



EDITORIAL

Apoptotic cell clearance and fibrotic lung disease

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Recognition and clearance of dying cells by phagocytes (a process known as efferocytosis) is essential for development, tissue homeostasis, and recovery from inflammation and injury. Under most circumstances, this process is so efficient that it can be difficult to detect, as illustrated by the fact that $>1 \times 10^{11}$ neutrophils are eliminated from the human circulation each day in a process that leaves no obvious trace [1]. Along similar lines, during community-acquired pneumonia there may be $>1.1 \times 10^6$ neutrophils per cubic millimetre of lung tissue, yet clearance of dying cells is so efficient that $<0.3\%$ of the neutrophils in the lungs are apoptotic [2]. While the consequences of apoptotic cell removal were initially thought to be immunologically silent, it is now recognised that efferocytosis can lead to the production of potent anti-inflammatory molecules, such as transforming growth factor (TGF)- β and interleukin-10, and growth factors that enhance tissue repair, such as hepatocyte growth factor (HGF) and vascular endothelial growth factor [3–5]. It is not surprising then that intentional injection of apoptotic cells into inflamed lungs or peritonea can enhance resolution of inflammation. In this issue of the *European Respiratory Journal*, LEE *et al.* [6] build on this foundation by demonstrating that a single administration of apoptotic cells into the lungs of bleomycin-injured mice reduces acute inflammation, attenuates activation of pro-apoptotic caspases and ameliorates the development of fibrosis. These striking results raise two important questions. How are these effects achieved and can these results be applied to human lung disease?

In answer to the first question, the results presented by LEE *et al.* [6] implicate HGF as a key molecule. Their results show that instillation of apoptotic cells into the lungs leads to an immediate increase in HGF gene expression and protein levels in the lungs. These findings are in line with previous work that shows that efferocytosis induces HGF production by macrophages [5, 7]. Accordingly, there is strong evidence suggesting that HGF upregulates antiapoptotic signalling pathways in epithelial and endothelial cells, rendering them less susceptible to oxidant and Fas-mediated apoptosis [8], both of which have been implicated in bleomycin-induced lung injury. Since epithelial injury is believed to be a prerequisite for the development of fibrosis, it is not surprising then that administration of HGF (either directly into the lungs or through systemic routes) attenuates fibrosis in bleomycin-treated rodents.

An interesting aspect of the work presented by LEE *et al.* [6] is that a single instillation of apoptotic cells resulted in enhanced expression of HGF in the lungs for up to 21 days. The mechanisms underlying this effect are unknown; however, it is enticing to postulate that ingestion of apoptotic cells altered alveolar macrophage activation states, a factor known to be important in fibrogenesis [9]. Along similar lines, it is important to note that instillation of apoptotic cells by LEE *et al.* [6] resulted in early, but not sustained, increases in TGF- β . This result may be considered ideal, since during acute inflammation, TGF- β exerts anti-inflammatory effects, whereas sustained expression of TGF- β in the lungs is generally regarded as pro-fibrotic. In this context, a balance between HGF and TGF- β may be beneficial to prevent epithelial apoptosis and promote repair of injured tissues without inducing fibrosis. Elegant studies from the liver and kidneys serve as an example for this paradigm wherein during resolution of inflammation, HGF suppresses TGF- β production and mitigates fibrosis [10–12].

Administration of exogenous HGF was once considered a promising therapeutic strategy for pulmonary fibrosis [13]. Unfortunately, the molecule is too labile in the circulation to maintain suitable levels for long periods and perform anti-fibrotic actions. As LEE *et al.* [6] show, administration of apoptotic cells may be a more favourable means of inducing HGF in lungs, since the effect appears to be sustained. Moreover, efferocytosis of apoptotic cells may lead to immune modulation, including regulation of TGF- β . While these effects may be important in animal models of fibrosis, it is unclear whether similar efficacy can be realised in idiopathic pulmonary fibrosis (IPF). Most patients with this disease have established fibrosis at the time of presentation and it is unlikely that administration of apoptotic cells would lead to disease reversal. Furthermore, the role of inflammation in the progression of IPF is unclear and anti-inflammatory therapies have shown disappointing results. Thus, it is overly optimistic to assume that administration of apoptotic cells might have similar efficacy in humans with IPF. With this in mind, it is important to note that the bleomycin model of lung injury also mimics many features of acute lung injury and the acute respiratory distress syndrome. Might it therefore be possible to administer autologous apoptotic cells to patients with acute inflammatory lung injury? More research is required to determine whether this is feasible or even prudent. In addition to further understanding the biological mechanisms by which efferocytosis modulates immunity, it would be important to determine a number of factors, including the appropriate route of delivery for cells, the optimum volume and concentration of cells, the frequency of treatment, the best type of cells to use and the best way to induce apoptosis.

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STATEMENT OF INTEREST

None declared.

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