Regulation of ferroptosis in severe asthma

Type 2 immune responses are triggered by allergens or by multicellular worm parasites (helminths). The cells and mediators involved in type 2 immunity are crucial for protective host defense against helminths as well as for the pathogenesis of type 2 inflammatory diseases such as asthma or allergies. The mechanisms that drive type 2 immunity (e.g. interleukin 4, IL-4) greatly increase the susceptibility to a partiular type of iron-dependent cell death, called ferroptosis. Thus, type 2 immune settings such as asthma and nasal polyposis represent *in vivo* settings with a unique susceptibility to lipid peroxidation and ferroptotic cell death. In our recent work, we have identified pathways that drive ferroptosis in key effector cells of type 2 immunity (macrophages and eosinophils). In this project, we will now study how ferroptosis can be modulated by drugs targeting IL-4 signaling (e.g. dupilumab) and how this may prevent tissue destruction, chronic inflammation and fibrosis. Using patient samples and mouse models of asthma, we will study the role of the IL-4 pathway in lipid peroxidation and ferroptotic cell death in type 2 airway inflammation. Type 2 activated macrophages are particularly susceptible to ferroptosis and we and others have identified key mechanisms (e.g. 15-lipoxygenase, nitric oxide synthase, IDO-1) that regulate macrophage ferroptosis. As type-2 activated macrophages drive host defense and tissue repair during helminth infection as well as airway inflammation and remodeling in asthma, we will particularly focus on this cell type as a promising target of ferroptosis modulation. The data generated in this PhD project will thus considerably advance our understanding of ferroptosis induction and modulation with direct implications for major human inflammmatory diseases.

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