DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

41° Cycle

Main research line

Title of the research: Investigating the role of Two Component Systems in the regulation of virulence gene expression in *Shigella*

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Summary

Two component signal transduction systems (TCSs) are widespread protein machineries, typically consisting of a histidine kinase membrane sensor and a cytoplasmic transcriptional regulator, that can sense and respond to environmental signals. TCSs are responsible for modulating genes involved in a multitude of bacterial functions, including cell division, motility, differentiation, biofilm formation, antibiotic resistance, and virulence. Pathogenic bacteria exploit the capabilities of TCSs to reprogram gene expression according to the different niches they encounter during host infection. *Shigella* is highly adapted intracellular human pathogen, mainly found in developing world and causing severe enteric syndrome. The hallmark of *Shigella* pathogenicity is its ability to penetrate the colonic epithelium, escape macrophages by inducing cell death, and, subsequently, invade colonocytes from the basolateral side and propagate infection through cell-to-cell spread, eventually causing the destruction of the intestinal barrier function.

The aim of this project is to discover new regulatory proteins involved in the activation and optimization of the invasive program of *Shigella*. This will be done by searching among the TCS systems conserved in the *Shigella* genome, novel regulators able to fine tune the expression of virulence genes in response to specific niche and in coordination with other factors. While some TCSs have already been shown to contribute to the regulation of virulence gene expression, no data are currently available on the potential roles of the QseBC and RcsBC systems, which have been demonstrated to be important in other pathogenic bacteria. Expanding our understanding of the TCSs utilized by *Shigella* is crucial for uncovering how the bacterium avoids wasteful expression of virulence factors while ensuring robust and timely activation when required. This is particularly significant as it may pave the way for innovative antibacterial therapies using compounds that directly inhibit TCS systems, thereby silencing the expression of TCS-controlled genes.

Pertinent Publications of the proponent (last 5 years)

1. Ishikawa T, Eguchi Y, Igarashi M, Okajima T, Mita K, Yamasaki Y, Sumikura K, Okumura T, Tabuchi Y, Hayashi C, Pasqua M, Coluccia M, Prosseda G, Colonna B, Kohayakawa C, Tani A, Haruta JI, Utsumi R. Synthesis and biochemical characterization of naphthoquinone derivatives targeting bacterial histidine kinases. J Antibiot (Tokyo). 2024 77(8):522-532.

2. Trirocco R, Pasqua M, Tramonti A, Grossi M, Colonna B, Paiardini A, Prosseda G. Fatty Acids Abolish *Shigella* Virulence by Inhibiting Its Master Regulator, VirF. Microbiol Spectr. 2023 15;11(3):e0077823.

3. Fanelli G, Pasqua M, Prosseda G, Grossi M, Colonna B. AcrAB efflux pump impacts on the survival of adherent-invasive Escherichia coli strain LF82 inside macrophages. Sci Rep. 2023 15;13(1):2692.

4. Pasqua M, Coluccia M, Eguchi Y, Okajima T, Grossi M, Prosseda G, Utsumi R, Colonna B. Roles of Two-Component Signal Transduction Systems in Shigella Virulence. Biomolecules. 2022 18;12(9):1321.

5. Pasqua M, Bonaccorsi di Patti MC, Fanelli G, Utsumi R, Eguchi Y, Trirocco R, Prosseda G, Grossi M, Colonna B. 2021. Host - Bacterial Pathogen Communication: The Wily Role of the Multidrug Efflux Pumps of the MFS Family. Front Mol Biosci. 8:723274.

6. Pasqua M, Grossi M, Zennaro A, Fanelli G, Micheli G, Barras F, Colonna B, Prosseda G. 2019 The Varied Role of Efflux Pumps of the MFS Family in the Interplay of Bacteria with Animal and Plant Cells. Microorganisms. 7:285.

7. Pasqua M, Grossi M, Scinicariello S, Aussel L, Barras F, Colonna B, Prosseda G. 2019 The MFS efflux pump EmrKY contributes to the survival of *Shigella* within macrophages. Sci Rep. 9(1):2906.