Modulation of SOCS3 in macrophages can enhance the clearance of dying cells in inflammation

Macrophages, from the Latin meaning "big eaters", are key cells of the immune system that have the ability to scan tissues in the body and engulf and destroy invading pathogens. They also play a housekeeping role, to maintain and restore tissue homeostasis by clearing apoptotic (dying) cells that would otherwise lead to secondary post apoptotic necrosis and inflammation. If apoptotic cell clearance is defective, it can lead to the development of autoimmune or inflammatory diseases. Therapeutic approaches designed to enhance clearance of apoptotic cells could therefore improve the resolution of inflammation and associated disorders.

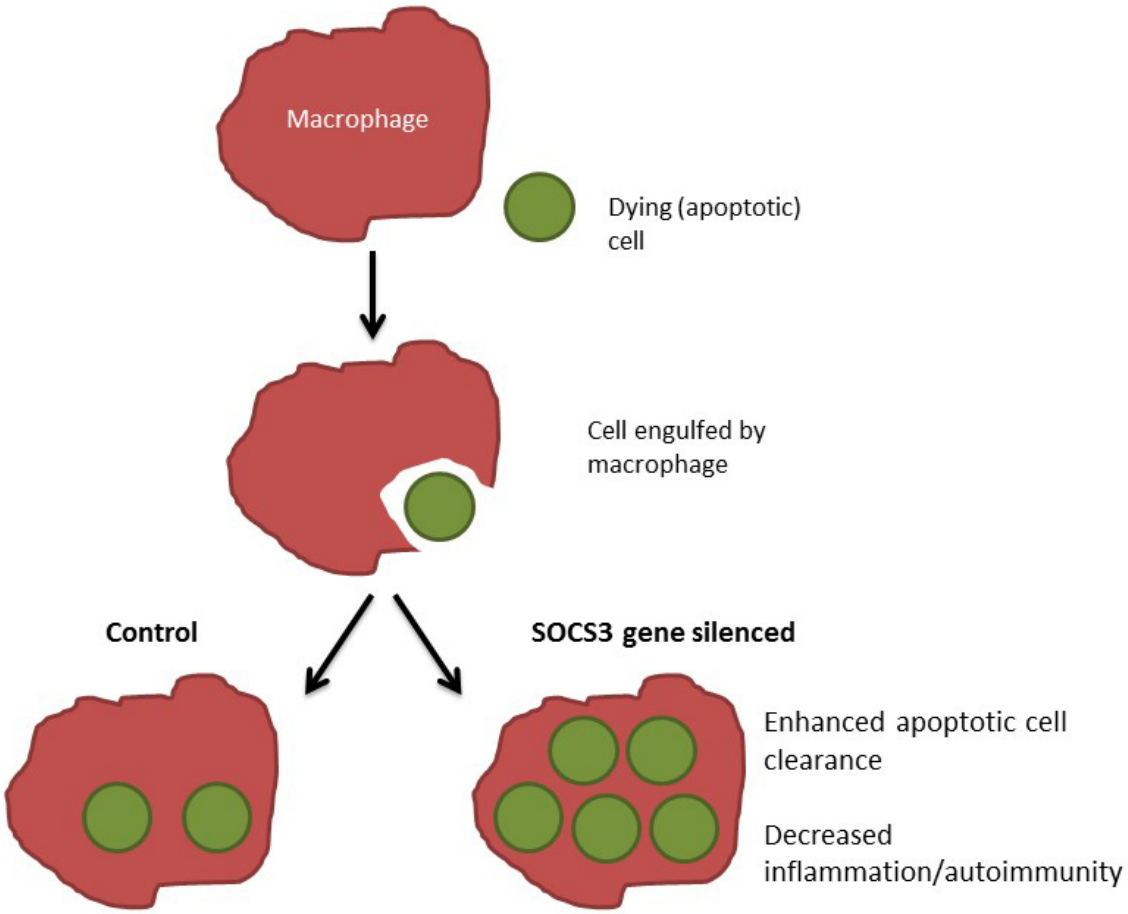

Fig. 1. Depletion of SOCS3 gene expression enhances the uptake of apoptotic (dying) cell clearance by macrophages.

Our recent work demonstrates that one molecule that resides inside macrophages, Suppressor of

Cytokine Signalling 3 (SOCS3), plays an important role in controlling the pathways driving uptake of dying apoptotic cells by macrophages. SOCSS proteins are key feedback inhibitor molecules modulating the inflammatory activities of macrophages and SOCS3 in particular is rapidly upregulated by human macrophages exposed to inflammatory conditions. When the SOCS3 gene was blocked using short interfering siRNA technology, it enhanced the ability of macrophages to engulf apoptotic cells. As well as this, by using video microscopy, we showed that the total number of apoptotic cell targets that were taken up by each macrophage increased. These two observations suggest that targeting SOCS3 *in vivo* would improve the clearance of apoptotic cells at sites of inflammation to encourage the healing and resolution process

One potential explanation for the enhanced uptake of apoptotic cells by SOCS3 depleted macrophages was that macrophages became more mobile and interacted at a greater rate with their target. Using the same microscopy movies, we studied how the macrophages moved, again with and without SOCS3 gene expression. However, the speed, total distance travelled and directionality (area covered) did not differ significantly in cells with or without SOCS3. This suggested that differences in macrophage engulfment rate would relate to events controlling the actin cytoskeleton structural scaffolding within the macrophages that dictates how well their target become consumed. When we analysed the activity of signalling elements inside the macrophages without SOCS3, we observed changes in specific signalling molecules (PI3K/Rac1/F-actin) that drive the engulfment process, indicating that the SOCS3 depleted macrophage can alter its shape more efficiently thus providing a mechanism for the ability of SOCS3 deleted macrophages to show better uptake.

To conclude, we have found that if the intracellular signalling regulator, SOCS3, is blocked in macrophages, they will be less inflammatory and be better at clearing dying cells and debris from inflammatory sites within tissue. Therefore strategies for SOCS3 modulation offer an opportunity for drug targeting to both restrict inflammatory responses and additionally to accelerate phagocytic clearance and resolution of inflammation. This would be important for diseases such as atherosclerosis or in chronic wounds where inflammation and defective clearance of apoptotic cells play a significant part.

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