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The role of a panel of pro-fibrogenic miRs in fibrotic lung disorders.

Simona Inghilleri¹, Patrizia Morbini², Elena Rossi², Stefano Di Carlo³, Emanuela Cova¹, Fiorella Calabrese⁴, Davide Piloni¹, Michele Zorzetto¹, Laura Divizia¹, Gianfranco Politano³, Alfredo Benso³, Bart Vanaudenaerde⁵, Romain Kessler⁶, Michele Porzio⁶ and Federica Meloni¹.

¹Respiratory Diseases Dpt., IRCCS San Matteo Foundation, Pavia, Italy; ²Molecular Medicine, University of Pavia, Pavia, Italy, ³Control and Computer Engineering Dpt., Politecnico di Torino, Torino, Italy,⁴Thoracic and Cardiovascular Sciences Dpt., University of Padua, Padua, Italy,⁵Dept. of Clinical and Experimental Medicine Division of Respiratory Diseases Lung Transplant Unit Leuven University of Leuven ⁶Department of Pneumology University Hospital of Strasbourg

Rationale Pulmonary idiopathic fibrosis (IPF), Cryptogenetic organizing pneumonia (COP) and bronchiolitis obliterans syndrome (BOS) are rare pulmonary disorders, linked by the presence of fibrotic lesions. In our previous work (Di Carlo, 2016) on BOS we computationally identified a panel of candidate miRNAs and demonstrated by in situ hybridization analysis (ISH) and qRT-PCR, a dysregulation of two highly ranked miRNAs, miR-21 and miR-34a; ISH confirmed abnormal miR-21 and miR-34a expression in BOS lesions; other miRNAs where indicated as potential candidates in BOS by computational analysis.

Aim We extended our previous work by analyzing the expression of miR-21, miR-34a and three other highly ranked miRNAs (miR-145, miR-146b-5p and miR-381) in BOS and other lung diseases associated with fibroblast activation/proliferation and collagen deposition. Identifying a specific profile of dysregulated miRNAs could provide useful diagnostic markers and potential therapeutic target.

Methods We evaluated miRNAs expression profile by ISH and RT-PCR quantification in a series of formalin-fixed and paraffin-embedded lung samples obtained from patients with IPF (n. 8), OP (n. 8), BOS (n. 12) and normal lung from organ donors.

Results In BOS, COP and IPF/UIP miR-21 and miR-145 were expressed in fibroblasts of BO lesions, OP plugs and in fibroblast foci respectively, and in reactive alveolar epithelia; miR-146b expression correlated to the amount of inflammatory cell infiltrates and epithelial activation in all cases, while a weak expression was evident in OP and IPF/UIP lesions. miR-34a overexpression was associated with the activation of alveolar epithelia and to a lesser extent with fibroblast lesions in OP. miR-381 showed a weak expression in all diseases, and was localized especially in inflammatory cells. ISH data have been confirmed by qRT-PCR analysis obtained on same samples.
Conclusions miR-21, miR-145 and miR-146b are over-expressed in fibroblasts in all the cases analyzed, but their expression is not disease-specific, although some differences are observed in different diseases. This finding underlies their role in non-specific fibrotic lung processes. ISH complements the results of qPCR, allows the precise cellular localization of miR expression, and improves correlations with cell-specific pathways.