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Review

How bacterial pathogens colonize their hosts and invade deeper tissues

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Abstract

Bacterial pathogens have evolved a wide range of strategies to colonize and invade human organs, despite the presence of multiple host defense mechanisms. In this review, we will describe how pathogenic bacteria can adhere and multiply at the surface of host cells, how some bacteria can enter and proliferate inside these cells, and finally how pathogens may cross epithelial or endothelial host barriers and get access to internal tissues, leading to severe diseases in humans.

Keywords: Bacterial invasion; Bacterial adhesion; Microbiota; Host barrier; Host–pathogen interactions; *Listeria*

1. Introduction

The human body harbors a large number of bacteria but their localization in healthy individuals is normally restricted to certain body areas such as the skin, the mucosae of buccal and nasal cavities, vagina and, most importantly, the gastrointestinal tract [1–6]. The internal tissues are normally sterile. In some circumstances, however, some opportunistic pathogens are able to enter the host by taking advantage of injuries or breaches in one of the different host barriers. In addition, *bona fide* pathogens have evolved mechanisms to cross host barriers and reach deeper organs where they proliferate and lead to severe disease for their host.

In this review, we will describe the diversity of mechanisms used by bacterial pathogens to colonize and invade human organs. We will first focus on the capacity of these bacteria to adhere and to proliferate at the surface of host cells and tissues, despite a wide-range of defense mechanisms used by the host. We will then present how some bacteria are able to enter and to proliferate inside host cells. Finally we will discuss how some pathogens can cross host barriers and get access to deeper tissues thereby promoting their dissemination inside their host.

2. Colonization of host surfaces

The respiratory, digestive and urogenital mucosa represent a surface area of approximately 300–400 square meters (*i.e.* 200-fold larger than that of the skin) and thus constitute major sites of contact with bacteria. These mucosa are composed of three layers: an epithelium, a layer of loose connective tissue called lamina propria, and a thin layer of smooth muscles. These surfaces constitute frontline barriers limiting the invasion by both commensal and pathogenic bacteria. Despite the different defense mechanisms occuring at the level of these barriers, pathogenic bacteria have evolved various molecular strategies to adhere to these epithelia and to proliferate at their surface.

2.1. Host epithelia and associated defense mechanisms

Epithelia of diverse organs in contact with the extracellular milieu, and thus with environmental bacteria, are covered by a

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mucus layer that allows a protection against intruders. The intestinal mucus layer, for example, plays a key role in limiting invasion by commensal bacteria of the microflora or by foodborne pathogenic bacteria [7] (Figs. 1 and 2). This mucus is mainly composed of glycoproteins called mucins, digestive enzymes, antimicrobial peptides and immunoglobulins. Bacteria are often found at the top of this intestinal mucus layer, where they interact with mucins, whereas the inner layer of mucus, where the concentration of antimicrobial compounds is high, is normally devoid of bacteria [8]. Mucins are produced and secreted in the intestine by goblet cells, a specialized cell-type of the intestinal epithelium. Their production can be modulated in response to microbial products or inflammation [7]. The level of antimicrobial peptides, predominantly secreted by Paneth cells from intestinal crypts, can also be regulated by the presence of microorganisms. Indeed, whereas α-defensins are constitutively expressed, other antimicrobial peptides such as REG3γ (Regenerating islet-derived protein 3γ) or cryptdins are produced in response to the detection of pathogen-associated molecular patterns (PAMPs) that activates TLR (Toll-like receptors) or NOD (nucleotide-binding oligomerization domain-containing protein) signaling pathways [9–12]. IgA, produced by B cells in the lamina propria and secreted into the mucus via epithelial cells, are

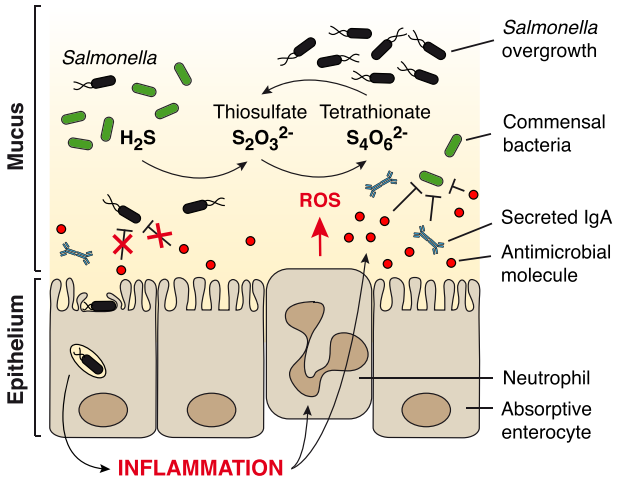

Fig. 2. Schematic representation of events leading to *Salmonella* overgrowth in the intestine. Invasion of intestinal epithelial cells by *Salmonella* triggers an inflammatory response leading to the release of antimicrobial peptides and the production of ROS (*R*eactive *O*xygen *S*pecies) by neutrophils. H_2S, a fermentation end product generated by commensal bacteria, is oxidized into thiosulfate by the colonic epithelium and then into tetrathionate by ROS. In contrast to fermenting bacteria of the microbiota, *Salmonella* can use this tetrathionate as a terminal electron acceptor to support growth in anaerobic conditions. The use of tetrathionate, in addition to *Salmonella* resistance to antimicrobial molecules, allow this pathogen to out-compete commensal bacteria in this inflamed context.

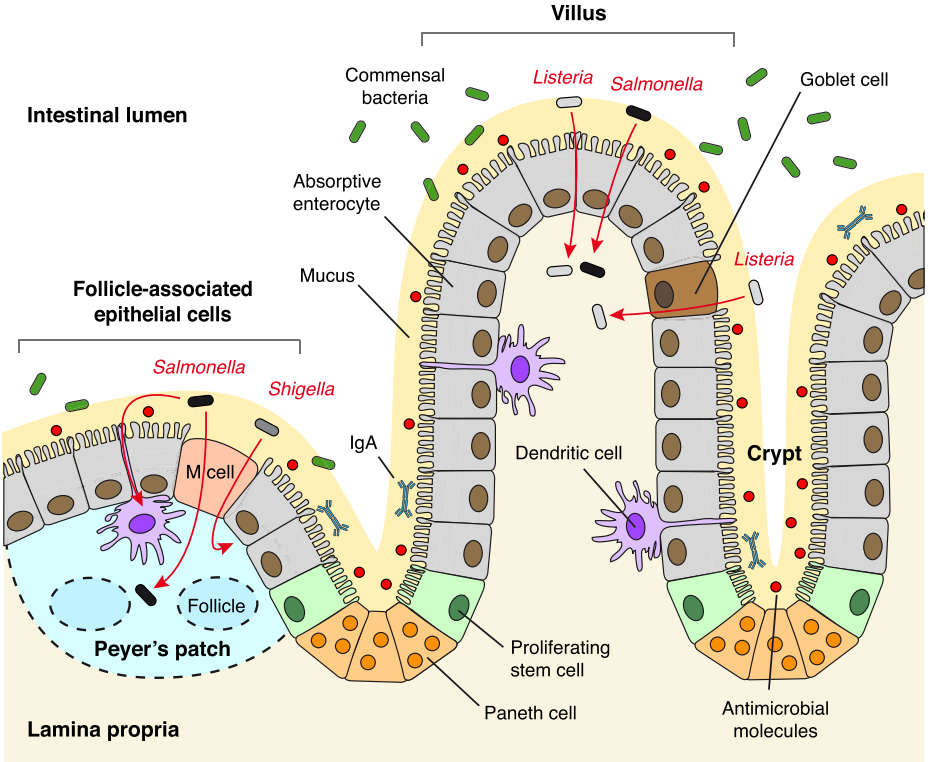

Fig. 1. Routes of invasion by enteric pathogens in the human small intestine. The epithelium of the small intestine is composed of absorptive enterocytes, mucus-producing goblet cells, M cells, as well as proliferating stem cells and Paneth cells located in intestinal crypts. The intestinal epithelium is covered by a mucus layer containing secreted IgA, antimicrobial peptides and other types of antimicrobial compounds that limit the colonization by commensal bacteria or foodborne pathogens. Peyer's patches and the overlaying follicle-associated epithelium, M cells and dendritic cells constitute specialized regions of the intestine that continuously sample the intestinal luminal content (adapted from Ref. [99]). *Listeria monocytogenes* can cross the host intestinal barrier at sites of cell extrusion at the tip of the villi or at junctions between goblet and absorptive epithelial cells. *Salmonella* Typhimurium can cross the intestinal epithelium by targeting absorptive cells, M cells of Peyer's patches or dendritic cells sampling the intestinal lumen. *Shigella flexneri* also target M cells for crossing the intestinal barrier and then re-infect epithelial cells basolaterally.