Review

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Three cheers for the goblet cell: maintaining homeostasis in mucosal epithelia

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Many organs throughout the body maintain epithelial homeostasis by employing a mucosal barrier which acts as a lubricant and helps to preserve a near-sterile epithelium. Goblet cells are largely responsible for secreting components of this mucosal barrier and represent a major cellular component of the innate defense system. In this review we summarize what is known about the signaling pathways that control goblet cell differentiation in the intestine, the lung, and the ocular surface, and we discuss a novel functional role for goblet cells in mucosal epithelial immunology. We highlight the cell type-specificity of the circuitry regulating goblet cell differentiation and shed light on how changes to these pathways lead to altered goblet cell function, a prominent feature of mucosa-associated diseases.

Mucosal epithelia employ specialized cell types to maintain tissue homeostasis

Throughout the body, internal organs and passages that come into contact with the exterior environment are lined by mucosal epithelium, which is required for lubrication and barrier function against outside pathogens and debris. The gastrointestinal tract, genitourinary system, upper and lower respiratory tract, and ocular surface are all vastly distinct tissues functionally, but they share common mucosal features. Mucosal epithelium differentiates (see Glossary) and functions uniquely for the processes required in each tissue type, but there are some important features common to the health and homeostasis of all mucosal epithelia.

Goblet cells are specialized secretory cells found throughout mucosal epithelia, and play an important role in maintaining tissue homeostasis by secreting a variety of factors, including proteins, trefoil factors, and mucins, all of which contribute to the mucus layer protecting mucosal epithelium. Mucins are large, high molecular weight glycoproteins that can be membrane bound or secreted, and over 20 mucin genes have been identified to date [1]. Combinations of membrane-bound and secreted mucins vary between tissues, with goblet cells being the main source of secreted gel-forming mucins in mucosal epithelia. The contents of goblet cells are tightly condensed and stored in secretory granules awaiting release. Goblet cells can secrete a small, baseline amount of mucins via exocytosis under physiologic conditions, but primarily release their entire secretory contents in an apocrine manner or compound exocytosis in response to external stimuli [2–8]. Release of mucins into the extracellular environment is controlled by microbial factors [6], growth factors [4,7,9], inflammatory cytokines [6,7], inflammasomes [8], and autonomic neural pathways, which are mediated in part by adrenergic and cholinergic receptors present on the surface of goblet cells [3,4,10–12]. Mucus is then moved through the gastrointestinal tract by peristalsis, through the respiratory epithelium by mucociliary clearance, and through the ocular surface by blinking [1,13,14]. Intestinal and conjunctival epithelia turn over within the span of a few days [15,16], whereas pulmonary epithelial cells have a much longer lifespan under homeostatic conditions [17]. The mucus layer of all three tissues turns over in a matter of hours [1], but goblet cells are capable of producing large mucin secretions multiple times within their lifespans, and may live much longer than their non-secretory epithelial neighbors, at least in the conjunctiva [16].

Glossary

Apocrine: mechanism of exocytosis in which secreted products bud off in plasma-membrane bound vesicles and are shed into the lumen.
Conjunctiva: the mucosal epithelium lining the inner surface of the eyelid; 'forniceal' refers to the folded region near the limbus and 'palpebral' refers to the flat region between the fornix and the eyelid epithelium.
Dendritic cells: antigen-presenting cells important in innate and adaptive immunity.
Differentiation: the process by which a multipotent stem or progenitor cell becomes restricted in function to become a more specialized cell type.
Exocytosis: mechanism of releasing secreted contents of a cell into the extracellular environment.
Homeostasis: process by which the cellular environment is kept stable and constant in response to fluctuating external conditions.
Lumina: the inner space of a cylindrical tube, such as the intestine.
Metaplasia: abnormal conversion of one mature differentiated cell type into a new differentiated cell type in response to stimuli.

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While the importance of goblet cells in mucosal biology has been appreciated for decades, the genetic regulation of goblet cell differentiation has only begun to be understood in the past 10 years. One gene that is of special interest in goblet cell differentiation is sterile α motif pointed domain epithelial specific transcription factor (*Spdef*). SPDEF was originally described as a prostate-specific transcription factor [18,19], but has since been shown to play an integral role in goblet cell differentiation in the intestine [20,21], the lung [22], and the conjunctiva [23,24] (Box 1). However, upstream regulators of *Spdef* vary contextually or have not been tested globally, thus hindering a complete understanding of goblet cell differentiation. Alterations in goblet cell number or secretory function is associated with many mucosal diseases (Table 1). In this review we highlight the current knowledge of genetic pathways regulating goblet cell differentiation, with special emphasis on how regulation of common genes differs contextually. We discuss the role of the goblet cell secreted mucus layer in innate defense and consider new evidence implicating goblet cells in immune surveillance. Lastly, we examine alterations of goblet cell gene expression, number, and function in disease states.

Box 1. SPDEF is a central player in goblet cell differentiation

SPDEF is required for proper goblet cell differentiation, maturation, and function in mucosal epithelia, making this transcription factor a focal point for studies of normal and abnormal goblet cell differentiation. Loss of *Spdef* results in impairment of goblet cell maturation in the intestine [20], failure of goblet cell induction in response to allergen in the lung [82], and complete loss of goblet cell differentiation in the conjunctiva [23]. Conversely, expression of SPDEF results in an expansion of goblet cells at the expense of other cell types in the intestine [21], the lung [22], and the conjunctiva [24]. It is clear that SPDEF plays an integral role in the differentiation and maturation of goblet cells; however, upstream regulators of *Spdef* vary substantially in a tissue-dependent manner. SPDEF functions downstream of many common genetic pathways, including the Notch pathway, Wnt/β-catenin/Tcf4 signaling, and TGF-β signaling (Figures 2A, 3A, 4A), and is tightly regulated to maintain mucosal homeostasis.

Mucosal epithelial architecture in the gastrointestinal tract, the airway, and the ocular surface

Mature goblet cells are integral components of the gastrointestinal tract, the airway epithelium, and the conjunctival epithelium (Figure 1), but their differentiation from progenitor cells and placement among other specialized cell types varies contextually.

The gastrointestinal tract is organized into functionally and anatomically distinct tissues which are specialized for nutrient uptake, including the mouth, esophagus, stomach, small intestine and colon. The epithelium of the small intestine is organized into villi and crypts, and is composed of a variety of differentiated cell types, including absorptive enterocytes and secretory cells, encompassing goblet cells, enteroendocrine cells, antibacterial Paneth cells, and tuft cells [25–30] (Figure 1). Colonic epithelium differs in that there are no Paneth cells, enterocytes are termed colonocytes, and the differentiated cells of the villi are flush with the luminal surface [25,31]. Both small and large intestinal epithelia are maintained by well-characterized stem cell pools located in the crypts [25,27,30]. Goblet cells are the most abundant secretory cell type within the intestinal epithelium [25] and mainly secrete trefoil factors and mucin 2 (Muc2) [1,6,32–34]. In the intestine, mucus plays dual roles as a lubricant and a physical barrier between luminal contents and the intestinal epithelium [35] (Table 1). Goblet cells are found in increasing numbers from the proximal small intestine to the distal colon as stool becomes compacted [27,29,36]. Both the small and large intestine are covered by mucus composed mainly of Muc2, but the mucus covering the small intestine is unattached and in a single layer, whereas the colon maintains a two-layered mucus gel, with the inner layer providing a bacteria-free environment adjacent to the epithelium and the luminal less-viscous layer harboring gut microflora [1,6,14,33].

The airway epithelium consists of the cartilaginous trachea which branches into primary bronchi, bronchioles, and alveolae, which are the sites of gas exchange [37,38] (Figure 1). The tracheobronchial epithelium contains basal cells, ciliated cells, club (Clara) cells, and goblet cells

Table 1. Goblet cell function in mucosal epithelial homeostasis and disease

	Intestine	Lung	Eye
Function	Lubrication Provide a bacteria-free environment Maintain a barrier between the sterile mucosal epithelium and the intestinal microbiota	Lubrication Contribute to the mucus layer Protect the respiratory epithelium from inhaled particles and pathogens	Lubrication Component of tears Maintain mucosal barrier integrity
Associated diseases	Ulcerative colitis: reduced number of goblet cells and thinner colonic mucus layer Crohn's disease: enhanced goblet cell differentiation due to inflammation and thicker colonic mucus layer Cystic fibrosis: increased number of goblet cells and thick mucus secretion	Asthma: increased number of goblet cells Chronic obstructive pulmonary disease: increased number of goblet cells Cystic fibrosis: increased number of goblet cells and thick mucus secretion	Sjögren's syndrome: autoimmune disease resulting in loss of goblet cells Keratoconjunctivitis sicca (dry eye): loss of goblet cells Allergic conjunctivitis: increased numbers of goblet cells Inverted mucoepidermoid papilloma: increased number of goblet cells