Microbial disruption drives metabolic rewiring in pulmonary macrophages and a dysregulated type 2 response in the lung.

The lung is constantly exposed to environmental stimuli that can potentially trigger inflammatory immune responses. Therefore, the pulmonary immune system is tightly regulated to avoid inappropriate inflammation; a breakdown in this tolerance can lead to asthma. Strong epidemiological evidence links antibiotic use early in life with increased susceptibility to asthma. However, the cellular mechanisms as to how this occurs are unclear. We show here that disruption of the microbiota with oral antibiotic use in mice did not alter macrophages in the lung during the treatment period. However, repopulation of the microbiota (recolonization) following antibiotics causes striking changes in the transcriptome of alveolar macrophages, with enhanced expression of the IL-13 receptor il13ra, reduced expression of the Th1-polarizing cytokine il27 and enhanced expression of co-stimulatory molecules cd80 and cd86. Flow cytometry confirmed increased expression of CD80/86 and MHC class II at protein level and also elucidated differential effects of recolonization post-antibiotics on alveolar (AMs) versus interstitial macrophages (IMs) in the lung with reduced expression of CD86 and MHC class II on IMs. These alterations in pulmonary macrophages in recolonized mice preceded the gradual development of a heightened type 2 response in the lung, indicated by increased numbers of Th2 cells, eosinophils and aberrant IL-13 productions by ILC2s, induced to a greater degree in recolonized mice during allergy challenge with house dust mite. AMs were metabolically less active than their IM counterparts but AMs from recolonized mice showed enhanced levels of oxidative phosphorylation, glycolysis and lipid metabolism. Further experiments will determine whether these metabolic changes in macrophages is related to heightened IL-13/IL-4 signalling in macrophages during recolonization as indicated by their transcriptomic changes, and will explore whether these macrophage-specific changes are responsible for the dysregulated type 2 immunity following antibiotic treatment. In summary, the microbiota is essential for maintaining macrophage-mediated pulmonary immune homeostasis and this process is disrupted by oral antibiotics, promoting susceptibility to type 2 inflammation. This work defines a direct link between the microbiota and pulmonary macrophage metabolism which has a profound effect on their function in type 2 immunity, and has important implications for broad spectrum antibiotic use in humans.

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