Role of small RNA-based regulatory systems in cystic fibrosis airways infection by Pseudomonas aeruginosa: a new frontier in the identification of molecular targets for novel antibacterials

Ferrara S[1], Macchi R[1], Falcone M[1], Rossi A[2], Ranucci S[2], Bragonzi A[2], Cigana C[2], Bertoni G[1]
[1]Department of Biosciences, Università degli Studi di Milano, Milan, Italy, [2]Infections and Cystic Fibrosis Unit, Division of Immunology, Transplantation and Infectious Diseases, San Raffaele Scientific Institute, Milan, Italy
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Background and rationale. In the field of CF airways infection by Pseudomonas aeruginosa, the comprehension of molecular mechanisms underlying the infection process is crucial to the design of new clinical protocols to prevent and contrast it. Anti-virulence therapies have become an attractive approach that may yield drugs with high specificity and narrow spectra, and in this perspective bacterial small RNAs (sRNAs) represent a largely unexploited category of potential targets for anti-virulence design. Interestingly, sRNAs have been shown to play key roles not only in modulating bacterial virulence but also microbial processes leading to antibiotic resistance.

Hypothesis and objectives. The main aims of this proposal were: i) to assess the involvement of three newly discovered P. aeruginosa sRNAs, named ErsA, ReaL and PesA (1, 2, 3), in regulatory mechanisms underlying antibiotics resistance; ii) to investigate the capability of mutants for these sRNAs to establish chronic infection in murine models.

Essential methods. To achieve these goals, sRNA-deleted mutants were subjected to i) Minimum Inhibitory Concentrations (MICs) determination of antibiotics commonly used in the clinical practice; ii) tests for virulence in murine models of chronic infection.

Results. Our results suggest that the sRNA ErsA is involved in regulatory mechanisms underlying resistance to certain antibiotics commonly used in the clinical practice. In addition, ErsA deletion strongly reduces virulence of P. aeruginosa in a murine model of chronic infection. This result correlates with the observation that an ErsA-deleted mutant is less pro-inflammatory than the wt and induces lower cell death in infected bronchial epithelial cells.

Spin-off for research and clinical purposes. The achievements of this project have the potential to foster the development of innovative antimicrobial strategies. In fact, illuminating the functional roles of sRNAs in host/pathogen interaction can provide the fundamental knowledge for the development of next-generation antibiotics using sRNAs and the virulence functions that they regulate as novel targets. In the case of the use of sRNAs as novel targets, the information resulting from mechanistic studies on the interactions with target genes will be invaluable for identifying drug molecules that can bind and inhibit sRNA functions. In addition, due to their specificity, these drugs would preserve CF patient healthy commensal flora.

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