The Company of **Biologists**

REVIEW

SUBJECT COLLECTION: MEMBRANE TRAFFICKING

Supply chain logistics – the role of the Golgi complex in extracellular matrix production and maintenance

John Hellicar[1,2,*], Nicola L. Stevenson[3,*], David J. Stephens[3,‡] and Martin Lowe[1,‡]

ABSTRACT

The biomechanical and biochemical properties of connective tissues are determined by the composition and quality of their extracellular matrix. This, in turn, is highly dependent on the function and organisation of the secretory pathway. The Golgi complex plays a vital role in directing matrix output by co-ordinating the post-translational modification and proteolytic processing of matrix components prior to their secretion. These modifications have broad impacts on the secretion and subsequent assembly of matrix components, as well as their function in the extracellular environment. In this Review, we highlight the role of the Golgi in the formation of an adaptable, healthy matrix, with a focus on proteoglycan and procollagen secretion as example cargoes. We then discuss the impact of Golgi dysfunction on connective tissue in the context of human disease and ageing.

KEY WORDS: Golgi complex, Collagen, Extracellular matrix, Glycosylation, Proteoglycans, Secretory pathway

Introduction

The extracellular matrix (ECM) is a complex, highly ordered network of proteins and attached carbohydrates, which provides structural support to tissues while dynamically influencing cellular processes, such as proliferation, differentiation and migration. The 'matrisome' itself consists of ~300 distinct proteins (Shao et al., 2020), the most abundant of which are the collagens. These form the basic support structure of tissues and thus determine their biomechanical properties, for example building long elastic fibres in tendons (Kannus, 2000) or a transparent layered lattice in the cornea (Meek, 2009). Collagens also provide a surface for integrin-mediated cell adhesion and can bind and store growth factors and other signalling molecules. Other major fibrous proteins contributing to ECM structure include fibronectin, elastin, laminins and tenascin (Frantz et al., 2010; Karamanos et al., 2021). The ECM also contains an abundance of proteoglycans, all composed of a core protein modified with one of six types of sulfated glycosaminoglycan (GAG) chains (Iozzo and Schaefer,

[1]School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, The Michael Smith Building, Oxford Road, Manchester, M13 9PT, UK. [2]Institute of Molecular and Cell Biology (IMCB), Agency for Science, Technology and Research (A*STAR), 61 Biopolis Drive, Proteos, Singapore, 138673. [3]Cell Biology Laboratories, School of Biochemistry, Faculty of Life Sciences, University Walk, University of Bristol, Bristol, BS8 1TD, UK.
*These authors contributed equally to this work

‡Author for correspondence (david.stephens@bristol.ac.uk; martin.p.lowe@manchester.ac.uk)

J.H., 0000-0001-5533-273X; N.L.S., 0000-0001-8967-7277; D.J.S., 0000-0001-5297-3240; M.L., 0000-0002-9331-8143

2015; Schwartz, 2000). These large linear polysaccharides have negatively charged carboxyl and sulfate groups, which are important for attracting water into tissues. They also regulate a wide range of biological functions as reviewed previously (Raman et al., 2005).

Matrix components are synthesised within the secretory pathway prior to exocytosis and assembly in the ECM. However, their size and extensive glycosylation pose many challenges for the cellular machinery. For example, fibrillar procollagen molecules can measure more than 300 nm in length (Bruns et al., 1979), far exceeding the diameter of traditional transport carriers, whereas the proteoglycan aggrecan accumulates ~100 GAG chains (Kiani et al., 2002), increasing in molecular mass 10-fold during transit. Furthermore, many ECM proteins, including procollagen, are synthesised as pro-proteins that need processing, and often carry post-translational modifications that must be tailored to suit specific tissues, developmental stage or injury (Frantz et al., 2010; Walma and Yamada, 2020).

The majority of the challenges of post-translational modification and processing of ECM proteins are met by the Golgi complex. Indeed, cells that produce large quantities of ECM, such as osteoblasts, chondrocytes and fibroblasts, have a prominent Golgi (Capulli et al., 2014; Florencio-Silva et al., 2015; Hascall, 1980) (Fig. 1; Movies 1 and 2). Although the capture of large ECM cargoes in endoplasmic reticulum (ER)-derived vesicles has previously attracted much attention (McCaughey and Stephens, 2019), the interplay between cargo modification and transit through the Golgi is an equally important topic, with errors in these processes leading to tissue malfunction. This Review will discuss the role of the Golgi as a central control point for ECM synthesis and maintenance, as well as the implications of this in health and disease. We will concentrate on two major classes of ECM proteins as case studies, namely the proteoglycans and fibrillar collagens. The Golgi is also relevant to matrix degradation, but this is not the focus here.

The central role of the Golgi complex

The Golgi complex acts as a hub for post-translational modification and sorting of cargo within the secretory pathway (Nakamura et al., 2012) (Fig. 2). In most vertebrate cells, the Golgi is comprised of stacked cisternae that are laterally connected to form a continuous ribbon located near the cell centre. Newly synthesised secretory cargo exits the ER in COPII-coated carriers and is delivered, via the ER-Golgi intermediate compartment (ERGIC) in vertebrates, to the entry, or *cis*-side, of the Golgi stack (Brandizzi and Barlowe, 2013). Cargo then moves across the Golgi stack, in a *cis* to *trans* direction, accessing the many Golgi-resident enzymes that carry out post-translational modification and processing of the cargo as it does so. Although the mechanism of cargo transit across the Golgi stack is still debated, most evidence, including analysis of procollagen trafficking (Bonfanti et al., 1998), favours the cisternal maturation model whereby cargo is retained within
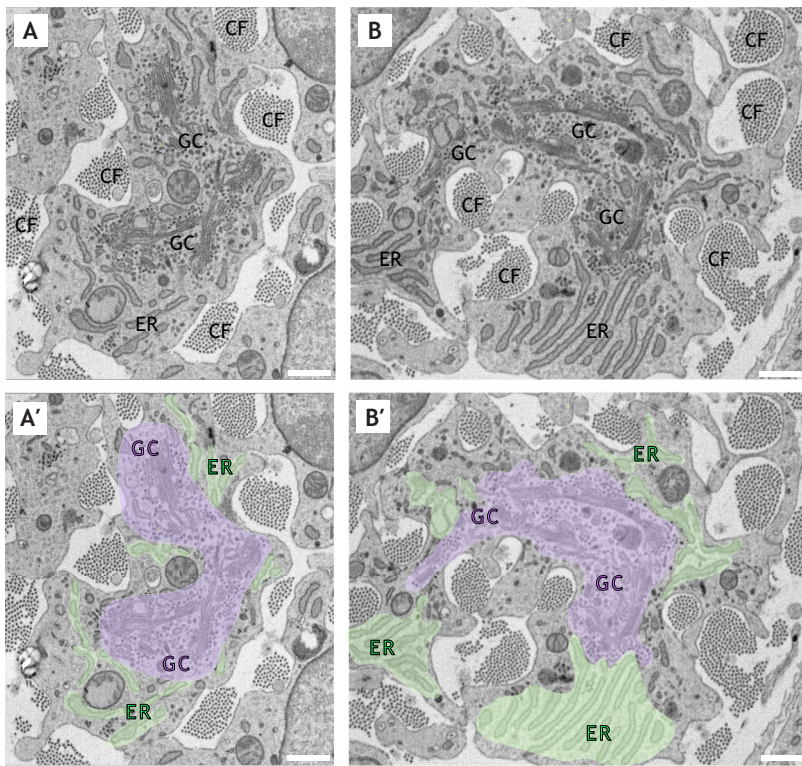
Fig. 1. Electron microscopy of the Golgi in mouse tendon fibroblast cells. (A,B) Images of two separate fibroblasts present in mouse tendon at embryonic day 17, imaged using high-resolution scanning electron microscopy. The Golgi complex (GC), endoplasmic reticulum (ER) and bundles of collagen fibres (CF) are indicated. A′ and B′ show colour-coded representations of A and B, respectively, with the Golgi highlighted in magenta and the ER in green. Note the prominent Golgi in the tendon fibroblasts, where it occupies a significant proportion of the cell area in the sections shown. The images were taken from 3D block face scanning electron microscopy series that are shown in Movies 1 and 2, respectively. Images courtesy of Professor Karl Kadler and Dr Yinhui Lu, Wellcome Centre for Cell-Matrix Research, University of Manchester, UK. Scale bars: 1 µm.

cisternae that progressively migrate and mature as they move across the stack (Glick and Nakano, 2009). Cisternal maturation is driven by the retrograde trafficking of COPI-coated transport vesicles that recycle Golgi-resident enzymes and other membrane constituents from later to earlier cisternae (Beck et al., 2009). COPI vesicles also mediate recycling of escaped ER residents, including chaperones, such as the major procollagen chaperone Hsp47 (also known as SERPINH1), from the *cis*-Golgi and ERGIC back to the ER. The machinery required for COPI trafficking is described in Box 1. The exit station of the Golgi is the *trans*-Golgi network (TGN), where cargo is sorted into carriers for delivery to the appropriate destination (Guo et al., 2014), which for ECM proteins is the cell exterior via exocytosis.

Golgi-based glycosylation
Golgi-resident enzymes mediate a wide range of post-translational modifications, including glycosylation, phosphorylation, sulfation and proteolytic processing (Baeuerle and Huttner, 1987; Moremen et al., 2012; Seidah et al., 2013; Yang et al., 2015). Glycosylation reactions within the Golgi involve the processing of N-linked glycans, whose synthesis is initiated at asparagine residues in the ER, as well as the initiation and processing of O-linked glycans that are attached to serine or threonine residues (Freeze, 2006; Schjoldager et al., 2020). These reactions are mediated by glycosyltransferases, of which there are at least 173 in humans (Schjoldager et al., 2020), and glycosidases, which promote the sequential modification and processing of glycan chains, respectively. Each enzyme has a specific distribution within the Golgi, which suggests a sequential function in glycan chain biosynthesis (Moremen et al., 2012; Schjoldager et al., 2020). Glycosylation is an abundant modification, with 2% of the eukaryotic proteome encoding for glycosylation machinery and ~85% of secretory proteins receiving this modification

(Schjoldager et al., 2020). This includes most ECM proteins, including the very highly glycosylated proteoglycans (PGNs), such as decorin (DCN) and biglycan (BGN) (see below). The combinatorial use of different enzymes allows a large variety of glycan structures to be produced, and the differential expression of enzymes allows the extent and nature of glycosylation to differ depending upon cell type and in response to functional needs (Moremen et al., 2012; Schjoldager et al., 2020).

Maintaining cisternal identity
Golgi enzymes and other resident proteins are maintained within specific regions of the Golgi despite the extensive flux of cargo through this organelle. This is ensured by COPI-mediated retrieval, which sorts residents into recycling COPI vesicles and delivers them back to the relevant cisternae by binding to golgin tethers (see Box 1). Transmembrane domain (TMD) length also plays a role in Golgi retention, allowing for energetically favourable partitioning of resident proteins into cisternal membranes of a similar bilayer thickness, which is known to increase in a *cis*- to *trans*-direction because of changes in lipid composition (Munro, 1995; Sharpe et al., 2010; Welch and Munro, 2019). It has also been found that Golgi proteins can segregate within cisternae, with Golgi enzymes residing towards the interior of cisternae at steady state, whereas the trafficking machinery is present at the rims (Tie et al., 2018). Bulky cargoes also appear to segregate from smaller soluble cargoes within cisternae (Tie et al., 2018). How intra-cisternal segregation of proteins is maintained is currently unclear, but likely involves lateral protein association, physical occlusion and possibly phase separation (Rebane et al., 2020; Rothman, 2019).

Golgi-based transcriptional control
In addition to its main role in post-translational modification and sorting of cargo, the Golgi participates in other cellular processes, including transcriptional regulation. An interesting example is that
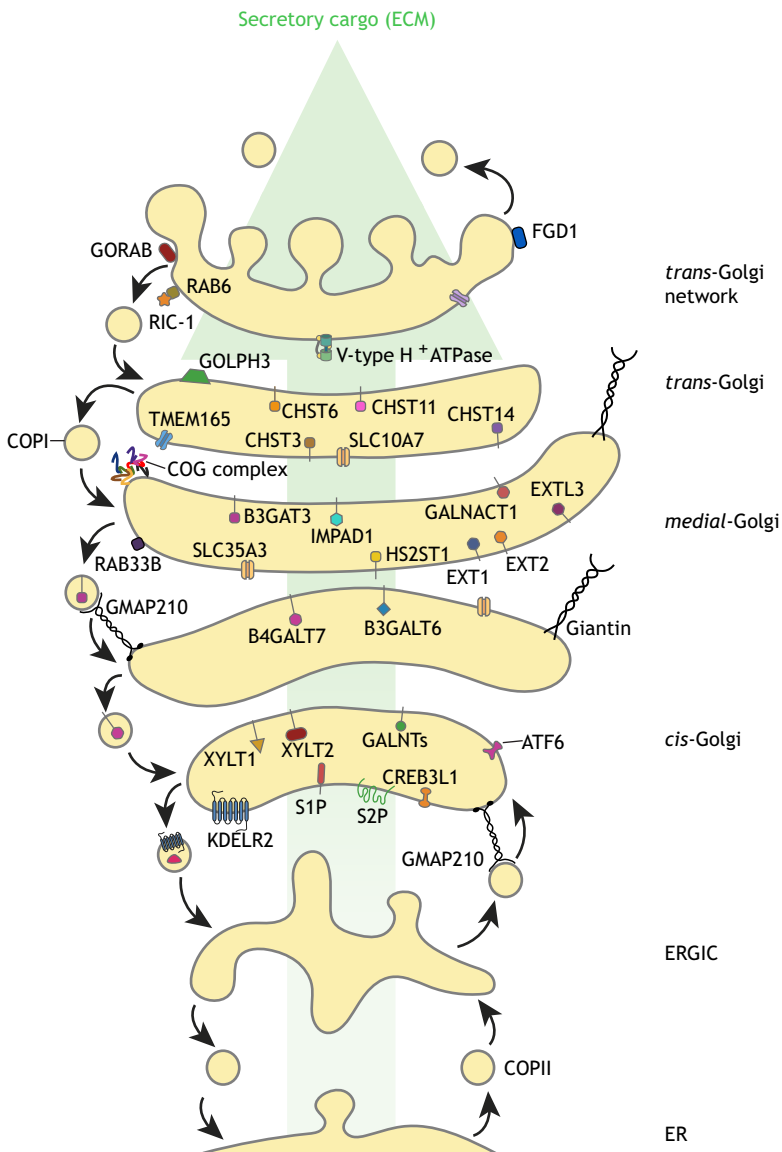
Fig. 2. The Golgi and Golgi proteins associated with ECM-related human disease. The Golgi acts as a hub for post-translational modification and cargo sorting within the cell. Cargo arrives at the *cis*-face of the Golgi from the endoplasmic reticulum (ER) via the ER-to-Golgi intermediate compartment (ERGIC). As it transports through the Golgi stacks, the cargo undergoes modification by a range of enzymes, which usually act sequentially. These enzymes are themselves trafficked within the Golgi in retrograde COPI-coated vesicles in order to maintain their retention and Golgi homeostasis. As cargo transits through the Golgi stacks, it reaches the *trans*-Golgi network, where it is sorted for delivery to its post-Golgi destination, which, in the case of ECM components, is the plasma membrane from where it is secreted. Shown in this diagram are some key Golgi proteins, including enzymes (depicted as lollipops), ion pumps and transporters, and trafficking proteins, that are known to be mutated in human diseases in which a matrix defect is a major component of the disease phenotype (Table 1).

of the membrane-tethered transcriptional factors CREB3L1 and CREB3L2 (cAMP responsive element-binding protein 3 like 1 and 2), which are important for bone and cartilage development (Caengprasath et al., 2021). In response to appropriate osteogenic or chondrogenic stimuli, these factors are cleaved in the Golgi by the zinc metalloproteases S1P and S2P [also known as membrane bound transcription factor peptidases site 1 and 2 (MBTPS1 and MBTPS2)] (Hino et al., 2014; Murakami et al., 2009). This releases N-terminal fragments of CREB3L1 and CREB3L2, which then enter the nucleus and stimulate transcription of procollagen and the COPII machinery required for ECM trafficking, notably Sec23A (Chen et al., 2014; Murakami et al., 2009; Saito et al., 2009a). Collagen synthesis in dermal fibroblasts is promoted by a similar mechanism (Ishikura-Kinoshita et al., 2012). Interestingly, it was recently shown that procollagen synthesis, including its secretory trafficking to and through the Golgi, is under circadian control, indicating another level of transcriptional regulation in matrix production (Chang et al., 2020). It is therefore clear that the ability of cells to produce ECM is sensitive to transcriptional regulation at the level of the Golgi, which can be in response to various physiological stimuli.

The importance of Golgi function in the production of ECM – GAG modification of proteoglycans
Synthesis of SLRP proteoglycans at the Golgi
The importance of Golgi organisation and function in producing matrix molecules, particularly with respect to glycosylation, is exemplified by the heavily glycosylated small leucine-rich repeat proteoglycans (SLRPs) biglycan (BGN) and decorin (DCN) (Chen and Birk, 2013). These proteoglycans consist of a core protein of 40 and 43 kDa, respectively, modified at the N-terminus by the addition of one (DCN) or two (BGN) chondroitin sulfate (CS) or dermatan sulfate (DS) GAG chains. They also carry N-linked glycans in their leucine-rich repeats (Chen and Birk, 2013).

The synthesis of CS or DS, as well as heparan sulfate (HS) and heparan, begins with the assembly of a common core tetrasaccharide followed by the addition of 100 or more GAG-specific repeating disaccharide units (Box 2). The sequential nature of GAG assembly is reflected in the organisation of Golgi enzymes. Chain initiation begins with the addition of xylose to specific serine residues in the core protein. Some studies report this might take place in the ER (Kearns et al., 1993; Vertel et al., 1993); however, it is likely the majority of xylose transfer occurs in the ERGIC and/or *cis*-Golgi

Box 1. Golgi trafficking machinery

Vesicle formation and cargo sorting

The small GTPase ARF1 (ARF3, ARF4 and ARF5 are also involved in Golgi trafficking) is activated by its guanine nucleotide exchange factors (GEFs) (GBF1 is the major ARF-GEF at the Golgi) (Claude et al., 1999; Sztul et al., 2019). As a result of binding GTP, ARF1 undergoes a conformational change and binds to the Golgi membrane, where it recruits the heptameric coatomer complex that assembles to form the COPI coat (Arakel and Schwappach, 2018). Additional scaffolding factors, such as SCYL1 and GORAB, also contribute to COPI recruitment and/or assembly (Hamlin et al., 2014; Witkos et al., 2019). Cargo is selected for inclusion into COPI vesicles by binding coatomer directly, or through binding to adaptor proteins that bridge the cargo to the coat. Adaptors include the KDEL receptor, which facilitates recycling of escaped resident proteins to the ER (Newstead and Barr, 2020), and GOLPH3, which mediates recycling of numerous Golgi enzymes proteins within the Golgi stack (Welch et al., 2021). Scission of COPI vesicles is poorly understood but appears to be promoted by ARF1 with possible involvement of additional factors such as CtBP/BARS (Arakel and Schwappach, 2018).

Vesicle tethering and fusion

COPI vesicles lose their coat following ARF-GAP activity and GTP hydrolysis, and become tethered to their target Golgi membrane. Tethering is mediated by the golgins, which are coiled-coil proteins found on the surface of the Golgi membrane (Gillingham and Munro, 2016; Witkos and Lowe, 2015). Different golgins localise to distinct Golgi regions and capture specific subsets of vesicles to direct transport and maintain cisternal identity (Gillingham and Munro, 2016; Witkos and Lowe, 2015). Additional interactions with RAB GTPases (Homma et al., 2021) and the multi-subunit tethering complex COG, which is a master coordinator of tethering and fusion (Blackburn et al., 2019), facilitate the transition from initial tethering to membrane fusion (Witkos and Lowe, 2017). Fusion represents the final step in transport and is catalysed by the SNARE proteins, which are short coiled-coil proteins that interact in a selective manner to drive membrane fusion (Wang et al., 2017). Post-fusion, RABs are recycled to the cytosol by RAB-GAPs, while SNARE complexes are dissociated by the AAA ATPase NSF and recycled back to the donor compartment to allow further rounds of transport (Homma et al., 2021; Wang et al., 2017).

(Jonsson et al., 2003; Kearns et al., 1993; Lohmander et al., 1989; Nuwayhid et al., 1986; Vertel et al., 1993). The core tetrasaccharide is then assembled in the *cis-medial* Golgi, while chain elongation and modification take place in the *medial-trans* Golgi (Prydz, 2015; Sugumaran et al., 1992; Sugumaran and Silbert, 1991). This organisation has been confirmed by multiple groups, showing that the machinery required for core tetrasaccharide assembly can be separated from that required for chain elongation and sulfation by using brefeldin A treatment (Calabro and Hascall, 1994; Jonsson et al., 2003; Spiro et al., 1991; Sugumaran et al., 1992; Sugumaran and Silbert, 1991; Uhlin-Hansen et al., 1997), which inhibits COPI transport and causes fusion of the early Golgi with the ER (Lippincott-Schwartz et al., 1989). Similarly, the addition of a KDEL sequence to DCN, which prevents its progression to the late Golgi, prevents chain elongation but not tetrasaccharide assembly (Jonsson et al., 2003). Sulfation is also ordered across the Golgi stack, with sulfation of the C6 and C4 positions in *N*-acetylgalactosamine occurring in the *trans*-Golgi (Hoppe et al., 1985; Sugumaran and Silbert, 1991). Meanwhile, epimerisation occurs specifically in the late *trans*-Golgi (Hoppe et al., 1985). This organisation likely ensures efficient glycan assembly and could regulate the nature or quantity of GAG chains produced.

The compartmentalisation of enzymes within cisternae also supports the formation of functional enzyme complexes to facilitate efficient substrate transfer between enzymes (Dick et al., 2012). In particular, epimerases and sulfotransferases have been observed in oligomeric complexes partitioned to distinct Golgi domains. The translocation of sugars from the cytosol into the lumen of specific cisternae also acts to increase precursor concentrations 50- to 100-fold in the vicinity of the relevant glycosyltransferases (Dick et al., 2012; Hirschberg and Snider, 1987). In the case of UDP-xylose, the Golgi itself acts as a site of synthesis, reducing the reliance of GAG initiation on sugar transporters (Kearns et al., 1991; Moriarity et al., 2002). Indeed, loss of the Golgi-resident UDP-xylose synthase leads to craniofacial defects in zebrafish (Eames et al., 2010). Cisternal pH is also important in GAG production, given that neutralisation with weak bases or proton pump inhibitors increases CS and DS sulfation (Grondahl et al., 2009; Harper et al., 1986).

The functional importance of SLRP proteoglycan synthesis

The presence, length, type and degree of sulfation of GAG chains is important for ECM and tissue function. In the case of DCN and BGN, CS is the main GAG in cartilage and bone, whereas DS is more prevalent in soft tissues, which might confer different properties relevant to the biomechanics of these tissues (Boskey et al., 1997; Yan et al., 2011). In bone, temporally regulated changes in SLRP expression during mineralisation (Takeuchi et al., 1990) and spatially regulated patterns of sulfate modification throughout the tissue (Takagi et al., 1991) all support the idea that Golgi GAG output is carefully controlled to orchestrate mineral deposition (Waddington et al., 2003). GAGs also affect the interaction of SLRPs with extracellular collagen. For example, binding to type I collagen is enhanced in the presence of GAG chains, at least *in vitro* (Schonherr et al., 1995), and DCN binds to type XII (Font et al., 1993, 1996), XIV (Ehnis et al., 1997) and VI (Nareyeck et al., 2004) collagen in a GAG-dependent way. The influence of GAG chains on fibrillogenesis, however, seems to be context specific; the presence of a DS chain on DCN can enhance (Kuc and Scott, 1997) or limit (Ruhland et al., 2007) fibril diameter *in vitro*, whereas dermatan sulfate epimerase I-null mice, which lack DS chains, have thicker fibrils in the skin (Maccarana et al., 2009).

Besides their direct influence on matrix structure, glycanated SLRPs also have important roles in signalling, which in turn is important for the differentiation and survival of matrix-producing cells. For example, BGN-mediated enhancement of bone morphogenic protein 4 (BMP-4) signalling, which is required for osteogenesis, is dependent on the presence of a GAG chain (Ye et al., 2012), and glycanation of BGN and DCN modulates availability and signalling of transforming growth factor β (TGF-β), which must be tightly controlled to maintain cell differentiation status (Hildebrand et al., 1994). A number of matrix diseases are attributable to defects in proteoglycan modification, as described further below (Table 1), underscoring the importance of this Golgi-localised process. Despite its obvious importance, we do not yet have a clear picture of how Golgi GAG chain output is controlled (reviewed in Mikami and Kitagawa, 2013).
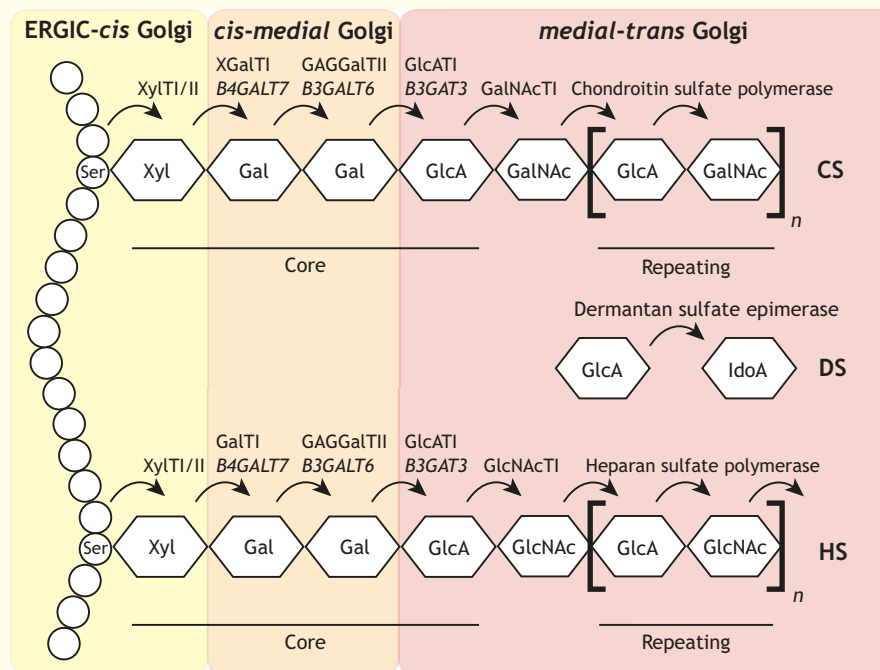
The importance of Golgi function in the production of ECM – transport and processing of procollagen

The Golgi plays a vital role in collagen production (Fig. 3). Additionally, studying this major fibrillar matrix protein has itself provided important insight into the processes of trafficking to and through the Golgi. Following its export from the ER in COPII-coated carriers, which involves several additional factors including TFG (McCaughey et al., 2016; Witte et al., 2011), TANGO1 (also known as MIA3) (Saito et al., 2009b) and cTAGE5 (also known as MIA2) (Saito

Box 2. GAG synthesis at the Golgi complex

As illustrated in the figure, the initiation of chondroitin sulfate (CS), dermatan sulfate (DS), heparan and heparan sulfate (HS) synthesis begins with the addition of xylose (Xyl) to specific serine residues in the core protein. This step is catalysed by xylosyltransferase I (XylTI) (Kearns et al., 1991) and II (Cuellar et al., 2007) in the ERGIC and early Golgi (Lohmander et al., 1989; Nuwayhid et al., 1986; Vertel et al., 1993). Two galactose residues (Gal) are then sequentially added in the *cis-medial* Golgi by β-1,4 galactosyltransferase 7 (XGalTI) and β-1,3 galactosyltransferase 6 (GAG GalTII), encoded by the *B4GALT7* and *B3GALT6* genes, respectively. Next, glucuronic acid (GlcA) is added by β-1,3-glucuronyltransferase 3 (GlcATI, encoded by *B3GAT3*) in the *medial-trans* Golgi (Pedersen et al., 2000). This completes the formation of the core tetrasaccharide linkage region common to all four GAGs. Mutations in any of the enzymes responsible for building this linkage cause a set of diseases termed linkeropathies (Mizumoto et al., 2013, 2015; Paganini et al., 2019). These are multisystemic disorders of connective tissues and skeletal structures, characterised by a loss of GAG content in the ECM (see Table 1 for a summary).

The addition of a fifth sugar in the *medial-trans* Golgi determines which GAG is built – the addition of N-acetyl-D-galactosamine (GalNAc) by GalNAc transferase I (GalNAcTI) (Rohrmann et al., 1985; Sato et al., 2003) initiates DS or CS synthesis, whereas the addition of N-acetyl-D-glucosamine (GlcNAc) by GlcNAc transferase I initiates HS or heparan synthesis. Chain elongation then proceeds with the addition of more than 100 chain-specific repeating disaccharide units – [4GlcAβ1-3GalNAcβ1] for CS or DS and [4GlcAβ1-4GlcNAcα1] for HS or heparan. CS and DS elongation is catalysed by the enzyme complex chondroitin sulfate polymerase. This complex includes a chondroitin sulfate polymerase (ChSy), which possesses both CS-GlcATII and GalNAcTII enzymatic activities, and the chaperone chondroitin polymerase factor (ChPF). DS is then created through the conversion of GlcA to IdoA within the chain by dermatan sulfate epimerase. Heparan chains are built by the heparan sulfate polymerase, consisting of EXT1 and EXT2, and can also undergo GlcA to IdoA conversion. All chains are sulfated in the *medial-trans* Golgi concurrent with chain elongation (Sugumaran and Silbert, 1990). GAG chain synthesis and sulfation, not discussed here, is reviewed in more detail in Silbert and Sugumaran (2002). The sulfotransferases associated with disease are also summarised in Table 1.

procollagen is delivered, via the ERGIC, to the *cis*-Golgi (McCaughey et al., 2021). Once in the Golgi, procollagen congregates in specific dilated domains of Golgi cisternae, as shown by EM studies (Fig. 3) (Bonfanti et al., 1998; Leblond, 1989; Marchi and Leblond, 1984; Mironov et al., 2001; Trelstad and Hayashi, 1979; Trucco et al., 2004). These procollagen aggregates are only observed within cisternae and never in vesicles or intra-Golgi tubules (Trucco et al., 2004), consistent with them being too large to fit into these carriers, and instead transiting the Golgi in maturing cisternae. In certain cell types, procollagen also aligns into parallel arrays as it progresses from the *cis*- to *trans*-Golgi (Bonfanti et al., 1998; Leblond, 1989; Marchi and Leblond, 1984; Mironov et al., 2001; Trelstad and Hayashi, 1979; Trucco et al., 2004), and it maintains this organisation as it buds off into post-Golgi carriers. Concentration and alignment of the procollagen molecules within Golgi distensions thus provides a means to organise them early in their synthesis to facilitate fibrillogenesis.

Simultaneously with aggregation, procollagen acquires sugar modifications upon reaching the more *trans*-cisternae (Leblond, 1989). There is also increasing evidence to suggest that proteolytic processing of procollagen begins within the Golgi (Canty-Laird et al., 2012; Humphries et al., 2008; Stevenson et al., 2021). Fibrillar procollagen molecules consist of a central triple helical domain flanked by globular N- and C-terminal propeptide domains that are removed prior to, or concomitant with, fibril formation (Canty and Kadler, 2005; Miyahara et al., 1984) (Fig. 3). Although these processing steps can occur in the extracellular environment, pulse-chase experiments with ^{14}C-labelled type I procollagen show that cleavage can start within the secretory pathway (Canty-Laird et al., 2012; Humphries et al., 2008). Consistent with this, N-propeptide cleavage can proceed in the presence of brefeldin A in tendon explants, indicating at least some N-propeptidase activity is localised to the early secretory pathway (Canty-Laird et al., 2012).

Table 1. Human diseases caused by mutation of Golgi-localised proteins where a major aspect of the disease phenotype is due to an impairment of ECM assembly or function

Protein	Protein function	Disease and MIM	Phenotype	References
Golgi enzymes				
β-1,3-galactosyltransferase 6 (B3GALT6)	Glycosyltransferase. Required for the third step in GAG biosynthesis – transfers galactose to galactose residue on the PGN tetrasaccharide linker region (Box 2).	Ehlers–Danlos syndrome, spondylodysplastic type 2 (EDSSPD2). Linkeropathy. MIM 615349	Skin hyperextensibility, articular hypermobility, tissue fragility, short stature, aged appearance, loose but elastic skin, craniofacial disproportion, osteopenia, defective wound healing, hypermobile joints, hypotonic muscles and developmental delay.	Nakajima et al., 2013; Van Damme et al., 2018
		Spondyloepimetaphyseal dysplasia with joint laxity 1, with or without fractures (SEMDJL1). Linkeropathy. MIM 271640	Bone disease characterised by vertebral abnormalities and ligamentous laxity that results in spinal misalignment and progressive severe kyphoscoliosis, thoraic asymmetry and respiratory compromise. Elbow deformities with radial head dislocation, dislocated hips, clubfeet and tapered fingers.	Malfait et al., 2013; Nakajima et al., 2013
		Al-Gazali syndrome (ALGAZ). Linkeropathy. MIM 609465	Prenatal growth retardation, joint contractures, camptodactyly, bilateral talipes equinovarus, small mouth, anterior segment eye anomalies and early lethality.	al Gazali et al., 1994; Ben-Mahmoud et al., 2018; Sellars et al., 2014
β-1,3-glucuronyltransferase 3 (B3GAT3)	Glycosyltransferase. Required for the fourth, step in GAG biosynthesis – transfers glucuronic acid to galactose residue on the PGN tetrasaccharide linker region (Box 2).	Multiple joint dislocations, short stature and craniofacial dysmorphism with or without congenital heart defects (JDSCD). Linkeropathy. MIM 245600	Dysmorphic craniofacial features, bilateral dislocations of the elbows, hips and knees, clubfeet and short stature alongside cardiovascular defects.	Baasanjav et al., 2011; Budde et al., 2015; Jones et al., 2015; von Oettingen et al., 2014
β-1,4-galactosyltransferase 7 (B4GALT7)	Glycosyltransferase. Required for the second step in GAG biosynthesis – transfers galactose to xylose on the PGN tetrasaccharide linker region (Box 2).	Ehlers–Danlos syndrome, spondylodysplastic type 1 (EDSSPD1). Linkeropathy. MIM 130070	Skin hyperextensibility, articular hypermobility, tissue fragility, short stature, developmental anomalies of the forearm bones and elbow and bowing of the extremities.	Okajima et al., 1999
Carbohydrate sulfotransferase 3 (CHST3)	Sulfotransferase. Catalyses the transfer of sulfate to position 6 of the GalNAc residue of chondroitin.	Spondyloepiphyseal dysplasia with congenital joint dislocations (SEDCJD). MIM 143095	Bone dysplasia characterised by dislocation of the knees and/or hips at birth, clubfoot, elbow joint dysplasia with sublaxation and limited extension, short stature and progressive kyphosis.	Hermanns et al., 2008; Thiele et al., 2004
Carbohydrate sulfotransferase 6 (CHST6)	Sulfotransferase. Catalyses the transfer of sulfate to position 6 of the GlcNAc residues of keratan.	Macular dystrophy, corneal (MCD). MIM 217800	Ocular disease characterised by bilateral, progressive corneal opacification and reduced corneal sensitivity. Caused by deposition of unsulfated keratan sulfate within both the intracellular space and in the extracellular corneal stroma.	Akama et al., 2000; Niel et al., 2003
Carbohydrate sulfotransferase 11 (CHST11)	Sulfotransferase Catalyses the transfer of sulfate to position 4 of the GalNAc residue of chondroitin.	Osteochondrodysplasia, brachydactyly, and overlapping malformed digits (OCBMD). MIM 618167	Bilateral symmetric skeletal defects primarily affecting the limbs. Mild short stature due to short lower leg bones and hand and foot malformations (predominantly brachydactyly and overlapping digits).	Shabbir et al., 2018

Table 1. Continued

Protein	Protein function	Disease and MIM	Phenotype	References
Carbohydrate sulfotransferase 14 (CHST14)	Sulfotransferase Catalyses transfer of sulfate to position 4 of the GalNac residue of dermatan.	Ehlers–Danlos syndrome, musculocontractural type 1 (EDSMC1). MIM 601776	Craniofacial dysmorphism, congenital contractures of thumbs and fingers, clubfeet, severe kyphoscoliosis, muscular hypotonia, hyperextensible thin skin, wrinkled palms, joint hypermobility and ocular involvement.	Dündar et al., 2009; Hirose et al., 2019; Malfait et al., 2010; Miyake et al., 2010
Chondroitin sulfate N-acetylgalactosaminyltransferase 1 (CSGALNACT1)	Transfers GalNAc to GlcUA. Involved in CS and DS biosynthesis (Box 2).	Skeletal dysplasia, mild, with joint laxity and advanced bone age (SDJLABA). MIM 618870	Skeletal dysplasia, short stature, short long bones, advanced bone age, joint laxity and facial dysmorphism.	Meyer et al., 2019; Mizumoto et al., 2020; Vodopiutz et al., 2017
Dermatan sulfate epimerase	Converts D-glucuronic acid into L-iduronic acid. DS biosynthesis (Box 2).	Ehlers–Danlos syndrome musculocontractural type 2 (EDSMC2). MIM 615539	Joint dislocation and deformities, skin hyperextensibility, skin bruisability and fragility, cardiac valvular, respiratory, gastrointestinal and ophthalmologic complications.	Müller et al., 2013
Exostosin-1 (EXT1)	HS-polymerase complex component. Involved in HS biosynthesis.	Hereditary multiple exostoses 1 (EXT1). MIM 133700	Skeletal disorder that primarily affects endochondral bone during growth. Characterised by numerous cartilage-capped, benign bone tumours, skeletal deformities and short stature.	Hecht et al., 1997; Philippe et al., 1997; Wuyts et al., 1998
		Chondrosarcoma (CHDSA). MIM 215300	Malignant neoplasm derived from cartilage cells, ranging from slow-growing, non-metastasising lesions to highly aggressive metastasising sarcomas.	Hecht et al., 1997
Exostosin-2 (EXT2)	HS-polymerase complex component. Involved in HS biosynthesis.	Hereditary multiple exostoses 2 (EXT2). MIM 133701	Skeletal disorder that primarily affects endochondral bone during growth. Characterised by numerous cartilage-capped, benign bone tumours, skeletal deformities and short stature.	Philippe et al., 1997
Exostosin-like 3 (EXTL3)	Glycosyltransferase. Involved in HS biosynthesis.	Immunoskeletal dysplasia with neurodevelopmental abnormalities (ISDNA). MIM 617425	Variable skeletal abnormalities and neurodevelopmental defects. Skeletal features include disproportionate short stature, cervical malformations, epiphyseal and metaphyseal dysplasia.	Oud et al., 2017; Volpi et al., 2017
Heparan sulfate 2-O-sulfotransferase 1 (HS2ST1)	Sulfotransferase. Transfers sulfate group to the C2-position of selected uronic acid residues within heparan sulfate.	Neurofacioskeletal syndrome with or without renal agenesis. MIM 619194	Developmental delay, corpus callosum hypoplasia or agenesis, facial dysmorphism and skeletal abnormalities including short stature, scoliosis and flexion contractures with broad fingertips and toes.	Schneeberger et al., 2020
IMPAD1	Nucleotide phosphatase. Role in sulfation of GAGs on PGNs.	Chondrodysplasia with joint dislocations, GRAPP type (CDP-GRAPP). MIM 614078	Congenital joint dislocations, chondrodysplasia with short stature, micrognathia and cleft palate and a distinctive face.	Vissers et al., 2011
S1P	Serine protease. Mediates regulated intramembrane proteolysis (RIP) of transcription factors.	Spondyloepiphyseal dysplasia, Kondo–Fu type (SEDKF). MIM 618392	Severely retarded growth, spondyloepiphyseal dysplasia, reduced bone mineral density, pectus carinatum, kyphosis, a waddling gate, brachydactyly and dysmorphic facial features.	Kondo et al., 2018

Table 1. Continued

Protein	Protein function	Disease and MIM	Phenotype	References
S2P	Zinc metalloprotease. Mediates regulated intramembrane proteolysis (RIP) of transcription factors.	IFAP syndrome with or without BRESHECK syndrome. MIM 308205	Follicular itchyosis, total or subtotal atrichia and photophobia.	Oeffner et al., 2009
		Keratosis follicularis spinulosa decalvans X-linked (KFSDX). MIM 308800	Thickening of the skin of the neck, ears and extremities, particularly the palms and soles. Loss of eyebrows, eyelashes and beard, thickening of the eyelids with blepharitis and ectropion and corneal degeneration.	Aten et al., 2010
		Olmsted syndrome, X-linked (OLMSX). MIM 300918	Bilateral mutilating palmoplantar keratoderma and periorificial keratotic plaques with severe itching. Diffuse alopecia, constriction of digits and onychodystrophy have also been reported.	Haghighi et al., 2013
		Osteogenesis imperfecta 19 (OI19). MIM 301014	Low bone mass, bone fragility, prenatal fractures, short stature, white sclerae, variable scoliosis and pectal deformity, striking tibial anterior angulation and generalised osteopenia.	Lindert et al., 2016
Soluble Ca^{2+}-activated nucleotidase 1 (CANT1)	Ca^{2+}-dependent nucleotidase. Involved in PGN synthesis.	Desbuquois dysplasia 1 (DBQD1). MIM 251450	Chondrodysplasia characterised by severe prenatal and postnatal growth retardation, joint laxity, short extremities, progressive scoliosis, round face, midface hypoplasia and prominent bulging eyes.	Faden et al., 2010; Huber et al., 2009; Laccone et al., 2011
		Epiphyseal dysplasia, multiple, 7 (EDM7). MIM 617719	Skeletal dysplasia characterised by joint pain, joint deformity, waddling gait, short stature and significant morbidity.	Balasubramanian et al., 2017
Xylosyltransferase 1 (XYLT1)	Glycosyltransferase. Required for the initial step in GAG biosynthesis – transfers xylose to serine residues on the PGN tetrasaccharide linker region (Box 2).	Desbuquois dysplasia 2 (DBQD2). Linkeropathy. MIM 615777	Chondrodyplasia characterised by severe prenatal and postnatal growth retardation, dislocations of large joints, joint laxity, short extremities, progressive scoliosis, round face, midface hypoplasia and prominent bulging eyes.	Al-Jezawi et al., 2017; Bui et al., 2014; Schreml et al., 2014
Xylosyltransferase 2 (XYLT2, XylT 2)	Glycosyltransferase. Required for the initial step in GAG biosynthesis – transfers xylose to serine residues on the PGN tetrasaccharide linker region (Box 2).	Spondyloocular syndrome (SOS). Linkeropathy. MIM 605822	Characterised by cataract, loss of vision due to retinal detachment, facial dysmorphism, facial hypotonia, short trunk, osteoporosis, immobile spine with thoracic kyphosis and reduced lumbar lordosis.	Munns et al., 2015
Ion pumps and transporters				
ATP6V0A2	V-type H^+ ATPase subunit. Acidifies the Golgi.	Cutis laxa autosomal recessive 2A (ARCL2A). MIM 219200	Excessive congenital skin wrinkling, a large fontanelle with delayed closure, a typical facial appearance with downslanting palpebral fissures, general connective tissue weakness and varying degrees of growth and developmental delays.	Kornak et al., 2008
		Wrinkly skin syndrome (WSS). MIM 278250	Wrinkling of the skin of the dorsum of the hands and feet, an increased number of palmar and plantar creases, wrinkled abdominal skin, multiple musculoskeletal abnormalities, microcephaly, growth failure and developmental delay.	Kornak et al., 2008

Table 1. Continued

Protein	Protein function	Disease and MIM	Phenotype	References
ATP6V1A	V-type H$^+$ ATPase subunit. Acidifies the Golgi.	Cutis laxa autosomal recessive 2D (ARCL2D). MIM 617403	Excessive congenital skin wrinkling, a large fontanelle with delayed closure, a typical facial appearance with downslanting palpebral fissures, general connective tissue weakness.	Van Damme et al., 2017
ATP6V1E1	V-type H$^+$ ATPase subunit. Acidifies the Golgi.	Cutis laxa autosomal recessive 2C (ARCL2C). MIM 617402	Excessive congenital skin wrinkling, a large fontanelle with delayed closure, a typical facial appearance with downslanting palpebral fissures, general connective tissue weakness.	Van Damme et al., 2017
ATP7A	ATP-driven copper ion pump of the TGN. Intracellular copper ion homeostasis.	Menkes disease (MNK). MIM 309400	Progressive neurodegeneration and connective tissue disturbances. Early growth retardation, cutis laxia, vascular complications and death in early childhood.	Møller et al., 2005; Skjørringe et al., 2017; Tümer et al., 1997
		Occipital horn syndrome (OHS). MIM 304150	Unusual facial appearance, skeletal abnormalities including occipital horns, short, broad clavicles, deformed radii, ulnae and humeri, narrowing of the rib cage, undercalcified long bones with thin cortical walls and coxa valga.	Dagenais et al., 2001; Ronce et al., 1997; Tang et al., 2006
SLC10A7	Potential Ca^{2+} transporter. Plays a role in protein glycosylation and transport of PGNs and glycoproteins to the ECM.	Short stature, amelogenesis imperfecta and skeletal dysplasia with scoliosis (SSASKS). MIM 618363	Disproportionate short stature, defective tooth enamel formation and skeletal dysplasia with severe scoliosis in some patients.	Ashikov et al., 2018; Dubail et al., 2018; Laugel-Haushalter et al., 2019
SLC35A3	UDP-GlcNAc transporter. Plays a role in protein glycosylation.	Arthrogryposis, mental retardation and seizures (AMRS). MIM 615553	Arthrogryposis, mental retardation, autism spectrum disorder, epilepsy, limb malformations, distal joint involvement, microcephaly, retromicrognathia and general muscle hypotonia.	Edvardson et al., 2013
TMEM165	Potential Ca^{2+} transporter. Plays a role in protein glycosylation and transport of PGNs and glycoproteins to the ECM.	Congenital disorder of glycosylation 2 K (CDG2 K). MIM 614727	Growth retardation, psychomotor retardation, short stature, dysmorphism, hypotonia, eye abnormalities, acquired microcephaly, hepatomegaly and skeletal dysplasia.	Foulquier et al., 2012; Rosnoblet et al., 2013; Zeevaert et al., 2013
Trafficking proteins				
Beta′-COP (COPB2)	Coatomer (COPI) subunit. Intra-Golgi and Golgi to ER trafficking.	Microcephaly 19. MIM 617800	Osteoporosis, osteopenia, fractures, developmental delay of varying severity and microcephaly.	DiStasio et al., 2017; Marom et al., 2021
COG1	COG complex subunit. Intra-Golgi trafficking.	Congenital disorder of glycosylation 2G (CDG2G). MIM 611209	Generalised hypotonia, growth retardation with rhizomelic short stature, mild psychomotor retardation, microcephaly, facial dysmorphism.	Foulquier et al., 2006
COG4	COG complex subunit. Intra-Golgi trafficking.	Saul–Wilson syndrome (SWILS). MIM 618150	Skeletal dysplasia with short stature, prominent forehead, prominent eyes with cataracts, narrow nasal bridge, micrognathia, clubfoot, brachydactyly and short distal phalanges of fingers.	Ferreira et al., 2018

Table 1. Continued

Protein	Protein function	Disease and MIM	Phenotype	References
COG7	COG complex subunit. Intra-Golgi trafficking.	Congenital disorder of glycosylation 2E (CDG2E). MIM 608779	Dysmorphism including low-set dysplastic ears, micrognathia, short neck and loose, wrinkled skin, in addition to skeletal dysplasia, generalised hypotonia and hepatosplenomegaly.	Wu et al., 2004
Delta-COP (COPD/ARCN1)	Coatomer (COPI) subunit. Intra-Golgi and Golgi to ER trafficking.	Short stature, rhizomelic, with microcephaly, micrognathia and developmental delay (SRMMD). MIM 617164	Facial dysmorphism, severe micrognathia, microcephaly, rhizomelic short stature and mild developmental delay.	Izumi et al., 2016
Dymeclin	Plays a role in trafficking of ECM components.	Dyggve–Melchior–Clausen syndrome (DMC). MIM 223800	Spondyloepimetaphyseal dysplasia characterised by progressive short trunk dwarfism, microcephaly, protruding sternum and psychomotor retardation.	Dimitrov et al., 2009; El Ghouzzi et al., 2003
		Smith–McCort dysplasia 1 (SMC1). MIM 607326	Osteochondrodysplasia characterised by short limbs and trunk with barrel-shaped chest.	Nakamura et al., 1997; Santos et al., 2009
FGD1	Cdc42 GEF. TGN trafficking.	Aarskog–Scott syndrome. 305400	Short stature and multiple facial, limb and genital abnormalities.	Orrico et al., 2000; Schwartz et al., 2000
GMAP210 (TRIP11)	Golgin. Anterograde and retrograde trafficking.	Achondrogenesis 1A (ACG1A). MIM 200600	Lethal chondrodysplasia characterised by deficient ossification in the lumbar vertebrae and absent ossification in the sacral, pubic and ischial bones.	Smits et al., 2010; Wehrle et al., 2019
		Odontochondrodysplasia (ODCD). MIM 184260	Mesomelic shortening of tubular bones, ligamentous laxity, scoliosis, detinogenesis imperfecta, trident pelvis, posteriorly flattened vertebrae and brachydactyly with cone-shaped epiphyses.	Wehrle et al., 2019
GORAB	COPI scaffold. Aids COPI assembly at the TGN.	Geroderma osteodysplasticum (GO). MIM 231070	Lax, wrinkled skin, joint laxity, typical face with a prematurely aged appearance, severe osteoporosis leading to frequent fractures, malar and mandibular hypoplasia and growth retardation.	Hennies et al., 2008
RAB33B	Rab GTPase. Functions in intra-Golgi transport and autophagy.	Smith–McCort dysplasia 2 (SMC2). MIM 15222	Short limbs and trunk with barrel-shaped chest, platyspondyly and kyphoscoliosis.	Dupuis et al., 2013
RIC-1	RAB6 GEF. Functions in various Golgi trafficking steps.	Cleft lip, cataract tooth abnormality, intellectual disability, facial dysmorphism, attention-deficit hyperactivity disorder syndrome (CATIFA). MIM 618761	Global developmental delay, intellectual disability and behavioural abnormalities. Craniofacial dysmorphism, cleft lip/palate, tooth abnormalities and visual impairment.	Patel et al., 2017; Unlu et al., 2020

Furthermore, loss of the *cis-medial*-golgin giantin (also known as GOLGB1) results in the loss of intracellular N-propeptide processing in cell culture, further implicating this compartment in this step (Stevenson et al., 2021).

The precise role of the *cis*-Golgi, and giantin, in regulating procollagen processing remains elusive; however, it is likely that this compartment is home to at least one procollagen N-propeptidase, which may require giantin for its localisation or processing. So far five N-propeptidases have been identified in mammals, which are all secreted: ADAMTS-2, -3 and -14, and meprin-α and -β (Bekhouche and Colige, 2015; Broder et al., 2013). These are all expressed as zymogens, which themselves need to be cleaved for activation. For the ADAMTS proteins, this is achieved by furin-like convertases in the TGN (Wang et al., 2003). In turn, the furin-like convertases are also expressed as inactive precursors that undergo autocatalytic activation in the TGN (Leduc et al., 1992). Interestingly, treatment of tendon explants with furin inhibitors does reduce, but does not eliminate, intracellular procollagen N-propeptide cleavage (Canty-Laird et al., 2012). Therefore, a furin-like convertase proteolytic cascade is required, at least in part, for intracellular procollagen

processing, but a stable pool of active propeptidase, or an unidentified furin-independent enzyme, must also exist within the early secretory pathway to explain the experimental observations.

Genetic disorders of the ECM linked to Golgi function

Given the importance of the Golgi in the production and maintenance of the ECM, as exemplified above, it is unsurprising that many genetic disorders caused by mutations in Golgi proteins result in matrix defects. These are typically rare, but give important insights into matrix biogenesis. In this section, we describe examples of such disorders to illustrate the different mechanisms that can underlie a matrix phenotype (Table 1, see also Fig. 2). Some of these

disorders lie within the larger class of disorders known as congenital disorders of glycosylation (CDGs), which arise from defects in glycosylation and often manifest as multisystemic phenotypes (Freeze and Ng, 2011; Péanne et al., 2018; Reily et al., 2019). These have been covered elsewhere, and here, we only highlight certain examples of CDGs that result in a major ECM defect.

Golgi enzymes

A number of disorders with a matrix phenotype can be attributed to mutations in Golgi enzymes (Table 1). For example, mutation of β-1,4-galactosyltransferase 7 (*B4GALT7*), involved in generating the tetrasaccharide linkage region of PGNs (Box 2), results
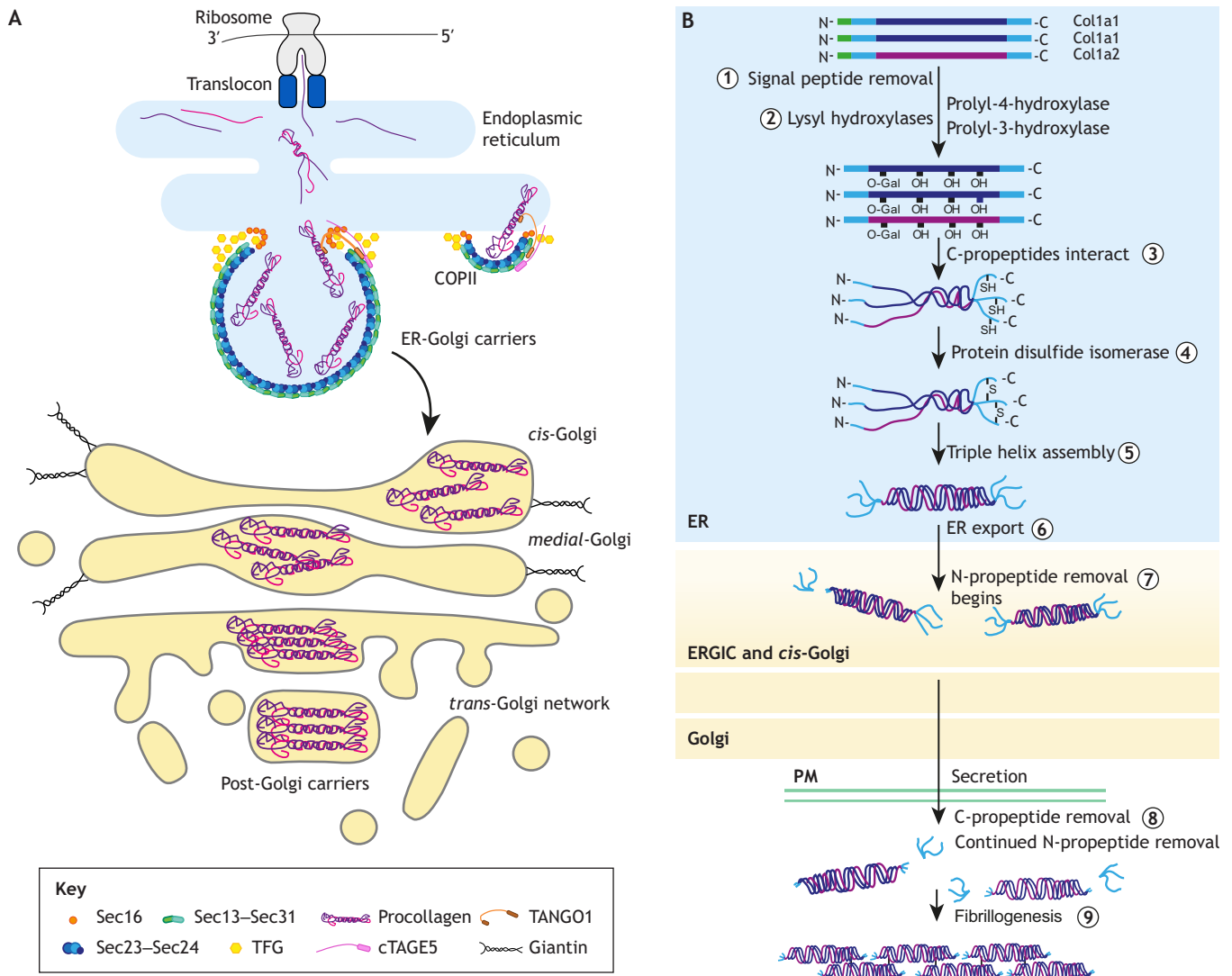

Fig. 3. Procollagen processing and trafficking. (A) Schematic overview of procollagen secretion. Procollagen molecules are co-translationally imported into the ER and assemble into a triple helix (see B). They are then exported from the ER in a COPII-dependent manner. COPII assembly is driven by the core coat subunits Sec23, Sec24, Sec13 and Sec31 and is facilitated by other factors, including Sec16 and TFG. The recruitment of procollagen to the carriers is enabled by the adaptors TANGO1 and cTAGE5. Once procollagen is transferred to the Golgi, it transits through the cisternae before packaging into post-Golgi carriers for transport to the cell surface. (B) Procollagen synthesis. Type I procollagen is synthesised as two Col1a1 chains and one Col1a2 chain, which are co-translationally imported into the ER. After import, signal peptides are removed (1) and key lysine residues in the triple helical domain of each chain are hydroxylated (2). Some glycosylation also takes place. Lysyl hydroxylation initiates the folding of the trimeric procollagen molecule, beginning with the interaction of the C-terminal ends of each chain (3) and stabilisation by disulfide bond formation (4). The chains then zipper up to form a triple helical molecule flanked by globular N- and C-terminal propeptide domains (5). Immature procollagen is exported from the ER (6) and progresses through the ERGIC to the cis-Golgi. Between these compartments, N-propeptide cleavage is initiated by an unknown enzyme (7). Procollagen then progresses through the Golgi and is secreted into the extracellular space where the C-propeptide is proteolytically cleaved by mTLD, TLL1, TLL2 or BMP1 (8). N-propeptides that escape intracellular processing are also proteolytically cleaved here by ADAMTS-2, -3, -14 and/or meprin-α or -β. Following processing, the mature triple helical collagen assembles into fibrils (9).

in defective glycosylation of DCN and BGN (Seidler et al., 2006) in the connective tissue disorder Ehlers–Danlos syndrome, spondylodysplastic type 1 (EDSSPD1) (Faiyaz-Ul-Haque et al., 2004; Götte and Kresse, 2005; Kresse et al., 1987; Okajima et al., 1999). Collagen fibril formation is severely perturbed in EDSSPD1 fibroblasts (Seidler et al., 2006), confirming the importance of both DCN and BGN glycosylation in this process. A similar outcome was seen with mutations in the gene encoding the related enzyme β-1,3-galactosyltransferase 6 (*B3GALT6*), which causes Ehlers–Danlos syndrome, spondylodysplastic type 2 (EDSSPD2) and spondyloepimetaphysical dyspasia with joint laxity 1 (SEMDJL1) (Malfait et al., 2013; Nakajima et al., 2013; Van Damme et al., 2018; Vorster et al., 2015). Other Golgi enzymes involved in the formation of the tetrasaccharide linkage region of PGNs have also been found to be responsible for connective tissue disorders, and collectively these disorders have been termed linkeropathies (Jones et al., 2015; Mizumoto et al., 2015; Ritelli et al., 2019).

Mutation of Golgi enzymes involved in processes other than glycan processing can also result in matrix defects. An interesting example is provided by the metalloprotease S2P (Caengprasath et al., 2021), whose mutation causes the X-linked bone disorder osteogenesis imperfecta 19 (OI19) (Lindert et al., 2016). Both of the S2P mutations that have so far been identified in OI19 patients are found in intramembrane residues critical for metal ion coordination (Lindert et al., 2016). Consequently, the cleavage of its substrate transcription factor CREB3L1 is impaired. This results in reduced synthesis and secretion of procollagen, explaining the bone phenotype seen in patients (Lindert et al., 2016).

Ion pumps and transporters

The Golgi relies on a variety of pumps and transporters to maintain correct luminal pH and ion composition, as well as to move sugars into the Golgi for glycosylation reactions. Golgi pH is crucial for the activity and localisation of glycosyltransferases (Guillard et al., 2009), and hence disruption of pH can have wide-ranging effects upon cargo modification. For example, mutation of ATP6V0A2, a subunit of the V-type H^+ ATPase that acidifies many organelles including the Golgi (Futai et al., 2000), leads to defects in both N- and O-linked glycosylation, impaired Golgi trafficking and disruption of Golgi structure (Hucthagowder et al., 2009; Kornak et al., 2008; Udono et al., 2015). These defects manifest as autosomal recessive cutis laxa 2 (ARCL2A) (Kornak et al., 2008), characterised by wrinkly, inelastic skin and bone abnormalities, consistent with ECM changes playing a prominent role in the disease aetiology.

Disruption of Golgi ion homeostasis can result in ECM defects in other ways. For example, mutation of ATP7A, a TGN-localised ATP-driven copper ion pump, causes occipital horn syndrome (OHS), an X-linked recessive disorder that affects the connective tissue, skeleton and nervous system (Dagenais et al., 2001; Ronce et al., 1997; Tang et al., 2006). The ECM abnormalities can be explained by reduced activity of the ATP7A substrate lysyl oxidase, a cuproenzyme required for initiation of cross-linking of collagen and elastin. ATP7A mutations also cause Menkes disease, a more severe disorder that is usually fatal in childhood with connective tissue defects and progressive neurodegeneration (Møller et al., 2005; Skjørringe et al., 2017; Tümer et al., 1997). The pathological mechanisms of OHS and Menkes disease are likely conserved, with Menkes arising from a complete loss of ATP7A activity, whereas in OHS there is residual activity, resulting in a milder phenotype.

Trafficking proteins

Mutations in Golgi trafficking machinery have been found to cause various ECM disorders (Table 1). For example, mutation of the COPI subunit β′-COP (COPB2), leading to haploinsufficiency, has recently been shown to cause a disorder characterised by osteoporosis and developmental delay (Marom et al., 2021). This is thought to be caused by disrupted procollagen trafficking to the Golgi, likely due to defective recycling of the machinery required to maintain anterograde flux of this cargo. Interestingly, mutations in β′-COP have also been attributed to the disorder microcephaly 19 (DiStasio et al., 2017). Given that recent work has shown a link between microcephaly and impaired ECM secretion (Esk et al., 2020), one might speculate that the underlying cause of microcephaly 19 could be improper trafficking of procollagen or other matrix proteins. Another disorder associated with defects in COPI traffic is the skin and bone disorder geroderma osteodysplastica (Hennies et al., 2008), caused by mutation of the COPI scaffolding protein GORAB (Witkos et al., 2019). DCN and BGN GAG chain synthesis is particularly sensitive to loss of GORAB, likely accounting for the fragility of collagen fibres in GO patients, and is also associated with altered TGF-β signalling and cell senescence within affected tissues (Chan et al., 2018).

Mutations in RIC-1, a subunit of the Golgi-localized guanine nucleotide exchange factor (GEF) for RAB6A, cause CATIFA (cleft lip, cataract, tooth abnormality, intellectual disability, facial dysmorphism, attention-deficit hyperactivity disorder) syndrome (Unlu et al., 2020). This is associated with defective procollagen secretion, accounting for the skeletal abnormalities seen in patients and RIC1-deficient animal models. Deficits in N-linked glycosylation of cartilage and neural ECM were also seen upon loss of RIC1 or its partner protein RGP1, consistent with a more widespread dysregulation of ECM production (Pusapati et al., 2012; Unlu et al., 2020).

Mutations in Golgi vesicle-tethering components can also cause disease. For example, mutation of the golgin GMAP210 (TRIP11) gives rise to two skeletal disorders in humans, namely achondrogenesis 1A (ACG1A) and odontochondrodysplasia (ODCD), which are both associated with defective trafficking and glycosylation of matrix proteins (Smits et al., 2010; Wehrle et al., 2019). ACG1A is characterised by severely deficient or absent ossification and is lethal, whereas ODCD has a milder skeletal phenotype that is accompanied by dental abnormalities. The milder phenotype of ODCD can be attributed to residual expression of GMAP210 in these patients and a milder trafficking and glycosylation defect compared to that seen with ACG1A, which is usually associated with a complete loss of GMAP210 expression (Wehrle et al., 2019). In addition to these genetic diseases, the Golgi has a key role in matrix maintenance throughout normal healthy ageing, as well as in chronic disease states such as cancer, as discussed below.

Cancer, wound healing and age-related degeneration

The ECM is critical for maintaining tissue homeostasis and health, and dysregulation of its production and maintenance is associated with common malignancies such as cancer. The ECM is also critical for wound healing, and it is known that ECM integrity deteriorates with age. The function of the Golgi plays an important role in these major aspects of ECM biology, which is described below.

Cancer

The ECM plays a major role in cancer (Cox, 2021). Changes in the matrix result in a number of biophysical and biochemical changes

that affect cell signalling, adhesion and migration, which together impact upon tumour initiation and progression (Egeblad et al., 2010; Winkler et al., 2020). The extent to which the Golgi can impact upon matrix remodelling in cancer is unclear but given its critical role in the production of matrix its importance is implicit.

A direct link between the Golgi and cancer comes from studies of protein glycosylation, which can influence many aspects of tumorigenesis (Rodrigues et al., 2018). The GALA pathway, which is a driver of tumorigenesis, involves the relocation of N-acetylgalactosaminyltransferases (GALNTs) from the Golgi to the ER as a consequence of increased Src activity that promotes retrograde COPI traffic (Chia et al., 2014; Gill et al., 2010). The consequence is elevated production of Tn antigen, a glycoconjugate associated with tumorigenesis (Springer, 1984). Although the full mechanisms by which the GALA pathway contributes to cancer remain to be determined, a known target is the matrix metalloproteinase MMP14 (Nguyen et al., 2017), which promotes metastasis by increasing localised ECM degradation, in turn facilitating cell migration and invasion (Castro-Castro et al., 2016). This may be further enhanced by GALA-dependent export of ER oxidoreductases to the cell exterior where they act upon matrix proteins to reduce disulfide binds and increase proteolytic degradation (Ros et al., 2020).

Another way in which changes in Golgi glycosylation can result in tumorigenesis is through GOLPH3, a COPI adaptor for numerous Golgi enzymes (Eckert et al., 2014; Rizzo et al., 2021; Tu et al., 2008; Welch et al., 2021). GOLPH3 is an oncoprotein and is overexpressed in a number of cancers. GOLPH3 likely exerts its tumorigenic properties by affecting glycosylation of various proteins and lipids that influence mitogenic signalling at the plasma membrane (Sechi et al., 2020). This can alter the expression of many proteins, but one protein of interest in the context of this review is MMP9, which degrades ECM to promote cell migration and invasion, and is upregulated when GOLPH3 is highly expressed (Bera et al., 2013; Dupouy et al., 2014; Li et al., 2015).

Wound healing and fibrosis

If tissue is damaged, upon injury for example, then wound healing takes place to repair the damage (Wight and Potter-Perigo, 2011). Wound healing relies on extensive synthesis and secretion of new matrix components and, as such, the secretory pathway plays a fundamental role in this process. However, the extent to which the secretory pathway, or the Golgi more specifically, changes during a wound healing response remains to be investigated. It is clear that the amount and composition of matrix deposited during wound healing is controlled, as excessive deposition of ECM, in particular fibrillar collagens, results in fibrosis, causing scarring and disrupting tissue homeostasis (Henderson et al., 2020). One of the symptoms associated with EDSSPD1, caused by mutation in B4GALT7, as mentioned above, is a delay in wound repair, indicating that Golgi-dependent glycosylation of DCN can influence wound healing (Seidler et al., 2006). Alongside data showing that changes in the concentration of CS and HS affect cell proliferation during wound repair (Elenius et al., 2004; Zou et al., 2004), this suggests a vital role for the Golgi in its role as a hub for post-translational modification of ECM components in the wound-healing process.

Ageing

Ageing leads to a gradual loss of structural integrity of skin and bone as time passes (Bonté et al., 2019; Farr and Khosla, 2019). In skin, the epidermis thins and there is increased wrinkling, while bone becomes more fragile, as seen in osteoporosis. During ageing, there are changes in the relative amount of each matrix component produced, as well as the post-translational modifications these proteins receive, consequently altering matrix composition (Ewald, 2020). Many of the changes can be accounted for, at least in part, by senescence, a key signature of ageing, which is characterised by cell cycle arrest and resistance to apoptosis (Di Micco et al., 2021). Both increases and decreases in the synthesis and secretion of the key matrix constituents are seen in senescent cells, depending upon the cell type and tissue affected (Levi et al., 2020). Senescent cells have an altered Golgi structure, which might reflect changes in the functionality of this organelle (Cho et al., 2011; Despres et al., 2019). Although the mechanisms underlying such changes in Golgi organisation remain poorly understood, reduced expression of the V-ATPase subunit ATP6V0A2 mentioned above may be relevant, which could also account for the changes in glycosylation seen in senescent cells (Udono et al., 2015). As well as changes in the production of ECM proteins, senescent cells also secrete various molecules, including pro-inflammatory cytokines and MMPs as part of the senescence-associated secretory phenotype (SASP), which can further impact upon ECM integrity (Campisi, 2013; Coppé et al., 2008; Franceschi et al., 2000).

The modification and abundance of PGNs is particularly sensitive to ageing and can be used as a marker of the ageing process. Reduced glycan chain lengths are observed as tissues get older, which may reflect reduced chain stability, but equally could be indicative of reduced modification in the Golgi (Derwin et al., 2001; Grzesik et al., 2002; Lee et al., 2016; Li et al., 2013; Miguez, 2020). Similarly, total GAG abundance and expression of PGNs are reduced in aged tissues, with the former again consistent with reduced Golgi-dependent modification (Derwin et al., 2001; Fedarko et al., 1992; Lee et al., 2016; Miguez, 2020; Wang et al., 2018). Such changes can impact the matrix in several ways, for example by reducing the amount of bound water and interactions between matrix components that are required to maintain tissue strength and integrity.

Conclusions and future directions

Clearly the Golgi plays a vital role in the production of the ECM. What is less clear is the extent to which Golgi function can be altered in response to regulatory cues, which may be intrinsic or environmental. Trafficking pathways to and from the Golgi are under circadian control (Chang et al., 2020), which is likely important for optimum production of the ECM. The Golgi also responds to its matrix-dependent mechanical environment to control lipid synthesis (Romani et al., 2019). Changes to Golgi structure and function based on the mechanical environment also impact cell migration (Pouthas et al., 2008; Thery et al., 2006; Tzima et al., 2003). These might be particularly important in wound healing, as well as in pathological situations where the tissue stiffness is typically increased, including fibrosis and cancer. Considerable data support the concept that the Golgi is not merely a permissive conduit for matrix production, but rather serves as an important control point in this process.

The control and coordination of matrix assembly remains poorly understood. Mathematical modelling of Golgi organisation and glycosylation (Fisher et al., 2019; Jaiman and Thattai, 2020; Vagne et al., 2020) presents key opportunities to understand the relative importance of different Golgi components in the process. It is also worth considering that self-correction mechanisms may exist at the Golgi, allowing for conservation of matrix homeostasis. For example, a glycan chain branching defect is corrected by the

production of a structurally distinct but functionally equivalent glycan chain at the Golgi (Mkhikian et al., 2016). Similarly, loss of the golgin giantin, which is important for procollagen-I production, results in altered Golgi enzyme expression, likely as an adaptive response to altered intra-Golgi traffic (Stevenson et al., 2017).

Considering the number of diseases associated with Golgi dysfunction and aberrant matrix production, a number of potential therapeutic strategies can be considered. For monogenic disorders, gene therapy is a promising strategy (Bulaklak and Gersbach, 2020). It may be possible to treat diseases caused by defective glycosylation reactions in the Golgi using other approaches, such as dietary sugar supplementation, as recently shown for GDP-L-fucose synthase (GFUS)-CDG (Feichtinger et al., 2021). In some circumstances, local or systemic modulation of the circadian rhythm might be a useful strategy. CRISPR-based screening approaches might help us to better understand the machinery required for matrix production and modification at the Golgi, allowing the identification of new possible therapeutic targets. High-throughput screening, as recently performed in the case of procollagen-I (Calverley et al., 2020), also provides opportunities to identify new means of manipulating matrix synthesis in a therapeutic context. The wide-ranging social and economic importance of matrix biology in human health and disease makes this a key area of study with ambition to have dramatic clinical impacts.

References

Akama, T. O., Nishida, K., Nakayama, J., Watanabe, H., Ozaki, K., Nakamura, T., Dota, A., Kawasaki, S., Inoue, Y., Maeda, N. et al. (2000). Macular corneal dystrophy type I and type II are caused by distinct mutations in a new sulphotransferase gene. *Nat. Genet.* **26**, 237-241. doi:10.1038/79987

al Gazali, L. I., al Talabani, J., Mosawi, A. and Lytle, W. (1994). Anterior segment anomalies of the eye, clefting and skeletal abnormalities in two sibs of consanguineous parents: Michels syndrome or new syndrome? *Clin. Dysmorphol.* **3**, 238-244.

Al-Jezawi, N. K., Ali, B. R. and Al-Gazali, L. (2017). Endoplasmic reticulum retention of xylosyltransferase 1 (XYLT1) mutants underlying Desbuquois dysplasia type II. *Am. J. Med. Genet. A* **173**, 1773-1781. doi:10.1002/ajmg.a.38244

Arakel, E. C. and Schwappach, B. (2018). Formation of COPI-coated vesicles at a glance. *J. Cell Sci.* **131**, jcs209890. doi:10.1242/jcs.209890

Ashikov, A., Abu Bakar, N., Wen, X. Y., Niemeijer, M., Rodrigues Pinto Osorio, G., Brand-Arzamendi, K., Hasadsri, L., Hansikova, H., Raymond, K., Vicogne, D. et al. (2018). Integrating glycomics and genomics uncovers SLC10A7 as essential factor for bone mineralization by regulating post-Golgi protein transport and glycosylation. *Hum. Mol. Genet.* **27**, 3029-3045. doi:10.1093/hmg/ddy213

Aten, E., Brasz, L. C., Bornholdt, D., Hooijkaas, I. B., Porteous, M. E., Sybert, V. P., Vermeer, M. H., Vossen, R. H., van der Wielen, M. J., Bakker, E. et al. (2010). Keratosis Follicularis Spinulosa Decalvans is caused by mutations in MBTPS2. *Hum. Mutat.* **31**, 1125-1133. doi:10.1002/humu.21335

Baasanjav, S., Al-Gazali, L., Hashiguchi, T., Mizumoto, S., Fischer, B., Horn, D., Seelow, D., Ali, B. R., Aziz, S. A., Langer, R. et al. (2011). Faulty initiation of proteoglycan synthesis causes cardiac and joint defects. *Am. J. Hum. Genet.* **89**, 15-27. doi:10.1016/j.ajhg.2011.05.021

Baeuerle, P. A. and Huttner, W. B. (1987). Tyrosine sulfation is a trans-Golgi-specific protein modification. *J. Cell Biol.* **105**, 2655-2664. doi:10.1083/jcb.105.6.2655

Balasubramanian, K., Li, B., Krakow, D., Nevarez, L., Ho, P. J., Ainsworth, J. A., Nickerson, D. A., Bamshad, M. J., Immken, L., Lachman, R. S. et al. (2017). MED resulting from recessively inherited mutations in the gene encoding calcium-activated nucleotidase CANT1. *Am. J. Med. Genet. A* **173**, 2415-2421. doi:10.1002/ajmg.a.38349

Beck, R., Rawet, M., Wieland, F. T. and Cassel, D. (2009). The COPI system: molecular mechanisms and function. *FEBS Lett.* **583**, 2701-2709. doi:10.1016/j.febslet.2009.07.032

Bekhouche, M. and Colige, A. (2015). The procollagen N-proteinases ADAMTS2, 3 and 14 in pathophysiology. *Matrix Biol.* **44-46**, 46-53. doi:10.1016/j.matbio.2015.04.001

Ben-Mahmoud, A., Ben-Salem, S., Al-Sorkhy, M., John, A., Ali, B. R. and Al-Gazali, L. (2018). A B3GALT6 variant in patient originally described as Al-Gazali syndrome and implicating the endoplasmic reticulum quality control in the mechanism of some β3GalT6-pathy mutations. *Clin. Genet.* **93**, 1148-1158. doi:10.1111/cge.13236

Bera, A., Zhao, S., Cao, L., Chiao, P. J. and Freeman, J. W. (2013). Oncogenic K-Ras and loss of Smad4 mediate invasion by activating an EGFR/NF-κB Axis that induces expression of MMP9 and uPA in human pancreas progenitor cells. *PLoS ONE* **8**, e82282. doi:10.1371/journal.pone.0082282

Blackburn, J. B., D'Souza, Z. and Lupashin, V. V. (2019). Maintaining order: COG complex controls Golgi trafficking, processing, and sorting. *FEBS Lett.* **593**, 2466-2487. doi:10.1002/1873-3468.13570

Bonfanti, L., Mironov, A. A., Jr, Martinez-Menarguez, J. A., Martella, O., Fusella, A., Baldassarre, M., Buccione, R., Geuze, H. J., Mironov, A. A. and Luini, A. (1998). Procollagen traverses the Golgi stack without leaving the lumen of cisternae: evidence for cisternal maturation. *Cell* **95**, 993-1003. doi:10.1016/S0092-8674(00)81723-7

Bonté, F., Girard, D., Archambault, J. C. and Desmoulière, A. (2019). Skin Changes During Ageing. *Subcell. Biochem.* **91**, 249-280. doi:10.1007/978-981-13-3681-2_10

Boskey, A. L., Spevak, L., Doty, S. B. and Rosenberg, L. (1997). Effects of bone CS-proteoglycans, DS-decorin, and DS-biglycan on hydroxyapatite formation in a gelatin gel. *Calcif. Tissue Int.* **61**, 298-305. doi:10.1007/s002239900339

Brandizzi, F. and Barlowe, C. (2013). Organization of the ER-Golgi interface for membrane traffic control. *Nat. Rev. Mol. Cell Biol.* **14**, 382-392. doi:10.1038/nrm3588

Broder, C., Arnold, P., Vadon-Le Goff, S., Konerding, M. A., Bahr, K., Muller, S., Overall, C. M., Bond, J. S., Koudelka, T., Tholey, A. et al. (2013). Metalloproteases meprin alpha and meprin beta are C- and N-procollagen proteinases important for collagen assembly and tensile strength. *Proc. Natl. Acad. Sci. USA* **110**, 14219-14224. doi:10.1073/pnas.1305464110

Bruns, R. R., Hulmes, D. J., Therrien, S. F. and Gross, J. (1979). Procollagen segment-long-spacing crystallites: their role in collagen fibrillogenesis. *Proc. Natl. Acad. Sci. USA* **76**, 313-317. doi:10.1073/pnas.76.1.313

Budde, B. S., Mizumoto, S., Kogawa, R., Becker, C., Altmüller, J., Thiele, H., Rüschendorf, F., Toliat, M. R., Kaleschke, G., Hämmerle, J. M. et al. (2015). Skeletal dysplasia in a consanguineous clan from the island of Nias/Indonesia is caused by a novel mutation in B3GAT3. *Hum. Genet.* **134**, 691-704. doi:10.1007/s00439-015-1549-2

Bui, C., Huber, C., Tuysuz, B., Alanay, Y., Bole-Feysot, C., Leroy, J. G., Mortier, G., Nitschke, P., Munnich, A. and Cormier-Daire, V. (2014). XYLT1 mutations in Desbuquois dysplasia type 2. *Am. J. Hum. Genet.* **94**, 405-414. doi:10.1016/j.ajhg.2014.01.020

Bulaklak, K. and Gersbach, C. A. (2020). The once and future gene therapy. *Nat. Commun.* **11**, 5820. doi:10.1038/s41467-020-19505-2

Caengprasath, N., Theerapanon, T., Porntaveetus, T. and Shotelersuk, V. (2021). MBTPS2, a membrane bound protease, underlying several distinct skin and bone disorders. *J. Transl. Med.* **19**, 114. doi:10.1186/s12967-021-02779-5

Calabro, A. and Hascall, V. C. (1994). Differential effects of brefeldin A on chondroitin sulfate and hyaluronan synthesis in rat chondrosarcoma cells. *J. Biol. Chem.* **269**, 22764-22770. doi:10.1016/S0021-9258(17)31711-8

Calverley, B. C., Kadler, K. E. and Pickard, A. (2020). Dynamic high-sensitivity quantitation of procollagen-i by endogenous CRISPR-Cas9 NanoLuciferase tagging. *Cells* **9**, 2070. doi:10.3390/cells9092070

Campisi, J. (2013). Aging, cellular senescence, and cancer. *Annu. Rev. Physiol.* **75**, 685-705. doi:10.1146/annurev-physiol-030212-183653

Canty, E. G. and Kadler, K. E. (2005). Procollagen trafficking, processing and fibrillogenesis. *J. Cell Sci.* **118**, 1341-1353. doi:10.1242/jcs.01731

Canty-Laird, E. G., Lu, Y. and Kadler, K. E. (2012). Stepwise proteolytic activation of type I procollagen to collagen within the secretory pathway of tendon fibroblasts in situ. *Biochem. J.* **441**, 707-717. doi:10.1042/BJ20111379

Capulli, M., Paone, R. and Rucci, N. (2014). Osteoblast and osteocyte: games without frontiers. *Arch. Biochem. Biophys.* **561**, 3-12. doi:10.1016/j.abb.2014.05.003

Castro-Castro, A., Marchesin, V., Monteiro, P., Lodillinsky, C., Rossé, C. and Chavrier, P. (2016). Cellular and molecular mechanisms of MT1-MMP-dependent cancer cell invasion. *Annu. Rev. Cell Dev. Biol.* **32**, 555-576. doi:10.1146/annurev-cellbio-111315-125227

Chan, W. L., Steiner, M., Witkos, T., Egerer, J., Busse, B., Mizumoto, S., Pestka, J. M., Zhang, H., Hausser, I., Khayal, L. A. et al. (2018). Impaired proteoglycan glycosylation, elevated TGF-β signaling, and abnormal osteoblast differentiation as the basis for bone fragility in a mouse model for gerodermia osteodysplastica. *PLoS Genet.* **14**, e1007242. doi:10.1371/journal.pgen.1007242

Chang, J., Garva, R., Pickard, A., Yeung, C. C., Mallikarjun, V., Swift, J., Holmes, D. F., Calverley, B., Lu, Y., Adamson, A. et al. (2020). Circadian control of the secretory pathway maintains collagen homeostasis. *Nat. Cell Biol.* **22**, 74-86. doi:10.1038/s41556-019-0441-z

Chen, S. and Birk, D. E. (2013). The regulatory roles of small leucine-rich proteoglycans in extracellular matrix assembly. *FEBS J.* **280**, 2120-2137. doi:10.1111/febs.12136

Chen, Q., Lee, C. E., Denard, B. and Ye, J. (2014). Sustained induction of collagen synthesis by TGF-β requires regulated intramembrane proteolysis of CREB3L1. *PLoS ONE* **9**, e108528. doi:10.1371/journal.pone.0108528

Chia, J., Tham, K. M., Gill, D. J., Bard-Chapeau, E. A. and Bard, F. A. (2014). ERK8 is a negative regulator of O-GalNAc glycosylation and cell migration. *Elife* **3**, e01828. doi:10.7554/eLife.01828

Cho, J. H., Saini, D. K., Karunarathne, W. K., Kalyanaraman, V. and Gautam, N. (2011). Alteration of Golgi structure in senescent cells and its regulation by a G protein γ subunit. *Cell. Signal.* **23**, 785-793. doi:10.1016/j.cellsig.2011.01.001

Claude, A., Zhao, B. P., Kuziemsky, C. E., Dahan, S., Berger, S. J., Yan, J. P., Arnold, A. D., Sullivan, E. M. and Melancon, P. (1999). GBF1: A novel Golgi-associated BFA-resistant guanine nucleotide exchange factor that displays specificity for ADP-ribosylation factor 5. *J. Cell Biol.* **146**, 71-84.

Coppé, J. P., Patil, C. K., Rodier, F., Sun, Y., Muñoz, D. P., Goldstein, J., Nelson, P. S., Desprez, P. Y. and Campisi, J. (2008). Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLoS Biol.* **6**, 2853-2868. doi:10.1371/journal.pbio.0060301

Cox, T. R. (2021). The matrix in cancer. *Nat. Rev. Cancer* **21**, 217-238. doi:10.1038/s41568-020-00329-7

Cuellar, K., Chuong, H., Hubbell, S. M. and Hinsdale, M. E. (2007). Biosynthesis of chondroitin and heparan sulfate in chinese hamster ovary cells depends on xylosyltransferase II. *J. Biol. Chem.* **282**, 5195-5200. doi:10.1074/jbc.M611048200

Dagenais, S. L., Adam, A. N., Innis, J. W. and Glover, T. W. (2001). A novel frameshift mutation in exon 23 of ATP7A (MNK) results in occipital horn syndrome and not in Menkes disease. *Am. J. Hum. Genet.* **69**, 420-427. doi:10.1086/321290

Derwin, K. A., Soslowsky, L. J., Kimura, J. H. and Plaas, A. H. (2001). Proteoglycans and glycosaminoglycan fine structure in the mouse tail tendon fascicle. *J. Orthop. Res.* **19**, 269-277. doi:10.1016/S0736-0266(00)00032-2

Despres, J., Ramdani, Y., di Giovanni, M., Bénard, M., Zahid, A., Montero-Hadjadje, M., Yvergnaux, F., Saguet, T., Driouich, A. and Follet-Gueye, M. L. (2019). Replicative senescence of human dermal fibroblasts affects structural and functional aspects of the Golgi apparatus. *Exp. Dermatol.* **28**, 922-932. doi:10.1111/exd.13886

Dick, G., Akslen-Hoel, L. K., Grondahl, F., Kjos, I. and Prydz, K. (2012). Proteoglycan synthesis and Golgi organization in polarized epithelial cells. *J. Histochem. Cytochem.* **60**, 926-935. doi:10.1369/0022155412461256

Di Micco, R., Krizhanovsky, V., Baker, D. and d'Adda di Fagagna, F. (2021). Cellular senescence in ageing: from mechanisms to therapeutic opportunities. *Nat. Rev. Mol. Cell Biol.* **22**, 75-95. doi:10.1038/s41580-020-00314-w

Dimitrov, A., Paupe, V., Gueudry, C., Sibarita, J. B., Raposo, G., Vielemeyer, O., Gilbert, T., Csaba, Z., Attie-Bitach, T., Cormier-Daire, V. et al. (2009). The gene responsible for Dyggve-Melchior-Clausen syndrome encodes a novel peripheral membrane protein dynamically associated with the Golgi apparatus. *Hum. Mol. Genet.* **18**, 440-453. doi:10.1093/hmg/ddn371

DiStasio, A., Driver, A., Sund, K., Donlin, M., Muraleedharan, R. M., Pooya, S., Kline-Fath, B., Kaufman, K. M., Prows, C. A., Schorry, E. et al. (2017). Copb2 is essential for embryogenesis and hypomorphic mutations cause human microcephaly. *Hum. Mol. Genet.* **26**, 4836-4848. doi:10.1093/hmg/ddx362

Dubail, J., Huber, C., Chantepie, S., Sonntag, S., Tüysüz, B., Mihci, E., Gordon, C. T., Steichen-Gersdorf, E., Amiel, J., Nur, B. et al. (2018). SLC10A7 mutations cause a skeletal dysplasia with amelogenesis imperfecta mediated by GAG biosynthesis defects. *Nat. Commun.* **9**, 3087. doi:10.1038/s41467-018-05191-8

Dündar, M., Müller, T., Zhang, Q., Pan, J., Steinmann, B., Vodopiutz, J., Gruber, R., Sonoda, T., Krabichler, B., Utermann, G. et al. (2009). Loss of dermatan-4-sulfotransferase 1 function results in adducted thumb-clubfoot syndrome. *Am. J. Hum. Genet.* **85**, 873-882. doi:10.1016/j.ajhg.2009.11.010

Dupouy, S., Doan, V. K., Wu, Z., Mourra, N., Liu, J., De Wever, O., Llorca, F. P., Cayre, A., Kouchkar, A., Gompel, A. et al. (2014). Activation of EGFR, HER2 and HER3 by neurotensin/neurotensin receptor 1 renders breast tumors aggressive yet highly responsive to lapatinib and metformin in mice. *Oncotarget* **5**, 8235-8251. doi:10.18632/oncotarget.1632

Dupuis, N., Lebon, S., Kumar, M., Drunat, S., Graul-Neumann, L. M., Gressens, P. and El Ghouzzi, V. (2013). A novel RAB33B mutation in Smith-McCort dysplasia. *Hum. Mutat.* **34**, 283-286. doi:10.1002/humu.22235

Eames, B. F., Singer, A., Smith, G. A., Wood, Z. A., Yan, Y. L., He, X., Polizzi, S. J., Catchen, J. M., Rodriguez-Mari, A., Linbo, T. et al. (2010). UDP xylose synthase 1 is required for morphogenesis and histogenesis of the craniofacial skeleton. *Dev. Biol.* **341**, 400-415. doi:10.1016/j.ydbio.2010.02.035

Eckert, E. S. P., Reckmann, I., Hellwig, A., Röhling, S., El-Battari, A., Wieland, F. T. and Popoff, V. (2014). Golgi Phosphoprotein 3 Triggers Signal-mediated Incorporation of Glycosyltransferases into Coatomer-coated (COPI) Vesicles. *J. Biol. Chem.* **289**, 31319-31329. doi:10.1074/jbc.M114.608182

Edvardson, S., Ashikov, A., Jalas, C., Sturiale, L., Shaag, A., Fedick, A., Treff, N. R., Garozzo, D., Gerardy-Schahn, R. and Elpeleg, O. (2013). Mutations in SLC35A3 cause autism spectrum disorder, epilepsy and arthrogryposis. *J. Med. Genet.* **50**, 733-739. doi:10.1136/jmedgenet-2013-101753

Egeblad, M., Rasch, M. G. and Weaver, V. M. (2010). Dynamic interplay between the collagen scaffold and tumor evolution. *Curr. Opin. Cell Biol.* **22**, 697-706. doi:10.1016/j.ceb.2010.08.015

Ehnis, T., Dieterich, W., Bauer, M., Kresse, H. and Schuppan, D. (1997). Localization of a binding site for the proteoglycan decorin on collagen XIV (undulin). *J. Biol. Chem.* **272**, 20414-20419. doi:10.1074/jbc.272.33.20414

Ghouzzi, E., Dagoneau, V., Kinning, N., Thauvin-Robinet, E., Chemaitilly, C., Prost-Squarcioni, W., Al-Gazali, C., Verloes, L. I., Le Merrer, A., Munnich, M. (2003). Mutations in a novel gene Dymeclin (FLJ20071) are responsible for Dyggve-Melchior-Clausen syndrome. *Hum. Mol. Genet.* **12**, 357-364. doi:10.1093/hmg/ddg029

Elenius, V., Götte, M., Reizes, O., Elenius, K. and Bernfield, M. (2004). Inhibition by the soluble syndecan-1 ectodomains delays wound repair in mice overexpressing syndecan-1. *J. Biol. Chem.* **279**, 41928-41935. doi:10.1074/jbc.M404506200

Esk, C., Lindenhofer, D., Haendeler, S., Wester, R. A., Pflug, F., Schroeder, B., Bagley, J. A., Elling, U., Zuber, J., von Haeseler, A. et al. (2020). A human tissue screen identifies a regulator of ER secretion as a brain-size determinant. *Science* **370**, 935-941. doi:10.1126/science.abb5390

Ewald, C. Y. (2020). The Matrisome during aging and longevity: a systems-level approach toward defining matreotypes promoting healthy aging. *Gerontology* **66**, 266-274. doi:10.1159/000504295

Faden, M., Al-Zahrani, F., Arafah, D. and Alkuraya, F. S. (2010). Mutation of CANT1 causes Desbuquois dysplasia. *Am. J. Med. Genet. A* **152a**, 1157-1160. doi:10.1002/ajmg.a.33404

Faiyaz-Ul-Haque, M., Zaidi, S. H. E., Al-Ali, M., Al-Mureikhi, M. S., Kennedy, S., Al-Thani, G., Tsui, L.-C. and Teebi, A. S. (2004). A novel missense mutation in the galactosyltransferase-I (B4GALT7) gene in a family exhibiting facioskeletal anomalies and Ehlers–Danlos syndrome resembling the progeroid type. *Am. J. Med. Genet. A* **128A**, 39-45. doi:10.1002/ajmg.a.30005

Farr, J. N. and Khosla, S. (2019). Cellular senescence in bone. *Bone* **121**, 121-133. doi:10.1016/j.bone.2019.01.015

Fedarko, N. S., Vetter, U. K., Weinstein, S. and Robey, P. G. (1992). Age-related changes in hyaluronan, proteoglycan, collagen, and osteonectin synthesis by human bone cells. *J. Cell. Physiol.* **151**, 215-227. doi:10.1002/jcp.1041510202

Feichtinger, R. G., Hullen, A., Koller, A., Kotzot, D., Grote, V., Rapp, E., Hofbauer, P., Brugger, K., Thiel, C., Mayr, J. A. et al. (2021). A spoonful of L-fucose-an efficient therapy for GFUS-CDG, a new glycosylation disorder. *EMBO Mol. Med.* **13**, e14332. doi:10.15252/emmm.202114332

Ferreira, C. R., Xia, Z. J., Clément, A., Parry, D. A., Davids, M., Taylan, F., Sharma, P., Turgeon, C. T., Blanco-Sánchez, B., Ng, B. G. et al. (2018). A Recurrent De Novo Heterozygous COG4 Substitution Leads to Saul-Wilson Syndrome, Disrupted Vesicular Trafficking, and Altered Proteoglycan Glycosylation. *Am. J. Hum. Genet.* **103**, 553-567. doi:10.1016/j.ajhg.2018.09.003

Fisher, P., Spencer, H., Thomas-Oates, J., Wood, A. J. and Ungar, D. (2019). Modeling glycan processing reveals golgi-enzyme homeostasis upon trafficking defects and cellular differentiation. *Cell Rep.* **27**, 1231-1243.e6. doi:10.1016/j.celrep.2019.03.107

Florencio-Silva, R., Sasso, G. R., Sasso-Cerri, E., Simões, M. J. and Cerri, P. S. (2015). Biology of bone tissue: structure, function, and factors that influence bone cells. *Biomed. Res. Int.* **2015**, 421746. doi:10.1155/2015/421746

Font, B., Aubert-Foucher, E., Goldschmidt, D., Eichenberger, D. and van der Rest, M. (1993). Binding of collagen XIV with the dermatan sulfate side chain of decorin. *J. Biol. Chem.* **268**, 25015-25018. doi:10.1016/S0021-9258(19)74565-7

Font, B., Eichenberger, D., Rosenberg, L. M. and van der Rest, M. (1996). Characterization of the interactions of type XII collagen with two small proteoglycans from fetal bovine tendon, decorin and fibromodulin. *Matrix Biol.* **15**, 341-348. doi:10.1016/S0945-053X(96)90137-7

Foulquier, F., Vasile, E., Schollen, E., Callewaert, N., Raemaekers, T., Quelhas, D., Jaeken, J., Mills, P., Winchester, B., Krieger, M. et al. (2006). Conserved oligomeric Golgi complex subunit 1 deficiency reveals a previously uncharacterized congenital disorder of glycosylation type II. *Proc. Natl. Acad. Sci. USA* **103**, 3764-3769. doi:10.1073/pnas.0507685103

Foulquier, F., Amyere, M., Jaeken, J., Zeevaert, R., Schollen, E., Race, V., Bammens, R., Morelle, W., Rosnoblet, C., Legrand, D. et al. (2012). TMEM165 deficiency causes a congenital disorder of glycosylation. *Am. J. Hum. Genet.* **91**, 15-26. doi:10.1016/j.ajhg.2012.05.002

Franceschi, C., Bonafè, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E. and De Benedictis, G. (2000). Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann. N. Y. Acad. Sci.* **908**, 244-254. doi:10.1111/j.1749-6632.2000.tb06651.x

Frantz, C., Stewart, K. M. and Weaver, V. M. (2010). The extracellular matrix at a glance. *J. Cell Sci.* **123**, 4195-4200. doi:10.1242/jcs.023820

Freeze, H. H. (2006). Genetic defects in the human glycome. *Nat. Rev. Genet.* **7**, 537-551. doi:10.1038/nrg1894

Freeze, H. H. and Ng, B. G. (2011). Golgi glycosylation and human inherited diseases. *Cold Spring Harb. Perspect Biol.* **3**, a005371. doi:10.1101/cshperspect.a005371

Futai, M., Oka, T., Sun-Wada, G., Moriyama, Y., Kanazawa, H. and Wada, Y. (2000). Luminal acidification of diverse organelles by V-ATPase in animal cells. *J. Exp. Biol.* **203**, 107-116. doi:10.1242/jeb.203.1.107

Gill, D. J., Chia, J., Senewiratne, J. and Bard, F. (2010). Regulation of O-glycosylation through Golgi-to-ER relocation of initiation enzymes. *J. Cell Biol.* **189**, 843-858. doi:10.1083/jcb.201003055

Gillingham, A. K. and Munro, S. (2016). Finding the Golgi: Golgin Coiled-Coil Proteins Show the Way. *Trends Cell Biol.* **26**, 399-408. doi:10.1016/j.tcb.2016.02.005

Glick, B. S. and Nakano, A. (2009). Membrane traffic within the Golgi apparatus. *Annu. Rev. Cell Dev. Biol.* **25**, 113-132. doi:10.1146/annurev.cellbio.24.110707.175421

Götte, M. and Kresse, H. (2005). Defective glycosaminoglycan substitution of decorin in a patient with progeroid syndrome is a direct consequence of two point mutations in the galactosyltransferase I (beta4GalT-7) gene. *Biochem. Genet.* **43**, 65-77. doi:10.1007/s10528-005-1068-2

Grondahl, F., Tveit, H. and Prydz, K. (2009). Neutralization of endomembrane compartments in epithelial MDCK cells affects proteoglycan synthesis in the apical secretory pathway. *Biochem. J.* **418**, 517-528. doi:10.1042/BJ20081179

Grzesik, W. J., Frazier, C. R., Shapiro, J. R., Sponseller, P. D., Robey, P. G. and Fedarko, N. S. (2002). Age-related changes in human bone proteoglycan structure. Impact of osteogenesis imperfecta. *J. Biol. Chem.* **277**, 43638-43647. doi:10.1074/jbc.M202124200

Guillard, M., Dimopoulou, A., Fischer, B., Morava, E., Lefeber, D. J., Kornak, U. and Wevers, R. A. (2009). Vacuolar H+-ATPase meets glycosylation in patients with cutis laxa. *Biochim. Biophys. Acta* **1792**, 903-914. doi:10.1016/j.bbadis.2008.12.009

Guo, Y., Sirkis, D. W. and Schekman, R. (2014). Protein sorting at the trans-Golgi network. *Annu. Rev. Cell Dev. Biol.* **30**, 169-206. doi:10.1146/annurev-cellbio-100913-013012

Haghighi, A., Scott, C. A., Poon, D. S., Yaghoobi, R., Saleh-Gohari, N., Plagnol, V. and Kelsell, D. P. (2013). A missense mutation in the MBTPS2 gene underlies the X-linked form of Olmsted syndrome. *J. Invest. Dermatol.* **133**, 571-573. doi:10.1038/jid.2012.289

Hamlin, J. N., Schroeder, L. K., Fotouhi, M., Dokainish, H., Ioannou, M. S., Girard, M., Summerfeldt, N., Melançon, P. and McPherson, P. S. (2014). Scyl1 scaffolds class II Arfs to specific subcomplexes of coatomer through the γ-COP appendage domain. *J. Cell Sci.* **127**, 1454-1463.

Harper, J. R., Quaranta, V. and Reisfeld, R. A. (1986). Ammonium chloride interferes with a distinct step in the biosynthesis and cell surface expression of human melanoma-type chondroitin sulfate proteoglycan. *J. Biol. Chem.* **261**, 3600-3606. doi:10.1016/S0021-9258(17)35689-2

Hascall, G. K. (1980). Ultrastructure of the chondrocytes and extracellular matrix of the swarm rat chondrosarcoma. *Anat. Rec.* **198**, 135-146. doi:10.1002/ar.1091980202

Hecht, J. T., Hogue, D., Wang, Y., Blanton, S. H., Wagner, M., Strong, L. C., Raskind, W., Hansen, M. F. and Wells, D. (1997). Hereditary multiple exostoses (EXT): mutational studies of familial EXT1 cases and EXT-associated malignancies. *Am. J. Hum. Genet.* **60**, 80-86.

Henderson, N. C., Rieder, F. and Wynn, T. A. (2020). Fibrosis: from mechanisms to medicines. *Nature* **587**, 555-566. doi:10.1038/s41586-020-2938-9

Hennies, H. C., Kornak, U., Zhang, H., Egerer, J., Zhang, X., Seifert, W., Kühnisch, J., Budde, B., Nätebus, M., Brancati, F. et al. (2008). Gerodermia osteodysplastica is caused by mutations in SCYL1BP1, a Rab-6 interacting golgin. *Nat. Genet.* **40**, 1410-1412. doi:10.1038/ng.252

Hermanns, P., Unger, S., Rossi, A., Perez-Aytes, A., Cortina, H., Bonafé, L., Boccone, L., Setzu, V., Dutoit, M., Sangiorgi, L. et al. (2008). Congenital joint dislocations caused by carbohydrate sulfotransferase 3 deficiency in recessive Larsen syndrome and humero-spinal dysostosis. *Am. J. Hum. Genet.* **82**, 1368-1374. doi:10.1016/j.ajhg.2008.05.006

Hildebrand, A., Romaris, M., Rasmussen, L. M., Heinegard, D., Twardzik, D. R., Border, W. A. and Ruoslahti, E. (1994). Interaction of the small interstitial proteoglycans biglycan, decorin and fibromodulin with transforming growth factor beta. *Biochem. J.* **302**, 527-534. doi:10.1042/bj3020527

Hino, K., Saito, A., Kido, M., Kanemoto, S., Asada, R., Takai, T., Cui, M., Cui, X. and Imaizumi, K. (2014). Master regulator for chondrogenesis, Sox9, regulates transcriptional activation of the endoplasmic reticulum stress transducer BBF2H7/CREB3L2 in chondrocytes. *J. Biol. Chem.* **289**, 13810-13820. doi:10.1074/jbc.M113.543322

Hirose, T., Takahashi, N., Tangkawattana, P., Minaguchi, J., Mizumoto, S., Yamada, S., Miyake, N., Hayashi, S., Hatamochi, A., Nakayama, J. et al. (2019). Structural alteration of glycosaminoglycan side chains and spatial disorganization of collagen networks in the skin of patients with mcEDS-CHST14. *Biochim. Biophys. Acta Gen. Subj.* **1863**, 623-631. doi:10.1016/j.bbagen.2018.12.006

Hirschberg, C. B. and Snider, M. D. (1987). Topography of glycosylation in the rough endoplasmic reticulum and Golgi apparatus. *Annu. Rev. Biochem.* **56**, 63-87. doi:10.1146/annurev.bi.56.070187.000431

Homma, Y., Hiragi, S. and Fukuda, M. (2021). Rab family of small GTPases: an updated view on their regulation and functions. *FEBS J.* **288**, 36-55. doi:10.1111/febs.15453

Hoppe, W., Glossl, J. and Kresse, H. (1985). Influence of monensin on biosynthesis, processing and secretion of proteodermatan sulfate by skin fibroblasts. *Eur. J. Biochem.* **152**, 91-97. doi:10.1111/j.1432-1033.1985.tb09167.x

Huber, C., Oulès, B., Bertoli, M., Chami, M., Fradin, M., Alanay, Y., Al-Gazali, L. I., Ausems, M. G., Bitoun, P., Cavalcanti, D. P. et al. (2009). Identification of CANT1 mutations in Desbuquois dysplasia. *Am. J. Hum. Genet.* **85**, 706-710. doi:10.1016/j.ajhg.2009.10.001

Hucthagowder, V., Morava, E., Kornak, U., Lefeber, D. J., Fischer, B., Dimopoulou, A., Aldinger, A., Choi, J., Davis, E. C., Abuelo, D. N. et al. (2009). Loss-of-function mutations in ATP6V0A2 impair vesicular trafficking, tropoelastin secretion and cell survival. *Hum. Mol. Genet.* **18**, 2149-2165. doi:10.1093/hmg/ddp148

Humphries, S. M., Lu, Y., Canty, E. G. and Kadler, K. E. (2008). Active negative control of collagen fibrillogenesis in vivo. Intracellular cleavage of the type I procollagen propeptides in tendon fibroblasts without intracellular fibrils. *J. Biol. Chem.* **283**, 12129-12135. doi:10.1074/jbc.M708198200

Iozzo, R. V. and Schaefer, L. (2015). Proteoglycan form and function: A comprehensive nomenclature of proteoglycans. *Matrix Biol.* **42**, 11-55. doi:10.1016/j.matbio.2015.02.003

Ishikura-Kinoshita, S., Saeki, H. and Tsuji-Naito, K. (2012). BBF2H7-mediated Sec23A pathway is required for endoplasmic reticulum-to-Golgi trafficking in dermal fibroblasts to promote collagen synthesis. *J. Invest. Dermatol.* **132**, 2010-2018. doi:10.1038/jid.2012.103

Izumi, K., Brett, M., Nishi, E., Drunat, S., Tan, E. S., Fujiki, K., Lebon, S., Cham, B., Masuda, K., Arakawa, M. et al. (2016). ARCN1 Mutations Cause a Recognizable Craniofacial Syndrome Due to COPI-Mediated Transport Defects. *Am. J. Hum. Genet.* **99**, 451-459. doi:10.1016/j.ajhg.2016.06.011

Jaiman, A. and Thattai, M. (2020). Golgi compartments enable controlled biomolecular assembly using promiscuous enzymes. *Elife* **9**, e49573. doi:10.7554/eLife.49573

Jones, K. L., Schwarze, U., Adam, M. P., Byers, P. H. and Mefford, H. C. (2015). A homozygous B3GAT3 mutation causes a severe syndrome with multiple fractures, expanding the phenotype of linkeropathy syndromes. *Am. J. Med. Genet. A* **167a**, 2691-2696. doi:10.1002/ajmg.a.37209

Jonsson, M., Eklund, E., Fransson, L. A. and Oldberg, A. (2003). Initiation of the decorin glycosaminoglycan chain in the endoplasmic reticulum-Golgi intermediate compartment. *J. Biol. Chem.* **278**, 21415-21420. doi:10.1074/jbc.M210977200

Kannus, P. (2000). Structure of the tendon connective tissue. *Scand. J. Med. Sci. Sports* **10**, 312-320. doi:10.1034/j.1600-0838.2000.010006312.x

Karamanos, N. K., Theocharis, A. D., Piperigkou, Z., Manou, D., Passi, A., Skandalis, S. S., Vynios, D. H., Orian-Rousseau, V., Ricard-Blum, S., Schmelzer, C. E. H. et al. (2021). A guide to the composition and functions of the extracellular matrix. *FEBS J.*. doi:10.1111/febs.15776

Kearns, A. E., Campbell, S. C., Westley, J. and Schwartz, N. B. (1991). Initiation of chondroitin sulfate biosynthesis: a kinetic analysis of UDP-D-xylose: core protein beta-D-xylosyltransferase. *Biochemistry* **30**, 7477-7483. doi:10.1021/bi00244a010

Kearns, A. E., Vertel, B. M. and Schwartz, N. B. (1993). Topography of glycosylation and UDP-xylose production. *J. Biol. Chem.* **268**, 11097-11104. doi:10.1016/S0021-9258(18)82097-X

Kiani, C., Chen, L., Wu, Y. J., Yee, A. J. and Yang, B. B. (2002). Structure and function of aggrecan. *Cell Res.* **12**, 19-32. doi:10.1038/sj.cr.7290106

Kondo, Y., Fu, J., Wang, H., Hoover, C., McDaniel, J. M., Steet, R., Patra, D., Song, J., Pollard, L., Cathey, S. et al. (2018). Site-1 protease deficiency causes human skeletal dysplasia due to defective inter-organelle protein trafficking. *JCI Insight* **3**, e121596. doi:10.1172/jci.insight.121596

Kornak, U., Reynders, E., Dimopoulou, A., van Reeuwijk, J., Fischer, B., Rajab, A., Budde, B., Nürnberg, P., Foulquier, F., Dobyns, W. B. et al. (2008). Impaired glycosylation and cutis laxa caused by mutations in the vesicular H+-ATPase subunit ATP6V0A2. *Nat. Genet.* **40**, 32-34. doi:10.1038/ng.2007.45

Kresse, H., Rosthøj, S., Quentin, E., Hollmann, J., Glössl, J., Okada, S. and Tønnesen, T. (1987). Glycosaminoglycan-free small proteoglycan core protein is secreted by fibroblasts from a patient with a syndrome resembling progeroid. *Am. J. Hum. Genet.* **41**, 436-453.

Kuc, I. M. and Scott, P. G. (1997). Increased diameters of collagen fibrils precipitated in vitro in the presence of decorin from various connective tissues. *Connect. Tissue Res.* **36**, 287-296. doi:10.3109/03008209709160228

Laccone, F., Schoner, K., Krabichler, B., Kluge, B., Schwerdtfeger, R., Schulze, B., Zschocke, J. and Rehder, H. (2011). Desbuquois dysplasia type I and fetal hydrops due to novel mutations in the CANT1 gene. *Eur. J. Hum. Genet.* **19**, 1133-1137. doi:10.1038/ejhg.2011.101

Laugel-Haushalter, V., Bär, S., Schaefer, E., Stoetzel, C., Geoffroy, V., Alembik, Y., Kharouf, N., Huckert, M., Hamm, P., Hemmerlé, J. et al. (2019). A New SLC10A7 Homozygous Missense Mutation Responsible for a Milder Phenotype of Skeletal Dysplasia With Amelogenesis Imperfecta. *Front. Genet.* **10**, 504. doi:10.3389/fgene.2019.00504

Leblond, C. P. (1989). Synthesis and secretion of collagen by cells of connective tissue, bone, and dentin. *Anat. Rec.* **224**, 123-138. doi:10.1002/ar.1092240204

Leduc, R., Molloy, S. S., Thorne, B. A. and Thomas, G. (1992). Activation of human furin precursor processing endoprotease occurs by an intramolecular autoproteolytic cleavage. *J. Biol. Chem.* **267**, 14304-14308. doi:10.1016/S0021-9258(19)49712-3

Lee, D. H., Oh, J.-H. and Chung, J. H. (2016). Glycosaminoglycan and proteoglycan in skin aging. *J. Dermatol. Sci.* **83**, 174-181. doi:10.1016/j.jdermsci.2016.05.016

Levi, N., Papismadov, N., Solomonov, I., Sagi, I. and Krizhanovsky, V. (2020). The ECM path of senescence in aging: components and modifiers. *FEBS J.* **287**, 2636-2646. doi:10.1111/febs.15282

Li, W., Qi, K., Wang, Z., Gu, M., Chen, G., Guo, F. and Wang, Z. (2015). Golgi phosphoprotein 3 regulates metastasis of prostate cancer via matrix metalloproteinase 9. *Int J Clin Exp Pathol* **8**, 3691-3700.

Li, Y., Liu, Y., Xia, W., Lei, D., Voorhees, J. J. and Fisher, G. J. (2013). Age-dependent alterations of decorin glycosaminoglycans in human skin. *Sci. Rep.* **3**, 2422. doi:10.1038/srep02422

Lindert, U., Cabral, W. A., Ausavarat, S., Tongkobpetch, S., Ludin, K., Barnes, A. M., Yeetong, P., Weis, M., Krabichler, B., Srichomthong, C. et al. (2016). MBTPS2 mutations cause defective regulated intramembrane proteolysis in X-linked osteogenesis imperfecta. *Nat. Commun.* **7**, 11920. doi:10.1038/ncomms11920

Lippincott-Schwartz, J., Yuan, L. C., Bonifacino, J. S. and Klausner, R. D. (1989). Rapid redistribution of Golgi proteins into the ER in cells treated with brefeldin A: evidence for membrane cycling from Golgi to ER. *Cell* **56**, 801-813. doi:10.1016/0092-8674(89)90685-5

Lohmander, L. S., Shinomura, T., Hascall, V. C. and Kimura, J. H. (1989). Xylosyl transfer to the core protein precursor of the rat chondrosarcoma proteoglycan. *J. Biol. Chem.* **264**, 18775-18780. doi:10.1016/S0021-9258(18)51534-9

Maccarana, M., Kalamajski, S., Kongsgaard, M., Magnusson, S. P., Oldberg, A. and Malmstrom, A. (2009). Dermatan sulfate epimerase 1-deficient mice have reduced content and changed distribution of iduronic acids in dermatan sulfate and an altered collagen structure in skin. *Mol. Cell. Biol.* **29**, 5517-5528. doi:10.1128/MCB.00430-09

Malfait, F., Syx, D., Vlummens, P., Symoens, S., Nampoothiri, S., Hermanns-Lê, T., Van Laer, L. and De Paepe, A. (2010). Musculocontractural Ehlers-Danlos Syndrome (former EDS type VIB) and adducted thumb clubfoot syndrome (ATCS) represent a single clinical entity caused by mutations in the dermatan-4-sulfotransferase 1 encoding CHST14 gene. *Hum. Mutat.* **31**, 1233-1239. doi:10.1002/humu.21355

Malfait, F., Kariminejad, A., Van Damme, T., Gauche, C., Syx, D., Merhi-Soussi, F., Gulberti, S., Symoens, S., Vanhauwaert, S., Willaert, A. et al. (2013). Defective initiation of glycosaminoglycan synthesis due to B3GALT6 mutations causes a pleiotropic Ehlers-Danlos-syndrome-like connective tissue disorder. *Am. J. Hum. Genet.* **92**, 935-945. doi:10.1016/j.ajhg.2013.04.016

Marchi, F. and Leblond, C. P. (1984). Radioautographic characterization of successive compartments along the rough endoplasmic reticulum-Golgi pathway of collagen precursors in foot pad fibroblasts of [3H]proline-injected rats. *J. Cell Biol.* **98**, 1705-1709. doi:10.1083/jcb.98.5.1705

Marom, R., Burrage, L. C., Venditti, R., Clement, A., Blanco-Sanchez, B., Jain, M., Scott, D. A., Rosenfeld, J. A., Sutton, V. R., Shinawi, M. et al. (2021). COPB2 loss of function causes a coatopathy with osteoporosis and developmental delay. *Am. J. Hum. Genet.* **108**, 1710-1724. doi:10.1016/j.ajhg.2021.08.002

McCaughey, J. and Stephens, D. J. (2019). ER-to-Golgi Transport: A Sizeable Problem. *Trends Cell Biol.* **29**, 940-953. doi:10.1016/j.tcb.2019.08.007

McCaughey, J., Miller, V. J., Stevenson, N. L., Brown, A. K., Budnik, A., Heesom, K. J., Alibhai, D. and Stephens, D. J. (2016). TFG Promotes Organization of Transitional ER and Efficient Collagen Secretion. *Cell Rep* **15**, 1648-1659. doi:10.1016/j.celrep.2016.04.062

McCaughey, J., Stevenson, N. L., Mantell, J. M., Neal, C. R., Paterson, A., Heesom, K. and Stephens, D. J. (2021). A general role for TANGO1, encoded by MIA3, in secretory pathway organization and function. *J. Cell Sci.* **134**, jcs259075. doi:10.1242/jcs.259075

Meek, K. M. (2009). Corneal collagen-its role in maintaining corneal shape and transparency. *Biophys Rev* **1**, 83-93. doi:10.1007/s12551-009-0011-x

Meyer, R., Schacht, S., Buschmann, L., Begemann, M., Kraft, F., Haag, N., Kochs, A., Schulze, A., Kurth, I. and Elbracht, M. (2019). Biallelic CSGALNACT1-mutations cause a mild skeletal dysplasia. *Bone* **127**, 446-451. doi:10.1016/j.bone.2019.07.016

Miguez, P. A. (2020). Evidence of biglycan structure-function in bone homeostasis and aging. *Connect. Tissue Res.* **61**, 19-33. doi:10.1080/03008207.2019.1669577

Mikami, T. and Kitagawa, H. (2013). Biosynthesis and function of chondroitin sulfate. *Biochim. Biophys. Acta* **1830**, 4719-4733. doi:10.1016/j.bbagen.2013.06.006

Mironov, A. A., Beznoussenko, G. V., Nicoziani, P., Martella, O., Trucco, A., Kweon, H. S., Di Giandomenico, D., Polishchuk, R. S., Fusella, A., Lupetti, P. et al. (2001). Small cargo proteins and large aggregates can traverse the Golgi by a common mechanism without leaving the lumen of cisternae. *J. Cell Biol.* **155**, 1225-1238. doi:10.1083/jcb.200108073

Miyahara, M., Hayashi, K., Berger, J., Tanzawa, K., Njieha, F. K., Trelstad, R. L. and Prockop, D. J. (1984). Formation of collagen fibrils by enzymic cleavage of precursors of type I collagen in vitro. *J. Biol. Chem.* **259**, 9891-9898. doi:10.1016/S0021-9258(17)42783-9

Miyake, N., Kosho, T., Mizumoto, S., Furuichi, T., Hatamochi, A., Nagashima, Y., Arai, E., Takahashi, K., Kawamura, R., Wakui, K. et al. (2010). Loss-of-function mutations of CHST14 in a new type of Ehlers-Danlos syndrome. *Hum. Mutat.* **31**, 966-974. doi:10.1002/humu.21300

Mizumoto, S., Ikegawa, S. and Sugahara, K. (2013). Human genetic disorders caused by mutations in genes encoding biosynthetic enzymes for sulfated glycosaminoglycans. *J. Biol. Chem.* **288**, 10953-10961. doi:10.1074/jbc.R112.437038

Mizumoto, S., Janecke, A. R., Sadeghpour, A., Povysil, G., McDonald, M. T., Unger, S., Greber-Platzer, S., Deak, K. L., Katsanis, N., Superti-Furga, A. et al. (2020). CSGALNACT1-congenital disorder of glycosylation: a mild skeletal dysplasia with advanced bone age. *Hum. Mutat.* **41**, 655-667. doi:10.1002/humu.23952

Mizumoto, S., Yamada, S. and Sugahara, K. (2015). Mutations in biosynthetic enzymes for the protein linker region of chondroitin/dermatan/heparan sulfate cause skeletal and skin dysplasias. *Biomed. Res. Int.* **2015**, 861752. doi:10.1155/2015/861752

Mkhikian, H., Mortales, C. L., Zhou, R. W., Khachikyan, K., Wu, G., Haslam, S. M., Kavarian, P., Dell, A. and Demetriou, M. (2016). Golgi self-correction generates bioequivalent glycans to preserve cellular homeostasis. *Elife* **5**, e14814. doi:10.7554/eLife.14814

Møller, L. B., Bukrinsky, J. T., Mølgaard, A., Paulsen, M., Lund, C., Tümer, Z., Larsen, S. and Horn, N. (2005). Identification and analysis of 21 novel disease-causing amino acid substitutions in the conserved part of ATP7A. *Hum. Mutat.* **26**, 84-93. doi:10.1002/humu.20190

Moremen, K. W., Tiemeyer, M. and Nairn, A. V. (2012). Vertebrate protein glycosylation: diversity, synthesis and function. *Nat. Rev. Mol. Cell Biol.* **13**, 448-462. doi:10.1038/nrm3383

Moriarity, J. L., Hurt, K. J., Resnick, A. C., Storm, P. B., Laroy, W., Schnaar, R. L. and Snyder, S. H. (2002). UDP-glucuronate decarboxylase, a key enzyme in proteoglycan synthesis: cloning, characterization, and localization. *J. Biol. Chem.* **277**, 16968-16975. doi:10.1074/jbc.M109316200

Müller, T., Mizumoto, S., Suresh, I., Komatsu, Y., Vodopiutz, J., Dundar, M., Straub, V., Lingenhel, A., Melmer, A., Lechner, S. et al. (2013). Loss of dermatan sulfate epimerase (DSE) function results in musculocontractural Ehlers-Danlos syndrome. *Hum. Mol. Genet.* **22**, 3761-3772. doi:10.1093/hmg/ddt227

Munns, C. F., Fahiminiya, S., Poudel, N., Munteanu, M. C., Majewski, J., Sillence, D. O., Metcalf, J. P., Biggin, A., Glorieux, F., Fassier, F. et al. (2015). Homozygosity for frameshift mutations in XYLT2 result in a spondylo-ocular syndrome with bone fragility, cataracts, and hearing defects. *Am. J. Hum. Genet.* **96**, 971-978. doi:10.1016/j.ajhg.2015.04.017

Munro, S. (1995). An investigation of the role of transmembrane domains in Golgi protein retention. *EMBO J.* **14**, 4695-4704. doi:10.1002/j.1460-2075.1995.tb00151.x

Murakami, T., Saito, A., Hino, S., Kondo, S., Kanemoto, S., Chihara, K., Sekiya, H., Tsumagari, K., Ochiai, K., Yoshinaga, K. et al. (2009). Signalling mediated by the endoplasmic reticulum stress transducer OASIS is involved in bone formation. *Nat. Cell Biol.* **11**, 1205-1211. doi:10.1038/ncb1963

Nakajima, M., Mizumoto, S., Miyake, N., Kogawa, R., Iida, A., Ito, H., Kitoh, H., Hirayama, A., Mitsubuchi, H., Miyazaki, O. et al. (2013). Mutations in B3GALT6, which encodes a glycosaminoglycan linker region enzyme, cause a spectrum of skeletal and connective tissue disorders. *Am. J. Hum. Genet.* **92**, 927-934. doi:10.1016/j.ajhg.2013.04.003

Nakamura, K., Kurokawa, T., Nagano, A., Nakamura, S., Taniguchi, K. and Hamazaki, M. (1997). Dyggve-Melchior-Clausen syndrome without mental retardation (Smith-McCort dysplasia): morphological findings in the growth plate

of the iliac crest. *Am. J. Med. Genet.* **72**, 11-17. doi:10.1002/(SICI)1096-8628(19971003)72:1<11::AID-AJMG3>3.0.CO;2-Y

Nakamura, N., Wei, J. H. and Seemann, J. (2012). Modular organization of the mammalian Golgi apparatus. *Curr. Opin. Cell Biol.* **24**, 467-474. doi:10.1016/j.ceb.2012.05.009

Nareyeck, G., Seidler, D. G., Troyer, D., Rauterberg, J., Kresse, H. and Schonherr, E. (2004). Differential interactions of decorin and decorin mutants with type I and type VI collagens. *Eur. J. Biochem.* **271**, 3389-3398. doi:10.1111/j.1432-1033.2004.04273.x

Newstead, S. and Barr, F. (2020). Molecular basis for KDEL-mediated retrieval of escaped ER-resident proteins - SWEET talking the COPs. *J. Cell Sci.* **133**, jcs250100. doi:10.1242/jcs.250100

Nguyen, A. T., Chia, J., Ros, M., Hui, K. M., Saltel, F. and Bard, F. (2017). Organelle specific O-glycosylation drives MMP14 activation, tumor growth, and metastasis. *Cancer Cell* **32**, 639-653. e6. doi:10.1016/j.ccell.2017.10.001

Niel, F., Ellies, P., Dighiero, P., Soria, J., Sabbagh, C., San, C., Renard, G., Delpech, M. and Valleix, S. (2003). Truncating mutations in the carbohydrate sulfotransferase 6 gene (CHST6) result in macular corneal dystrophy. *Invest. Ophthalmol. Vis. Sci.* **44**, 2949-2953. doi:10.1167/iovs.02-0740

Nuwayhid, N., Glaser, J. H., Johnson, J. C., Conrad, H. E., Hauser, S. C. and Hirschberg, C. B. (1986). Xylosylation and glucuronosylation reactions in rat liver Golgi apparatus and endoplasmic reticulum. *J. Biol. Chem.* **261**, 12936-12941. doi:10.1016/S0021-9258(18)69252-X

Oeffner, F., Fischer, G., Happle, R., König, A., Betz, R. C., Bornholdt, D., Neidel, U., Boente Mdel, C., Redler, S., Romero-Gomez, J. et al. (2009). IFAP syndrome is caused by deficiency in MBTPS2, an intramembrane zinc metalloprotease essential for cholesterol homeostasis and ER stress response. *Am. J. Hum. Genet.* **84**, 459-467. doi:10.1016/j.ajhg.2009.03.014

Okajima, T., Fukumoto, S., Furukawa, K. and Urano, T. (1999). Molecular basis for the progeroid variant of Ehlers-Danlos syndrome. Identification and characterization of two mutations in galactosyltransferase I gene. *J. Biol. Chem.* **274**, 28841-28844. doi:10.1074/jbc.274.41.28841

Orrico, A., Galli, L., Falciani, M., Bracci, M., Cavaliere, M. L., Rinaldi, M. M., Musacchio, A. and Sorrentino, V. (2000). A mutation in the pleckstrin homology (PH) domain of the FGD1 gene in an Italian family with faciogenital dysplasia (Aarskog-Scott syndrome). *FEBS Lett.* **478**, 216-220. doi:10.1016/S0014-5793(00)01857-3

Oud, M. M., Tuijnenburg, P., Hempel, M., van Vlies, N., Ren, Z., Ferdinandusse, S., Jansen, M. H., Santer, R., Johannsen, J., Bacchelli, C. et al. (2017). Mutations in EXTL3 Cause Neuro-immuno-skeletal Dysplasia Syndrome. *Am. J. Hum. Genet.* **100**, 281-296. doi:10.1016/j.ajhg.2017.01.013

Paganini, C., Costantini, R., Superti-Furga, A. and Rossi, A. (2019). Bone and connective tissue disorders caused by defects in glycosaminoglycan biosynthesis: a panoramic view. *FEBS J.* **286**, 3008-3032. doi:10.1111/febs.14984

Patel, N., Anand, D., Monies, D., Maddirevula, S., Khan, A. O., Algoufi, T., Alowain, M., Faqeih, E., Alshammari, M., Qudair, A. et al. (2017). Novel phenotypes and loci identified through clinical genomics approaches to pediatric cataract. *Hum. Genet.* **136**, 205-225. doi:10.1007/s00439-016-1747-6

Péanne, R., de Lonlay, P., Foulquier, F., Kornak, U., Lefeber, D. J., Morava, E., Pérez, B., Seta, N., Thiel, C., Van Schaftingen, E. et al. (2018). Congenital disorders of glycosylation (CDG): Quo vadis? *Eur. J. Med. Genet.* **61**, 643-663. doi:10.1016/j.ejmg.2017.10.012

Pedersen, L. C., Tsuchida, K., Kitagawa, H., Sugahara, K., Darden, T. A. and Negishi, M. (2000). Heparan/chondroitin sulfate biosynthesis. Structure and mechanism of human glucuronyltransferase I. *J. Biol. Chem.* **275**, 34580-34585. doi:10.1074/jbc.M007399200

Philippe, C., Porter, D. E., Emerton, M. E., Wells, D. E., Simpson, A. H. and Monaco, A. P. (1997). Mutation screening of the EXT1 and EXT2 genes in patients with hereditary multiple exostoses. *Am. J. Hum. Genet.* **61**, 520-528. doi:10.1086/515505

Pouthas, F., Girard, P., Lecaudey, V., Ly, T. B., Gilmour, D., Boulin, C., Pepperkok, R. and Reynaud, E. G. (2008). In migrating cells, the Golgi complex and the position of the centrosome depend on geometrical constraints of the substratum. *J. Cell Sci.* **121**, 2406-2414. doi:10.1242/jcs.026849

Prydz, K. (2015). Determinants of Glycosaminoglycan (GAG) Structure. *Biomolecules* **5**, 2003-2022. doi:10.3390/biom5032003

Pusapati, G. V., Luchetti, G. and Pfeffer, S. R. (2012). Ric1-Rgp1 complex is a guanine nucleotide exchange factor for the late Golgi Rab6A GTPase and an effector of the medial Golgi Rab33B GTPase. *J. Biol. Chem.* **287**, 42129-42137. doi:10.1074/jbc.M112.414565

Raman, R., Sasisekharan, V. and Sasisekharan, R. (2005). Structural insights into biological roles of protein-glycosaminoglycan interactions. *Chem. Biol.* **12**, 267-277. doi:10.1016/j.chembiol.2004.11.020

Rebane, A. A., Ziltener, P., LaMonica, L. C., Bauer, A. H., Zheng, H., López-Montero, I., Pincet, F., Rothman, J. E. and Ernst, A. M. (2020). Liquid–liquid phase separation of the Golgi matrix protein GM130. *FEBS Lett.* **594**, 1132-1144. doi:10.1002/1873-3468.13715

Reily, C., Stewart, T. J., Renfrow, M. B. and Novak, J. (2019). Glycosylation in health and disease. *Nat. Rev. Nephrol.* **15**, 346-366. doi:10.1038/s41581-019-0129-4

Ritelli, M., Cinquina, V., Giacopuzzi, E., Venturini, M., Chiarelli, N. and Colombi, M. (2019). Further defining the phenotypic spectrum of B3GAT3 mutations and literature review on linkeropathy syndromes. *Genes (Basel)* **10**, 631. doi:10.3390/genes10090631

Rizzo, R., Russo, D., Kurokawa, K., Sahu, P., Lombardi, B., Supino, D., Zhukovsky, M. A., Vocat, A., Pothukuchi, P., Kunnathully, V. et al. (2021). Golgi maturation-dependent glycoenzyme recycling controls glycosphingolipid biosynthesis and cell growth via GOLPH3. *EMBO J.* **40**, e107238. doi:10.15252/embj.2020107238

Rodrigues, J. G., Balmaña, M., Macedo, J. A., Poças, J., Fernandes, Â., de-Freitas-Junior, J. C. M., Pinho, S. S., Gomes, J., Magalhães, A., Gomes, C. et al. (2018). Glycosylation in cancer: Selected roles in tumour progression, immune modulation and metastasis. *Cell. Immunol.* **333**, 46-57. doi:10.1016/j.cellimm.2018.03.007

Rohrmann, K., Niemann, R. and Buddecke, E. (1985). Two N-acetylgalactosaminyltransferase are involved in the biosynthesis of chondroitin sulfate. *Eur. J. Biochem.* **148**, 463-469. doi:10.1111/j.1432-1033.1985.tb08862.x

Romani, P., Brian, I., Santinon, G., Pocaterra, A., Audano, M., Pedretti, S., Mathieu, S., Forcato, M., Bicciato, S., Manneville, J. B. et al. (2019). Extracellular matrix mechanical cues regulate lipid metabolism through Lipin-1 and SREBP. *Nat. Cell Biol.* **21**, 338-347. doi:10.1038/s41556-018-0270-5

Ronce, N., Moizard, M. P., Robb, L., Toutain, A., Villard, L. and Moraine, C. (1997). A C2055T transition in exon 8 of the ATP7A gene is associated with exon skipping in an occipital horn syndrome family. *Am. J. Hum. Genet.* **61**, 233-238. doi:10.1016/S0002-9297(07)64297-9

Ros, M., Nguyen, A. T., Chia, J., Le Tran, S., Le Guezennec, X., McDowall, R., Vakhrushev, S., Clausen, H., Humphries, M. J., Saltel, F. et al. (2020). ER-resident oxidoreductases are glycosylated and trafficked to the cell surface to promote matrix degradation by tumour cells. *Nat. Cell Biol.* **22**, 1371-1381. doi:10.1038/s41556-020-00590-w

Rosnoblet, C., Legrand, D., Demaegd, D., Hacine-Gherbi, H., de Bettignies, G., Bammens, R., Borrego, C., Duvet, S., Morsomme, P., Matthijs, G. et al. (2013). Impact of disease-causing mutations on TMEM165 subcellular localization, a recently identified protein involved in CDG-II. *Hum. Mol. Genet.* **22**, 2914-2928. doi:10.1093/hmg/ddt146

Rothman, J. E. (2019). Jim's View: Is the Golgi stack a phase-separated liquid crystal? *FEBS Lett.* **593**, 2701-2705. doi:10.1002/1873-3468.13609

Ruhland, C., Schonherr, E., Robenek, H., Hansen, U., Iozzo, R. V., Bruckner, P. and Seidler, D. G. (2007). The glycosaminoglycan chain of decorin plays an important role in collagen fibril formation at the early stages of fibrillogenesis. *FEBS J.* **274**, 4246-4255. doi:10.1111/j.1742-4658.2007.05951.x

Saito, A., Hino, S., Murakami, T., Kanemoto, S., Kondo, S., Saitoh, M., Nishimura, R., Yoneda, T., Furuichi, T., Ikegawa, S. et al. (2009a). Regulation of endoplasmic reticulum stress response by a BBF2H7-mediated Sec23a pathway is essential for chondrogenesis. *Nat. Cell Biol.* **11**, 1197-1204. doi:10.1038/ncb1962

Saito, K., Chen, M., Bard, F., Chen, S., Zhou, H., Woodley, D., Polischuk, R., Schekman, R. and Malhotra, V. (2009b). TANGO1 facilitates cargo loading at endoplasmic reticulum exit sites. *Cell* **136**, 891-902. doi:10.1016/j.cell.2008.12.025

Saito, K., Yamashiro, K., Ichikawa, Y., Erlmann, P., Kontani, K., Malhotra, V. and Katada, T. (2011). cTAGE5 mediates collagen secretion through interaction with TANGO1 at endoplasmic reticulum exit sites. *Mol. Biol. Cell* **22**, 2301-2308. doi:10.1091/mbc.e11-02-0143

Santos, H. G., Fernandes, H. C., Nunes, J. L. and Almeida, M. R. (2009). Portuguese case of Smith-McCort syndrome caused by a new mutation in the Dymeclin (FLJ20071) gene. *Clin. Dysmorphol.* **18**, 41-44. doi:10.1097/MCD.0b013e32831868ea

Sato, T., Gotoh, M., Kiyohara, K., Akashima, T., Iwasaki, H., Kameyama, A., Mochizuki, H., Yada, T., Inaba, N., Togayachi, A. et al. (2003). Differential roles of two N-acetylgalactosaminyltransferases, CSGalNAcT-1, and a novel enzyme, CSGalNAcT-2. Initiation and elongation in synthesis of chondroitin sulfate. *J. Biol. Chem.* **278**, 3063-3071. doi:10.1074/jbc.M208886200

Schjoldager, K. T., Narimatsu, Y., Joshi, H. J. and Clausen, H. (2020). Global view of human protein glycosylation pathways and functions. *Nat. Rev. Mol. Cell Biol.* **21**, 729-749. doi:10.1038/s41580-020-00294-x

Schneeberger, P. E., von Elsner, L., Barker, E. L., Meinecke, P., Marquardt, I., Alawi, M., Steindl, K., Joset, P., Rauch, A., Zwijnenburg, P. J. G. et al. (2020). Bi-allelic pathogenic variants in HS2ST1 cause a syndrome characterized by developmental delay and corpus callosum, skeletal, and renal abnormalities. *Am. J. Hum. Genet.* **107**, 1044-1061. doi:10.1016/j.ajhg.2020.10.007

Schonherr, E., Witsch-Prehm, P., Harrach, B., Robenek, H., Rauterberg, J. and Kresse, H. (1995). Interaction of biglycan with type I collagen. *J. Biol. Chem.* **270**, 2776-2783. doi:10.1074/jbc.270.6.2776

Schreml, J., Durmaz, B., Cogulu, O., Keupp, K., Beleggia, F., Pohl, E., Milz, E., Coker, M., Ucar, S. K., Nürnberg, G. et al. (2014). The missing "link": an

autosomal recessive short stature syndrome caused by a hypofunctional XYLT1 mutation. *Hum. Genet.* **133**, 29-39. doi:10.1007/s00439-013-1351-y

Schwartz, N. (2000). Biosynthesis and regulation of expression of proteoglycans. *Front. Biosci.* **5**, D649-D655. doi:10.2741/A540

Schwartz, C. E., Gillessen-Kaesbach, G., May, M., Cappa, M., Gorski, J., Steindl, K. and Neri, G. (2000). Two novel mutations confirm FGD1 is responsible for the Aarskog syndrome. *Eur. J. Hum. Genet.* **8**, 869-874. doi:10.1038/sj.ejhg.5200553

Sechi, S., Frappaolo, A., Karimpour-Ghahnavieh, A., Piergentili, R. and Giansanti, M. G. (2020). Oncogenic roles of GOLPH3 in the physiopathology of Cancer. *Int. J. Mol. Sci.* **21**, 933. doi:10.3390/ijms21030933

Seidah, N. G., Sadr, M. S., Chrétien, M. and Mbikay, M. (2013). The multifaceted proprotein convertases: their unique, redundant, complementary, and opposite functions. *J. Biol. Chem.* **288**, 21473-21481. doi:10.1074/jbc.R113.481549

Seidler, D. G., Faiyaz-Ul-Haque, M., Hansen, U., Yip, G. W., Zaidi, S. H. E., Teebi, A. S., Kiesel, L. and Götte, M. (2006). Defective glycosylation of decorin and biglycan, altered collagen structure, and abnormal phenotype of the skin fibroblasts of an Ehlers–Danlos syndrome patient carrying the novel Arg270Cys substitution in galactosyltransferase I (β4GalT-7). *J. Mol. Med.* **84**, 583-594. doi:10.1007/s00109-006-0046-4

Sellars, E. A., Bosanko, K. A., Lepard, T., Garnica, A. and Schaefer, G. B. (2014). A newborn with complex skeletal abnormalities, joint contractures, and bilateral corneal clouding with sclerocornea. *Semin. Pediatr. Neurol.* **21**, 84-87. doi:10.1016/j.spen.2014.04.007

Shabbir, R. M. K., Nalbant, G., Ahmad, N., Malik, S. and Tolun, A. (2018). Homozygous CHST11 mutation in chondrodysplasia, brachydactyly, overriding digits, clino-symphalangism and synpolydactyly. *J. Med. Genet.* **55**, 489-496. doi:10.1136/jmedgenet-2017-105003

Shao, X., Taha, I. N., Clauser, K. R., Gao, Y. T. and Naba, A. (2020). MatrisomeDB: the ECM-protein knowledge database. *Nucleic Acids Res.* **48**, D1136-D1144. doi:10.1093/nar/gkz849

Sharpe, H. J., Stevens, T. J. and Munro, S. (2010). A comprehensive comparison of transmembrane domains reveals organelle-specific properties. *Cell* **142**, 158-169. doi:10.1016/j.cell.2010.05.037

Silbert, J. E. and Sugumaran, G. (2002). Biosynthesis of chondroitin/dermatan sulfate. *IUBMB Life* **54**, 177-186. doi:10.1080/15216540214923

Skjørringe, T., Amstrup Pedersen, P., Salling Thorborg, S., Nissen, P., Gourdon, P. and Birk Møller, L. (2017). Characterization of ATP7A missense mutants suggests a correlation between intracellular trafficking and severity of Menkes disease. *Sci. Rep.* **7**, 757. doi:10.1038/s41598-017-00618-6

Smits, P., Bolton, A. D., Funari, V., Hong, M., Boyden, E. D., Lu, L., Manning, D. K., Dwyer, N. D., Moran, J. L., Prysak, M. et al. (2010). Lethal skeletal dysplasia in mice and humans lacking the golgin GMAP-210. *N. Engl. J. Med.* **362**, 206-216. doi:10.1056/NEJMoa0900158

Spiro, R. C., Freeze, H. H., Sampath, D. and Garcia, J. A. (1991). Uncoupling of chondroitin sulfate glycosaminoglycan synthesis by brefeldin A. *J. Cell Biol.* **115**, 1463-1473. doi:10.1083/jcb.115.5.1463

Springer, G. F. (1984). T and Tn, general carcinoma autoantigens. *Science* **224**, 1198-1206. doi:10.1126/science.6729450

Stevenson, N. L., Bergen, D. J. M., Skinner, R. E. H., Kague, E., Martin-Silverstone, E., Robson Brown, K. A., Hammond, C. L. and Stephens, D. J. (2017). Giantin-knockout models reveal a feedback loop between Golgi function and glycosyltransferase expression. *J. Cell Sci.* **130**, 4132-4143.

Stevenson, N. L., Bergen, D. J. M., Lu, Y., Prada-Sanchez, M. E., Kadler, K. E., Hammond, C. L. and Stephens, D. J. (2021). Giantin is required for intracellular N-terminal processing of type I procollagen. *J. Cell Biol.* **220**, e202005166. doi:10.1083/jcb.202005166

Sugumaran, G. and Silbert, J. E. (1990). Relationship of sulfation to ongoing chondroitin polymerization during biosynthesis of chondroitin 4-sulfate by microsomal preparations from cultured mouse mastocytoma cells. *J. Biol. Chem.* **265**, 18284-18288. doi:10.1016/S0021-9258(17)44750-8

Sugumaran, G. and Silbert, J. E. (1991). Subfractionation of chick embryo epiphyseal cartilage Golgi. Localization of enzymes involved in the synthesis of the polysaccharide portion of proteochondroitin sulfate. *J. Biol. Chem.* **266**, 9565-9569. doi:10.1016/S0021-9258(18)92857-7

Sugumaran, G., Katsman, M. and Silbert, J. E. (1992). Effects of brefeldin A on the localization of chondroitin sulfate-synthesizing enzymes. Activities in subfractions of the Golgi from chick embryo epiphyseal cartilage. *J. Biol. Chem.* **267**, 8802-8806. doi:10.1016/S0021-9258(19)50350-7

Sztul, E., Chen, P. W., Casanova, J. E., Cherfils, J., Dacks, J. B., Lambright, D. G., Lee, F. S., Randazzo, P. A., Santy, L. C., Schurmann, A. et al. (2019). ARF GTPases and their GEFs and GAPs: concepts and challenges. *Mol. Biol. Cell* **30**, 1249-1271. doi:10.1091/mbc.E18-12-0820

Takagi, M., Maeno, M., Kagami, A., Takahashi, Y. and Otsuka, K. (1991). Biochemical and immunocytochemical characterization of mineral binding proteoglycans in rat bone. *J. Histochem. Cytochem.* **39**, 41-50. doi:10.1177/39.1.1898498

Takeuchi, Y., Matsumoto, T., Ogata, E. and Shishiba, Y. (1990). Isolation and characterization of proteoglycans synthesized by mouse osteoblastic cells in culture during the mineralization process. *Biochem. J.* **266**, 15-24. doi:10.1042/bj2660015

Tang, J., Robertson, S., Lem, K. E., Godwin, S. C. and Kaler, S. G. (2006). Functional copper transport explains neurologic sparing in occipital horn syndrome. *Genet. Med.* **8**, 711-718. doi:10.1097/01.gim.0000245578.94312.1e

Thery, M., Racine, V., Piel, M., Pepin, A., Dimitrov, A., Chen, Y., Sibarita, J. B. and Bornens, M. (2006). Anisotropy of cell adhesive microenvironment governs cell internal organization and orientation of polarity. *Proc. Natl. Acad. Sci. USA* **103**, 19771-19776. doi:10.1073/pnas.0609267103

Thiele, H., Sakano, M., Kitagawa, H., Sugahara, K., Rajab, A., Höhne, W., Ritter, H., Leschik, G., Nürnberg, P. and Mundlos, S. (2004). Loss of chondroitin 6-O-sulfotransferase-1 function results in severe human chondrodysplasia with progressive spinal involvement. *Proc. Natl. Acad. Sci. USA* **101**, 10155-10160. doi:10.1073/pnas.0400334101

Tie, H. C., Ludwig, A., Sandin, S. and Lu, L. (2018). The spatial separation of processing and transport functions to the interior and periphery of the Golgi stack. *Elife* **7**, e41301. doi:10.7554/eLife.41301

Trelstad, R. L. and Hayashi, K. (1979). Tendon collagen fibrillogenesis: intracellular subassemblies and cell surface changes associated with fibril growth. *Dev. Biol.* **71**, 228-242. doi:10.1016/0012-1606(79)90166-0

Trucco, A., Polishchuk, R. S., Martella, O., Di Pentima, A., Fusella, A., Di Giandomenico, D., San Pietro, E., Beznoussenko, G. V., Polishchuk, E. V., Baldassarre, M. et al. (2004). Secretory traffic triggers the formation of tubular continuities across Golgi sub-compartments. *Nat. Cell Biol.* **6**, 1071-1081. doi:10.1038/ncb1180

Tu, L., Tai, W. C. S., Chen, L. and Banfield, D. K. (2008). Signal-Mediated Dynamic Retention of Glycosyltransferases in the Golgi. *Science* **321**, 404-407. doi:10.1126/science.1159411

Tümer, Z., Lund, C., Tolshave, J., Vural, B., Tønnesen, T. and Horn, N. (1997). Identification of point mutations in 41 unrelated patients affected with Menkes disease. *Am. J. Hum. Genet.* **60**, 63-71.

Tzima, E., Kiosses, W. B., del Pozo, M. A. and Schwartz, M. A. (2003). Localized cdc42 activation, detected using a novel assay, mediates microtubule organizing center positioning in endothelial cells in response to fluid shear stress. *J. Biol. Chem.* **278**, 31020-31023. doi:10.1074/jbc.M301179200

Udono, M., Fujii, K., Harada, G., Tsuzuki, Y., Kadooka, K., Zhang, P., Fujii, H., Amano, M., Nishimura, S.-I., Tashiro, K. et al. (2015). Impaired ATP6V0A2 expression contributes to Golgi dispersion and glycosylation changes in senescent cells. *Sci. Rep.* **5**, 17342. doi:10.1038/srep17342

Uhlin-Hansen, L., Kusche-Gullberg, M., Berg, E., Eriksson, I. and Kjellen, L. (1997). Mouse mastocytoma cells synthesize undersulfated heparin and chondroitin sulfate in the presence of brefeldin A. *J. Biol. Chem.* **272**, 3200-3206. doi:10.1074/jbc.272.6.3200

Unlu, G., Qi, X., Gamazon, E. R., Melville, D. B., Patel, N., Rushing, A. R., Hashem, M., Al-Faifi, A., Chen, R., Li, B. et al. (2020). Phenome-based approach identifies RIC1-linked Mendelian syndrome through zebrafish models, biobank associations and clinical studies. *Nat. Med.* **26**, 98-109. doi:10.1038/s41591-019-0705-y

Vagne, Q., Vrel, J. P. and Sens, P. (2020). A minimal self-organisation model of the Golgi apparatus. *Elife* **9**, e47318. doi:10.7554/eLife.47318

Van Damme, T., Gardeitchik, T., Mohamed, M., Guerrero-Castillo, S., Freisinger, P., Guillemyn, B., Kariminejad, A., Dalloyaux, D., van Kraaij, S., Lefeber, D. J. et al. (2017). Mutations in ATP6V1E1 or ATP6V1A cause autosomal-recessive cutis laxa. *Am. J. Hum. Genet.* **100**, 216-227. doi:10.1016/j.ajhg.2016.12.010

Van Damme, T., Pang, X., Guillemyn, B., Gulberti, S., Syx, D., De Rycke, R., Kaye, O., de Die-Smulders, C. E. M., Pfundt, R., Kariminejad, A. et al. (2018). Biallelic B3GALT6 mutations cause spondylodysplastic Ehlers-Danlos syndrome. *Hum. Mol. Genet.* **27**, 3475-3487. doi:10.1093/hmg/ddy234

Vertel, B. M., Walters, L. M., Flay, N., Kearns, A. E. and Schwartz, N. B. (1993). Xylosylation is an endoplasmic reticulum to Golgi event. *J. Biol. Chem.* **268**, 11105-11112. doi:10.1016/S0021-9258(18)82098-1

Vissers, L. E., Lausch, E., Unger, S., Campos-Xavier, A. B., Gilissen, C., Rossi, A., Del Rosario, M., Venselaar, H., Knoll, U., Nampoothiri, S. et al. (2011). Chondrodysplasia and abnormal joint development associated with mutations in IMPAD1, encoding the Golgi-resident nucleotide phosphatase, gPAPP. *Am. J. Hum. Genet.* **88**, 608-615. doi:10.1016/j.ajhg.2011.04.002

Vodopiutz, J., Mizumoto, S., Lausch, E., Rossi, A., Unger, S., Janocha, N., Costantini, R., Seidl, R., Greber-Platzer, S., Yamada, S. et al. (2017). Chondroitin Sulfate N-acetylgalactosaminyltransferase-1 (CSGalNAcT-1) deficiency results in a mild skeletal dysplasia and joint laxity. *Hum. Mutat.* **38**, 34-38. doi:10.1002/humu.23070

Volpi, S., Yamazaki, Y., Brauer, P. M., van Rooijen, E., Hayashida, A., Slavotinek, A., Sun Kuehn, H., Di Rocco, M., Rivolta, C., Bortolomai, I. et al. (2017). EXTL3 mutations cause skeletal dysplasia, immune deficiency, and developmental delay. *J. Exp. Med.* **214**, 623-637. doi:10.1084/jem.20161525

von Oettingen, J. E., Tan, W. H. and Dauber, A. (2014). Skeletal dysplasia, global developmental delay, and multiple congenital anomalies in a 5-year-old boy-report of the second family with B3GAT3 mutation and expansion of the phenotype. *Am. J. Med. Genet. A* **164a**, 1580-1586. doi:10.1002/ajmg.a.36487

Vorster, A. A., Beighton, P. and Ramesar, R. S. (2015). Spondyloepimetaphyseal dysplasia with joint laxity (Beighton type); mutation analysis in eight affected South African families. *Clin. Genet.* **87**, 492-495. doi:10.1111/cge.12413

Waddington, R. J., Roberts, H. C., Sugars, R. V. and Schonherr, E. (2003). Differential roles for small leucine-rich proteoglycans in bone formation. *Eur. Cell Mater.* **6**, 12-21. discussion 21. doi:10.22203/eCM.v006a02

Walma, D. A. C. and Yamada, K. M. (2020). The extracellular matrix in development. *Development* **147**, dev175596. doi:10.1242/dev.175596

Wang, T., Li, L. and Hong, W. (2017). SNARE proteins in membrane trafficking. *Traffic* **18**, 767-775. doi:10.1111/tra.12524

Wang, W. M., Lee, S., Steiglitz, B. M., Scott, I. C., Lebares, C. C., Allen, M. L., Brenner, M. C., Takahara, K. and Greenspan, D. S. (2003). Transforming growth factor-beta induces secretion of activated ADAMTS-2. A procollagen III N-proteinase. *J. Biol. Chem.* **278**, 19549-19557. doi:10.1074/jbc.M300767200

Wang, X., Hua, R., Ahsan, A., Ni, Q., Huang, Y., Gu, S. and Jiang, J. X. (2018). Age-related deterioration of bone toughness is related to diminishing amount of matrix glycosaminoglycans (GAGS). *JBMR Plus* **2**, 164-173. doi:10.1002/jbm4.10030

Wehrle, A., Witkos, T. M., Unger, S., Schneider, J., Follit, J. A., Hermann, J., Welting, T., Fano, V., Hietala, M., Vatanavicharn, N. et al. (2019). Hypomorphic mutations of TRIP11 cause odontochondrodysplasia. *JCI Insight* **4**, e124701. doi:10.1172/jci.insight.124701

Welch, L. G. and Munro, S. (2019). A tale of short tails, through thick and thin: investigating the sorting mechanisms of Golgi enzymes. *FEBS Lett.* **593**, 2452-2465. doi:10.1002/1873-3468.13553

Welch, L. G., Peak-Chew, S.-Y., Begum, F., Stevens, T. J. and Munro, S. (2021). GOLPH3 and GOLPH3L are broad-spectrum COPI adaptors for sorting into intra-Golgi transport vesicles. *J. Cell Biol.* **220**, e202106115. doi:10.1083/jcb.202106115

Wight, T. N. and Potter-Perigo, S. (2011). The extracellular matrix: an active or passive player in fibrosis? *Am. J. Physiol. Gastrointest. Liver Physiol.* **301**, G950-G955. doi:10.1152/ajpgi.00132.2011

Winkler, J., Abisoye-Ogunniyan, A., Metcalf, K. J. and Werb, Z. (2020). Concepts of extracellular matrix remodelling in tumour progression and metastasis. *Nat. Commun.* **11**, 5120. doi:10.1038/s41467-020-18794-x

Witkos, T. M. and Lowe, M. (2015). The Golgin family of coiled-coil tethering proteins. *Front. Cell Dev. Biol.* **3**, 86.

Witkos, T. M. and Lowe, M. (2017). Recognition and tethering of transport vesicles at the Golgi apparatus. *Curr. Opin. Cell Biol.* **47**, 16-23. doi:10.1016/j.ceb.2017.02.003

Witkos, T. M., Chan, W. L., Joensuu, M., Rhiel, M., Pallister, E., Thomas-Oates, J., Mould, A. P., Mironov, A. A., Biot, C., Guerardel, Y. et al. (2019). GORAB scaffolds COPI at the trans-Golgi for efficient enzyme recycling and correct protein glycosylation. *Nat. Commun.* **10**, 127. doi:10.1038/s41467-018-08044-6

Witte, K., Schuh, A. L., Hegermann, J., Sarkeshik, A., Mayers, J. R., Schwarze, K., Yates, J. R., III, Eimer, S. and Audhya, A. (2011). TFG-1 function in protein secretion and oncogenesis. *Nat. Cell Biol.* **13**, 550-558. doi:10.1038/ncb2225

Wu, X., Steet, R. A., Bohorov, O., Bakker, J., Newell, J., Krieger, M., Spaapen, L., Kornfeld, S. and Freeze, H. H. (2004). Mutation of the COG complex subunit gene COG7 causes a lethal congenital disorder. *Nat. Med.* **10**, 518-523. doi:10.1038/nm1041

Wuyts, W., Van Hul, W., De Boulle, K., Hendrickx, J., Bakker, E., Vanhoenacker, F., Mollica, F., Lüdecke, H. J., Sayli, B. S., Pazzaglia, U. E. et al. (1998). Mutations in the EXT1 and EXT2 genes in hereditary multiple exostoses. *Am. J. Hum. Genet.* **62**, 346-354. doi:10.1086/301726

Yan, J., Stringer, S. E., Hamilton, A., Charlton-Menys, V., Gotting, C., Muller, B., Aeschlimann, D. and Alexander, M. Y. (2011). Decorin GAG synthesis and TGF-beta signaling mediate Ox-LDL-induced mineralization of human vascular smooth muscle cells. *Arterioscler. Thromb. Vasc. Biol.* **31**, 608-615. doi:10.1161/ATVBAHA.110.220749

Yang, Y. S., Wang, C. C., Chen, B. H., Hou, Y. H., Hung, K. S. and Mao, Y. C. (2015). Tyrosine sulfation as a protein post-translational modification. *Molecules* **20**, 2138-2164. doi:10.3390/molecules20022138

Ye, Y., Hu, W., Guo, F., Zhang, W., Wang, J. and Chen, A. (2012). Glycosaminoglycan chains of biglycan promote bone morphogenetic protein-4-induced osteoblast differentiation. *Int. J. Mol. Med.* **30**, 1075-1080. doi:10.3892/ijmm.2012.1091

Zeevaert, R., de Zegher, F., Sturiale, L., Garozzo, D., Smet, M., Moens, M., Matthijs, G. and Jaeken, J. (2013). Bone dysplasia as a key feature in three patients with a novel congenital disorder of glycosylation (CDG) Type II due to a deep intronic splice mutation in TMEM165. *JIMD Rep* **8**, 145-152. doi:10.1007/8904_2012_172

Zou, X. H., Foong, W. C., Cao, T., Bay, B. H., Ouyang, H. W. and Yip, G. W. (2004). Chondroitin sulfate in palatal wound healing. *J. Dent. Res.* **83**, 880-885. doi:10.1177/154405910408301111