The involvement of the *ami* operon in *Pseudomonas aeruginosa* virulence regulation and biofilm formation reveals new functions for the amidase AmiE.

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We have previously shown that the C-type Natriuretic Peptide (CNP), a peptide produced by the lung, prevents *Pseudomonas aeruginosa* biofilm formation. In the present study, we identified AmiC as the bacterial target explaining CNP effects, and we studied the involvement of the aliphatic amidase AmiE in these effects.

Comparison of 3D structures of human natriuretic peptide receptors and *Pseudomonas* proteins revealed that the bacterial protein AmiC shows significant similarity with the human C-type natriuretic peptide receptor (hNPR-C). Recombinant protein AmiC was purified and protein/peptide interactions assessed using MicroScale Thermophoresis. Results showed that both CNP and hNPR-C agonists bind the AmiC protein. The *amiC* gene belongs to the *ami* operon. This operon also encodes the aliphatic amidase AmiE which hydrolyses short-chain aliphatic amides to their corresponding organic acids. We investigated AmiE potential alternative functions in *P. aeruginosa*. We observed that over expression of AmiE protein altered biofilm formation, bacterial motilities and quorum sensing molecules production. Using several infection models, we demonstrated that AmiE over-production led to a strong decrease in *P. aeruginosa* virulence both *in vitro* and *in vivo*, suggesting that in addition to its carbon-nitrogen metabolic process activities, AmiE would have multiple other functions.

We demonstrate that the bacterial protein AmiC is an ortholog of the eukaryotic receptor hNPR-C, acting as a CNP sensor in *P. aeruginosa*. Our data show that the whole *ami* operon has new functions in bacteria, allowing to modulate the switch between chronic and acute infection depending on exposition to host factors.