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Biofilm-induced type 2 innate immunity in a cystic fibrosis model of Pseudomonas aeruginosa

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Background: Biofilm-producing strains of *Pseudomonas aeruginosa* are a major cause of morbidity and mortality in cystic fibrosis (CF) patients. Several studies in CF patients have shown increased IL-17 levels, but also increased levels of IL-5 and IL-13 along with arginase (Arg)-positive macrophages in bronchoalveolar lavage fluid. While IL-17 is a strong proinflammatory cytokine associated with host defence against bacterial and fungal infections, IL-5 and IL-13 as well as Arg-positive M2 macrophages are parts of anti-inflammatory type 2 (Th2) immunity. In this study, we analysed whether these Th2 cytokines and M2 macrophages that are elevated in lungs of CF patients, are an induced response against biofilm extracellular polymeric structures frequently observed in CF patients colonized by *P. aeruginosa.*

Material/methods: To study the host biofilm response, an agarose bead-embedded *P. aeruginosa* rat model commonly employed in *in vivo* studies of biofilm was utilized. Animals were intra-tracheally instilled with either sterile agarose beads that mimic biofilm-matrix or agar beads loaded with *P.*

aeruginosa for chronic pneumonia development. Lung transcript levels for main Th1 (IFNγ, TNFα, IL-1β, IL-12a), Th2 (IL-5, IL-13) and Th17 cytokines (IL-17A, IL-17F, IL-22, IL-23a) were analysed at day 1 and day 3 post-instillation. Macrophage polarization phenotypes were assessed on lung (immuno)histopathology and confocal immunofluorescence microscopy.

Results: We showed that 'sterile' agarose bead-instillation in rat caused notably increased lung transcript levels of IL-5 and IL-13 at both day 1 and day 3. Concurrently, increased infiltration of type 2 innate cells such as eosinophils and arginase-1 positive (Arg1+CD68+) M2 macrophages was also observed at day 1 and day 3 while the proportion of M1 macrophages (iNOS+CD68+) at these time-points decreased. In contrast, *P. aeruginosa*-loaded beads caused a drastic elevation of proinflammatory Th1 and antibacterial Th17 cytokines at day 1 post infection along with high influx of neutrophils and M1 macrophages while the anti-inflammatory Th2 cytokines drastically declined. Most interestingly, at day 3, both proinflammatory Th1 and Th17 cytokines sharply declined and at this time-point IL-13 was the only cytokine that showed a significantly increased expression over baseline control animals and also corroborated with decreased M1 and increased M2 macrophages.

Conclusions: To conclude, we clearly showed here that the Th2-mediated anti-inflammatory milieu, which is also observed in CF patients, is primarily driven by biofilm matrix structures and not by the accompanying pathogen, i.e. *P. aeruginosa*. These results suggest a potential for blocking Th2 signalling and or use of these cytokines as biomarkers to detect impending infection/colonization. We also showed that the high IL-17 levels are directly linked to episodes of acute exacerbations of *P. aeruginosa* infection and have important implications for clinical management of CF patients.