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REVIEW

Exocrine gland structure-function relationships

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ABSTRACT

Fluid secretion by exocrine glandular organs is essential to the survival of mammals. Each glandular unit within the body is uniquely organized to carry out its own specific functions, with failure to establish these specialized structures resulting in impaired organ function. Here, we review glandular organs in terms of shared and divergent architecture. We first describe the structural organization of the diverse glandular secretory units (the end-pieces) and their fluid transporting systems (the ducts) within the mammalian system, focusing on how tissue architecture corresponds to functional output. We then highlight how defects in development of end-piece and ductal architecture impacts secretory function. Finally, we discuss how knowledge of exocrine gland structure-function relationships can be applied to the development of new diagnostics, regenerative approaches and tissue regeneration.

KEY WORDS: Exocrine glands, Branching morphogenesis, Lacrimal glands, Mammary glands, Salivary glands, Structure-function

Introduction

Glands in the body generate secretory fluids necessary for the function and/or maintenance of the target tissue. Glands are classified as either endocrine or exocrine: endocrine glands deliver their secretions, such as hormones, into the bloodstream, while exocrine glands deliver secretions directly into body cavities (e.g. oral cavity) or onto external surfaces (e.g. skin). Exocrine glands can be characterized as unicellular, where a single cell is secretory in nature, or multicellular, where an array of epithelial cells organize themselves into sub-structures (Van Lommel, 2003). Multicellular exocrine glands can be further defined based on their mode of secretion (Table 1): merocrine glands secrete secretory contents into the gland lumen via exocytosis without damage to the secreting cell; apocrine glands operate by pinching off small parts of the cell that contain the secretory product; finally, holocrine glands secrete product through apoptosis (the secreting cell dies, emptying its product into the gland lumen). The shape of the tissue (e.g. branched or coiled), as well as the secretory product released (e.g. aqueous, lipid or protein), can also be used to classify exocrine glands (Table 1).

In this Review, we examine the exocrine gland literature in detail. Exocrine gland development has been characterized in numerous organ systems, including the mammary gland (Paine and Lewis, 2017), salivary gland [comprising parotid, sublingual and submandibular components (de Paula et al., 2017; Takeuchi et al., 1978)], pancreas (O'Dowd and Stocker, 2013), prostate (Thomson and Marker, 2006), ocular glands [including meibomian (eyelid) and lacrimal (tear duct) (Garg and Zhang, 2017; Nien et al., 2010)], sebaceous (Niemann and Horsley, 2012) glands, uterine (Kelleher et al., 2019; Spencer et al., 2019) and sweat (including apocrine-sweat and eccrine-sweat) (Lu and Fuchs, 2014) glands. The location of these glands and developmental progression of five representative glands is shown in Fig. 1. The timing of gland initiation and differentiation differs between glandular systems and is largely dependent on the formation of tissues/organs that they serve (Table 2). In all glands, development begins with the formation of a placode or bud (Fig. 1). The epithelial placode or bud extends into the mesenchymal tissue to form a bulb-shaped structure, which then undergoes morphogenesis via coiling or branching (Box 1). In all cases, glands must contain 'end-pieces' (required for the synthesis of glandular secretions) and 'ducts' (required for fluid transport and regulation of tonicity).

In this Review, we discuss shared and distinct features in gland architecture that contribute to dynamic function and highlight major developmental pathways that give rise to these features. The literature is diverse and, depending on the context, some exocrine glands are better studied than others. Our Review accommodates this heterogeneity by highlighting common themes, where possible, and noting gaps in the literature where more research is needed.

End-pieces: functional secretory units

End-pieces can be classified as acinar, alveolar or tubular, and are composed of secretory epithelial cells (Fig. 2). Here, we discuss the distinction between each type of end-piece, their secretory cell types, their organization and their secretion profiles, supplemented with examples from relevant exocrine glands (Table 1).

Acinar end-pieces: salivary, lacrimal, pancreas, meibomian and sebaceous glands

Acinar end-pieces (commonly referred to as acini) are lobules consisting of secretory cells that are present in a variety of glandular organs, including salivary glands (de Paula et al., 2017), the exocrine pancreas (Cleveland et al., 2012), the lacrimal glands (Makarenkova and Dartt, 2015), the sebaceous glands (Niemann and Horsley, 2012) and the meibomian glands (Knop et al., 2011) (Fig. 2A). Glands containing acinar end-pieces produce secretions necessary for homeostasis and thus acinar end-pieces are constitutively associated with secretory activity.

Acinar end-piece organization and composition of secretory content

Acinar secretory cells can be divided into serous, mucous or lipid-enriched cell types based on the composition of their secretion.

(1) Serous cells secrete a watery, protein-rich fluid that is essentially devoid of mucins. They have a pyramidal shape with secretory granules in the apical cytoplasm and round distinct nuclei. Two of the three major salivary glands (parotid and submandibular), the pancreatic exocrine gland

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Table 1. Classification of exocrine glands based on mode of secretion, branch pattern and type of secretion product

Gland(s)	Mode of secretion	Shape	Secretory cell type and product	References
Exocrine pancreas	Merocrine	Compound tubuloacinar	Serous: proteinaceous (digestive enzymes and zymogens).	Longnecker et al. (2018); Motta et al. (1997)
Lacrimal	Merocrine	Compound tubuloacinar	Serous: tears (aqueous layer of ocular tear film)	Singh and Basu, (2020)
Mammary	Apocrine	Compound tubuloalveolar*	Serous: milk	McManaman et al. (2006); Murphrey and Vaidya (2020)
Meibomian	Holocrine	Tubuloacinar	Lipid (lipid layer of ocular tear film)	Knop and Knop (2009)
Prostate	Apocrine and merocrine	Compound tubuloalveolar*	Serous: alkaline compound mixture of hormones, carbohydrates, lipids and fibrolysin (liquefies semen).	Aumüller and Adler (1979); Fullwood et al. (2019); Thomson and Marker (2006)
Salivary (parotid, submandibular and sublingual)	Merocrine	Compound tubuloacinar	Sublingual: mucous, sialic acid Submandibular: mixed Parotid: serous, α amylase	de Paula et al. (2017); Porcheri and Mitsiadis (2019)
Sebaceous	Holocrine	Simple acinar‡	Lipid-enriched: sebum	Thody and Shuster (1989)
Sweat (apocrine)	Apocrine	Simple coiled tubular	Serous: protein, lipid, steroids, water and electrolytes	Lu and Fuchs (2014); Saga (2002); Wilke et al. (2007)
Sweat (eccrine)	Merocrine	Simple coiled tubular	Serous: sweat, antimicrobial proteins, lipids, lactate, urea, sodium and potassium	Cui and Schlessinger (2015); Freeman et al. (2020); Saga (2002)
Uterine	Merocrine	Compound tubular	Serous: crucial signaling molecules (LIF), glucose, fructose, lipids and protein	Arora et al. (2016); Kelleher et al. (2019); Kojima and Selander (1970); Vue et al. (2018)

*The literature describes the prostate and mammary gland as 'tubuloacinar'; however, we have termed them 'tubuloalveolar' here to reflect our clarification of the differences in alveolar and acinar end-pieces.

‡The literature describes the sebaceous gland as simple tubular, but the structure of the sebaceous gland is essentially an acinus connected to a hair follicle shaft or to a skin pore; hence, the 'simple acinar' nomenclature.

(Fig. 2Aa) and the lacrimal glands, are primarily composed of serous cells. Secretory serous cells generate digestive enzymes, such as amylase in the salivary glands, trypsinogen in the pancreas, and lysozyme and peroxidase in the lacrimal glands (Cleveland et al., 2012; Paulsen, 2006; Porcheri and Mitsiadis, 2019; Rocha et al., 2008).

(2) Mucous cells produce a thick viscous fluid rich in highly glycosylated proteins called mucins, and are formed by secretory structures containing mucin granules in the apical cytoplasm that push the flat nuclei to the basal surface (de Paula et al., 2017) (Fig. 2Ab). The sublingual salivary gland comprises mucous cells that produce mucins rich in sialic acid, helping keep the pH of the saliva neutral (Porcheri and Mitsiadis, 2019).

(3) Lipid-enriched acinar cells serve to maintain lubrication of external surfaces and are found in meibomian and sebaceous glands. In the meibomian glands, the acinar end-pieces contain an accumulation of secretory cells called meibocytes that secrete lipid-rich fluid (meibum) onto the ocular surface as part of the tear film (Knop et al., 2011) (Fig. 2Ac). In the sebaceous glands the secretory cells called sebocytes secrete sebum which is an integral component of the epithelial barrier and skin immune system (Zouboulis, 2004). Meibocytes and sebocytes undergo a disintegration of their nucleus and degradation of the cell membrane, resulting in the release of the entire secretory contents of the cell (meibum/sebum), which is characteristic of their holocrine method of secretion (Knop et al., 2011). While mucous or serous secretory end-pieces use a merocrine mode of secretion, lipid secretions correlate with a holocrine mechanism of secretion and it is unclear why this happens.

Beyond synthesized product, serous and mucous acinar cells (except pancreatic acinar end-pieces) contribute fluid and ions to their secretions through diffusion. Upon an external stimulus, neurotransmitters are released by nerve cells, causing an increase in intracellular calcium in the acinar cells. This activates voltage-gated chloride channels resulting in a net negative charge in the lumen, which triggers paracellular sodium influx through tight junctional complexes. Higher sodium chloride concentration in luminal fluid, along with other gland-specific secretions, leads to increased hypertonicity, causing osmosis through water channels and fluid accumulation (Catalán et al., 2015; Cui and Schlessinger, 2015; Ding et al., 2010; Hanukoglu et al., 2017; Ousingsawat et al., 2009; Schnipper et al., 2020; Walcott, 1998; Yu et al., 2016). Although lipid-rich secretions from meibomian and sebaceous glands are devoid of serous content (ions and aqueous fluid) (Esler et al., 2019; Picardo et al., 2009; Shrestha et al., 2011), pancreatic secretions acquire ions and fluids primarily from the ducts instead of the acinar end-pieces (Lee et al., 2012; Tóth-Molnár and Ding, 2020).

Regulation of acinar cell secretion

A subset of epithelial cells called myoepithelial cells often surround the end-piece epithelium. These cells possess contractile activity and thus aid in expulsion of the secreted product for delivery to the target organ. Both serous and mucous acinar end-pieces of all the major salivary (de Paula et al., 2017) and lacrimal (Makarenkova and Dartt, 2015) glands have myoepithelial cells. However, myoepithelial cells are more abundant in glands enriched in mucous rather than in serous acinar end-pieces (e.g. sublingual compared to submandibular salivary glands) (Hardy and Kramer, 1998) and are lacking in the exocrine pancreas (Pandol, 2010). Myoepithelial cells are also found around lipid-rich meibomian but not lipid-rich sebaceous acinar end-pieces (Mescher, 2016). Presence of myoepithelial cells depends on a requirement of contractile function for secretion delivery. This explains why mucous (more dense secretions), but not serous and meibomian (more distance for secretion to travel) and sebaceous acinar end-pieces, possess myoepithelial cells.

The stimulus for acinar end-piece secretion can be either neuronal or hormonal. Salivary glands are differently innervated depending on acinar cell type: serous cells respond to muscarinic agonists

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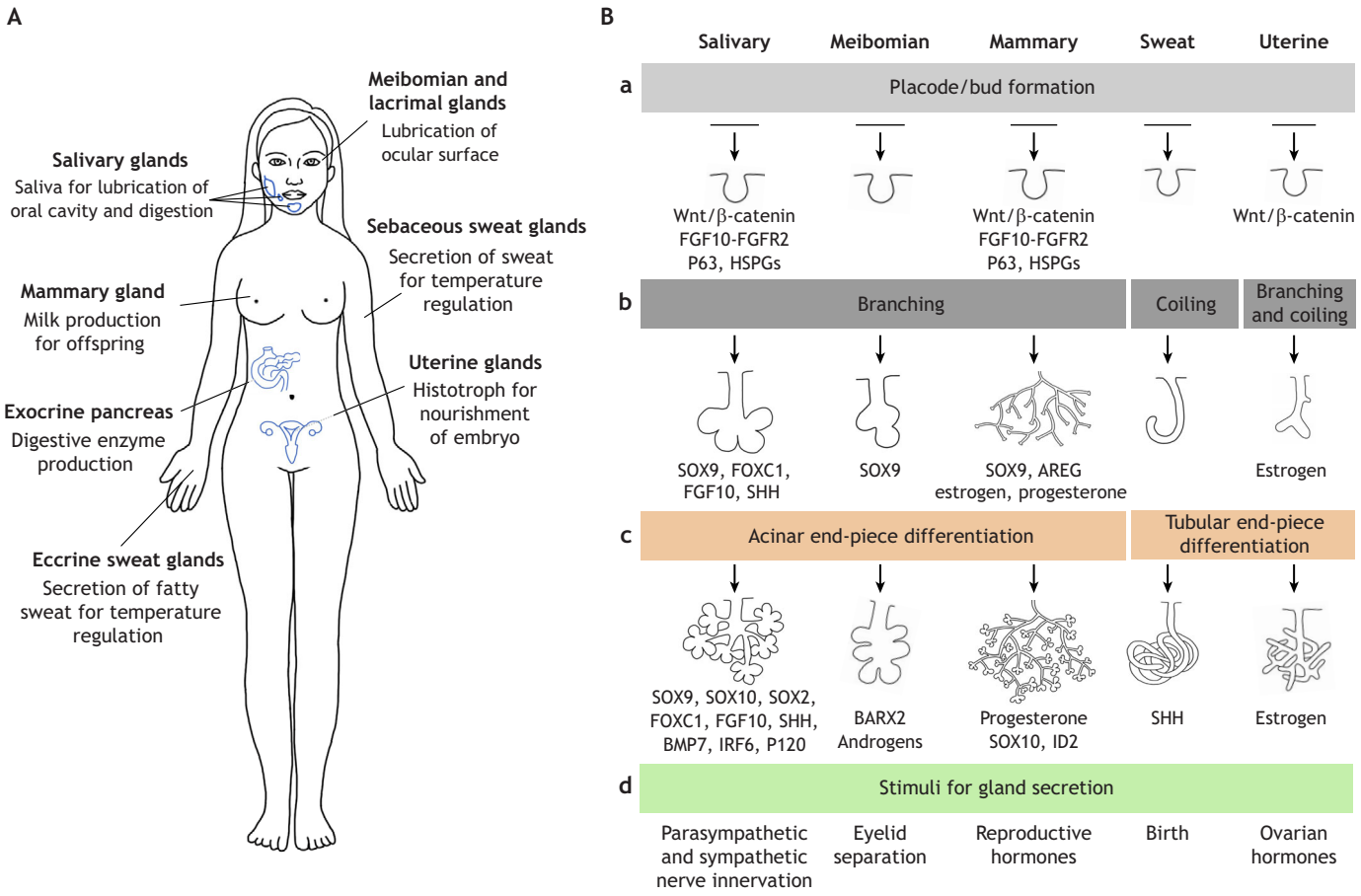

Fig. 1. Diversity in exocrine gland development. (A) Location of different exocrine glands and their secretions in the human body. (B) Five different exocrine glands (salivary, meibomian, mammary, sweat and uterine) represent diversity in shape, branching or coiling patterns, in proteins involved in growth and differentiation, and in stimuli for gland formation. (Ba) Glands are formed from an epithelial bud or placode that invaginates in response to cues/growth factors from the mesenchyme. (Bb) The bud then undergoes branching (e.g. salivary, meibomian, mammary and uterine) or coiling (sweat) morphogenesis to elongate the gland and form a ductal system. (Bc) Differentiation of end-pieces (Fig. 2) occurs at the end of each duct. (Bd) Secretory cells in the end-pieces respond to stimuli to secrete gland-specific material.

(acetylcholine), while mucous cells respond to α and β-adrenergic agonists (Porcheri and Mitsiadis, 2019). Lacrimal glands differ in innervation type and density across species but universally respond to α-1-adrenergic agonists (Dartt, 2009). Oxytocin stimulation is required for myoepithelial cell contraction in the lacrimal context (Hawley et al., 2018). Exocrine pancreas secretion is hormonally regulated by cholecystokinin, secretin and gastrin, and neurally regulated through cholinergic input from vagal nerves (Pandol, 2010). The presence of many neurotransmitters across the sympathetic and parasympathetic systems have been correlated with increase in meibomian production, but the literature does not yet describe a causal link (Cox and Nichols, 2014). Sebaceous gland production has been shown to be stimulated by multiple neurotransmitters and hormones *in vitro*, including dihydrotestosterone, prolactin, adrenocorticotropic hormone, growth hormone, alpha-melanocyte stimulating hormone, acetylcholine and substance P, but whether these contribute to *in vivo* sebaceous secretory activity is not clear (Clayton et al., 2020).

Alveolar end-pieces: mammary and prostate

Alveolar end-pieces (commonly referred to as alveoli) are found in the mammary glands (Cole and Parkes, 1933) and prostate gland (Gilloteaux and Afolayan, 2014; Risbridger and Taylor, 2006) (Fig. 2B). While alveolar end-pieces may secrete constitutively, their secretions are not required for homeostasis and are only released upon an appropriate stimulus, such as lactation for mammary glands and ejaculation for prostate glands. Here, we discuss structural features of the alveolar end-pieces that support this on demand functional activity.

Alveolar end-piece organization

In the literature, ‘acini’ and ‘alveoli’ are often used interchangeably, causing significant confusion. Histologically, unlike acini, alveoli possess a large, dilated lumen that allows accumulation of large volumes of secretions to be released upon appropriate stimulus (Gilloteaux and Afolayan, 2014; Macias and Hinck, 2012; Richert et al., 2000).

Alveolar end-pieces are composed of two cell layers that differ depending on gland type: in the mammary gland, a single layer of secretory epithelial cells is surrounded by a layer of myoepithelial cells (Oakes et al., 2006) (Fig. 2Ba); in the prostate, a layer of secretory epithelial cells is surrounded by undifferentiated basal epithelial cells (Srigley et al., 1990) (Fig. 2Bb).

The layer of mammary myoepithelium is intermittent to enable contact between the luminal cells and the basement membrane. These myoepithelial cells not only display contractile properties to enable fluid secretion, but they also influence the differentiation, polarity, proliferation and invasion/migration of adjacent luminal

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Table 2. Timing of gland formation

Gland	Species	Bud formation	Elongation and branching	End-piece specification	Onset of function	References
Salivary	Human	6 weeks	13-16 weeks	20 weeks	Birth	Chatzeli et al. (2017); Knosp et al. (2012); Knox and Hoffman (2008); Patel et al. (2006); Tucker (2007)
	Mouse	E12.5	E18.5	E18.5	Birth	
Lacrimal	Human	7 weeks	10 weeks	10 weeks	Birth	Garg and Zhang (2017); Penbharkkul et al. (1962); Esmaeelpour et al. (2011)
	Mouse	E16.5	E16.5	E19.5	Birth	
Exocrine pancreas	Human	6 weeks	8 weeks	16 weeks	24 weeks	Pictet et al. (1972); Pan and Brissova (2014); McClean and Weaver (1993)
	Mouse	E9.5	E12.5-birth	E14.5-birth	Birth	
Meibomian	Human	9 weeks	12 weeks	15 weeks	30 weeks	Nien et al. (2010); Millar et al. (2017)
	Mouse	E18.5	P5	P5	P15	
Sebaceous	Human	13 weeks	No elongation	16 weeks	21 weeks	Niemann and Horsley (2012); Smith and Thiboutot (2008)
	Mouse	P0	No elongation	P3-P4	>P4	
Mammary	Human	9 weeks	Second trimester	Post-puberty	Lactation	Javed and Lteif (2013); Sternlicht (2006)
	Mouse	E10	E15.5	Post-puberty	Lactation	
Prostate	Human	8 weeks	10 weeks	12 weeks	Puberty	Cunha et al. (2018); Aumuller (1991); Toivanen and Shen (2017)
	Mouse	E13	E16	Birth	Puberty	
Sweat	Human	12 weeks	15 weeks	22 weeks	Birth	Lu and Fuchs (2014)
	Mouse	E17.5	E18.5-birth	Birth-P21	P21	Cui and Schlessinger (2015)
Uterine	Human	*In utero*	*In utero*	Unknown	Pregnancy	Jin (2019); Kelleher et al. (2019)
	Mouse	P4-P7	P7-puberty	Unknown	Pregnancy	

E, embryonic day; P, postnatal day; weeks, weeks *in utero*.

epithelial cells (Bello-DeOcampo et al., 2001; Gudjonsson et al., 2005; Makarenkova and Dartt, 2015). The basal layer of the prostate contributes stem cells for ductal integrity, for differentiation and survival of luminal cells, for postnatal prostate regeneration (Fullwood et al., 2019; Kurita et al., 2004; Ousset et al., 2012) and for neurogenic function (Zhang et al., 2016). Prostate alveolar end-pieces lack myoepithelial cells and the surrounding fibromuscular stroma aids in the expulsion of the alveolar contents into the prostatic ducts (Srigley et al., 1990).

Composition of alveolar secretions

Similar to acinar end-pieces, alveolar end-pieces generate organ-specific secretions. In the mammary gland, milk secretions are largely composed of proteins, lipids and lactose. Alveolar cells also regulate fluid and ion concentration of the secretions through diffusion mechanisms. The high lactose and milk sugar content of the mammary luminal secretion draws transcellular water and ions across the alveolar epithelium. In addition, non-alveolar proteins, such as albumin and IgA, found in the interstitial space are accumulated in the alveolar lumen by transcytosis (Mobasheri and Barrett-Jolley, 2014). Unlike acinar cell secretions that primarily contain monovalent ions, such as sodium, chloride and potassium, alveolar cells accumulate both monovalent and bivalent ions, such as calcium, copper and iron in mammary secretions; and calcium, magnesium and zinc ions in prostate secretions (Ackland et al., 1999; Dang et al., 2017; Faddy et al., 2008; McManaman and Neville, 2003; Michalczyk et al., 2000; Neville et al., 1994; Pinnix et al., 2010; Reinhardt et al., 2000). Prostate alveolar end-pieces function similarly to mammary alveolar end-pieces, but instead of milk, prostatic secretions mostly consist of citric acid, lipids and enzymes (such as fibrolysin and acid phosphatase) (Huggins and Neal, 1942).

Regulation of alveolar cell secretion

Mammary gland secretion is hormonally stimulated by prolactin and oxytocin. Prolactin causes lactogenesis and the production of milk by the alveolar end-pieces while oxytocin stimulates the contraction of myoepithelial cells surrounding the alveolar end-pieces, resulting in milk ejection (‘lactation’) (Crowley, 2014). Regulation of prostatic secretion is relatively understudied, but studies have shown that secretion occurs when smooth muscle surrounding the alveoli is stimulated by α-adrenergic agonists and cholinergic agonists (Ventura et al., 2002; Wang et al., 1991). For prostate alveolar end-pieces, hormones, such as testosterone, have only been implicated in regulating prostate structure; a role in prostate secretion has not been identified (Wang et al., 1991).

Neither prostatic fluid nor mammary milk is entirely serous; they both contain additional proteins and electrolytes intended for the nourishment of the sperm or the offspring, respectively. In contrast to the merocrine and holocrine mode of secretion for acinar end-pieces, an apocrine mode of secretion supports release of protein and lipid content from alveolar end-pieces (Freeman et al., 2020; Murphrey and Vaidya, 2020; Nicander et al., 1974). This may be because, unlike water and ions that can be quickly accumulated by diffusion, proteins require time for transcription and translation. Thus, alveolar secretions are accumulated over time and released only upon the required stimulus.

Tubular end-pieces: sweat and uterine glands

Tubular end-pieces, present in the sweat and uterine glands, are bilayered structures consisting of a hollow luminal center surrounded by secretory luminal cells, and an outer layer of contractile myoepithelial cells in sweat glands (Fig. 2Ca) or an outer layer of basal epithelial cells in uterine glands (Fig. 2Cb).

Tubular end-piece organization

Tubular end-pieces possess a secretory layer of cells, which consist of ciliated ‘clear’ cells interspersed with ‘dark’ cells that are highly granulated (Sato et al., 1989). The function of these cells varies slightly depending on the exocrine gland. For example, the secretory function of sweat glands is fulfilled by the clear cells, although, more recently, there are reports that clear and dark cells may both be secretory (Cui and Schlessinger, 2015; Kurata et al., 2017). Conversely, dark cells in the uterine gland become increasingly granulated, generating more secretory material from early to mid-pregnancy (Amso et al., 1994; Perry and Crombie, 1982).

Composition and regulation of tubular secretion

Sweat glands secrete factors such as lactate, urea, sodium, potassium, bicarbonate and water to maintain skin hydration. They also secrete several antimicrobial peptides, and contain

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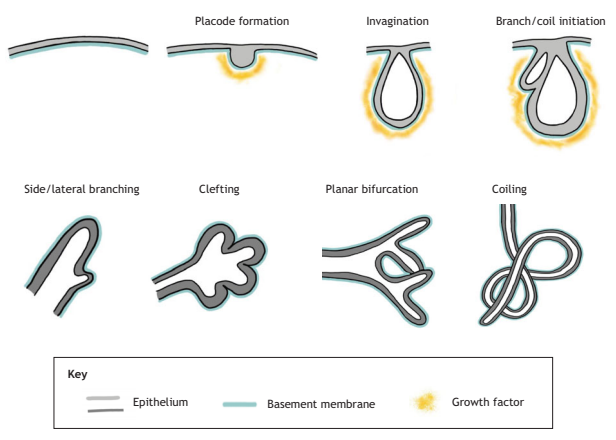
Box 1. Coiling and branching morphogenesis

In contrast to a simple single tip outgrowth mode during coiling, as occurs in sweat glands (Lu and Fuchs, 2014), epithelial branching takes place through three primary modes: side/lateral branching, clefting and bifurcations. During side or lateral branching in the newly emerged epithelium of the developing pancreas (Iber and Menshykau, 2013), mammary gland (Sternlicht et al., 2006), seminal vesicles (Risbridger and Taylor, 2006) and meibomian glands (Nien et al., 2010), new buds appear perpendicular to the main axis of the elongating primary bud. Clefting of the epithelium of the salivary (Hsu and Yamada, 2010) or lacrimal gland occurs as a result of the elongating bud splitting into two or more non-identical buds in the plane of elongation, with subsequent cycles of clefting of the new buds exponentially expanding bud number (Sakai, 2009). Finally, the elongating mammary (Sternlicht et al., 2006) or prostate gland buds (Risbridger and Taylor, 2006) undergo bifurcation. Bifurcations occur in the plane of elongation through the splitting of the single bud into two new buds that then elongate and undergo further bifurcation to generate the immature glandular tree.



secreted IgA and cytokines that likely contribute to skin immune defense and inflammatory reactions (Cui and Schlessinger, 2015). Myoepithelial cells in the bilayered sweat glands are arranged longitudinally parallel to the secretory tubule and are surrounded by nerve fibers, suggesting that myoepithelial cells contract synchronously to expel the secretory contents of the coil (Kurata et al., 2017) (Fig. 2C). Eccrine sweat glands primarily respond to sympathetic cholinergic stimulation, but may respond to adrenergic stimulation albeit to a much lesser extent (Baker, 2019). Apocrine sweat gland innervation is poorly understood, but these glands secrete in response to β-adrenergic receptor agonists, sexual excitement and emotional stress (Hu et al., 2018).

Uterine glands become secretory under the influence of ovarian hormone progesterone. These glands secrete amino acids, ions, glucose, lipids and proteins (including cytokines, enzymes, hormones, growth factors, proteases and their inhibitors) and transporters likely necessary for early embryo and pregnancy survival (Spencer, 2014). Uterine gland tubular end-pieces of the rat and human, but not the mouse, are surrounded by smooth muscle actin-positive basal cells, but whether these cells are myoepithelial in nature and possess contractile properties for regulating secretion, has not been determined (Czernobilsky et al., 1993; Shimomoto et al., 2005).

Apocrine sweat glands secrete using an apocrine mode, while eccrine sweat glands secrete in a merocrine fashion (Freeman et al., 2020). Such differences in mode of secretion can be explained by the difference in secretory product: apocrine sweat contains more protein and lipid content, whereas eccrine-sweat is mostly salt and water (Baker, 2019). Ultrastructural studies of the uterine glands are few, but the existing literature suggests a merocrine mode of secretion (Akinloye and Oke, 2015; Tunón et al., 1995).

Similarities and differences amongst glandular end-pieces

The elements of cell-type diversity, shape, secretory activity and mode of secretion reflect the ways in which end-pieces are uniquely structured to accomplish their respective functions. The following themes have emerged from our review of the literature.

Cell diversity

Acinar end-pieces contain a diverse set of secretory cell types (i.e. mucous, serous and lipid-enriched), which allows them to produce a varied set of secretions that range from highly serous, such as saliva and tears, to highly lipid based, such as meibum and sebum. This extent of diversity is absent in alveolar and tubular end-pieces, which possess a single cell-type for secretion.

Shape

In acinar and alveolar end-pieces, multiple units are arranged in secretory lobules, while tubular end-pieces are linear structures that act individually. This arrangement conserves space in the tubular exocrine glands (Freeman et al., 2020).

Volume of individual end-piece secretion

In contrast to acinar or alveolar end-pieces, tubular end-pieces possess substantially less luminal space to hold the secretory product (Gilloteaux and Afolayan, 2014). This is possibly an adaptation to the physiological context surrounding function, as tubular glands (both uterine and sweat) appear as one unit among a population of many. As the population of glands can collectively produce a large volume of secretion, each individual gland may not require the secretory capacity of an acinar or alveolar end-piece.

Constitutive versus stimulus-induced secretory activity

Acinar and alveolar end-pieces mainly differ in their capacity to hold secretions. We hypothesize that alveolar end-pieces are selected in physiological contexts where it is necessary to store secretions, whereas acinar secretions have homeostatic roles, and are constantly being produced to some extent without a need to 'store' the secretion. Tubular glands serve a similar homeostasis-based physiological role, but we predict that their morphology is tailored toward limited secretory volume; the number of glandular units together provide enough secretions for gland function.

Mode of secretion

The merocrine mode of secretion is shared by the salivary, lacrimal, exocrine pancreas and uterine end-pieces. The secretions of these glands contain relatively higher water content than those of the apocrine (prostate, mammary and apocrine sweat) or holocrine (sebaceous and meibomian) glands. Increase in protein content correlates with an increase in diameter for glands using apocrine mode of secretion. Thus, it appears that alveolar cells have a larger diameter compared with serous acinar cells (Gilloteaux and Afolayan, 2014). This is further supported by the distinction between the eccrine and apocrine sweat glands. Although they share identical structure, the diameter of the apocrine sweat gland secretory coil is larger than the eccrine sweat gland secretory coil, presumably because apocrine sweat generates higher lipid and

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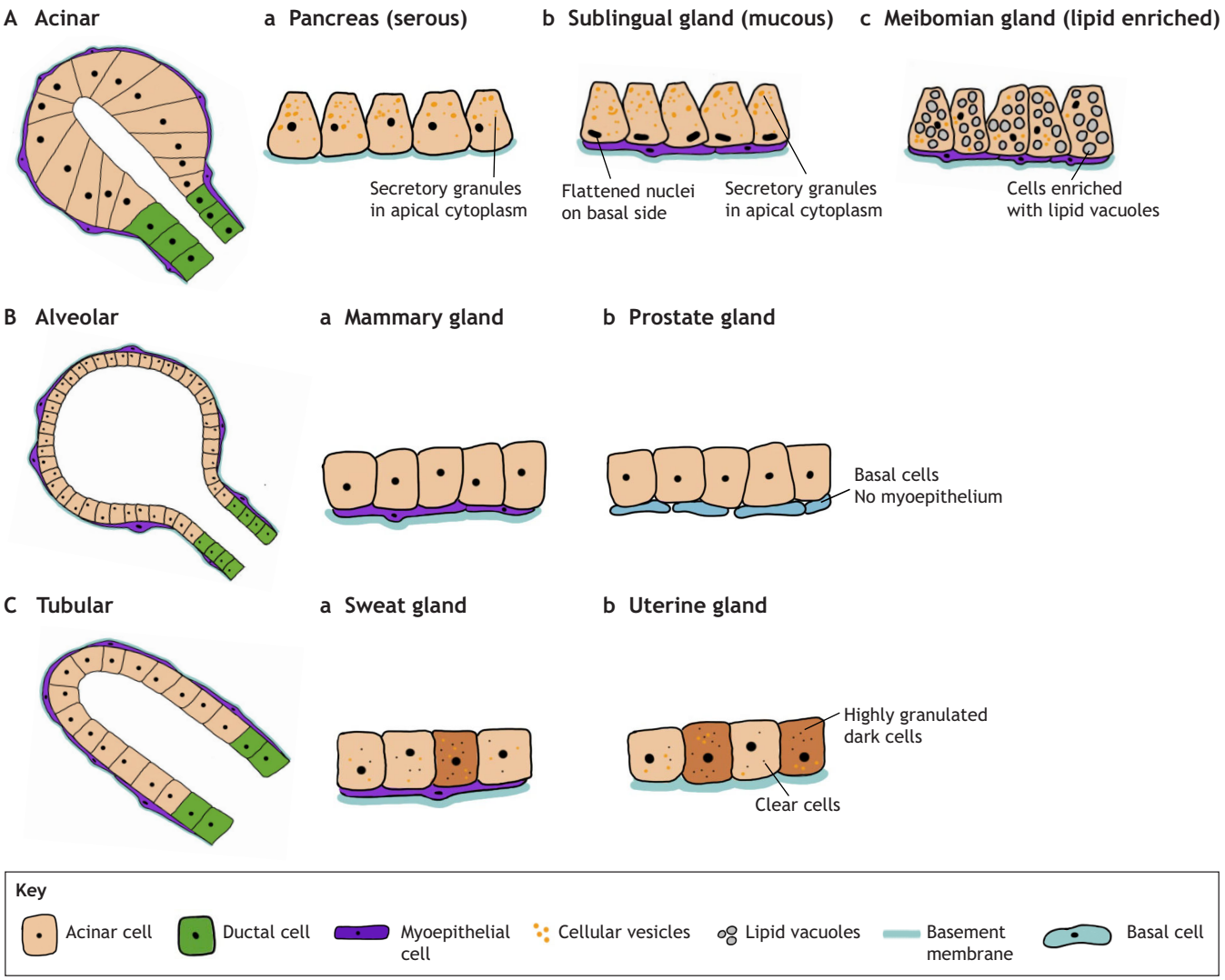

Fig. 2. Morphologically defined exocrine gland end-pieces. (A) Acinar end-pieces are made up of wedge-shaped acinar cells that form lobules and produce a characteristic serous, mucous, mixed or lipid-enriched secretion, and are found in pancreatic exocrine glands (Aa), sublingual glands (Ab) and meibomian glands (Ac). (B) Alveolar end-pieces consist of a wide lumen lined with cuboidal secretory epithelial cells that will eventually blossom into alveolar buds. They are found in the mammary gland (Ba), where they are capable of milk secretion during pregnancy, and in the prostate glands (Bb). (C) Tubular end-pieces exhibit a bilayered structure lined with cuboidal secretory luminal cells and are found in skin eccrine (sweat) glands (Ca) and uterine glands (Cb). Although different cell types line the inside of the end-piece, contractile myoepithelial cells surrounding certain end-pieces facilitate contraction and squeezing of the secretory material into the luminal space and the ductal system. Myoepithelial cells run longitudinally parallel to the tubular end-pieces. Myoepithelial cells are absent in the pancreatic exocrine gland, prostate gland and rodent uterine glands.

protein secretory content (Baker, 2019; Wilke et al., 2007). For meibomian and sebaceous glands, we propose that the holocrine mechanism of secretion where the secretory cell undergoes lysis, generates the space required to hold the lipid-rich secretion. End-pieces are a crucial aspect of exocrine glands, being primarily responsible for producing and transporting the secretion into the ductal space. Available evidence collectively demonstrates a close relationship between structure and function for exocrine gland end-pieces.

Ducts modify and transport glandular secretions

The ductal system of exocrine glands is responsible for the delivery of fluid to the target organ. However, in addition to this role, the vast majority of secretions from the end-pieces undergo further modifications as they transit through the ducts (Fig. 3). Ductal structure has been studied in greater detail than end-piece structure; hence, we organize this section by individual gland type. We discuss the morphology and function of compound (branched) and simple ductal networks, and compare ductal cells and their contribution to secretions within glandular organs (Table 1).

Exocrine glands with compound ductal networks: salivary, lacrimal, pancreas and mammary

The large ductal networks of the exocrine pancreas, salivary, lacrimal and mammary glands possess similar architecture: the end-piece is attached to a small duct, which fuses with successively larger ducts to form an extensive branched network. Unlike the secretory end-pieces of these glands, ductal architectures are mostly similar between organ types, with some differences discussed below.

Salivary gland

In the salivary gland, acinar cells secrete the bulk of the fluid and the ducts themselves are water impermeable under physiological

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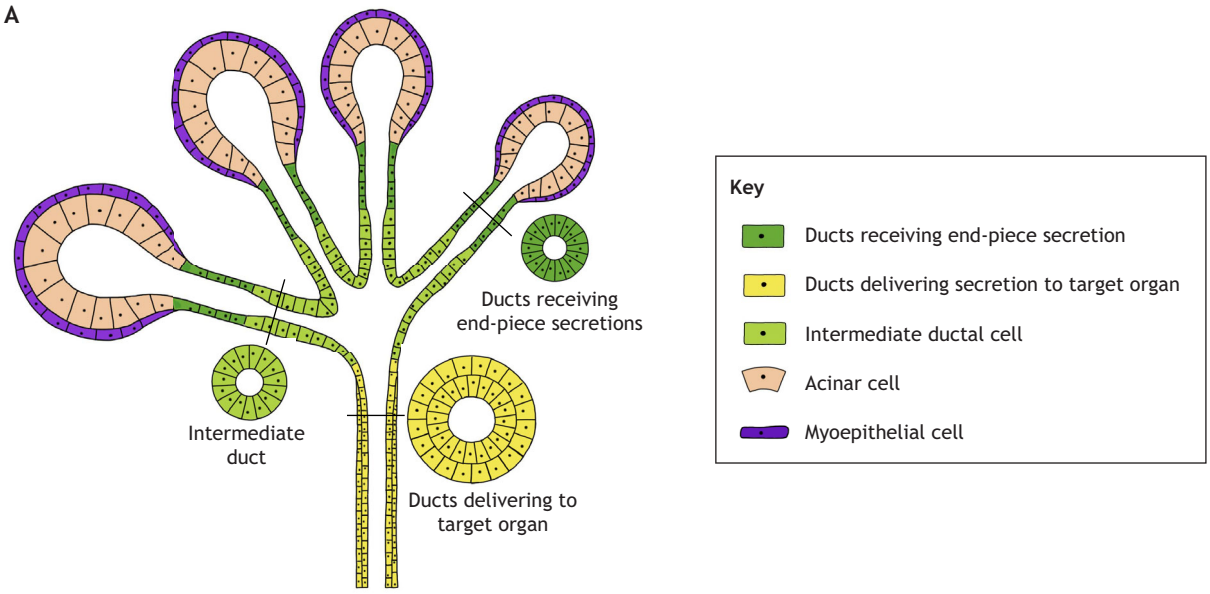

B

	a Salivary gland	b Lacrimal gland	c Exocrine pancreas	d Mammary gland
Duct(s) receiving end-piece secretion	Intercalated duct	Intercalated duct Intralobular duct	Intercalated duct	Terminal duct
Intermediate duct(s)	Striated duct	Interlobular duct Intralobar duct	Intralobular duct Interlobular duct	Subsegmental duct Segmental duct
Duct(s) delivering secretions to target organ	Excretory duct	Interlobar duct	Main pancreatic duct	Collecting duct
Key features of the ductal system	Passive absorption followed by active secretory and resorptive modifications to secretory content; impermeable to water	Secretion of K^+ and Cl^- ion-rich fluid contribute to final secretion volume	Hormone regulated ductal secretions contribute to bulk of the final secretion volume	No resorptive or secretory properties; ducts are impermeable to milk constituents

Fig. 3. Complex ductal organization in exocrine glands. Models of multi-level duct organization with respect to acinar end-pieces in exocrine glands. (A) The ductal system of the salivary glands has been studied in detail and forms the basis of ductal system nomenclature for other exocrine gland systems. Ductal systems are divided into three segments: ducts receiving secretions directly from the end-piece, intermediate ducts and ducts delivering secretions to the target organ. (B) Summary of ductal organization of the salivary gland (Ba), lacrimal gland (Bb), exocrine pancreas (Bc) and mammary gland (Bd). Each ductal system has unique features of secretion release, resorption and modification of secretory contents, all catered to the role of individual exocrine gland.

conditions. Small ducts formed by simple cuboidal epithelium are responsible for the passive absorption of ions, and lead to larger striated ducts that are responsible for modifying the electrolyte composition of saliva (Fig. 3Ba). These larger ducts are composed of columnar cells possessing an extensive basolateral surface area due to membrane infoldings, giving them a striated appearance (Amano et al., 2012) (Fig. 3Ba). These columnar cells are packed with mitochondria, allowing a higher yield of energy required for their major role in secreting bicarbonate and potassium, and reabsorbing sodium and chloride using Cl^--HCO_3^- and Na^+-K^+ pumps (Ding et al., 2010; Lee et al., 2012; Tandler et al., 2001). In addition to modifying the ionic content, striated duct cells of both humans and rodents contain apical vesicles that are responsible for transcytosis of secretory immunoglobin IgA from basolateral to apical lumen, an

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essential first line of defense against microorganisms. Resorption of sodium and chloride ions in the salivary striated ducts leads to the formation of hypotonic saliva; however, bicarbonate secretion from the acinar end-pieces and the ducts ensures a neutral pH (Tandler et al., 2001). Hypotonic saliva then moves to the excretory ducts that serve to further alter the ionic composition before emptying into the oral cavity (Proctor, 2016).

Lacrimal glands and exocrine pancreas

For the lacrimal glands (Ding et al., 2010) and pancreas (Egerbacher and Böck, 1997), the starting intercalated ducts extend into the lumen of the acinus as opposed to the salivary gland starting ducts that stop at the end-piece ductal junction (Fig. 3Bb,Bc) (Gokcimen, 2019). Furthermore, striated ducts have not been identified for either the pancreatic or the lacrimal exocrine glands. In both these glands, secretions move from intercalated ducts into intralobular ducts that drain several lobules (Egerbacher and Böck, 1997; Gokcimen, 2019). Both of the intercalated and intralobular ducts are lined solely by cuboidal epithelium. Smaller interlobular ducts are lined with cuboidal epithelium, whereas larger ducts are lined with columnar epithelium. From the interlobular ducts, the secretions are delivered into the major duct to be delivered to the eye surface (in case of the lacrimal glands) and to the duodenum (in case of the pancreas) (Ding et al., 2010; Egerbacher and Böck, 1997).

In the lacrimal gland, the entire ductal network modifies the lacrimal fluid by secreting potassium- and chloride-rich fluid contributing to about 30% of the final volume of lacrimal secretions in physiological conditions (Ding et al., 2010; Gresz, 2006). Unlike salivary and lacrimal glands, the bulk of the secretion in the pancreas comes from the ducts and not the acinar end-pieces. In the intercalated ducts of the exocrine pancreas, squamous-shaped cells nearest to the acinar cells, termed centroacinar cells, secrete an aqueous bicarbonate-rich solution under stimulation by the hormone secretin to flush the enzymes through the ducts and to neutralize the acid within the small intestine (Hart and Conwell, 2021) (Fig. 3Bc). More central cuboidal duct cells are rich in mitochondria and contribute bicarbonate and fluids to the pancreatic secretions.

Mammary gland

The ductal system of the mammary gland is very similar in structure to the ducts discussed above, although different nomenclature is used (Fig. 3Bd). The mammary gland ductal network comprises the starting ducts called terminal ductal-lobular units (TDLU), to which the alveolar end-piece lobules connect (Howard and Gusterson, 2000; Macias and Hinck, 2012). Milk flows from the TDLU into the subsegmental duct (similar to intralobular ducts), then to the segmental duct (similar to interlobular ducts), then to the lactiferous sinus and then collects in the collecting duct (similar to the excretory duct) connected to the nipple (Allred, 2010). The mammary ductal system is also lined by cuboidal or columnar epithelial cells (Fig. 3Bd). The mammary ductal epithelium is unique in that it neither possesses resorptive nor secretory properties, and it is impermeable to the main soluble constituents of milk (including ions and water). This allows the ductal system to store large quantities of milk while maintaining the integrity of the epithelial cells lining the ducts (Linzell and Peaker, 1971).

Exocrine glands with simple ductal networks: meibomian, sebaceous, sweat and uterine glands

Hierarchical organization and complexity of ducts may depend on the type of secretion, the changes that the secretions need to undergo through the ductal system, and the distance between the site of secretion and the target organ. Acinar and alveolar end-pieces arranged in large globular units tend to correlate with compound ductal networks, whereas relatively small glandular units correlate with a simplified ductal network as described below.

Meibomian gland

In the meibomian glands, several acinar units are connected to a central collecting duct. The central duct moves the secretions toward the terminal part of the duct, which is often dilated to receive the secretions before moving them to the excretory duct to deliver it to the ocular surface. During this transport, triglycerides in the lipids are broken down into monoglycerides, diglycerides and fatty acids, partly by bacteria present in the ductal system (Knop et al., 2011). The meibomian gland duct likely has no effect on its secretions because it is lined by stratified squamous epithelial cells that are neither absorptive nor secretory (Montagna, 1974).

Sebaceous gland

The sebaceous gland is simple, comprising one or more acinar units connected to an excretory duct shared with the follicle shaft or secreting directly onto the skin surface, in some cases (Thody and Shuster, 1989). Similar to meibomian glands, sebaceous glands are lined with stratified squamous epithelial cells, implying that the duct does not contribute to secretion or reabsorption (Montagna, 1974).

Sweat gland

In the sweat glands, secretions move from the coiled end-piece into the sweat duct that consists of two layers of cuboidal cells, suprabasal (luminal) and basal (Cui and Schlessinger, 2015). The sweat duct then empties into the intraepidermal duct that finally delivers the secretory material to the surface of the skin. The serous secretions of the apocrine and eccrine sweat gland undergo reabsorption in the ductal system, where ion transporters reduce the loss of salt and electrolytes before sweat is delivered to the skin surface (Ready and Quinton, 1994).

Uterine glands

Uterine gland structure has been poorly studied relative to the other discussed glands. One major constraint to discussion of ductal structure and function is the lack of a protein marker separating the uterine gland duct from its end-piece. The uterine glands bud off the uterine lumen. Thus, one unexplored possibility is that the uterine lumen acts as a large collecting duct and each uterine gland serves as an end-piece contributing secretions into the lumen.

Similarities and differences amongst ductal networks

Number of glands

Compound ductal systems appear where a few individual glands with serous or mucous acinar end-pieces or alveolar end-pieces are present (e.g. salivary with three glands, pancreas and mammary as a single gland). The individual gland possesses large amounts of space to form a complex branched network. In contrast, simple ductal systems appear in glands that are numerous with less space to occupy, such as the lipid-enriched acinar and tubular glands. Lipid-enriched sebaceous glands possess a very short duct leading to the hair follicle shaft or directly onto the skin surface. Tubular sweat glands address the space constraint by coiling.

Secretory content modification

The secretory and resorptive capacity of the ductal structure depends on the water content of the secretion and a need to secrete or retain

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water and ions during ductal transport. For example, sebaceous and meibomian acinar end-pieces secrete entirely lipid product and lack any resorption or secretory function within their ducts (Picardo et al., 2009; Shrestha et al., 2011). On the other hand, serous and mucous-secreting glands, such as salivary, lacrimal and eccrine sweat glands, possess ductal networks that highly modify the secretions en route to the target organ.

Ductal structure is selected based on the constraints of surrounding tissue, on space available for the ductal network, on the number of individual glandular units and on the final composition of gland secretions, highlighting ductal structure-function relationships that are necessary for exocrine gland function.

Developmental mechanisms controlling exocrine gland development, structure and function

Although exocrine organs have been studied for over 100 years, we are only at the beginning of understanding the mechanisms regulating gland structure formation and the acquisition of tissue function. Here, we discuss factors that have shared roles in regulating the development of at least two exocrine glands, as demonstrated by mouse genetic mutant studies (Fig. 1). Factors specific to a gland that have either not been studied in other systems or do not contribute to development of other glandular systems are highlighted in Table 3 but not discussed below. For example, salivary and lacrimal glands possess a longer history of investigation from a developmental perspective; thus, these glands are mentioned more frequently than others, such as sebaceous glands.

Bud formation

Bud formation in several exocrine organ systems (salivary, lacrimal, sebaceous, exocrine pancreas and mammary gland) is mediated by mesenchymal expression of fibroblast growth factor 10 (FGF10) and its receptor FGFR2B, which is expressed by epithelial cells (Bhushan et al., 2001; Donjacour et al., 2003; Jaskoll et al., 2005; Mailleux et al., 2002; Makarenkova et al., 2000; Puk et al., 2009; Villasenor et al., 2010). Evidence from mice shows that activation of FGFR2B is crucial for the development of the sebaceous glands (Grose et al., 2007), as well as induction of four out of five of the mammary placodes and the formation of the white adipose tissue essential for mammary growth (Rivetti et al., 2020). In the salivary gland, FGF10-FGFR2 signaling activates extracellular signal-regulated kinase (ERK) to initiate bud elongation through the transcription factor SOX9 (Chatzeli et al., 2017; Patel et al., 2017). Conversely, in the lacrimal gland, SOX9 augments the expression of heparan sulfate-synthesizing enzymes, which facilitates localized FGF10 expression to regulate budding and outgrowth (Chen et al., 2014).

Bone morphogenetic protein (BMP) signaling is crucial in determining exocrine gland cell fate because treatment with, or ectopic expression of, the BMP antagonist noggin alters epithelial cell identity. With noggin, meibomian glands are replaced by pilosebaceous glands and ectopic cilia (Plikus et al., 2004), eccrine sweat glands are replaced by pilosebaceous glands and hair follicles (Plikus et al., 2004), mammary gland display ectopic hair follicles (Mayer et al., 2008), and the pancreas displays excessive endocrine differentiation at the expense of the exocrine pancreas (Jennings et al., 2015). Members of the BMP signaling pathway can both promote or inhibit exocrine gland growth, depending on the ligand and the gland. For example, signaling through BMPR1A is essential for eccrine sweat gland formation (Leung et al., 2013). Contrastingly, in the lacrimal gland, BMP4 suppresses FGF10-induced bud outgrowth (Dean et al., 2004).

Canonical Wnt signaling mediated by β-catenin is essential for bud formation in sweat, uterine, mammary and meibomian glands (Dunlap et al., 2011; Sima et al., 2016; Xu et al., 2017). In the mammary glands, canonical Wnt signaling mediated by WNT10B (Macias and Hinck, 2012) and the effector LEF1 regulates parathyroid hormone-related protein (PTHRP) expression, which is essential for bud formation (Hiremath and Wysolmerski, 2013).

Meibomian, sweat, salivary, lacrimal and mammary glands require ectodysplasin A (EDA) signaling (Kunisada et al., 2009; Melnick et al., 2009; Monreal et al., 1998; Wang et al., 2016) for bud formation.

Genetic evidence from mouse models indicates essential roles for a number of transcription factors in exocrine gland development. The most commonly used transcription factor is P63, which is enriched in the basal epithelial cells of the early epithelium of the mammary, salivary, lacrimal, prostate and sebaceous glands (Signoretti et al., 2000; Yang et al., 1999). The ablation of epithelial P63 prevents the initiation of bud formation in all these glands (Signoretti et al., 2000; Yang et al., 1999).

Developmental gland growth

Similar to bud formation, branching and the extent of branching morphogenesis is regulated by FGF10 signaling; depletion of FGF10 or receptors FGFR2 reduces branching in salivary glands (Jaskoll et al., 2005; Ohuchi et al., 2000), prostate gland (Grishina et al., 2005) and the exocrine pancreas (Bhushan et al., 2001; Miralles et al., 1999; Pulkkinen et al., 2003).

EDA signaling is required after the bud stage in the salivary gland because EDA mutations result in glands that are smaller in size and produce less saliva with altered chemical composition (Jaskoll et al., 2003). Contrastingly, increased EDA receptor signaling results in enlarged meibomian and sebaceous glands, and excessive branching in mammary and salivary glands. Branching in salivary and mammary glands downstream of EDA signaling occurs via NF-κB (Häärä et al., 2011).

BMP4, through its receptor BMP1RA, activates transcription factor MSX2, allowing growth of the mammary tree (Hens et al., 2007). BMP7 positively regulates branching in the lacrimal gland (Dean et al., 2004; Garg and Zhang, 2017) and salivary gland (Miletich, 2010), but negatively regulates branching in the prostate gland (Grishina et al., 2005). This may be due to the different cell types targeted by BMP7. In the prostate, BMP7 binds to receptors in the epithelium and reduces branching by inhibiting Notch signaling during formation of prostatic buds (Grishina et al., 2005). However, in lacrimal and salivary glands, BMP7 signaling in the mesenchyme is necessary to induce glandular growth (Dean et al., 2004; Jaskoll et al., 2002).

Hedgehog signaling promotes gland expansion in salivary glands (Jaskoll et al., 2004), mammary glands (Monkkonen and Lewis, 2017) and sweat glands (Cui et al., 2014). In the salivary gland, complete loss of SHH results in a rudimentary submandibular salivary gland with a few branches (Elliott et al., 2018; Jaskoll et al., 2004). Furthermore, in salivary gland organ culture, SHH regulates branching morphogenesis by promoting epithelial cell proliferation and by modulating FGF8 signaling. In mammary glands, overexpression of Smoothened, the effector of canonical Hedgehog signaling, causes over-proliferation of epithelial cells and hyperbranching (Visbal and Lewis, 2010). Loss of SHH in the sweat glands does not affect bud formation but disrupts coiling morphogenesis, resulting in a rudimentary coil that fails to extend into the mesenchyme and eventually leads to a sweat-deficiency phenotype (Cui et al., 2014).

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Table 3. Genetic mutations causing defects in developing exocrine gland structure and function

Factor	Protein name (human syndrome)	Exocrine gland	Phenotype*	References
Growth factor	FGF10 (aplasia of lacrimal and salivary glands, lacrimoauriculodentodigital syndrome)	Salivary; lacrimal; sebaceous; mammary; prostate; pancreas	Absence of bud (salivary, lacrimal, sebaceous and mammary); reduced branching in signaling with heparan sulfate proteoglycans (salivary, prostate and pancreas)	Bhushan et al. (2001); Donjacour et al. (2003); Entesarian et al. (2005); Grishina et al. (2005); Grose et al. (2007); Jaskoll et al. (2005); Mailleux et al. (2002); Makarenkova et al. (2000); Milunsky et al. (2006); Miralles et al. (1999); Puk et al. (2009); Pulkkinen et al. (2003); Rivetti et al. (2020); Rohmann et al. (2006); Villasenor et al. (2010)
Signaling molecule	Amphiregulin	Mammary	Reduced branching.	Macias and Hinck (2012)
	β-Catenin	Apocrine sweat; eccrine sweat; uterine; meibomian; prostate; lacrimal	No bud formation (sweat, uterine and meibomian); unelongated/undeveloped buds (prostate); excessive branching (lacrimal)	Dean et al. (2005); Dunlap et al. (2011); Sima et al. (2016); Simons et al. (2012); Xu et al. (2017)
	BMP4	Mammary; eccrine-sweat; lacrimal	Deficient ductal development (mammary); formation of hair follicle instead of sweat gland (eccrine sweat); excessive bud outgrowth (lacrimal)	Dean et al. (2004); Hens et al. (2007); Leung et al. (2013)
	BMP7	Lacrimal; salivary; prostate	Reduced branching (lacrimal, salivary); excessive branching (prostate)	Dean et al. (2004); Grishina et al. (2005); Miletich (2010)
	EDA	Meibomia; apocrine-sweat; eccrine-sweat; lacrimal; mammary; salivary	No bud formation (meibomian and sweat); reduced terminal differentiation (lacrimal); decreased branching, reduced ductal development (mammary and salivary); reduced size (salivary)	Häärä et al. (2011); Jaskoll et al. (2003); Kunisada et al. (2009); Kuony et al. (2019); Voutilainen et al. (2012); Wang et al. (2016)
	EGFR	Salivary	Reduced branching	Jaskoll and Melnick (1999)
	LEF1	Mammary	No bud formation	Hiremath and Wysolmerski (2013)
	Noggin	Meibomian; eccrine-sweat; mammary; pancreas	Replacement by hair follicles, glands do not form (meibomian, eccrine sweat and mammary); reduced branching, excessive endocrine differentiation (pancreas)	Jennings et al. (2015); Mayer et al. (2008); Plikus et al. (2004)
	Notch signaling	Lacrimal	Increased number of acinar end-pieces	Dvoriantchikova et al. (2017)
	PTHRP	Mammary	Lack of mammary ducts	Jobert et al. (1998)
	RANKL	Mammary	Decreased side branching, no alveolar end-piece formation	Beleut et al. (2010)
	Scribble	Mammary	No alveolar formation	Aikawa et al. (2020)
	SHH	Apocrine-sweat; eccrine-sweat; salivary	Deficient secretory coil development (sweat); reduced branching (salivary)	Cui et al. (2014); Elliott et al. (2018); Jaskoll et al. (2004)
	SMAD4	Lacrimal	Reduced size and reduced number of acinar end-pieces	Liu and Lin (2014)
	SMO	Mammary	Overexpression results in over-proliferation and hyperplasia	Visbal and Lewis (2010)
	WNT5A	Mammary	Increased ductal extension, proliferation and branching	Roarty and Serra (2007)
Transcription factors	BARX2	Lacrimal; meibomian	Shorter buds with deficient branching (lacrimal); poorly developed acinar end-pieces (meibomian)	Tsau et al. (2011)
	ELF5	Mammary	No alveolar development	Zhou et al. (2005)
	EYA6 (branchio-oto-renal syndrome 1, brachio-otic syndrome 3)	Lacrimal	Narrowed ducts	Abdelhak et al. (1997); Ruf et al. (2004)
	FOXC1	Salivary; lacrimal	Induces salivary gland cell fate in organoids; induces gland branching in lacrimal	Jaskoll et al. (2005); Tanaka et al. (2018)
	HNF6	Pancreas	Cystic dilation of interlobular and intralobular ducts	Cleveland et al. (2012)

Continued

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Table 3. Continued

Factor	Protein name (human syndrome)	Exocrine gland	Phenotype*	References
Transcription factors	ID2	Mammary	No acinar end-pieces	Mori et al. (2003); Sakikubo et al. (2018)
	IRF6	Salivary	Disorganized branching	Metwalli et al. (2018)
	MIST1	Pancreas	Lack of acinar differentiation	Direnzo et al. (2012)
	OTX1	Lacrimal	Absence of gland	Acampora et al. (1996)
	PAX1 (oto-facio-cervical syndrome 2)	Lacrimal	No animal studies	Pohl et al. (2013)
	PAX6	Lacrimal; salivary	Absent bud (lacrimal) and reduced branching (salivary)	Jaskoll et al. (2002); Makarenkova et al. (2000)
	PREP1	Mammary	Reduced branching	Sicouri et al. (2018)
	PTF1A	Pancreas	No pancreas organogenesis	Kawaguchi et al. (2002)
	P63	Salivary; lacrimal; mammary	Absence of gland	Yang et al. (1999)
	P120	Salivary	No acinar end-pieces	Davis and Reynolds (2006)
	RUNX1, RUNX2 and RUNX3	Lacrimal	Reduced branching	Voronov et al. (2013)
	SIX1	Lacrimal	Reduced branching (lacrimal)	Laclef et al. (2003)
	SOX2	Salivary	No acinar end-pieces	Emmerson et al. (2017)
	SOX9	Salivary; pancreas; meibomian; mammary	Reduced branching	Chen et al. (2013); Malhotra et al. (2014); Seymour et al. (2007); Tanaka et al. (2018)
	SOX10 (Waardenburg syndrome)	Salivary; lacrimal; mammary.	Reduced branching and decreased acinar formation	Athwal et al. (2019); Elmaleh-Bergès et al. (2013)
	TBX3	Mammary; apocrine-sweat	Absence of gland (mammary), structural defects that have not yet been histologically characterized (apocrine sweat)	Davenport et al. (2003)
Extracellular matrix	Heparan sulfate	Salivary	Reduction in branching	Nakanishi et al. (1993)
	HPSE	Mammary	Excessive hyperbranching	Zcharia et al. (2009)
	HS2ST	Mammary	Decreased side-branching and end-piece formation	Patel et al. (2017)
	HS6ST1, HS6ST2 and HS2ST	Lacrimal	No bud formation (in knockout of all three for lacrimal)	Qu et al. (2011)
	MMP14	Salivary	Reduction in branching	Oblander et al. (2005)
	NDST1	Mammary; lacrimal	Reduced end-piece development (mammary) and reduced bud formation (lacrimal)	Crawford et al. (2010); Pan et al. (2008)
	NDST2	Mammary; lacrimal	Mild increase in branching (mammary), reduced bud formation (lacrimal); deletion of both *Ndst1* and *Ndst2* results in moderate increase in branching (mammary) or complete loss of bud formation (lacrimal)	Bush et al. (2012); Pan et al. (2008)
Hormone receptor	ESR1	Mammary	Reduced branching	Glidewell-Kenney et al. (2007); Javed and Lteif (2013); Quaynor et al. (2013)
	PR	Mammary; uterine	Reduced ductal side branching and lobuloalveolar development in mammary glands; decreased secretion of leukemia inhibitory factor in uterine glands	Mulac-Jericevic et al. (2003); Wetendorf et al. (2017)
Transport proteins	CFTR (cystic fibrosis)	Pancreas; lacrimal; salivary; eccrine sweat	Congenital atrophy (pancreas); decreased fluid secretion (pancreas and lacrimal); higher salinity secretion (salivary); higher chloride concentration in secretion (eccrine sweat)	Berczeli et al. (2018); Catalán et al. (2010); Mickle et al. (1998); Wilschanski and Novak (2013)
	FATP (ichthyosis prematurity syndrome)	Sebaceous; meibomian	Sebaceous gland dystrophy; enlarged opening and thicker ducts of meibomian glands	Lin et al. (2013)
	TMEM16A	Salivary	No salivary secretion	Catalán et al. (2015)

*In some cases, mouse mutant phenotypes are not replicated in humans.

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Similar to SHH, β-catenin-deficient mice also display arrested development of the sweat gland coil that fails to extend beyond the bud stage. Bud elongation in the prostate gland also relies on canonical Wnt signaling, because β-catenin-deficient mice have anterior lobes with thin primary buds, and ventral and dorsolateral lobes with small buds with no evidence of elongation or branching (Simons et al., 2012). Unlike other exocrine glands, β-catenin knockdown in cultured lacrimal glands leads to increased FGF10 expression and branching, suggesting an inhibitory role for Wnt signaling (Dean et al., 2005; Garg and Zhang, 2017).

SOX9 is a key transcriptional factor essential for branching in several exocrine organs: *Sox9* deletion reduces epithelial branching in salivary glands *in vitro*, and in meibomian, pancreatic and prepubertal mammary glands *in vivo* (Chen et al., 2013; Malhotra et al., 2014; Seymour et al., 2007; Tanaka et al., 2018).

Post-pubertal gland growth

Branching in reproductive glands differs from other exocrine glands because formation of a fully branched structure takes place after birth and not during embryonic stages. These glands are steroid hormone-responsive; however, they do not branch in response to maternal hormones *in utero* but initiate branching postnatally (Bigsby and Cunha, 1985; Cooke et al., 2013). In the mammary glands, with the onset of puberty, cycling ovarian hormones promote the formation of terminal buds and increase branching of the pre-pubertal ductal tree. Increasing levels of progesterone with successive mouse estrous cycles promotes lateral branching in the mature adult gland (Atwood et al., 2000; Sternlicht, 2006). Homozygous mutation in the estrogen receptor 1 (*Esr1*) gene results in estrogen resistance and mammary gland branching arrest in mice (Glidewell-Kenney et al., 2007). Although pre-pubertal treatment with estrogen and progesterone diminishes uterine gland development in mice (Stewart et al., 2011), rats display variable effects depending on age and the dose of exogenous estrogen (Branham et al., 1985a,b). The exact branching pattern of uterine glands into adulthood and pregnancy remains a mystery. In both rodents and humans, systemic androgens, testosterone and dihydrotestosterone initiate branching morphogenesis in the prostate gland (Thomson and Marker, 2006). The prostate gland is rudimentary at birth and branches postnatally in rodents, but the human prostate gland begins to branch 10-12 weeks into gestation (Banerjee et al., 2018; Risbridger and Taylor, 2006). Although commitment of the urogenital sinus to a prostatic fate and the induction of prostatic buds is androgen dependent (Cunha et al., 2018; Donjacour and Cunha, 1988), a majority of ductal branching in the prostate takes place before puberty, when androgen levels are low.

Overall, there are common and distinct morphogenetic factors responsible for exocrine gland growth. Formation of a branched network appears generally conserved across exocrine glands that develop embryonically; however, this does not apply to reproductive glands that develop post-pubertally.

End-piece differentiation, maturation and secretory function

Functional variation between exocrine glands is highly driven by end-pieces that contribute the secretory material. Many transcription factors play specific roles in end-piece epithelial cell differentiation. Although most are gland-specific (Table 3), at least three transcription factors (SOX10, MIST1 and FOXA1) regulate end-piece function in more than one exocrine gland. SOX10 is a regulator of end-piece formation in salivary, lacrimal and mammary glands (Athwal et al., 2019). MIST1 is essential for pancreatic acinar cell differentiation because *Mist1*$^{-/-}$ mice display significant acinar disorganization and decreased secretory output (Direnzo et al., 2012). In the salivary gland mesenchyme, MIST1 overexpression induces expression of salivary acinar cell marker AMY1 (Mona et al., 2019). Using large-scale gene expression analysis, FOXA1 has been identified as a possible candidate gene that regulates lacrimal and prostate end-piece cell fate identity (Li et al., 2018a; Toivanen and Shen, 2017), although this has not been validated *in vivo*.

Wnt signaling regulates the timing of ductal and acinar differentiation in the salivary gland. In early stages of gland development, Wnt signaling promotes duct formation while inhibiting acinar differentiation. In the later stages, Wnt signals suppress ductal fate and promote acinar maturation (Matsumoto et al., 2016). In the sweat gland, Wnt and EDA lie upstream of SHH signaling to promote the formation of the secretory coil (Cui et al., 2014).

In the pancreas, Notch signaling regulates epithelial cell fate between acinar end-pieces and ductal cells. Increased Notch signaling causes epithelial cells to acquire a ductal cell fate with the absence of acinar end-pieces (Greenwood et al., 2007; Kopinke et al., 2011), while the absence of Notch signaling causes ductal cells to assume acinar identity (Kopinke et al., 2012). Similarly, in the mammary gland, hormone-driven inhibition of Notch signaling results in alveolar end-piece cell fate (Oakes et al., 2008).

Steroid hormones guide functional differentiation of reproductive exocrine glands. For example, uterine glands become secretory and mammary alveolar end-pieces become functional under the influence of progesterone (Fata et al., 2004; Macias and Hinck, 2012; Oakes et al., 2006; Spencer, 2014). Steroid hormones also regulate secretory output in non-reproductive glands, such as lacrimal, meibomian and salivary glands (Ablamowicz et al., 2016; Azzarolo et al., 1997). For example, lack of androgens reduces the volume of pre-ocular tears and decrease the rate of tear turnover in meibomian glands (Liu et al., 2018). Sex-steroid receptors are expressed in mature meibomian glands and may regulate differential sex-based gene expression and alter secretory function, causing a higher propensity of Sjogren's syndrome (and related salivary and eye dysfunction) in women than in men (Konttinen et al., 2010).

Ion channels and water channels [aquaporins (AQPs)] are essential for transcellular ion and water secretion in the end-pieces of some exocrine glands. TMEM16A is an anion channel that is expressed in the lacrimal (Evans and Marty, 1986), mammary (Gruber et al., 1999) and salivary glands; however, only salivary phenotypes with reduced saliva production have been reported in TMEM16A-deficient mice (Catalán et al., 2015). Loss of AQP5 in the sweat glands causes hypohidrosis (Song et al., 2002) and AQP5 is also required for water resorption or water secretion in the acinar cells of the lacrimal and salivary glands (Tóth-Molnár and Ding, 2020). On the other hand, AQP3 – but not AQP5 – is essential for water resorption in mammary gland alveolar end-pieces (Mobasheri et al., 2011).

Ductal differentiation, maturation and secretory function

Developmental factors regulate aspects of ductal growth both structurally, by regulating formation of the mature ductal tree, and functionally, by enabling ductal cells to differentiate and perform roles, such as resorption and altering concentration of the secretions being transported to the target tissue. Membrane transporters present on the surface of ductal cells are responsible for electrolyte reabsorption. Most prominent are the Na^+/K^+ ATPase pump and the cystic fibrosis transmembrane conductance regulator (CFTR),

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both of which are responsible for reabsorbing chloride ions from saliva (Lu and Fuchs, 2014; Matsui et al., 2000; Weber et al., 2011), for sodium chloride resorption from sweat gland secretions (Zhang et al., 2014) and for isotonic bicarbonate rich-fluid production in the pancreas. Human mutations in CFTR transporter elevate sweat chloride concentrations and is a diagnostic marker for cystic fibrosis (Mickle et al., 1998; Pagin et al., 2020; Quinton, 1983).

In addition to end-pieces, AQPs play an important role in water resorption in the ducts. Pancreatic ducts express AQP1 and AQP5, which are responsible for bicarbonate and fluid secretion into the lumen. Lacrimal gland ducts express low levels of AQP5 and high levels of AQP4, and these channels promote water resorption through the lacrimal gland ductal system (Tóth-Molnár and Ding, 2020). Although AQPs are essential to water resorption, their deficiency does not cause notable phenotypes in exocrine glands, likely due to functional redundancy or genetic compensation in mutants. In the context of lipid production, mice lacking fatty acid transport protein have underdeveloped meibomian glands with thick ducts and abnormal sebaceous glands with a thick skin barrier.

As highlighted by growth factors, signaling pathways and transcription factors, there are commonalities during the development and specification of the ducts versus the end-pieces. However, as expected, end-piece function is responsible for variation between glandular secretions, and is largely governed by unique gland-specific factors, a detailed discussion of which is beyond the scope of this Review.

Aberrations in adult exocrine gland structure-function relationships

Analogous to developmental perturbations, pathological or physiological perturbations may alter the structure of the mature functional gland (Fig. 4A). To further elucidate the structure-function relationship of exocrine glands, we group these perturbations into three broad categories (Table 4).

Ductal occlusion

Ductal occlusion is the narrowing of a ductal lumen or its complete blockage by a foreign object (Fig. 4B). It functionally presents as an absence of, or change in, the flow rate of secretions in the gland. Ductal occlusion often leads to the dilation of the ductal passageway and causes second-order effects, such as inflammation and end-piece atrophy. One of the most prominent examples is meibomian gland dysfunction, where unusually opaque meibum secretion and hyperkeratinization of the gland passage result in gland dropout and further contribute to dry eye, due to the lack of meibum (Knop et al., 2011).

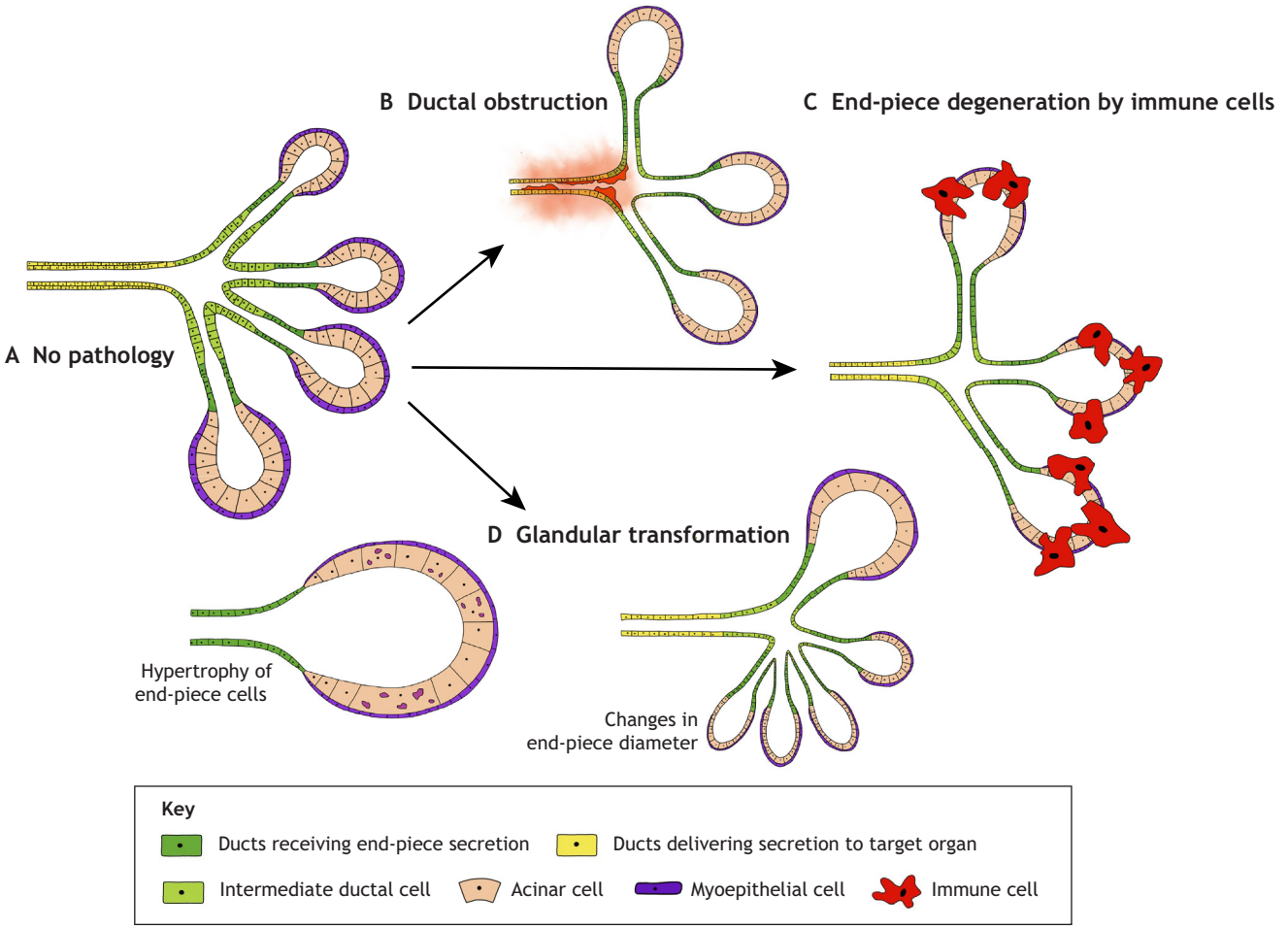

Fig. 4. Modes of alteration of normal exocrine gland structure. (A) Normal ductal and end-piece morphology with no pathology. (B) Ductal obstruction where build-up of material causes a narrowing of the ductal lumen and inflammation (red). (C) End-piece degeneration where end-piece units are destroyed by macrophages (red cells). (D) Glandular distortion displaying either hypertrophy of individual end-piece acinar cells or changes in end-piece diameter causing altered secretory capacity.

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Table 4. Changes in mature exocrine gland structure causing altered function

Pathology type	Organ system	Gland type	Causative agent	Functional outcome	References
Ductal occlusion	Digestive	Pancreatic exocrine	Ductal ligation of bile duct to duodenal wall	Decreased enzyme content in pancreatic fluid; decreased serum glucose	Pham and Forsmark (2018)
		Pancreatic exocrine	Cystic fibrosis causes gland plugging, gland obstruction and enzyme insufficiency	Pancreatitis; endocrine pancreas insufficiency	Gibson-Corley et al. (2016); Wilschanski and Novak (2013)
		Salivary	Mineralized intraductal mass caused by secretion or food debris; sialolithiasis	Increased salivary flow; pain	Harrison (2009); Jardim et al. (2011); Marchal et al. (2001)
		Salivary	Actinomycosis; bacterial infection of duct causes enlargement	Hyposalivation leading to dental caries	Mortazavi et al. (2014)
	Eye	Harderian	Exophthalmos block duct causes eye protrusion	Increased exophthalmos	Hittmair et al. (2014)
		Meibomian	Waxy secretions block ducts of glands (obstructive meibomian gland dysfunction)	Dry eye; inflammation of eyelid (blepharitis), cornea and gland (meibomitis)	Knop et al. (2011); Tomlinson et al. (2011)
	Female reproductive	Mammary	Intraductal mass; mammary duct ectasia	Bloody nipple discharge and inflammation	D'Alfonso et al. (2015)
	Male reproductive	Prostate	Ejaculatory duct obstruction caused by prostatic cysts, infection and stones	Reduced sperm count; reduced male fertility	Avellino et al. (2019); Pryor and Hendry (1991); Simpson and Rausch (2009)
	Skin	Apocrine	Blockage of apocrine-follicle opening	Hidradenitis suppurativa	Attanoos et al. (1995)
		Eccrine sweat	Type 2 diabetes causes narrower sweat ducts	Reduced gland function and less sweating	Ishibashi et al. (2014)
		Eccrine sweat	Miliaria; tight clothing causes rash due to duct blockage	Rash; sweat build-up in raised papules	Carter et al. (2011)
		Eccrine sweat	Aluminum salts in anti-perspirants precipitate in excretory duct	Sweat build-up and irritation	Hölzle and Braun-Falco (1984)
End-piece degeneration	Digestive	Salivary	Degeneration of duct cells and acinar cell metaplasia in systemic lupus erythematosus	Reduced salivary flow causing xerostomia	Bologna et al. (2018)
		Salivary	Radiation therapy for head/neck cancer	Salivary hypofunction, reduced oral health and difficulty swallowing	Brown et al. (1975); Dreizen et al. (1977); Dusek et al. (1996)
		Pancreas	Radiation therapy for gastric cancer	Pancreatic insufficiency; steatorrhea; limited animal or human studies looking at acinar end-pieces directly, but functional outcome correlated with radiation treatment	Wydmanski et al. (2016)
	Eye	Lacrimal	Lymphocytes infiltrate into end-piece cells and cause atrophy	Decreased tear flow and resultant dry eye	Izumi et al. (1998)
		Meibomian	Sjogren's syndrome	Dry eye, less robust tear film on ocular surface	Tomlinson et al. (2011); Zang et al. (2018)
Glandular transformation	Digestive	Exocrine pancreas	Alcohol consumption, smoking causes calcification resulting in pancreatitis	Reduced pancreatic juice; pancreatic insufficiency and steatorrhea	Lesniak et al. (2002); Majumder and Chari (2016)
		Exocrine pancreas	Pancreatic adenocarcinoma; tumor serves as ductal blockage	Pancreatic insufficiency and steatorrhea	Panozzo et al. (1995); Pham and Forsmark (2018)
		Salivary	Fibrosis of salivary glands in scleroderma	Reduced salivary flow causing xerostomia	Albilia et al. (2007)

Continued

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Table 4. Continued

Pathology type	Organ system	Gland type	Causative agent	Functional outcome	References
Glandular transformation	Eye	Meibomian	Long-term contact lens wear	Dry eye; less robust tear film on ocular surface	Gu et al. (2020)
		Meibomian	Glands significantly shortened or extinguished in granular corneal dystrophy type 2	Phospholipid deposits on the cornea from meibomian glands	Sakimoto (2015)
		Lacrimal	Aging causes changes in end-piece cells	Decreased tear production	Draper et al. (1999)
		Lacrimal	Sleep deprivation	Mouse model: gland hypertrophy and lipid droplets in end-piece cells	Li et al. (2018b)
	Male reproductive	Seminal vesicles	Agenesis of seminal vesicles	Reduced sperm count; reduced male fertility	Bouzouita et al. (2014)
	Female reproductive	Mammary gland	Mammary duct ectasia: build-up of fibrotic tissue causes blockage	Narrowed lumen, bloody nipple discharge and inflammation	D'Alfonso et al. (2015); Jiang et al. (2020)
	Skin	Eccrine-sweat	Decreased surface area of end-pieces of patients with growth hormone deficiency	Hypohidrosis	Lange et al. (2001)
		Eccrine-sweat	Heat-acclimated glands secrete more sweat when stimulated	Hyperhidrosis from heat-acclimated glands	Sato et al. (1990)
		Eccrine-sweat	Decreased volume of end-piece in 'poor sweaters'	Decreased sweat rate	Sato and Sato (1983)

End-piece degeneration

Atrophy or damage to the end-pieces themselves (Fig. 4C) is, generally, secondary to ductal occlusion but can arise independently, due to autoimmune causes and external trauma, such as radiation therapy for cancers. Autoimmune disorders (such as lupus, rheumatoid arthritis and Sjogren's syndrome) affect exocrine gland end-pieces through common mechanisms where lymphocytes infiltrate the acinus, and cause inflammation and cell death, leading to end-piece degeneration. Degeneration has been observed in meibomian (Zang et al., 2018), lacrimal (Izumi et al., 1998) and salivary (Bologna et al., 2018) glands. End-piece degeneration reduces gland function and causes symptoms, such as dry mouth (for salivary glands) and dry eye (for ocular glands) (Nair and Singh, 2017).

Glandular transformation

Glandular transformation involves a change in the structure or cellular composition of the duct or end-pieces that affects gland function (Fig. 4D). Although ductal occlusion is caused by an external agent, glandular transformation is due to a change in the gland tissue itself. Glandular transformation is not always a result of pathology, but also occurs as a physiological adaptation to adverse environmental conditions to maintain homeostasis. For example, Patas monkeys acclimatize to prolonged heat exposure by modifying their sweat gland structure and secretory function. Their maximum sweat rate increases; this correlates with changes in the secretory coil structure, including longer tubular length, increased tubular diameter and increased tubular volume (Sato et al., 1990). Thus, similar to developmental defects, adult pathology and physiology impacts structure-function relationships found in exocrine glands.

Implications of understanding exocrine gland structure-function relationships

Comprehensive understanding of exocrine gland morphogenesis combined with emerging bioengineering techniques show promise for advances across the life sciences. High-resolution imaging can provide reproducible details on structure, which can be used for diagnostic purposes when gland shape deviates from normal. Additionally, detailed knowledge of structure serves as a basis for bioengineering scaffolds to seed stem cells and promote gland regeneration (discussed below).

Whole-mount immunofluorescent imaging has allowed discovery of novel uterine gland organization in pre-implantation mice, supporting gland function in embryo survival (Arora et al., 2016), human uterine gland organization during the menstrual cycle (Yamaguchi et al., 2021), and structure-function relationships between sweat gland morphology and sweat rate (Kurata et al., 2017; Sato et al., 1990). Clinically, structure-based imaging is an alternative to invasive biopsies for diagnosis of various exocrine gland pathology. *In vivo* laser-scanning confocal microscopy can provide quantitative morphological lacrimal gland data as an indicator of dry eye (Zhao et al., 2016). Imaging salivary glands using sialography and magnetic resonance imaging is instrumental in tracking changes in gland shape post-radiation therapy (Wu and Leung, 2019). Imaging can also measure sweat gland structure distortion in the diagnosis of anhidrotic ectodermal dysplasia (Reinholz et al., 2016).

A better understanding of exocrine gland structure-function relationships will promote therapies that replace or regenerate organs with impaired ducts or end-pieces to restore organ function (Hirayama, 2018; Wang et al., 2017). Restoration of both salivary and lacrimal gland function has been successfully achieved in adult mice by orthotopic transplantation of embryonic 'organ germs' (Hirayama et al., 2013; Ogawa et al., 2013). Epithelial progenitor cells have also been successfully engrafted into the ductal and acinar compartments in ocular glands in a Sjogren's syndrome mouse model to improve tear secretion (Gromova et al., 2017). In addition, the exocrine pancreas shows regenerative capacity upon damage to acinar cells in acute pancreatitis in animal models (Zhou and Melton, 2018). Finally, burn victims are often treated using skin

grafts from epidermal sheets of their own unburned skin; however, sweat glands fail to regenerate, causing patients to experience heat intolerance. Therefore, methods for gland regeneration are required. The future of regenerative medicine for exocrine glands lies in understanding enough detail about the development of the gland structure to induce pluripotent stem cells to generate end-piece and ductal cells to restore function to the damaged glandular tissue.

Conclusions

We have summarized the current understanding of exocrine gland structure-function relationships often derived from careful morphological analyses across different exocrine glands. Through genetic mutations that display gland structure defects, we highlight key common factors that underlie gland morphogenesis across different glands and additional factors that underlie gland-specific differentiation and function. We identify glands where exocrine gland structure-function relationships are used for diagnostics of pathology, and we highlight the application of gland structure-function relationships for regeneration of exocrine glands.

Although a lot has been discovered, unanswered questions in the field remain including: (1) how or why some glandular shapes (coiling versus branching), end-pieces (tubular, acinar and alveolar) and ductal trees (simple versus complex) are evolutionarily selected for preparation and delivery of glandular material; (2) how the nature of gland secretions and the distance they need to travel influence the choice of gland shape; and (3) whether pathological abnormalities are easier to detect in certain glands due to their easy access or to the nature of gland structure and secretions. We highlight the need for applying novel molecular imaging to promote development of diagnostics in organs that have not yet been targeted. Improved diagnostics could then be used to track structural changes in exocrine glands as a marker for aging and disease. Finally, we suggest that detailed structure-function information obtained from high-resolution imaging could lead to development of precise scaffolds with the goal of using stem cells in creating regenerative patches for degenerating exocrine glands.

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Competing interests

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