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MACROPHAGES

Shaping good eating habits

Both professional and non-professional phagocytes contribute to the clearance of apoptotic cells and tissue debris, but it has been unclear how these populations coordinate their actions. Kodi Ravichandran and colleagues now report that tissue macrophages regulate phagocytosis and inflammatory responses in non-professional phagocytes by secreting insulin-like growth factor 1 (IGF1) and microvesicles.

In initial experiments, the authors tested whether factors linked to tissue repair affect the uptake of apoptotic cells by non-professional phagocytes. They found that IGF1 inhibited apoptotic cell uptake by fibroblasts from the LR73 cell line and also the uptake of apoptotic cells by airway epithelial cell lines and an endothelial cell line. Inhibition of IGF1 receptor (IGF1R) signalling restored the ability of these non-professional phagocytes to engulf apoptotic cells. By contrast, IGF1 treatment enhanced the uptake of liposomes (150–200 nm in size) by non-professional phagocytes. However, macrophages were resistant to the effect of IGF1 with respect to the uptake of apoptotic cells or liposomes, despite expressing IGF1R. Therefore, IGF1 seems to regulate phagocytosis specifically in non-professional phagocytes, limiting their uptake of apoptotic cells while reciprocally enhancing the uptake of smaller particles.

The authors found that peritoneal macrophages exposed to interleukin-4 (IL-4) or apoptotic cells produced IGF1, and this macrophage-derived IGF1 also suppressed apoptotic cell uptake by LR73 fibroblasts. Intranasal administration of IL-4, IL-13 or apoptotic cells also led to the upregulation of IGF1 production in the lungs of wild-type mice but not in mice with a myeloid cell-specific deletion of IGF1. This suggested that myeloid cells are the primary source of inducible IGF1 in the lungs. In the airways, the authors found that IGF1R is expressed predominantly by epithelial cells but also at lower levels by alveolar macrophages. In agreement with their *in vitro* findings, intranasal administration of IGF1 decreased apoptotic cell uptake and increased liposome uptake by airway epithelial cells, but did not affect phagocytic responses in alveolar macrophages.

They next used a model of house dust mite (HDM) allergen-induced airway inflammation to explore how IGF1 shapes phagocyte responses in inflamed tissues. Compared with controls, mice with an airway epithelial cell-restricted deletion of IGF1R showed exaggerated airway inflammation following sensitization with HDM allergen; this was associated with enhanced inflammatory cell infiltrates, greater mucus accumulation and increased airway hyperreactivity. These findings were surprising, as the authors had predicted that IGF1R-deficient epithelial cells would show greater uptake of apoptotic cells, thereby attenuating airway inflammation. They examined the temporal requirement for IGF1R signalling and found that inhibition of IGF1R signalling during allergen sensitization exacerbated airway inflammation, whereas deletion of IGF1R after the sensitization phase had no effect on disease. Levels of IL-6 and TSLP were increased in bronchoalveolar lavage fluid from mice with IGF1R-deficient epithelial cells during HDM sensitization, suggesting that IGF1 limits inflammatory cytokine production by epithelial cells during the sensitization phase. The authors propose that the presence of apoptotic cells or the production of IL-4 by other lung-resident immune cells may induce IGF1 production by alveolar macrophages during allergen sensitization.

Finally, as alveolar macrophages have been shown to release microvesicles containing anti-inflammatory mediators during lung injury, the authors examined whether this occurs during HDM sensitization. Indeed, they found that alveolar macrophages increased their secretion of microvesicles in response to IL-4 treatment, and that the uptake of these microvesicles by airway epithelial cells was enhanced by IGF1. Notably, the macrophage-derived microvesicles suppressed epithelial cell expression of several genes linked with airway inflammation and asthma.

In summary, this study shows that macrophages can communicate with non-professional phagocytes in the local environment by releasing IGF1 and microvesicles; importantly, this seems to be crucial for limiting excessive tissue inflammation.

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> “tissue macrophages regulate phagocytosis and inflammatory responses in non-professional phagocytes”

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