Host-pathogen-microbiota interactions at the first stages of *Salmonella* infection

Salmonella infections are one of the most important epidemiological issues worldwide, affecting directly about 200 million people globally, as well as a serious economic problem with an estimated cost as high a 3 billion euros per year only in European Union.

Salmonella genus includes more than 2600 serovars infecting many animal species, from reptiles to birds and mammals. Depending on the serovar and the infected host, they can cause diseases with different clinical symptoms, ranging from alimentary tract disturbances to invasive typhoid-like diseases. The majority of pathogenic serovars, so-called generalists, can infect many different species, with symptoms usually limited to the alimentary tract. In contrast, specialist serovars are host-specific, and infection causes severe systemic diseases with enteric fever and bacteremia.

The complex process of the *Salmonella* infection depends on its initial stages – adhesion followed by invasion of host cells. Adhesion to host tissues allows bacteria to survive in the hostile environment of the animal intestine by avoiding mechanical removal by the host's intestine peristaltic activity, and as a consequence, multiplication and further invasion. Among the number of adhesive structures, type 1 fimbriae (T1F), long, thin structures present at the surface of bacteria and directly responsible for binding to host cells, are one of the most extensively studied. Based on the ability to bind structures presented at the host's cell surface, there are several T1F variants determined by small changes in the T1F structure.

The majority of works regarding the first stages of *Salmonella* infection are focused on direct interaction with host cells. However, colonization of the gastrointestinal tract by enteric pathogens always occurs in a broader context, strongly determined by host-specific gut microflora, which can impact host-pathogen interactions. The gastrointestinal tract is occupied by billions of symbiotic microbes which can act as a physical barrier against invading bacteria by blocking pathogen access to the intestine epithelial layer. Therefore, a complete infection model should include interactions between the host, its microbiota, and infecting pathogen.

The proposed research aims to investigate the role of *Salmonella* T1F variants under the light of the interaction between *Salmonella*, the intestinal microbiota, and the host during the first stages of infection. The *Salmonella* infection process can be affected by additional, non-pathogenic microbes called probiotics, which can have a beneficial effect on the host health. Therefore, to stop or limit *Salmonella* infection at its initial stages, we are planning to supplement natural microflora with genetically modified probiotics. This modification will enhance probiotics adhesion properties, and therefore act as a physical barrier against invading bacteria by blocking pathogen access to the host's tissues.

To achieve those goals, we are going to approach several different infection models, including cultures of intestinal cell lines, 3D intestine simulating structures - organoids, up to mice model of infection. We will investigate the type and strength of interactions between *Salmonella* serovars with different host specificity and different T1F variants with host cells in the presence of human and mice intestinal microbiome. We will investigate the host innate immune response using the abovementioned infection models. We will characterize the microbiota profile before, during, and after infection using advanced genomic tools. Finally, we will track the course of infection in the presence of modified probiotics bacterial strains.

This project aims to understand the role of the microbiome during the first stages of *Salmonella* infection. Proposed models allow us to answer if and how microbiome modification helps to prevent or treat infection at an early stage of the disease. Understanding these complex interactions between the host, microbiota, and invading pathogen will enable the development of better therapies against *Salmonella* infections.