VEGF-C/VEGFR-3 signalling in macrophages ameliorates acute lung injury

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VEGF-C/VEGFR-3 signals on macrophages ameliorate acute lung injury *via* multiple functions, including increased anti-inflammatory cytokine production and increased efferocytosis, and VEGFR-3 expression on macrophages is impaired in human ARDS https://bit.ly/3D8Au3j

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Abstract

Background Successful recovery from acute lung injury requires inhibition of neutrophil influx and clearance of apoptotic neutrophils. However, the mechanisms underlying recovery remain unclear. We investigated the ameliorative effects of vascular endothelial growth factor (VEGF)-C/VEGF receptor 3 (VEGFR-3) signalling in macrophages in lipopolysaccharide (LPS)-induced lung injury.

Methods LPS was intranasally injected into wild-type and transgenic mice. Gain and loss of VEGF-C/VEGFR-3 signalling function experiments employed adenovirus-mediated intranasal delivery of VEGF-C (Ad-VEGF-C vector) and soluble VEGFR-3 (sVEGFR-3) or anti-VEGFR-3 blocking antibodies and mice with a deletion of VEGFR-3 in myeloid cells.

Results The early phase of lung injury was significantly alleviated by the overexpression of VEGF-C with increased levels of bronchoalveolar lavage (BAL) fluid interleukin-10 (IL-10), but worsened in the later phase by VEGFR-3 inhibition upon administration of Ad-sVEGFR-3 vector. Injection of anti-VEGFR-3 antibodies to mice in the resolution phase inhibited recovery from lung injury. The VEGFR-3-deleted mice had a shorter survival time than littermates and more severe lung injury in the resolution phase. Alveolar macrophages in the resolution phase digested most of the extrinsic apoptotic neutrophils and VEGF-C/VEGFR-3 signalling increased efferocytosis *via* upregulation of integrin α_v in the macrophages. We also found that incubation with BAL fluid from acute respiratory distress syndrome (ARDS) patients, but not from controls, decreased VEGFR-3 expression and the efficiency of IL-10 expression and efferocytosis in human monocyte-derived macrophages.

Conclusions VEGF-C/VEGFR-3 signalling in macrophages ameliorates experimental lung injury. This mechanism may also provide an explanation for ARDS resolution.