Apoptotic cells are rapidly phagocytosed by macrophages, a process that represents a critical step in tissue remodeling, immune responses, and the resolution of inflammation. In 1998, Peter Henson, Donna Bratton, and colleagues at National Jewish Health demonstrated that phagocytosis of apoptotic cells actively suppresses inflammation by inhibiting the production of inflammatory cytokines and inducing production of anti-inflammatory factors, including TGF-β and prostaglandin E2. Here they discuss the evolving relationship among apoptosis, phagocytosis, and inflammation.

In the course of our longstanding investigation of the inflammatory response, in the early 1980s we began to focus on its normal resolution, especially on the disposition of the accumulated granulocytes. This led to showing removal of “effete” neutrophils by uptake into macrophages (1). The observation was, in effect, a re-recognition of Metchnikov’s observations of macrophages phagocytosing microphages in the 1890s. The arrival in our program of Chris Haslett, who had worked previously with Andrew Wylie, brought appreciation that the target cells were in fact undergoing apoptosis (2), a form of programmed cell death (PCD) previously described in the now-classic 1972 paper by Kerr, Wylie, and Currie (3). Addressing the question of how apoptotic cells were recognized as “foreign” enough to initiate their phagocytosis led a graduate student in our laboratory, Valerie Fadok, to the key observation that exposure of phosphatidylserine (PS) on the outer membrane leaflet of apoptotic cells was thereby contrasted to other forms of cell death, being either “good” (apoptotic and silent) or “bad” (necrotic, proinflammatory, and immunogenic).

The original experiments implicated the multifunctional mediator TGF-β in this inflammosuppressive, as well as prostaglandin E2 (PGE2), which was later shown to result in part from secondary effects of TGF-β (11). TGF-β has become a well-known contributor to multiple tissue processes, from blockade of inflammatory mediator production to complex shaping of immune responses, alteration of epithelial functions, and induction of fibrosis. As such, its induction in response to the recognition of apoptotic cells brings to the fore a process that is far from silent and that has much broader potential roles in normal tissue remodeling, modulation of the immune response, and induction or suppression of neoplasia and metastasis (Figure 1B).

Many questions concerning the anti-inflammatory effects of apoptotic cells remain. For example, while blockade of PS on the apoptotic cell surface prevents many of the antiinflammatory consequences, the spectrum of PS “receptors” involved in these responses is not at all clear. Because actual uptake of the apoptotic cell is not required for the inflammosuppressive switch, receptors signaling for these two different effects may be distinct. It has also become increasingly clear that there is substantial heterogeneity in PCD/apoptotic processes (12), and it is likely that different forms of PCD will lead to different responses from the responding cell. Here too, it appears that the recognition and response to apoptotic cells is more general and by no means confined to the monocyte.

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Antiinflammatory effects of apoptotic cells

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The increasing recognition that macrophages derive from two quite different ontological sources and are highly plastic with regard to their programing in different tissue environments (and, we hypothesize, shaped in part by exposure to apoptotic cells or cells exposing PS as part of their activation responses) opens up a fascinating field for study of dynamic effects of apoptotic cells in both normal tissue maintenance and circumstances of injury and infection (Figure 1). The importance of these processes also clearly raises questions regarding the consequences of abnormalities or blockade of apoptotic cell recognition and removal, as altered response to apoptotic cells clearly contributes to a host of diseases, including tissue destruction, as in emphysema, and/or autoimmunity, as in systemic lupus erythematosus.

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