Lung-specific innate immune memory controls reactivity of mononuclear phagocytes to acute and chronic inflammation

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The lung, the body's largest surface constantly exposed to the environment, frequently encounters immune-stimulatory microbial components. How this sub-clinical stimulation shapes and regulates the susceptibility and severity of subsequent acute and chronic lung inflammation remains elusive.

To investigates this, we used high-dimensional flow cytometry and single-cell RNA sequencing (scRNA-seq) paired with functional assays to enable a spatio-temporal characterisation of the functional specialisation of myeloid cells within the mouse lung microenvironment.

Intranasal exposure to the environmental fungal component beta-glucan resulted in a profound Dectin-1 dependent margination of Ly6c+ monocytes in the lung, accompanied by an increase in homeostatic TNF-alpha, IL1beta, IL1alpha and GM-CSF production alongside an influx of monocyte-derived alveolar macrophages (AM) within the extra-pulmonal space with no clinical pathology. Moreover, scRNA-seq reveals the co-existence of a monocyte-derived AM population alongside with embryonic-derived AMs after beta-glucan pre-stimulation. These monocyte-derived AMs display a unique transcriptomic signature. Furthermore, the acute response to intranasal LPS 7 days after the initial challenge is enhanced after beta-glucan pre-stimulation marked by increased CCR2 dependent generation of inflammatory AMs and increased production of IL1beta, IL1alpha and GM-CSF. However, beta-glucan treatment 7 days before the induction of lung fibrosis mitigates fibrosis development and ameliorates fibrosis.

Taken together these data demonstrate for the first time a lung-specific inflammatory memory and unravel its molecular contribution to the development of lung pathologies, including acute lung injury and fibrosis.

Keywords : trained immunity, myeloid cells, inflammation, lung
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