A physiological role for $\alpha_2$-HS glycoprotein: stimulation of macrophage uptake of apoptotic cells

**ABSTRACT**

This comment describes the study by Jersmann and co-workers in this issue of *Clinical Science* reporting the results of a study of the role of the serum glycoprotein fetuin in the uptake of apoptotic cells by macrophages. They show that fetuin is able to stimulate the macropinocytosis of apoptotic cells *in vivo*, which would be therapeutically useful following chemotherapy when the increased numbers of apoptotic cells could exceed the capacity of the macrophage network.

Despite being a significant $\alpha$ globulin component of serum the physiological role of $\alpha_2$-Heremans–Schmid ($\alpha_2$-HS) glycoprotein (human fetuin) has not been adequately explored. Several functions, including the regulation of bone remodelling [1] and insulin signalling [2], have been proposed based upon the study of fetuin knockout mice. That fetuin might function as a bacterial opsonin was proposed as early as 1974 [3], and both neutrophil and monocyte uptake of particulate material could be stimulated by this protein [1,4]. However, it appeared unlikely that this was the major function of fetuin as levels of this serum protein fall during acute inflammation, and antibody and complement C3b/iC3b were established as the major bacterial opsonins triggering phagocytosis of pathogens by cells of the innate immune system. In addition, fetuin had been shown to inhibit the phagocytosis of *Helicobacter pylori* by macrophages [5]. In this issue of *Clinical Science*, Jersmann et al. [6] report that fetuin was able to stimulate the uptake of apoptotic neutrophils by macrophages and thus plays a key role in the prevention of chronic inflammation.

Resolution of inflammation is achieved by the induction of apoptosis in these cells, and the dysregulation of this process is thought to contribute significantly to tissue damage in chronic inflammatory diseases such as rheumatoid arthritis [7]. Apoptotic cells are recognized by macrophages and their uptake induces the secretion of anti-inflammatory cytokines, including transforming growth factor-$\beta$ (TGF-$\beta$) [8]. The efficient recognition and uptake of apoptotic cells by macrophages is therefore central to the termination of the inflammatory response. Exactly how apoptotic cells are recognized and ingested by macrophages has been the subject of intense research over the last decade, and the study by Jersmann et al. [6] now identifies the serum protein fetuin as a potent stimulator of the uptake process itself.

The uptake of apoptotic cells by macrophages involves two stages, firstly, the recognition and tethering of the apoptotic cell by the macrophage, and secondly, its ingestion and destruction within the macrophage (reviewed in [9]). The external surface of a cell undergoing apoptosis changes dramatically revealing structures that are recognized directly or indirectly by macrophages. For example, phosphatidylserine (PS), a phospholipid normally restricted to the inner leaflet of the lipid bilayer, is flipped to the outer leaflet and is recognized by the macrophage PS receptor. Also, lysocephosphatidylcholine, generated by the actions of Ca$^{2+}$-independent phospholipase A$_2$ (iPLA$_2$) during apoptosis, is ligated by serum IgM, leading to activation of the classical complement pathway and opsonization.

Key words: apoptosis, fetuin, macrophage, neutrophil, phagocytosis.
of apoptotic cells with C3b and uptake by macrophages [10]. Ligation of these molecules and others on the surface of apoptotic cells is able to then stimulate uptake by macrophages. Jersmann et al. [6] now show that the basal rate of uptake can be increased by 70% in the presence of fetuin. This finding has particular relevance during times of increased cell apoptosis in the body, when basal levels of macrophage uptake of apoptotic cells may be inadequate and there is a risk of cells progressing to secondary necrosis leading to persistence of inflammation. This situation would apply not only during the resolution of inflammation, but also during chemotherapy when tumour cell death via apoptosis places a sudden and potentially excessive burden on the macrophage network.

Exactly how fetuin stimulates uptake of apoptotic cells is not known. Fetuin is a sialylated glycoprotein and this study shows that its sialic acid residues are required for stimulating uptake of apoptotic cells. However, this was not due to a non-specific effect of sialic acid, as sialylated lactose or BSA could not mimic the effect of fetuin. Moreover, fetuin had to be present at the time of incubation of macrophages with apoptotic cells and was therefore not merely either opsonizing apoptotic cells or priming the macrophages for cell engulfment. Instead, fetuin was able to stimulate macropinocytosis, the process already proposed to mediate uptake of apoptotic cells by macrophages [6]. As a specific receptor for fetuin has not been identified, it is not possible at this stage to propose how macropinocytosis could be augmented by this glycoprotein. Macropinocytosis can be stimulated by a variety of factors, including growth factors and cytokines [11,12], and involves membrane ruffling to surround the target, followed by formation of a large phagosome containing extracellular fluid. Signalling through cell-membrane-bound receptors may be able to target the monomeric Rho family of GTPases involved in membrane ruffling and macropinocytosis, but further studies are clearly required to determine the molecular processes targeted by fetuin.

The study by Jersmann and co-workers [6] has thus revealed a key role for fetuin in the removal of apoptotic cells. Although fetuin is not the only external factor able to promote the macropinocytosis of apoptotic cells, the same group and others have shown previously that corticosteroids and lipoxins [13,14] have a similar effect, this serum protein is present at high levels in adults (0.5 mg/ml) and is likely to play a key homeostatic role in the removal of apoptotic cells from a variety cell lineages. Moreover, fetuin has therapeutic potential which may be realized in the treatment of diseases associated with inadequate removal of apoptotic cells, e.g. Lupus [15] or during cancer chemotherapy, when the basal rate of macrophage uptake of apoptotic cells may be inadequate.

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REFERENCES