

Hot topics from the Assemblies

Monocyte-derived alveolar macrophages drive lung fibrosis and persist in the lung over the life span

Authors: Misharin AV, Morales-Nebrada L, Reyfman PA, *et al.*

J Exp Med 2017; 214: 2387–2404.

Summary: Tissue-resident alveolar macrophages (TR-AM) are depleted from the lung during the early stages of bleomycin-induced lung injury and fibrosis. The recovery of the population of macrophages after bleomycin could be completely attributable to the recruitment and differentiation of monocyte-derived alveolar macrophages (Mo-AM). The authors used multiple lineage-trace mouse models where they selectively depleted TR-AM or Mo-AM and induced fibrosis with bleomycin. Deletion of TR-AM had no effect on the severity of the fibrotic phenotype. However, when Mo-AM were depleted animals showed attenuated fibrosis as evidenced by normalised collagen levels and recovered lung compliance.

The study of the gene expression in these cell populations using RNA sequencing indicated that genes are differently regulated through time, pointing towards Mo-AM gradually changing their gene profile to the expression of TR-AM genes. In addition, differences in expression of activation state genes showed no evidence of two different populations, but rather a complex and heterogeneous population. While in a healthy mouse the contribution of Mo-AM to the macrophage population is minimal (<5%) after 1 year of life, animals suffering and recovering from fibrosis showed a 50% contribution of Mo-AM to the macrophage population. On the basis of these results, the authors suggest consideration of the differentiation pathway from Mo-AM to TR-AM as a target for the therapy of fibrosis, rather than systemic depletion or inhibition of recruitment of monocytes. Since many pathways are specific for differentiation of alveolar macrophage (*e.g.* caspase 8 and RIPK3), targeting these pathways is predicted to slow down fibrosis development, without affecting circulating monocytes or resident macrophages.

Reviewed by: Elena Lopez Rodriguez (Germany, Assembly 3)

Airway mucosal host defense is key to genomic regulation of cystic fibrosis lung disease severity

Authors: Polineni D, Dang H, Gallins PJ, *et al.*

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Severity of lung disease can vary widely amongst people with cystic fibrosis (CF), even within populations possessing the same genotype. Addressing the key disease modifying factors has the potential to offer much better outcomes for individuals undergoing more rapid disease progression. Studies to identify these factors have, to date, performed genome-wide association studies (GWAS) and interpreted gene signatures against cohort clinical data or functional data obtained from immune cell lines.

To improve upon these studies, a new collaborative effort by POLINENI *et al.* performed RNA sequencing on 134 primary nasal epithelial tissue biopsies and married the transcriptomic data to both lung disease severity and GWAS signatures. They hypothesised that this approach would reveal novel gene networks driving extent of disease severity.

A key finding was that the 18 top ranked genes common to both the transcriptomic activity in nasal epithelia and GWAS pathways were nearly all associated with airway mucosal host-defence. The top five genes for a severe CF lung phenotype were EDN1, TLR2, HLA-DRB1, IL8 and EDN2. Importantly, these 18 genes and their biological pathways all relate to processes understood to be defective in CF – innate immunity, antiviral host-defence and apoptosis. Furthermore, transcriptomic data highlighted pathways that have been shown elsewhere to correlate with CF disease severity, for example the methionine salvage pathway.

Because nasal sampling is well tolerated, there is potential to apply this methodology to cohorts of other respiratory diseases such as asthma or chronic obstructive pulmonary disease, which often display significant variability in phenotypes and progression. The “omics” era heralds significant promise for tackling complex respiratory diseases.

Reviewed by: Luke Garratt (Australia, Assembly 7)

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Hot topics are short (approx. 200 words) summaries of recent important articles in respiratory medicine written by Early Career ERS members. To become a hot topic author, please contact Aran Singanayagam: e-mail: aransinga@gmail.com



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