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Lung stromal dysregulation by excess dietary lipids

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The consumption of western-type diets with high lipid and sugar content contributes to the development of many prevalent non-communicable diseases. Obesity has been correlated to the development of airway hyperresponsiveness (AHR) in several epidemiological studies. AHR is defined as the excessive airway narrowing in response to non-specific stimuli. The presence of AHR is associated with decreased lung function and increased risk of developing asthma. Besides airway inflammation and contractility of the airway smooth muscle surrounding the airways, the structural airway remodeling of the lung is described as reason for AHR. As stromal cells organize the structure of the lung, we investigated how lipid accumulation in the lung affects the stromal compartment.
To mimic airway hyperresponsiveness in obese patients, we used a diet-induced obesity model that results in expected weight gain and increased airway resistance upon methacholine challenge.
Based on flow cytometry, we observed a rearranged stromal compartment with reduced fibroblast counts. ScRNAseq of lung stromal cells revealed 8 subpopulations of mesenchymal stroma, among them 4 different fibroblast subsets in lean and obese lungs. Proteomics of total lung tissue showed dysregulated metabolism and extracellular matrix-related changes.
Based on our findings, we hypothesize that lung stromal cells are dysregulated by the fat accumulation in the lung and fail to organize an intact extracellular matrix as well as maintain the alveolar niche for immune cells. This could indicate a potential new pathway that plays a role in aggravating the asthma phenotype in obese patients.