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A Synthesis Concerning Conservation and Divergence of Cell Types across Epithelia

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Advances in single-cell RNA-seq (scRNA-seq) and computational analysis have enabled the systematic interrogation of the cellular composition of tissues. Combined with tools from developmental biology, cell biology, and genetics, these approaches are revealing fundamental aspects of tissue geometry and physiology, including the distribution, origins, and inferred functions of specialized cell types, and the dynamics of cellular turnover and differentiation. By comparing different tissues, such studies can delineate shared and specialized features of cell types and their lineage. Here, we compare two developmentally related murine epithelia, the airway and the small intestinal epithelia, which are both derived from the embryonic endodermal gut tube. We examine how airway and intestine generate and functionalize common archetypal cell types to fulfill similar shared physiologic functionalities. We point to cases in which similar cell types are repurposed to accommodate each tissue's unique physiologic role, and highlight tissue-specific cells whose specializations contribute to the distinct functional roles of each organ. We discuss how archetypal and unique cell types are incorporated within a cellular lineage, and how the regulation of the proportions of these cell types enables tissue-level organization to meet functional demands and maintain homeostasis.

Epithelia are sheets of polarized cells that serve to partition the body's internal milieu from the outside environment. During vertebrate development, all three primordial germ layers give rise to epithelia that serve a panoply of essential functions, including barrier maintenance, absorption and secretion, sensation, and immunity.

The diverse cells comprising a tissue must function together in a well-orchestrated manner to meet the tissue's functional demands and maintain homeostasis (Kotas and Medzhitov 2015). During evolution, distinct epithelia have redeployed several archetypal cell types. We broadly define an archetypal cell as a cell type

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that, despite its occurrence in distinct tissues, is easily recognized because of the presence of a shared set of recurring molecular and/or morphologic motifs that allow the given archetypal cell to subtend a shared epithelial function that is required in diverse physiologic contexts. Not all epithelia take advantage of every archetype cell. Moreover, epithelia also rely upon "unique" cell types (Chan et al. 2009).

Despite the fact that cells are the fundamental units of tissue structure, epithelial classification thus far has not been based on cell-type composition per se. Instead, the classical categorization of epithelia is based on tissue architecture and location in the body (Table 1; Wheater and Burkitt 1987). In the near future, we expect that epithelia will be increasingly understood through the lens of a newfound molecular understanding of each component cell. Just as cytology moved from morphologic to molecular definitions of cell types, we can now anticipate moving from morphologic to molecular definitions of tissues as composite structures.

The molecular definition of tissues is now beginning with the systematic identification of all the component cell types of a tissue through comprehensive profiling of each cell type's characteristic expression patterns (Regev et al. 2017). In particular, massively parallel single-cell genomics, especially single-cell RNA-seq (scRNA-seq) and single-cell assay for transposase accessible chromatin-seq (scATAC-seq), currently provide the most readily available methods for comparing distinct cell types, even for rare cells, and aligning cells by their features across tissues. Profiling methods allow us to recover comprehensive sets of expressed marker genes with no prior knowledge, in contrast to the one to four preselected markers classically deployed in developmental biology and histopathology. Furthermore, computational analysis of scRNA-seq and scATAC-seq data allows for the modeling of complex composite properties of tissues, such as networked intercellular signaling within a tissue and lineage (Chen et al. 2019; Luecken and Theis 2019). In this way, we can assemble an aggregate picture of how component cells contribute to specific physiologic functions, how those cells establish an ancestor–descendent order, whether those cell states are plastic, how these properties change with perturbation or disease, and, finally, how intercellular interactions within the tissue and between tissues orchestrate global physiology (Kotas and Medzhitov 2015). With the advances in spatial genomics methods (Ståhl et al. 2016; Moor and Itzkovitz 2017; Rodriques et al. 2019), we should further expect enhanced integrated understanding of the cellular and histological levels.

THE AIRWAY AND INTESTINAL EPITHELIAL ENSEMBLES

The airway and intestinal epithelia share many essential functions, including barrier defense and the management of microbes and immune cells, but they also fulfill entirely unique physiological roles. Cells of the small intestinal epithelium are arranged in a simple columnar fashion, accommodating digestion and nutrient absorption. In contrast, the cells of the airway

Table 1. Structural classification of epithelia

Structural type	Organ
Simple cuboidal	Small ducts of kidney and pancreas
Simple columnar (ciliated)	Female reproductive tract
Simple columnar (nonciliated)	Small intestine, Stomach
Pseudostratified columnar (ciliated)	Large airways of the respiratory system
Simple squamous	Alveolar lung, endothelium, mesothelium
Stratified squamous	Oral cavity, pharynx, esophagus
Stratified squamous (keratinizing)	Skin
Stratified cuboidal	Excretory ducts of salivary glands and sweat glands
Transitional	Urothelium

Data based on Wheater and Burkitt (1987).

epithelium are arranged in a simple pseudostratified epithelium, consisting of a single layer of cells attached to the basement membrane (Fig. 1A). The airway epithelium appears stratified because of the varying height of nuclei and because not all airway epithelial cells reach the luminal surface. This epithelium is generally classified as a simple epithelium, but the basally located stem cells are shielded from direct exposure to the lumen by differentiated luminal cells. This arrangement of cells allows for mucus production and clearance. At a higher order, the pseudostratified epithelium of the airway occurs as a simple cylindrical sheet that lines the mucosal surface of the respiratory tubes (Fig. 1A, left panel). In contrast, the columnar epithelium of the gut is folded into crypts and villi, presumably to protect the buried stem cell population (Kaiko et al. 2016) while also maximizing the surface area of enterocyte cells that absorb nutrients from the gut lumen (Fig. 1A, right panel).

Reflecting their physiological distinctions, the airway and the gut epithelia share multiple archetype cell types that are adapted to their organ-specific location, as well as some unique cell types. In some cases, an aggregate tissue function, such as immune regulation, is distributed over multiple archetype cells in complex ways that likely relate to organ-specific functionality. In some cases, evolution has repurposed archetype cells with minor modifications, whereas in others, entirely new cell types arose that accommodate unique physiologic demands. We now describe and categorize by function the cells of these two epithelia.

UNIQUE EPITHELIAL CELLS CHARACTERISTIC OF EITHER AIRWAY OR INTESTINE

Intestinal Enterocytes

Enterocytes are essential for performing nutrient absorption, the cardinal physiologic function of the intestinal epithelium, and to transport ions and water across the small intestinal epithelium to maintain fluid homeostasis. Consistent with this, the enterocyte is also the most abundant cell type in the intestinal epithelium, covering a large fraction of the villus surface. To support their unique function of high-volume nutrient absorption, enterocytes possess microvilli, morphologic specializations that increase the cells' surface area. As an abundant cell type, enterocytes must also contribute to barrier defense and produce antimicrobials, a feature shared by many cell types in both the airway and intestinal epithelia.

Airway Multiciliated Cells

The multiciliated cell, defined by motile cilia, is an archetype lung cell not found in the intestine. Motile cilia have a highly stereotyped structure, which is very similar to the flagella of the last common eukaryotic ancestor (Mitchell 2007). They are anchored along the luminal surface of ciliated cells and beat rhythmically to clear mucus and debris up and out of the airways in a process termed mucociliary clearance. Failure to clear mucus results in persistent lung infection (Tilley et al. 2015; Reiter and Leroux 2017). Motile ciliated cells fulfill similar purposes in other organs. For example, they are responsible for the flow of cerebrospinal fluid and transport along the fallopian tubes toward the uterus (Mitchison and Valente 2017). Despite their high degree of structural conservation across tissues and organisms, we speculate that ciliated cells from these distinct tissues may occur as flavors of a ciliated archetype cell adapted to different contexts. We hypothesize that scRNA-seq of ciliated cells across organs will reveal distinct expression programs that reflect the tuning of an archetype cell to a particular physiologic role.

There is no intestinal cell directly comparable with the ciliated cell. In the intestine, the propulsion of luminal contents is mediated by an entirely different mechanism: surrounding smooth muscle contraction (Feher 2012). Indeed, ciliated cells are unlikely to be able to produce sufficient force to transport the bulky contents of the intestine.

Airway Epithelial Ionocytes

Pulmonary ionocytes are rare epithelial cells in the airways whose identity was only recently described by scRNA-seq of mouse and human airways, and whose exact function requires

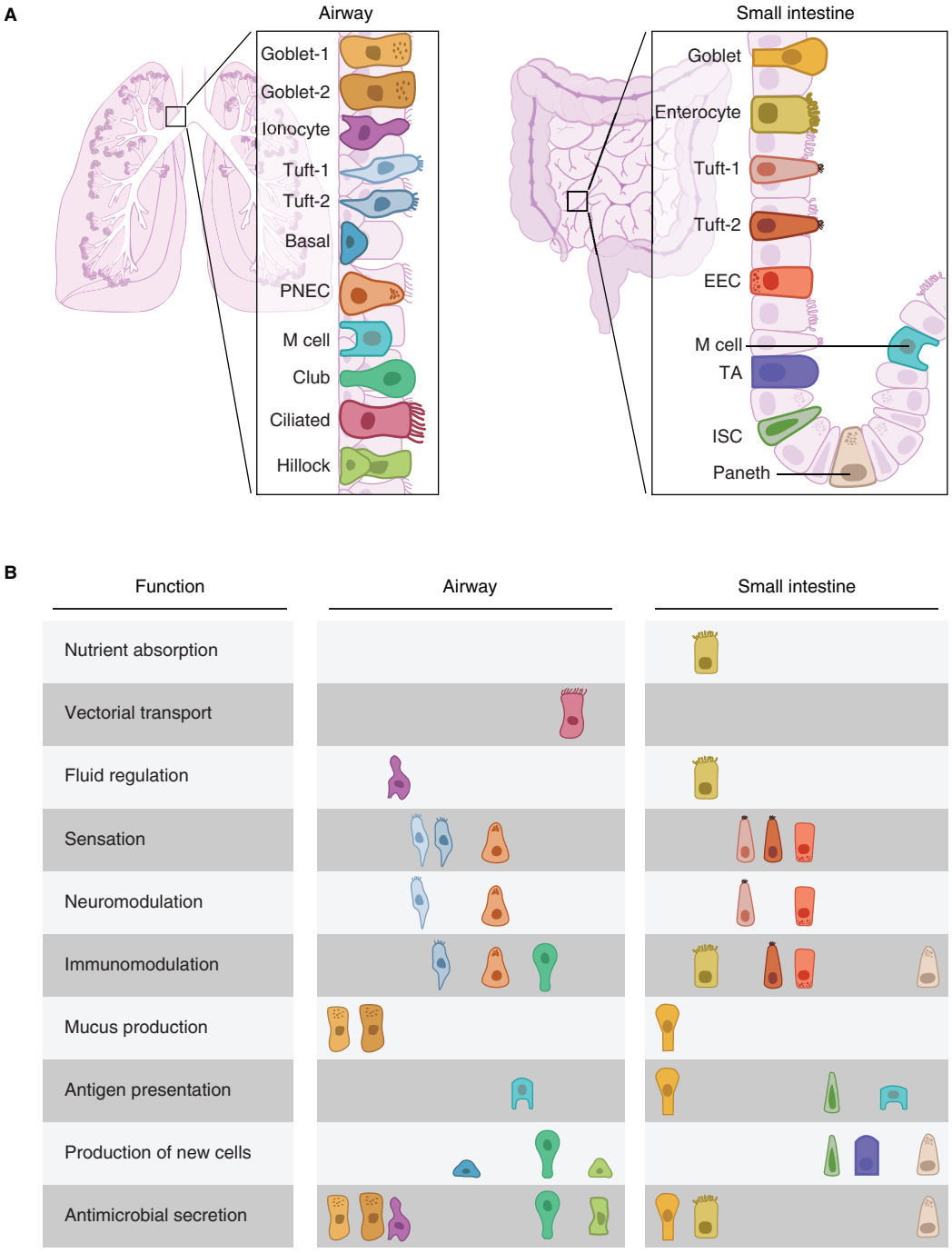

Figure 1. Functional specialization of epithelial subtypes. (*A*) Schematic comparison of the tissue architecture and cell types of murine airway (*left*) and small intestinal (*right*) epithelia. (*B*) Compartmentalization of epithelial tissue functions mapped onto component cell types in the two epithelia. (PNEC) pulmonary neuroendocrine cells, (EEC) enteroendocrine cell, (TA) transit-amplifying, (ISC) intestinal stem cell.

further scrutiny (Hawkins and Kotton 2018; Montoro et al. 2018; Plasschaert et al. 2018; Travaglini and Krasnow 2018). Ionocytes are characterized by the specific expression of the transcription factor (TF) FOXI1, specialized subunits of proton-transporting V-ATPases, and the chloride/bicarbonate channel cystic fibrosis (CF) transmembrane conductance regulator (CFTR). The high expression of CFTR by ionocytes is consistent with prior observations of rare airway epithelial cells with particularly high CFTR expression (Engelhardt et al. 1992; Jiang and Engelhardt 1998).

Interestingly, FOXI1 and V-ATPase subunits are also coexpressed in intercalated cells of the kidney, FORE cells of the endolymphatic epithelium of the inner ear, and narrow and clear cells of the epididymis (Vidarsson et al. 2009). All of these cells express V-ATPase subunits that localize to the plasma membrane and secrete protons into the extracellular fluid. We speculate that pulmonary ionocytes similarly regulate the composition and properties of the fluid and mucus layer at the surface of the mammalian airway epithelium (Montoro et al. 2018). The conservation of functional markers of ionocytes in distinct mammalian tissues suggests that they are an archetype cell that regulates hydration, pH, and ion transport in several tissue contexts and across phyla.

The specific and high expression of CFTR by ionocytes contrasts with the diffuse expression of CFTR in many of the cell types within the intestinal epithelium (Haber et al. 2017; Montoro et al. 2018). Despite the different expression patterns of CFTR in the intestine and airway, both tissues are loci of disease in CF patients (Jiang and Engelhardt 1998; De Lisle and Borowitz 2013). How these different patterns of CFTR tissue expression reflect the distinct physiology of these tissues remains to be clarified.

CELLS FOUND IN BOTH THE INTESTINAL AND AIRWAY EPITHELIA

Intestinal and Airway Tuft Cells

Tuft cells, also called brush cells or solitary chemosensory cells, were first recognized in the airway as cells with apical microvillar appendages. These microvilli, which are strikingly different from those of enterocytes (Banerjee et al. 2018), were believed to represent a sensory appendage, but the precise role of tuft cells continued to be mysterious for decades (Reid et al. 2005). Airway tuft cells express genes associated with taste reception, neuromodulation, and immunomodulation, suggesting that they may survey chemicals in the airway lumen and evoke airway defenses (Krasteva et al. 2011). Tuft cells in the small intestine similarly express various components of chemosensory pathways (Bezençon et al. 2008). Immunologically, they initiate type 2 immune responses to helminth infections (Gerbe et al. 2016; Howitt et al. 2016; von Moltke et al. 2016), by regulating the activity of group 2 innate lymphoid cells (ILC2s) via secretion of the cytokine interleukin-25 (IL-25). This effect is amplified by a dramatic increase in tuft cell numbers following infection.

scRNA-seq of tuft cells in the airways and small intestine (Haber et al. 2017; Montoro et al. 2018) allows cross-organ comparison, and reveals remarkable similarity in expression profiles of tuft cells in the two tissues. This includes expression of fate-specifying TFs, chemosensory G-protein-coupled receptors (GPCRs), and immunomodulatory cytokines (Schneider et al. 2019). Both airway and intestinal tuft cells are the predominant epithelial source of *Il25*. IL-25 is a central mediator of the inflammatory response in allergic asthma, so its production by tuft cells implicates them in asthma pathophysiology. T helper 2 (Th2)-mediated responses associated with allergic asthma are believed to reflect an aberrant deployment of Th2 immunity in the control of lung parasitic infection, implicating conserved functionality within a shared archetype cell population. Thus, despite the distinct luminal environments of the intestine and airway, the tuft cell archetype is likely involved in both tissues in bridging chemosensation, immunity, and the need to defend against specific types of pathogens.

Tuft cells in both epithelia occur as one of two specialized subsets: a tuft-1 subset more strongly expressing chemosensation and neuromodulation genes, and a tuft-2 subset expressing

inflammatory genes. Both express shared tuft-cell TFs, but each subset is also associated with distinct TFs (Montoro et al. 2018). Whether cells of each subset are capable of interconversion remains to be seen. Because they share many features and are conserved in both intestinal and airway epithelia, we propose that tuft-1 and tuft-2 subsets represent different flavors of the same archetype cell. Furthermore, just as specialized subsets of many immune cell types are capable of fulfilling distinct physiological functions (Fang et al. 2018), we speculate that tuft cell specialization is an important feature of their functionality.

Intestinal Enteroendocrine Cells (EECs) and Airway Pulmonary Neuroendocrine Cells (PNECs)

Both EECs and PNECs were once believed to arise from the neural crest, but both cell types have since been shown to be of endodermal origin and are locally maintained (Kuo and Krasnow 2015; Noguchi et al. 2015; Montoro et al. 2018). Rare enteroendocrine cells of the intestinal epithelium are specialized for sensing the luminal environment and transmitting information locally and systemically. The expression of many different GPCRs on their cell surfaces enables EECs to detect luminal nutrients and various endogenous and pathogen-associated metabolites (Gribble and Reimann 2016; Yu et al. 2019). EECs transduce these stimuli and relay signals to enteric neurons, endothelial cells, and neighboring epithelial cells via secreted cytokines and peptide hormones (McCauley 2020). EECs also send long-range signals through the bloodstream. Historically, EECs were classified by their expression of a particular dominant hormone. Recent scRNA-seq analysis of the small intestinal epithelium revealed a greater diversity of EEC subsets than previously believed. Instead of an association with one hormone, each EEC subset is distinguished by expression of a particular combination of hormones (Haber et al. 2017).

Intestinal EECs and airway PNECs share many functional attributes, including chemosensory capabilities (Gu et al. 2014). PNECs also produce peptide hormones, but in contrast to the numerous distinct hormone production programs that demarcate distinct EEC subsets, PNECs of the airway preliminarily appear to be less diverse (Montoro et al. 2018). Although a PNEC-derived peptide hormone may shape the type 2 immune response to asthma (Sui et al. 2018; Wallrapp et al. 2019), it is unclear why airway PNECs would display a more limited hormone repertoire than their counterparts in the intestine.

Aside from hormone expression, PNEC diversity is also reflected in their physical distribution as either solitary cells or as clusters of neuroepithelial bodies (NEBs). These clustered structures are notably absent in the intestinal epithelium, but are reminiscent of the aggregated NECs that compromise pancreatic islets. NEBs are often located at airway branch points, in which they may be ideally poised to sample the concentrations of oxygen and volatile compounds in inspired and expired gases. Of note, some PNECs found in NEBs act as facultative multipotent stem cells (Ouadah et al. 2019). Molecular signatures that distinguish structurally distinct PNEC populations are yet to be defined and spatial transcriptomics approaches should help resolve these.

Additional examples of conserved cells found in both airway and intestinal epithelia, but that we do not discuss in detail, include lymphoid-associated antigen-presenting M cells and mucus-producing goblet cells (Table 2; Fig. 1B).

EPITHELIAL FUNCTIONS DISTRIBUTED AMONG DIVERGENT CELL TYPES IN A TISSUE-SPECIFIC PATTERN

Some epithelial functions are distributed among divergent cell types in a pattern unique to each tissue (Table 2; Fig. 1B). For instance, both the airways and the intestines must produce antimicrobial agents to defend against pathogens. Many cell types participate in generating each tissue's respective battery of antimicrobial agents, likely attributable to the myriad types of pathogens. These cells include, but are not limited to, Paneth cells, enterocytes, and goblet cells in the intestinal epithelium, and club cells,

Table 2. The distribution of epithelial tissue functions onto component cell types corresponding to Figure 1

Function	Airway cell type	Specific role	Small intestinal cell type	Specific role
Nutrient absorption	N/A		Enterocyte	Absorption of carbohydrates (e.g., Lct) and lipids, bile resorption
Vectorial transport	Ciliated cells	Directional propulsion of mucus	N/A	
Fluid regulation	Ionocyte	Chloride (Cftr), sodium (ENaC), potassium (Kcnma1) transport	Enterocyte	Sodium (Slc5a1, Sglt1)
Sensation	Tuft cells	Chemosensation, possible innervation	Tuft cells	Chemosensation of parasites (Trpm5, Gnat3)
	PNEC	Oxygen sensation, stretch, innervation	Enterochromaffin cells	Detection of irritants, metabolites, and catecholamines
Neuromodulation	PNEC	Hormones, innervated	Enterochromaffin	Serotinergic activation of sensory nerves (Tph1, Tac1)
	Tuft-1	Neurotransmitter production (ChAT)	Enteroendocrine	Regulation of satiety (Ghrelin, Pyy) and mood (Gastrin, Cck)
			Tuft-1	Neurotransmitter production (ChAT)
Immunomodulation	PNEC	Allergic response (Cgrp, Gaba)	Enteroendocrine cells	Cck, Glp-1 substance P, neurokinin A, and neurokinin B
	Tuft-2	Allergic response (leukotrienes, IL-25, Tslp)	Tuft-2	Leukotrienes, Il25, Tslp
	Club	Tnf	Paneth Enterocytes	Tnfα Il18
Mucus production	Goblet	Mucins (Muc5b, Muc5ac)	Goblet cells	Mucins (Muc2)
Antigen presentation	Microfold cells		Microfold cells Intestinal stem cells Goblet	
Production of new cells	Basal cells	Production of club and rare cell types	Intestinal stem cells	Production of transit-amplifying cells, Paneth cells
		Production of differentiation factors to club cells	Transit-amplifying	Production of differentiated cells
	Club cells	Production of ciliated cells and goblet cells	Paneth cells	Stem cell niche factors WNT (Wnt3,11), Notch (Dll4)
	Hillock basal cells	Production of hillock club cells		
	PNEC	Reserve stem cell		

Continued

Table 2. *Continued*

Function	Airway cell type	Specific role	Small intestinal cell type	Specific role
Antimicrobial secretion	Ionocytes	Secretion of cochlin	Paneth cells	Antimcrobial peptides—α defensins, lysozyme, angiogenin4, Mmp7, interlectin-1
	Club	Surfactants (Sftpd, Scgb3a2), antimicrobial (Ltf, Lyz2)	Enterocytes	Antimcrobial peptides—C-type lectins (Reg3b, Reg3g)
	Hillock club	Surfactants (Sftpd), antimicrobial (Ltf, Lyz2)		
	Goblet		Goblet	Antiparasitic immunity—Retnlb

hillock club cells, goblet cells, and ionocytes in the airway epithelium (Table 2; Fig. 1). These unique arrangements might reflect the need to contend with distinct pathogens and toxins associated with either food consumption or air-breathing.

Intestinal stem cells (ISCs) and airway basal cells both serve as stem cells, but they have distinct markers, occupy unique niches, and use distinct signaling pathways to self-renew and differentiate. Additionally, they display very different stem cell kinetics that reflect high (intestine) or low (airway) homeostatic cell turnover. Furthermore, in the intestine, stem cells give rise to transit-amplifying (TA) cells in the crypt (Gehart and Clevers 2019) TA cells in turn serve as workhorse progenitors, rapidly proliferating and differentiating to support the rapid replacement of differentiated villus cell types. In contrast, airway club cells are long-lived progenitors found throughout the entire length of the airway. Perhaps because they are not continuously cycling (Clevers and Watt 2018), they are able to support a differentiated cell machinery that is used to detoxify contaminants.

INFERRING CELLULAR DYNAMICS AND LINEAGE RELATIONSHIPS IN EPITHELIA

Epithelial homeostasis involves cell turnover and differentiation. In the airways and small intestine, this results in a spectrum of transitional cell states as a progenitor cell is converted into another cell type. These transitional cells are captured in scRNA-seq experiments and they can be used to model differentiation paths. Computational methods can order cells collected at a single time point into a pseudotemporal ordering that arranges transitional cells along trajectories in gene-expression space (Trapnell et al. 2014; Schiebinger et al. 2019). The ordering allows for inferences concerning parent–progeny relationships between cells (Fig. 2A). Pseudotemporal ordering cannot be used to directly infer directionality, but the inferred relationships can be directly verified using lineage tracing. In one such application, we previously performed genetic lineage tracing of airway epithelial stem cells followed by scRNA-seq of epithelial cells at various time points after the initial lineage labeling. This "pulse-seq" strategy allowed us to revise previous models of cellular differentiation (Montoro et al. 2018). For example, tuft cells were previously believed to represent long-lived cells, but were found to be continuously produced during homeostasis (Saunders et al. 2013). Furthermore, pulse-seq analysis established a new cellular hierarchy in which stem cells directly produce tuft cells, solitary PNECs, and ionocytes. The number of methods for tracking the clonal histories of cells is rapidly growing (Habib et al. 2016; Alemany et al. 2018; Raj et al. 2018; Spanjaard et al. 2018), and these

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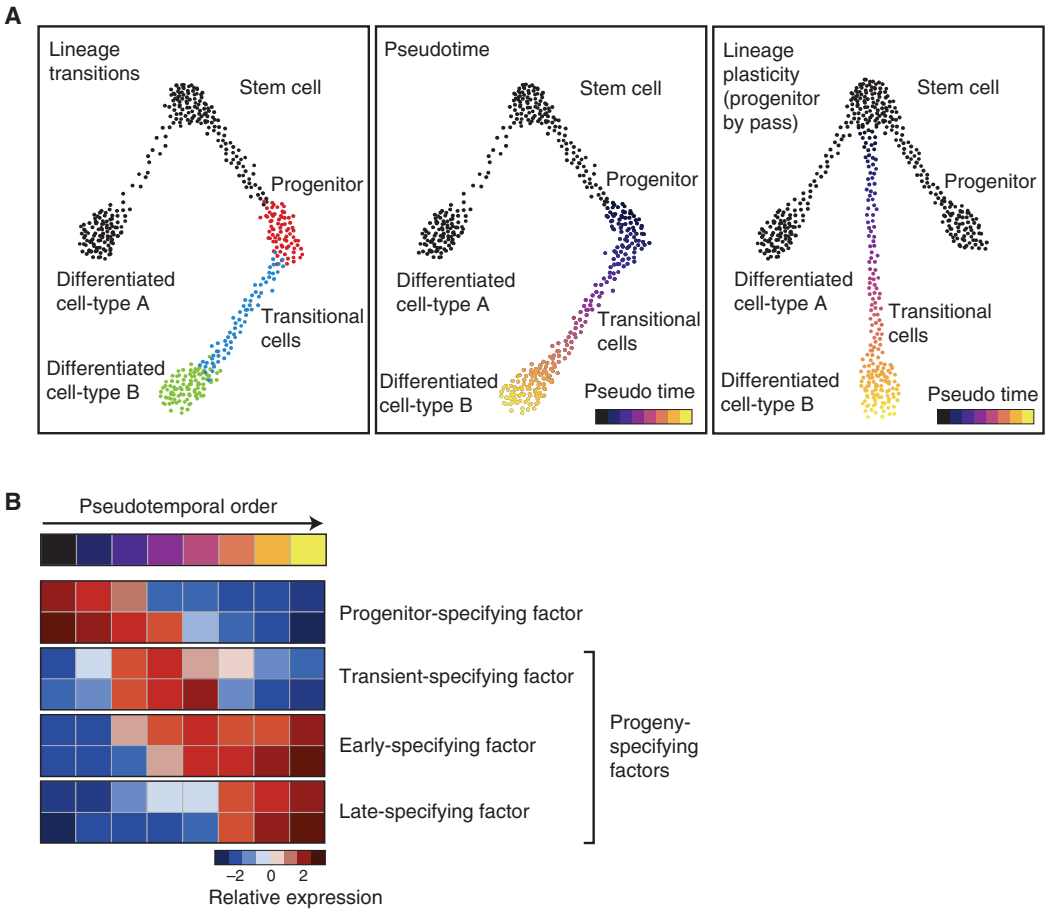

Figure 2. Modeling lineage and differentiation dynamics with single-cell RNA (scRNA)-seq data. (*A*) Identifying cellular transition states (*left* panel, blue dots) associated with differentiation from a progenitor cell type (*left* panel, red dots) to a differentiated cell type (*left* panel, green dots) using pseudotemporal ordering of cells (*middle* panel). Injury-induced lineage plasticity can be mapped by observing altered differentiation trajectories (*right* panel) as compared with those during homeostasis (*left* panel). (*B*) Pseudotemporal ordering allows inferences concerning the sequence of putative fate-specifying genes that govern differentiation from a progenitor cell to a mature differentiated cell.

will enable finer analyses of cell lineages and differentiation.

Epithelial differentiation is dynamically modulated to increase the production of particular cell types in response to injury or infection. As mentioned above, tuft cell numbers are greatly increased in the small intestinal epithelium in response to parasitic infection (Gerbe et al. 2016; Howitt et al. 2016; von Moltke et al. 2016). Similarly, goblet cell numbers are increased in airway epithelial diseases like allergic asthma (Chen et al. 2009; Roy et al. 2014; Whitsett 2018). These processes likely represent the increased production of one particular cell type from its usual progenitor cell. Injury also evokes lineage plasticity, with complex reorchestrations of normal lineage paths. For example, airway club cell progenitors dedifferentiate into basal stem cells in response to basal stem cell depletion (Tata et al. 2013), and, in response to inhaled injury (Pardo-Saganta et al. 2015), stem cells in the airway directly produce differentiated ciliated cells, bypassing the normal secretory cell intermediate associated with homeostatic

ciliated cell differentiation (Fig. 2A). Similar lineage plasticity is also seen in hematopoiesis, in which hematopoietic stem cells can directly produce differentiated myeloid cells by circumventing the intervening multipotent progenitor state (Yamamoto et al. 2018).

By analyzing changes in transcription along any pseudotemporal path of differentiation, one can infer which TFs are responsible for progressive differentiation (Fig. 2B; Biton et al. 2018). The sequential expression of differentiation factors has been of long-standing interest to developmental biologists and the ready identification of these putative fate-specifying genes should facilitate cellular reprogramming (Spence et al. 2011; Mou et al. 2012; Wong et al. 2012; Pagliuca et al. 2014).

ARCHETYPE CELLS AND EVOLUTION

Archetype cells are also identifiable across phyla. For example, rodlet cells are rare epithelial secretory cells that were identified in the intestines of teleost fish in 1892 (Leino 1974; Manera and Dezfuli 2004; Reite 2005). They were originally believed to be a protozoan parasite because of their unique extended cellular morphology, but they were later identified as bona fide intestinal epithelial cells. These mysterious cells greatly increase in number following helminth infections. Rodlet cells are also implicated in the recruitment of mast cells and eosinophilic granule cells through the agency of various secreted factors. Thus, rodlet cells are reported to be epithelial sensors of parasitic infection that then mediated an inflammatory response (Reite 2005). Many defining features of rodlet cells match those of tuft cells, including their extended cell morphology, their localization in the intestinal epithelium, their hyperplasia in response to helminth infection, and their observed role as sensors and mediators of host defense. Amazingly, the characterization of rodlet cells preceded the functional characterization of tuft cells in the gut by more than two decades. scRNA-seq now affords an opportunity to compare these and other cell types across evolutionary time.

In a remarkable parallel, ionocytes were only recently identified as Foxi1-expressing epithelial cells that regulate mammalian airway fluid homeostasis (Montoro et al. 2018; Plasschaert et al. 2018; Travaglini and Krasnow 2018). Although cells with similar gene expression were found in the mammalian kidney, epididymis, and inner ear a decade before (Vidarsson et al. 2009), a comparison with archetype cells in frogs and fish laid a foundation for our interpretation of ionocyte function in the airway. In fish gills, mitochondria-rich ionocytes are specified by Foxi1 and express apical plasma membrane V-ATPases. These fish ionocytes were so named because they contribute to ion and fluid homeostasis through the secretion and absorption of ions (Esaki et al. 2009). In frog multiciliated skin, ionocytes are again specified by a Foxi1 ortholog and express apical plasma membrane V-ATPases. Frog ionocytes contribute to pH and osmoregulation through the regulation of protons, bicarbonate, and chloride (Quigley et al. 2011). Indeed, these prior insights were crucial in putting forward the hypothesis that pulmonary ionocytes act as regulators of airway hydration (Montoro et al. 2018).

As an atlas of cells comprising the human body is assembled (Regev et al. 2017), we will be able to revisit the question of archetype cells across human organs and indeed across species. This body of data will certainly form the basis for a broader understanding of cell-type evolution. These same evolutionary insights will serve as a foundation for establishing methods to regulate archetype cells throughout the body in the case of systemic disease, and subtle differences in archetype cells may point the way toward deciphering tissue-specific biology and therapy.

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