Postdoc Journal
Vol. 3, No. 12, December 2015

Journal of Postdoctoral Research
www.postdocjournal.com

FFC Proceedings 2015

13th Convention of Investigators in Cystic Fibrosis – Italian Cystic Fibrosis Research Foundation (FFC)

Pathophysiological relevance of glycosaminoglycans in *Pseudomonas aeruginosa* chronic lung infections and validation of new therapeutic approaches to modulate inflammation and tissue remodelling

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Background. P. aeruginosa chronic colonization of CF airways is associated to physical changes, characterized by mucus hypersecretion, degradation of extracellular matrix, and high levels of sulphated glycosaminoglycans (sGAG).

Hypothesis and objectives. We hypothesized that during P. aeruginosa chronic lung infection there is an increasing concentration and sulphation of different sGAG, contributing to inflammation and tissue damage. Thus the objectives of this project were to establish the role of sGAG during P. aeruginosa chronic infection and to modulate the vicious inflammation-damage cycle using modified polysaccarides (PS) derived from heparin.

Methods. P. aeruginosa clinical strains were used in vitro and to induce acute and chronic lung infection in CF and non-CF mice. sGAG were quantified by dyebinding assay in murine lungs and sputum from CF patients and correlated to biochemical and clinical markers. The high performance liquid chromatography-mass spectrometry was used to distinguish different sGAG species in murine lungs. PS were ad-hoc synthesized and tested subcutaneously in mice during P. aeruginosa lung infection.

Results. During chronic colonization, mice infected with *P. aeruginosa* showed higher levels of sGAG and, in particular, heparin/heparan sulfate compared to control mice. Interestingly, CF mice showed the presence of different heparin/heparan sulphate chains. C23, a compound selected from a library of PS with attenuated anticoagulant properties, inhibited markers of inflammation and tissue damage induced by P. aeruginosa acute and chronic lung infection in murine models. Analysis in human respiratory samples showed that sGAG are present in the airways of CF patients and they correlate with markers of airways disease progression and with the length of P. aeruginosa colonization.

Spin-off for research & clinical purposes. These findings prompt to further investigate the potential use of sGAG as non-invasive prognostic biomarkers of lung injury in CF patients. In addition, these data support the further evaluation and pre-clinical testing of the compound C23 as a novel therapeutic molecule to counteract excessive inflammation and tissue damage induced by P. aeruginosa pulmonary infections in CF patients.

Acknowledgment. FFC #14/2013: funded by FFC, supported by Delegazione FFC di Milano