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Review

Autonomous immunity in mucosal epithelial cells: fortifying the barrier against infection

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Abstract

Mucosal epithelial cells express an autonomous innate immune response that controls the overgrowth of invaded bacteria, mitigates the harmful effects of the bacteria carried within, and does not rely on other external arms of the immune response. Epithelial cell autonomous innate immunity "respects" the social biology of invading bacteria to achieve symbiosis, and is the primary protective mechanism against pathogens.
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Keywords: Innate immunity; Mucosal epithelium; Antimicrobial proteins; Cell signaling; Infection

1. Introduction

> "The power which resides in him is new in nature, and none but he knows what that is which he can do, nor does he know until he has tried."
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> — Ralph Waldo Emerson, *Self-Reliance*

The social lives of bacteria demand that they colonize mucosal surfaces in humans and animals. Bacteria can reside inside or outside of mucosal epithelial cells as they attempt to find adequate nutrition to survive and multiply. In general, bacteria do not seek to kill their hosts; death of the host eliminates the ability of human pathogens to survive too. Mucosal symbionts survive on and in mucosal epithelial cells but are controlled by innate and adaptive immune responses that target the mucosal surface and the interior of mucosal epithelial cells. Indeed, there is no adaptive immune response to many symbionts. By invading mucosal epithelial cells, symbionts and some pathobionts become largely protected against the adaptive immune response and innate immune factors found in the secretions that bathe the mucosal surfaces, including lysozyme, lactoferrin and lactoperoxidase. As we come to appreciate that the interior of mucosal epithelial cells contains communities of infectious bacteria, we raise the question of how the interior of the cell is protected and why we do not die of an ever-growing ulcer or abscess. Furthermore, significant gastrointestinal pathogens such as Listeria and Salmonella first encounter the oral mucosa while contaminated food is being chewed and swallowed; yet infection of the oral mucosa does not occur. The oral mucosa is a formidable barrier against infection by pathological bacteria such as Listeria and Salmonella, yeasts including *Candida albicans*, and viruses such as HIV-1. The gastrointestinal mucosa is somewhat more permissive to infection by "true" pathogens like Listeria and Salmonella, responding with antimicrobial proteins produced by the intestinal epithelial cells and mucous from goblet cells [1]. Intestinal barrier function is enhanced when the epithelium senses metabolites such as taurine from the microbiota, activating the inflammasome and increasing production of IL-18 [2,3]. IL-18

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signals in an autocrine manner to increase production of antimicrobial proteins, maintain diversity of the microbiome, and prevent dysbiosis [2,3]. When other microbiome metabolites such as spermine are sensed, the epithelium ceases production of antimicrobial proteins, IL-18 autocrine signaling prevents development of goblet cells, and a dysbiotic, disease-causing microbiome emerges [2,3]. This contemporary example of cell autonomous epithelial immunity may serve as a paradigm for studies of other epithelial tissues.

This review will focus largely on the autonomous mechanisms of the squamous epithelia that line the oral cavity, oropharynx and the genitourinary tracts enabling resistance to infection by pathogens. Autonomous mechanisms function without reliance on the innate and adaptive immune mechanisms provided by white blood cells [4–6]. Cell autonomous immunity is a widely expressed system of self-defense that functions in many cell types and appears to be protective against a wide range of pathogens. For the host to defend against durable pathogens such as *Mycobacterium tuberculosis*, several defensive strategies are required [7]. Some of these mechanisms reflect the co-evolution of the pathogen and the host and examples exist in virtually all phyla. Indeed, bacteria protect against infection by bacteriophage with an innate adaptive mechanism, the clustered regularly interspaced short palindromic repeats (CRISPR) system, which recognizes and excises foreign DNA in a sequence-specific manner [8]. Bacteria also defend nutritional territory by production of toxic peroxides [9,10] and bacteriocins [11].

2. The mucosal epithelial barrier

In epithelia, the innate autonomous immune capacity of each cell contributes collectively to the barrier function of the tissue. Protecting the connective tissues from environmental insults including pathogens, the barrier function is both biological and physical [12]. The physical barrier is constructed by intercellular attachment structures that bond each epithelial cell to one another and to the basement membrane. Apically, tight junctions loosely stitch the cells to one another to form a semi-permeable barrier. Formed by cadherin adhesive proteins ringing the apical aspect of each cell, adherens junctions also bind cells together. Extending across the plasma membrane to the cytoplasmic face of the cells, adherens junctions also connect to the actin-based cytoskeleton. A third structure that attaches neighboring epithelial cells together is the desmosome. Desmosomes form rigid plaques that create strong “spot-welds” between cells. In membrane regions lacking attachment structures, epithelial cells are separated by a gap of about 30 nm. To keep the epithelial syncytia tightly attached to and covering the underlying connective tissue, hemidesmosomes cement the basal aspect of the cells to the basement membrane. These several attachment structures enable the epithelium to resist abrasion during typical functional activities like mastication and speech, respiratory air movement during exercise or coughing, gastrointestinal peristalsis, and genitourinary activity.

Gap junctions also bridge mucosal epithelial cells. Formed by complexes of proteins of the connexin family, these proteins organize into transmembrane gated-hemichannels. When hemichannels align between adjacent cells, a gap junction forms. The gap junction facilitates intercellular communication mediated by transfer of small molecules from one cell to its neighbor. Similarly, unaligned hemichannels can release biologically active small molecules to be bound and signal via proximal cell receptors. Bacteria and other microbes can very rapidly stimulate release of stored small molecules from hemichannels and gap junctions. To the extent that such signaling contributes to innate defense of the epithelium, this signaling mechanism may be the most rapid of any that are known to contribute to innate autonomous immunity.

Mucosal epithelial tissues in different anatomic sites show many similar activities and responses but can also differ markedly depending on the anatomic site. Indeed, the mucosal epithelia in various anatomic sites contains epithelial cells of either of two morphologies: squamous and cuboidal/columnar. In some locations, cells between mucosal tissues show transitional morphologies and some variations in size and shape.

2.1. Squamous epithelium

In the oral cavity, oropharynx and genitourinary tissues, the mucosal epithelium is an interdigitating stack of squamous cells, developed from basal cells, including stem cells, at the basement membrane. As the basal cells differentiate, new cells emanate from the basal layer to the mucosal surface in regions of increasing maturity. As they mature and migrate to the surface of the epithelium, squamous cells lose the ability to synthesize protein and divide, eventually to be sloughed. Between the squamous epithelial cells are sandwiched intraepithelial lymphoid cells in low abundance including Langerhans cells, γδ T cells and intraepithelial lymphocytes [13] These cells appear to provide immune surveillance of the mucosal surface and facilitate regional or central processing of antigen. These lymphoid cells, however, are unlikely to function directly as innate immune effectors in the control of mucosal commensals and pathogens.

2.2. Columnar/cuboidal epithelium

The pulmonary and gastrointestinal mucosae form from a single layer of epithelial cells with morphologies ranging in shape from columnar to cuboidal. The single cell thick epithelium contrasts to the stratified squamous mucosal epithelia. In both epithelia, cells connect to one another and the basement membrane similarly, recapitulating the same attachment organelles and functions. In the unicellular layer of pulmonary and gastrointestinal (GI) epithelia, intraepithelial lymphoid cells are more sparse than in squamous mucosal epithelium. The GI epithelial layer, however, contains M cells, which can recognize and translocate antigens and bacteria from the lumen to be processed by the gut-associated lymphoid tissue (GALT) on the serosal side of the epithelium [14]. Also residing in crypts within the epithelial layer,