CURRENT CONCEPTS OF SALMONELLOSIS PATHOGENESIS: THE ROLE OF VIRULENCE FACTORS AND IMMUNE RESPONSE

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Abstract. Salmonellosis is one of the most important foodborne bacterial infections and is characterized by a broad clinical spectrum ranging from self-limited acute gastroenteritis to severe invasive and systemic disease. Current concepts of salmonellosis pathogenesis emphasize the complex interaction between the virulence determinants of *Salmonella enterica*, the intestinal epithelial barrier, the gut microbiota, and the host immune system. A central role is played by Salmonella pathogenicity islands SPI-1 and SPI-2, which encode type III secretion systems responsible for delivering bacterial effector proteins directly into host cells. SPI-1 primarily promotes intestinal epithelial invasion and inflammatory responses, whereas SPI-2 facilitates intracellular bacterial survival and replication, particularly within macrophages.

Keywords: salmonellosis, *Salmonella enterica*, pathogenesis, virulence factors, pathogenicity islands, SPI-1, SPI-2, type III secretion system, immune response, inflammasome, macrophages, gut microbiota.

Introduction. Salmonellosis remains a major bacterial infection of global public health importance. Human disease is predominantly caused by *Salmonella enterica*, a species that includes numerous serovars with different host ranges, virulence characteristics, and clinical manifestations. Non-typhoidal *Salmonella* most commonly causes acute gastroenteritis, whereas typhoidal serovars,

particularly *S. Typhi* and *S. Paratyphi*, are associated with systemic enteric fever [1,2].

The pathogenesis of salmonellosis is considerably more complex than simple penetration of the intestinal mucosa by a pathogenic microorganism. Successful infection requires coordinated bacterial adaptation to the gastrointestinal environment, adhesion to host cells, epithelial invasion, intracellular survival, manipulation of host signaling pathways, and evasion or modification of immune responses. A particularly important feature of *Salmonella* is its ability to regulate virulence according to the anatomical location and stage of infection. Two major pathogenicity islands, SPI-1 and SPI-2, encode type III secretion systems (T3SS) that deliver bacterial effector proteins into host cells. These systems have complementary functions: SPI-1 is primarily associated with epithelial invasion, whereas SPI-2 supports intracellular survival and systemic dissemination [2,3].

The normal microbiota provides colonization resistance, while Salmonella-induced inflammation can alter the intestinal ecological environment and create conditions favorable for pathogen expansion [4].

Virulence factors of Salmonella. The first challenge encountered by *Salmonella* after ingestion is survival in the gastrointestinal tract. Gastric acidity, bile, antimicrobial peptides, oxidative stress and competition with commensal microorganisms constitute major barriers to infection. Salmonella possesses adaptive regulatory mechanisms that allow it to respond rapidly to these environmental stresses. Adhesion to intestinal epithelial cells is an essential stage preceding invasion. Fimbriae and other adhesins facilitate attachment to the epithelial surface, while flagella provide motility and contribute to interactions with host cells. One of the most important determinants of Salmonella virulence is SPI-1. The SPI-1-encoded T3SS functions as a

molecular apparatus that injects bacterial effector proteins directly into epithelial cells. These proteins alter the actin cytoskeleton and induce membrane ruffling, facilitating bacterial internalization [3,5]. After internalization, Salmonella is enclosed within a specialized compartment known as the Salmonella-containing vacuole (SCV). At this stage, the SPI-2 system becomes particularly important. SPI-2-encoded T3SS effectors modify intracellular trafficking, vesicular transport and host-cell organelles, creating an intracellular environment that supports bacterial survival and replication [2,5].

Role of Salmonella effector proteins. The effector proteins delivered by Salmonella T3SS represent major molecular determinants of host-pathogen interaction. They interfere with cytoskeletal organization, intracellular trafficking, inflammatory signaling, apoptosis, autophagy and cellular metabolism. SPI-1 effectors facilitate epithelial invasion and stimulate signaling pathways involved in the recruitment of inflammatory cells. This contributes to the development of intestinal inflammation and the clinical manifestations of gastroenteritis [3,5].

In contrast, SPI-2 effectors are particularly important for intracellular persistence. They modify the SCV and interfere with normal antimicrobial mechanisms of epithelial cells and macrophages. As a result, bacteria can survive in cells that would normally participate in their elimination [5].

Interaction with the intestinal epithelium and microbiota. The intestinal epithelium is an essential component of host defense. Tight junctions, mucus, antimicrobial peptides, secretory IgA and the resident microbiota collectively limit the ability of invasive bacteria to colonize the intestinal tract.Salmonella infection disrupts this equilibrium and stimulates a pronounced inflammatory response. Epithelial cells and immune cells produce chemokines and cytokines that recruit neutrophils and other leukocytes to the site of infection. The

interaction between inflammation and the microbiota is particularly important. Inflammation changes the chemical and metabolic environment of the intestine and can reduce the competitive advantage normally provided by commensal bacteria. Salmonella can exploit of these changes to expand within the intestinal lumen [4].

Innate immune response. The innate immune system represents the first major immunological barrier against Salmonella. Host cells recognize pathogen-associated molecular patterns through pattern-recognition receptors (PRRs), including Toll-like receptors, NOD-like receptors and other cytosolic sensors. Tumor necrosis factor-α, IL-1β, IL-6 and chemokines contribute to recruitment and activation of neutrophils, macrophages and other immune cells. Neutrophils eliminate bacteria through phagocytosis, reactive oxygen species, antimicrobial proteins and other mechanisms.

Macrophages play a particularly complex role. They engulf bacteria and produce antimicrobial mediators but may also become a cellular niche for Salmonella persistence. The ability of Salmonella to modify the SCV through SPI-2 effectors allows intracellular bacteria to resist several antimicrobial mechanisms [5].

Inflammasomes and pyroptosis The NAIP/NLRC4 inflammasome can recognize bacterial flagellin and components of the T3SS. Its activation results in caspase-1 activation, maturation of IL-1β and IL-18, and pyroptosis of infected cells [6]. The NLRP3 inflammasome can also participate in Salmonella recognition. Its activation is associated with cellular stress signals such as potassium efflux, mitochondrial reactive oxygen species and lysosomal damage. Recent research emphasizes that NLRC4 and NLRP3 may operate at different stages and in different cellular compartments during infection. Pyroptosis contributes to host defense by eliminating infected cells and releasing

inflammatory mediators. Nevertheless, excessive inflammasome activation can contribute to tissue damage.

Conclusion. Current knowledge indicates that salmonellosis is a complex infectious process resulting from continuous interaction between *Salmonella enterica*, the intestinal epithelium, the microbiota and the host immune system.The pathogenicity of Salmonella is determined by a coordinated set of virulence factors. SPI-1 and SPI-2 are central to this process: SPI-1 promotes epithelial invasion and inflammatory signaling, while SPI-2 supports intracellular survival and replication. Effector proteins delivered through these secretion systems modify host-cell signaling, cytoskeletal organization, intracellular trafficking and immune responses.

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