Identification and characterization of LPS-neutralizing human peptides: potential tools to control inflammation in cystic fibrosis lung disease

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Background. Host defence peptides (HDPs) are short cationic molecules produced by the immune systems of most multicellular organisms. They exhibit a wide range of biological activities from direct killing of invading pathogens to modulation of immunity. Chronic infection with P. aeruginosa is the main proven perpetrator of lung function decline and ultimate mortality in CF patients. HDPs, acting as anti-inflammatory molecules, could be able to block LPS pro-inflammatory activity attenuating inflammation and so limiting damage to host tissues. New potential HDPs have been identified by an in silico method and their biochemical and pharmacological features are under investigation.

Hypothesis and objectives. It has been demonstrated that many human proteins, with functions not necessarily related to host defense, are reservoirs of active host defense peptides. The aim of this study was to characterize structural propensity, antimicrobial activity, LPS neutralizing and anti-inflammatory properties of new human HDPs identified by a bioinformatic procedure that we have developed.

Methods. Human HDPs were obtained both by an effective procedure for the production of recombinant peptides in E. coli (1) and by synthetic procedures. These agents have been extensively analyzed to verify their ability to bind LPS by circular dichroism, NMR and light scattering as well as their antimicrobial, toxicity and immunological properties (2).

Results. Our bioinformatics procedure allowed to identify several novel human cryptic cationic HDPs, some of which have shown interesting LPS binding abilities. These promising LPS binding molecules showed also a broad spectrum antimicrobial activity on Gram positive and negative bacteria including several CF clinical strains, no toxicity on different human cell lines and significant propensity to mitigate cytokine and chemokine expression on human and murine LPS treated macrophages. Next steps will be to verify these LPS neutralizing properties in CF murine models.

Spin-off for research clinical purposes. We have obtained encouraging results confirming our general idea that human proteome represents a rich source of HDPs. Indeed some of novel HDPs we identified show significant anti-inflammatory effects and intriguing LPS binding ability. These evidences open suggestive perspectives on topic therapeutic use of these bioactive peptides. Innovative anti-inflammatory drugs are crucially required for the treatment of CF lung disease and a systematic approach voted to the identification of natural immunomodulating peptides well suits to this demanding task.

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