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Endothelial cells as regulators of cytokine storms during influenza infection

The morbidity and mortality of severe influenza infections has been attributed to excessive inflammatory cytokine production and early innate immune cell recruitment. This study highlights the pulmonary endothelium as a central regulator of the cytokine storm, in particular demonstrating the role of the sphingosine-1-phosphate (S1P1) signalling system.

S1P1 receptor specific agonists were shown to significantly reduce cytokine responses and innate inflammation following infection of mice with mouse adapted influenza virus. Similar results were found using mice infected with a virulent isolate of the H1N1 pandemic influenza virus. S1P1 agonism also led to a reduction in mouse mortality.

Using an eGFP-S1P1 receptor knockin mouse and flow cytometry, high levels of S1P1 expression were detected in lung lymphatic and vascular endothelium, CD4 T cells and B cells. However, S1P1 agonist treatment of knockin mice did not alter the expression levels suggesting an effect through functional activation rather than receptor degradation. Furthermore, S1P1 treatment of virus infected lymphocyte deficient mice inhibited the innate inflammatory response, proposing pulmonary endothelium cells as the main regulators of this process. LysM-GFP mice were employed to demonstrate that S1P1 mediated inhibition of cellular infiltration occurs as a result of cytokine downregulation. However, cytokine production and cell recruitment were shown to be distinct events.

Using a variety of chemical and genetic methods, this study provides data to support the pulmonary endothelium as a key orchestrator of the cytokine storm. Manipulation of the cellular signalling pathways involved may have broad therapeutic implications.

► **Teijaro JR**, Walsh KB, Cahalan S, *et al.* Endothelial cells are central orchestrators of cytokine amplification during influenza virus infection. *Cell* 2011;**146**:980–91.

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