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Apoptotic Cell Clearance: An Orchestra With Still Too Many Unknown Players

Editorial

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Apoptotic cells are removed by a process involving recognition and phagocytosis by professional phagocytes or neighbouring cells, followed by the induction of an active anti-inflammatory response. These events are critical for efficient corpse elimination and to prevent the release of potentially cytotoxic cellular contents that could elicit an autoimmune response: defects in apoptotic cell clearance are often associated with autoimmune or chronic inflammatory diseases [1]. Moreover, high levels of cell death occur within a tumour environment and the mechanisms through which dying tumour cells are removed can considerably influence tumour-specific immunity [2].

It is indisputable that several new studies had shed new light in the molecular mechanisms leading to phosphatidylserine (PtdSer) exposure and recognition. For example, different PtdSer receptors on macrophage are continuously being identified, in addition to the original PtdSer receptor cloned by Fadok and colleagues [3]: TIM-1 and TIM-4 [4], stabilin-2 [5] and bridging molecules like MFG-E8 in mammalian cells [6] or TTR-52 in *Caenorhabditis Elegans* [7] are shown to be able to interact with PtdSer and influence the removal of the cell corpse.

Different lipid transporter activities have been implicated in the generation, maintenance and alteration of phospholipid asymmetry in the plasma membrane which are essential for regulating a plethora of cellular events [8]. However, the challenge for scientists remains to assign these activities to specific molecular entities, since often discrepancies are found. According to one study [9] the transmembrane protein 16F (TMEM16F) has the calcium dependent phospholipid scramblase activity and when lymphoma cells were transformed with a constitutively active form of TMEM16F, they expose levels of PtdSer comparable to that observed in apoptotic cells. More recently it was demonstrated that TMEM16F forms a Ca (2+) activated cation channel required for lipid scrambling since TMEM16F KO mice are defective in PtdSer exposure, hemostasis and thrombosis [10]. Another controversy is on the role of apoptotic blebbing in promoting cell clearance: *in vitro* studies reported that inhibition of apoptotic blebbing compromised clearance by macrophages [11]. However, impaired corpse clearance following defective blebbing could be easily rescued by the PtdSer-bridging protein MFG-E8 suggesting the presence of redundancy in clearing mechanisms [12]. It should be underlined the similarity between the worm *C Elegans* and humans since the human blebs, which focalize factors that promote clearance, resemble the extracellular PtdSer vesicles, which lead to the exoplasmic leaflet expression on phagocytes via TTR-52 and CED-1 [7]. Therefore it seems that a better understanding of cell clearance could be derived from further studies in *C Elegans*, in addition to our actual knowledge on the apoptotic process, based on pioneering studies performed by Horvitz and colleagues [13]. But which points need to be addressed primarily? As well as an orchestra, programmed cell clearance is composed of several players acting synergistically under the supervision of a director. Despite the director in apoptotic cell clearance has been identified as PtdSer exposure, the key signal promoting this process, rising evidences suggest that other players are essential "to play". Identification of these players is the basis for therapeutic intervention by a selective targeting which must always take into consideration the specific pathology, since, under the current state of knowledge, there is no drug that modulates programmed cell death, effective for different diseases. Furthermore, attention should be focused also on the phagocytes factors that may influence continued clearance: recently it was shown that the mitochondrial membrane potential of the phagocyte critically controls engulfment capacity, with lower potential enhancing engulfment and vice versa [14]. This finding has a remarkable importance since suggests that mitochondria are crucial organelles in the programmed cell clearance [15] acting at both sides of the 'phagocytic synapse'.

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