

MEETING REVIEW

Cellular plasticity at the nexus of development and disease

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ABSTRACT

In October 2020, the Keystone Symposia Global Health Series hosted a Keystone eSymposia entitled ‘Tissue Plasticity: Preservation and Alteration of Cellular Identity’. The event synthesized groundbreaking research from unusually diverse fields of study, presented in various formats, including live and virtual talks, panel discussions and interactive e-poster sessions. The meeting focused on cell identity changes and plasticity in multiple tissues, species and developmental contexts, both in homeostasis and during injury. Here, we review the key themes of the meeting: (1) cell-extrinsic drivers of plasticity; (2) epigenomic regulation of cell plasticity; and (3) conserved mechanisms governing plasticity. A salient take-home conclusion was that there may be conserved mechanisms used by cells to execute plasticity, with autodegradative activity (autophagy and lysosomes) playing a crucial initial step in diverse organs and organisms.

KEY WORDS: Metaplasia, Paligenesis, Dedifferentiation, Transdifferentiation, Reprogramming

Introduction

There is abundant emerging evidence to suggest that cells can change their identity in order to respond to physiological or pathological signals. The first large, broad-spectrum meeting concerning such cellular plasticity was a Keystone Symposium held in early 2019. This inaugural symposium gathered investigators from seemingly disparate fields to share concepts about cell fate transitions, and to provide a conceptual and organizational foundation for this newly self-recognized field. The meeting also included a workshop on the use of terminology relating to the term ‘plasticity’, which was summarized in a recently published white paper (Mills et al., 2019). At the workshop, there was general agreement that ‘dedifferentiation’ is the process by which a mature cell returns to a progenitor or stem cell-like state, but questions were raised about what defines cellular ‘maturity’ and whether the ‘progenitor state’ has to exactly resemble that exhibited by homeostatic progenitor cells. ‘Transdifferentiation’ was recognized as the conversion of a mature cell to a different cell identity, but it was noted that it may occur with or without reversion to a transient immature state. In addition, the term ‘paligenesis’ was coined to define the evolutionarily conserved cellular and molecular program that cells use to change their identity.

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The second meeting in the plasticity series took place in October 2020. This eSymposium entitled ‘Tissue Plasticity: Preservation and Alteration of Cellular Identity’, with ~200 participants from 22 countries, was expertly organized by Ophir Klein (University of California, San Francisco, CA, USA), Ramesh A. Shivdasani (Harvard University, Cambridge, MA, USA) and Stacey S. Huppert (Cincinnati Children’s Hospital, OH, USA). Here, we summarize the work and key themes emerging from this meeting.

Cell-extrinsic drivers of plasticity

Cell plasticity research has often centered on cell-intrinsic mechanisms within the cells undergoing the identity change. Clearly, though, the complex microenvironment or cellular niche must also shape developmental trajectories and guide cell fate transitions (Fig. 1A). Magdalena Zernicka-Goetz (California Institute of Technology, Pasadena, USA and University of Cambridge, UK) delivered the eSymposium Keynote, detailing how the cellular niche shapes the developing embryo and highlighting how current lack of *in vitro* models hinders detailed studies of early embryonic development. An early embryo comprises three cell types – epiblast, trophectoderm and primitive endoderm – that can all now be cultured and maintained *in vitro* in differing conditions (Bedzhov and Zernicka-Goetz, 2014; Evans and Kaufman, 1981; Morris et al., 2012; Ramos-Mejia et al., 2005; Shahbazi et al., 2016, 2017, 2020; Tanaka et al., 1998). Dr Zernicka-Goetz showed how faithful *in vitro* modeling using stem cells for these three tissues has now helped us decipher some of the key plasticity events in embryonic development, including those occurring during lumenogenesis/rosette formation, symmetry breaking/cell fate transitions and germ layer self-organization (Harrison et al., 2017; Kyrianiou et al., 2020; Sozen et al., 2018).

Aaron Zorn (Cincinnati Children’s Hospital Medical Center, OH, USA) detailed how single-cell transcriptomic analyses have revealed the complex paracrine signaling networks coordinating epithelial and mesenchymal cell lineages in the developing mouse foregut. His lab has leveraged this molecular ‘roadmap’ to direct organ-specific mesoderm progenitors to differentiate from human induced pluripotent cells (iPSCs) (Han et al., 2020). Edward Morrisey (University of Pennsylvania, Philadelphia, USA) similarly used single cell RNA-sequencing (sc-RNA seq), sc-ATAC seq and single-cell chromatin accessibility and pathway expression (SCAPE) analyses to describe a transcriptional ‘roadmap’ of epithelial and mesenchymal compartments during lung development (Frank et al., 2019; Zepp and Morrisey, 2019; Zepp et al., 2017). The work showed, for example, how AT1 epithelial cells are signaling hubs that secrete ligands like PDGFA and VEGFA to communicate with mesenchymal cells like secondary crest myofibroblasts, which can, in turn, signal to AT1 cells by increasing tension during alveogenesis.

Leanne Jones (University of California, Los Angeles, USA) detailed her lab’s work studying extrinsic cues that signal to germline stem cells in the *Drosophila* testes. Lineage-tracing approaches have shown a close lineage relationship between critical support cells in the testis – the somatic hub cells – and somatic stem cells. Indeed, hub

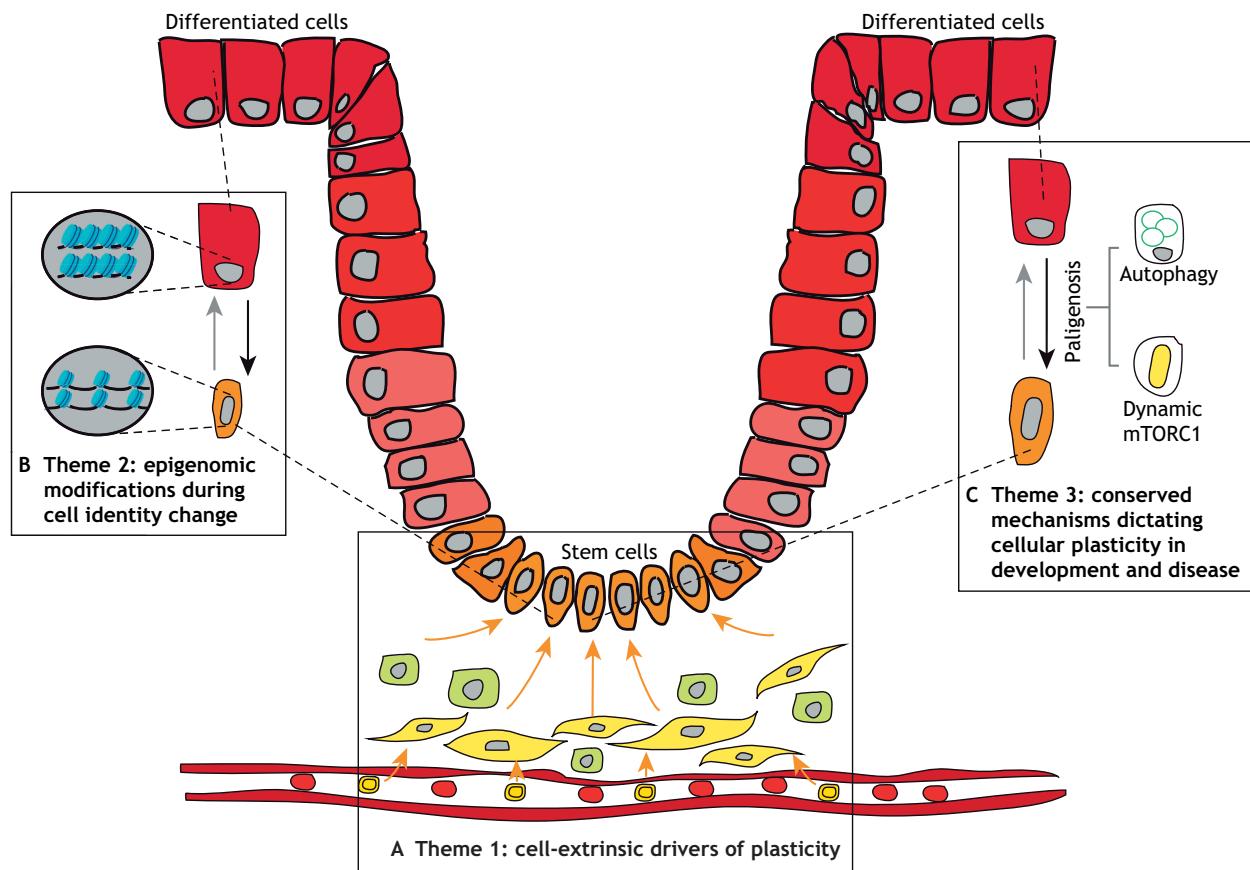


Fig. 1. Principal themes of tissue plasticity. The mechanisms driving cell fate specification and cell identity changes during development and disease states, presented during the eSymposium, can be grouped into three themes, which are illustrated here using the intestinal crypt as an example. (A) Theme 1: surrounding cell types and niche components (yellow) send signals to guide cell fate decisions in stem cells (orange). (B) Theme 2: interconversions between multipotent stem cells (orange) and differentiated cells (red) are characterized by changes in chromatin accessibility (i.e. shifts between heterochromatin and euchromatin) at distinct genetic loci. (C) Theme 3: shared mechanisms, including dynamic shifts in mTORC1 activity and autophagy, enable cellular plasticity; paligenesis specifically describes the autophagy-dependent dedifferentiation and proliferation of mature cell types after injury. Figure created with BioRender.com.

cells can differentiate into somatic cyst cells (Hetie et al., 2014; Voog et al., 2008, 2014). Escargot (Esg), a member of the Snail transcription factor family, maintains somatic stem cells by blocking their differentiation and decreasing epidermal growth factor signaling to maintain hub cells (Voog et al., 2014).

The niche also governs cellular plasticity after infection or inflammation. Ophir Klein discussed the interplay between niche components and epithelial cell identity in response to mouse helminth (*Hligmosomoides polygyrus*) infections. This parasite causes intestinal granulomas and induces adjacent intestinal crypt hyperproliferation. Following infection, reactive epithelial cells decrease expression of adult intestinal stem cell markers (e.g. LGR5 and OLFM4) and increase expression of markers (e.g. SCA1) that characterize fetal intestine (Nusse et al., 2018). Thus, in response to a damaging external stimulus, the epithelium reprograms into a more ‘developmental-like’ state to aid repair. Dr Klein also discussed how intestinal ATOH1⁺ secretory cells reprogram into multipotent stem cells after injury, giving rise to all colonic epithelial lineages after ablation of *Lgr5*⁺ stem cells (Castillo-Azofeifa et al., 2019).

Talks from Indira Mysorekar (Washington University School of Medicine, St Louis, MO, USA), Juanita Merchant (University of Arizona College of Medicine, Tucson, USA), Shruti Naik (New York University, USA) and Bo Wang (Stanford University, CA, USA) expanded upon the theme of inflammation and infection as niche-

derived cues for plasticity. Dr Mysorekar’s group focuses on how uropathogenic *Escherichia coli* (UPEC) infection and aging affect urothelial plasticity and regeneration. Host countermeasures to infection include exfoliation of infected epithelial cells and activation of underlying stem cells. For example, her group has shown that mesenchymal cells elaborate BMPs that activate p27kip1 to promote differentiation and regenerate lost epithelial cells. Contrastingly, decreased estrogen signaling (as occurs in aging) impairs such stem cell plasticity (Ligon et al., 2020; Wang et al., 2013). Dr Merchant discussed how sonic hedgehog regulates *Helicobacter*-induced gastric inflammation and gastric epithelial cell plasticity. *Gli1*-expressing myeloid-derived immune suppressive cells are recruited during stomach metaplasia (El-Zaatari et al., 2013) and schlafen 4 (*Slf4*) is a direct GLI1 target (Ding et al., 2016; Merchant and Ding, 2017). SLF4-expressing myeloid suppressor cells in the stomach promote metaplasia in part via the microRNA miR130b, which activates pro-inflammatory NF-κB signaling (Ding et al., 2020). Dr Shruti Naik shared her lab’s developing story about the interplay between immune cells and epithelial plasticity, wherein a recruited population of T cells helps fuel epidermal wound healing. Dr Wang described work in highly regenerative planaria, generating chimeras by fusing two separate genetic strains. In this context, the chimeric planaria exhibit deficient regeneration after injury. Cells from one strain see the cells of the other strain as ‘non-self’ and

increase activin signaling, which governs both the Wnt-responsive regenerative program and innate immunity through the p38 pathway.

The microenvironment also governs plasticity during carcinogenesis. Valerie Weaver (University of California, San Francisco, USA) described how, unlike normal breast tissue, breast cancers are embedded within a fibrotic, stiff extracellular matrix (ECM) (Acerbi et al., 2015; Maller et al., 2020 preprint). Inhibiting collagen crosslinking decreases circulating tumor cells, lung metastases and tumor grade (Levental et al., 2009; Mouw et al., 2014; Pickup et al., 2013), while increased ECM tension invokes tumor stem cell characteristics and an epithelial-to-mesenchymal transition (EMT) phenotype. These effects are mediated through integrin signaling and Rho kinase, pathways that can be targeted by drugs, potentially opening new therapeutic avenues (Northey et al., 2020; Paszek et al., 2005; Visvader and Stingl, 2014).

Finally, Emmanuelle Passegué (Columbia University, NY, USA) examined niche-mediated regulation of hematopoietic stem cell (HSC) plasticity during aging. Old HSCs exhibit cell-intrinsic alterations, such as replication stress and altered autophagy responses (Ho et al., 2017), that are not reverted by conserved systematic interventions that ‘rejuvenate’ other somatic stem cell compartments, such as heterochronic parabiosis, injection of young plasma, exercise or calorie restriction. Moreover, young HSC niches fail to rejuvenate old HSCs in heterochronic parabiosis experiments, suggesting that the hematopoietic system is surprisingly refractory to systemic rejuvenation interventions. These findings indicate that the old HSC state, once reached, is intrinsically stable and cannot yet be reversed by extrinsic interventions.

Epigenomic modifications during cell identity change

Cell fate switches that define cellular plasticity are often governed by epigenomic changes (Fig. 1B). Xin Sun (University of California, San Diego, USA) detailed how mitochondrial protein quality control defects caused by mutant *LONP1* (encoding a mitochondrial protease) lead to a striking increase of progenitor basal cells at the expense of differentiated cells in the airway due to altered expression of histone modifiers. Emily Zion (Xin Chen Lab, Johns Hopkins University, Baltimore, MD, USA) demonstrated that when *Drosophila* intestinal stem cells divide asymmetrically to produce another stem cell and an enteroblast (a more differentiated progeny), histones segregate based on age (i.e. time elapsed since they were first translated): ‘old’ histones segregate to the stem cell and ‘new’ histones to the enteroblast. Moreover, disrupting histone segregation causes tumor-like expansion of stem cell clones (Xie et al., 2015; Zion and Chen, 2020 preprint).

Ben Stanger (University of Pennsylvania, Philadelphia, USA) discussed the epigenome during cancer progression. Moderately differentiated tumors, with a partial EMT phenotype, invade as clusters of cells that retain expression of epithelial proteins sequestered in recycling endosomes. By contrast, poorly differentiated tumors, which invade as single cells, have more classical EMT phenotypes and exhibit transcriptional downregulation of epithelial genes (Aiello et al., 2018). Such plasticity appears to involve histone methylation: NSD2, a histone methyltransferase, impairs EMT, whereas KDM2A, a histone demethylase, impairs the reverse process of mesenchymal-to-epithelial transition (MET) (Yuan et al., 2020). Increased methylation correlates with a mesenchymal phenotype via activation of transcription factors such as Snail and Zeb1/2.

Barrett’s esophagus (BE) is a metaplasia in which normal squamous esophageal epithelial cells are lost in favor of a columnar mucosal epithelium, usually featuring cells with an intestinal phenotype. Ramesh Shivdasani’s lab found that BE has a pattern of

enhancer H3K4me2 marks resembling that of the intestine and stomach, but unlike that of normal squamous esophagus. This epigenomic pattern suggests that BE derives from gastric epithelium-derived cells with varying degrees of ‘hybrid’ intestinal transcriptional expression patterns subsequently superimposed.

Conserved mechanisms dictating cellular plasticity in development and disease

Another theme at the meeting was that diverse tissues – including mesenchymal and neural lineages – exhibit plasticity programs. Moreover, it is not just the phenomenon of plasticity that is conserved across tissues: much of the molecular and cellular machinery that coordinates plasticity events is also conserved (Fig. 1C), akin to how there is a shared program for cell division and cell death.

Yingzi Yang (Harvard School of Dental Medicine, Boston, MA, USA) showed how multiple signaling pathways regulate mesenchymal plasticity in the skeleton. The G-protein-coupled receptor subunit, encoded by the gene *Gnas*, coordinates both Wnt and Hedgehog signaling. People with *GNAS* mutations can exhibit progressive ectopic bone deposition. Dr Yang reported that, in mice, induced loss of *Gnas* increases sonic hedgehog secretion by a YAP/TAZ-dependent mechanism, with the secreted Hedgehog inducing osteogenesis non-cell-autonomously (Khan et al., 2018; Regard et al., 2013; Xu et al., 2018).

Shashank Gandhi (Marianne Bronner Lab, California Institute of Technology, Pasadena, USA) presented work on neural crest plasticity, showing that proper cardiac neural crest specification and septation of the cardiac outflow tract require the transcription factor *Tgif1* (Gandhi et al., 2020). Using sc-RNA-Seq, the Bronner Lab is piecing together how cardiac neural crest progenitors differentiate into downstream lineages via complex, combinatorial expression of transcription factors. They found that *Tgif1*, together with *Ets1* and *Sox8*, comprises a cardiac crest specific subcircuit that can be used to reprogram other neural crest populations toward a cardiac neural crest fate.

Adipocyte plasticity was discussed by Shingo Kajimura (University of California, San Francisco, USA) and Farnaz Shamsi (Yu-Hua Tseng Lab, Joslin Diabetes Center, Boston, MA, USA). The Kajimura Lab used a β-adrenergic receptor null mouse model (Bachman et al., 2002) to show that the pro-muscle transcription factor MyoD marks a subset of beige adipocytes, which they term ‘glycolytic beige’ (g-beige) cells. Their findings suggest that myoblasts have plasticity that allows them to switch from muscle to g-beige adipocytes after prolonged cold exposure or in response to pathological conditions such as tissue injury (Chen et al., 2019). These g-beige fat cells can act as a glucose sink to buffer blood glucose. Dr Shamsi showed that vascular smooth muscle-derived adipocyte progenitors are the cellular origin for cold-induced brown adipocytes. Such *Trpv1*⁺ precursors are a distinct population spawning brown adipocytes with increased mitochondrial/thermogenic gene expression (Shamsi et al., 2020 preprint).

As noted earlier, Ophir Klein explored how ATOH1⁺ secretory cells in the intestine could reprogram in different injury-induced contexts. The *Drosophila* posterior midgut (PMG) shows similar injury-induced plasticity. Normally, the gut houses multipotent intestinal stem cells (ISCs) that differentiate into polyploid enteroblasts and enterocytes (Ohlstein and Spradling, 2006). Benjamin Ohlstein (UT Southwestern Medical Center, Dallas, TX, USA) detailed how injury-induced ISC depletion can trigger ISC regeneration from differentiated cells in a process involving ploidy reduction known as ‘amitosis’ (Lucchetta and Ohlstein, 2017). Similarly, Dr Morrissey showed how injury in adult lung

causes AT2 surfactant-producing cells to regenerate lost AT1 cells (Zepp and Morrisey, 2019). Conversely, in neonatal hyperoxic injury, AT1 cells can regenerate AT2 cells (Leach and Morrisey, 2018), possibly because the pro-plasticity Hippo pathway effectors YAP/TAZ are uniquely expressed in AT1 cells. This Hippo-dependent AT1-to-AT2 plasticity is also seen in the adult lung, with loss of YAP and TAZ triggering the conversion.

Adult liver, like lung, lacks dedicated stem cells. Stacey Huppert discussed how hepatocytes transdifferentiate to regenerate cholangiocytes if bile ducts are lost. Mice with altered Notch signaling due to deletion of *RbpJ* and *Hnf6* display extreme intrahepatic bile duct paucity (Sparks et al., 2010; Vanderpool et al., 2012; Walter et al., 2014) but rebuild their ductular tree with age (Schaub et al., 2018). Differentiated hepatocytes fuel this *de novo* bile duct formation. Specifically, TGF β (via loss of *Hnf6*) unlocks the transdifferentiation potential of hepatocytes (Huppert and Iwafuchi-Doi, 2019), with TGFBR2 being required in hepatocytes (Schaub et al., 2018). Also focusing on the liver, Tianliang Sun (Novartis Institutes for BioMedical Research, Switzerland) showed how mTOR and YAP1 signaling control biliary epithelial cell (BEC)-driven regeneration (Planas-Paz et al., 2019; Sun et al., 2019). He further demonstrated that hepatocytes throughout the liver upregulate AXIN2 and LGR5 following injury and contribute to liver regeneration on demand, without zonal dominance of a putative pericentral stem cell population (Sun et al., 2020a,b).

During epithelial plasticity, ‘hybrid’ cell states can form, often characterized by the co-expression of mature and progenitor markers. Accordingly, Angela Nieto (Instituto de Neurociencias de Alicante, CSIC-UMH, Spain) discussed EMT as a transient and reversible process characterizing embryonic development and adult pathology (Nieto, 2013; Ocana et al., 2012), highlighting how partial or hybrid EMT phenotypes that favor plasticity have been found in primary tumors and in organ fibrosis (Grande et al., 2015; Nieto et al., 2016).

Hybrid cell states also characterize chronic, precancerous lesions such as metaplasia. The cells of origin fueling BE are unknown but Ramesh Shivdasani’s presentation (discussed above) indicates that BE may harbor a ‘hybrid’ identity, displaying concomitant stomach and intestinal characteristics arising from reparative stomach epithelium. Dr Shivdasani also reported that two intestine-promoting transcription factors, HNF4A and CDX2, play a key role in imposing intestinal identity.

Towards a common program governing cellular plasticity

Our group (Mills lab, Washington University School of Medicine, St Louis, MO, USA) has shown that many of the cellular plasticity events discussed above – including those involved in metaplasia – may be governed by a common cellular and molecular program termed paligenesis (Fig. 1C), similar to how apoptosis is a conserved program for cell death. Using acute drug injury models that induce mature cells to re-enter the cell cycle in both the pancreas and stomach (Willet et al., 2018), Dr Mills’ presentation showed that paligenesis occurs via distinct stages involving genetic/metabolic checkpoints. In stage 1, mTORC1 deactivates and autophagic mechanisms are activated. In stage 2, embryonic genes/metaplastic markers are expressed (i.e. SOX9, CD44v, nuclear YAP1, TFF2 and MUC6). Stage 3 is defined by mTORC1 reactivation and cell cycle re-entry. Given the conserved nature of paligenesis, there may be paligenesis-dedicated genes that are expected to be injury induced, cross-species/-tissue conserved, and not required for development or everyday stem cell homeostasis. Accordingly, Dr Mills explained that *IFRD1* is one such paligenesis gene that

licenses cell cycle re-entry (Miao et al., 2020), acting between stages 2 and 3 by repressing p53. *IFRD1* is highly conserved, also helping recruit *Drosophila* gut stem cells after injury. Dr Mysorekar’s talk discussed an analogous role for *IFRD1* in the urothelium: UPEC infection rapidly activates *IFRD1* as regenerative cells are recruited. Loss of *Ifrd1* causes aberrant injury response and a premature aging phenotype. *Ddit4* is another paligenesis gene that, as highlighted by Dr Mills, silences mTORC1 and regulates the initial induction of lysosomes and autophagy. Because *IFRD1* and p53 coordinate to license only healthy cells to re-enter the cell cycle, *Ddit4*^{-/-} cells, which have constitutively active mTORC1, escape licensing, are prone to enter the cell cycle even with DNA damage and cause increased tumorigenesis (Miao et al., 2021).

Other talks supported the existence of conserved features of plasticity. Dynamic regulation of mTORC1 and autophagy were recurring themes. Rashmi Mishra (Duc Dong Lab, Sanford Burnham Prebys Medical Discovery Institute, San Diego, CA, USA) showed that autophagy is required for and can enhance zebrafish skeletal muscle cell to endoderm lineage transdifferentiation. Autophagic puncta accumulate in these reprogramming cells, and autophagy inhibition blocks transdifferentiation initiation, whereas autophagy stimulation (by blocking mTORC1) increases its efficiency and efficacy. The requirement of autophagy for plasticity may be universal as even plant cells use autophagy for climatic adaptation (Rodriguez et al., 2020). Accordingly, Dr Mishra showed that autophagy is also required for transdifferentiation of pancreatic duct cells into endocrine cells. Similarly, Dr Kajimura showed that mitophagy (i.e. the targeted destruction of mitochondria by autophagy) fuels the beige-to-white fat conversion that occurs after cold-adapted mice are returned to homeostatic temperatures (Altshuler-Keylin et al., 2016; Lu et al., 2018; Sarraf and Youle, 2018). Adam Pietrobon (William Stanford Lab, Ottawa Hospital Research Institute, Canada) showed that aberrant mTORC1 activation via TSC1/2 loss induces kidney proliferation and differentiation defects. Finally, Valerie Horsley (Yale University, New Haven, CT, USA) showed a role for lipolysis in adipocyte reprogramming during skin repair. Wound bed adipocyte precursors lose adipogenic potential after injury and give rise to a population of myofibroblasts (Shook et al., 2018); inhibiting lipolysis impairs this process, resulting in wound repair phase defects. These data suggest that when adipocyte precursors change fate after injury, losing their adipogenic potential and differentiating into pro-regenerative myofibroblasts, they must also first reshape their cellular architecture by an autodegradative mechanism.

Conclusions

The quality and diversity of the presentations at this Keystone eSymposium reflected the rapidly growing cellular plasticity field. Universal themes are beginning to emerge: recurring roles for certain signaling pathways (e.g. YAP/TAZ), dynamic mTORC1-mediated energetic shifts and autodegradation of cell architecture as a key first step. Interestingly, early pathologists noted that differentiated cell architecture must be dismantled before returning to a progenitor state, and also predicted that dynamic energetic changes must characterize reprogramming (Adami, 1900). Over one century later, we are beginning to prove them right. The eSymposium also raised many new exciting questions. For example, embryonic development is necessarily plastic, but do adult plasticity events recapitulate this embryonic plasticity or do adult cells have their own unique built-in specialized plasticity mechanisms (e.g. paligenesis)? How is aberrant plasticity linked to diseases like cancer or processes like ageing? Are certain epigenomic changes conserved across plasticity events? The

meeting drove home the point that a vast array of cells from every tissue exhibit plasticity, but if there are also cells that cannot switch identity, what stops them? Clearly, we are just at the beginning of this exciting and expanding field!

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Competing interests

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