What makes a dead cell attractive?

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CONGESTIVE HEART FAILURE represents the end stage of various cardiac disease etiologies, including hypertension, myocardial infarction/ischemia from atherosclerosis, viral myocarditis, valvular insufficiency, or mutations in genes encoding sarcomeric proteins (1, 10, 11). These events trigger neurohumoral and cellular signaling cascades, ultimately resulting in myocardial adaptation, typically cardiac growth or hypertrophy, to compensate for any contractile detriments imparted by the disease. The transition from compensated to decompensated cardiac hypertrophy signifies a critical step in the progression to heart failure. However, as pharmacological and surgical treatment modalities improve mortality from cardiovascular disease, this transition becomes prolonged and less clearly defined, resulting in an ever-increasing clinical diagnosis of heart failure (10).

Multiple mechanisms have been implicated in the progressive deterioration of contractile function during heart failure, such as desensitization of β-adrenergic receptor signaling, dysregulation of excitation-contraction coupling, and activation of aberrant signaling pathways (6, 8, 12). In addition, experimental evidence exists for a causal role of myocardial cell loss as a mechanism underlying this transition to heart failure (for review, see Ref. 4). Cardiac cell death can occur by two primary mechanisms, apoptosis or necrosis. Although apoptosis is accepted as the more prominent mode of cell death (4, 7), necrosis has gained acceptance as a significant mediator of heart failure (13). Apoptosis is a highly regulated process of cell suicide that is mediated by extrinsic (ligand dependent) and intrinsic (mitochondrial dependent) pathways (4). Necrotic cell death is initiated by ischemic injury or perturbations in Ca²⁺ signaling accompanied by depletion of high-energy stores (3). Whereas necrosis immediately results in mitochondrial swelling and cell rupture, stimulating a robust inflammatory response, apoptotic cells are rapidly removed, presumably by phagocytic processes following activation of the death signal (14, 15).

Clearance of apoptotic cells is an active process and involves alterations in cell surface motifs such as exposure of phosphatidylserine, leading to recognition by phagocytes (9). In their study in the Journal of Applied Physiology, Kobara et al. (7a) demonstrate that apoptotic cells may recruit phagocytic cells through the release of chemokines, specifically monocyte chemotactrant protein-1 (MCP-1). MCP-1 regulates the recruitment of inflammatory cells into tissue during acute inflammatory events (2). In this study (7a), in vitro treatment of rat neonatal ventricular myocytes with staurosporine induces a robust and dose-dependent apoptotic response. These cells show an elevation of MCP-1 gene expression with concomitant MCP-1 protein expression. Interestingly, the culture medium from the staurosporine-treated cells is able to recruit more monocytes than that from the control cells. The authors also suggest that this upregulation may be initiated by interleukin-1, a well-known inducer of MCP-1 (16).

Next, to test the relevance of these in vitro findings to the intact heart, the authors exposed the hearts of male rats to an ischemia-reperfusion protocol. Following 24 h of reperfusion, the ischemic border region demonstrates significant apoptosis as detected by both terminal deoxynucleotidyltransferase-mediated dUTP nick-end labeling (TUNEL)-positive cells and DNA fragmentation. Furthermore, MCP-1 protein is evident along with infiltrating monocytes in this ischemic region.

The studies performed by Kobara et al. (7a) demonstrate two novel points: 1) the production and release of a soluble factor that may contribute to the clearance of apoptotic cells, and 2) a point of overlap between apoptotic and necrotic cell death. The first point contradicts previous work that found no evidence for the release of a soluble factor by apoptotic cells (5, 17). Regarding the second point, even though distinct signaling pathways mediate the initiation of apoptosis and necrosis, the recognition and clearance of “dying” cells involves a common inflammatory chemokine, MCP-1. Kobara et al. (7a) demonstrate that apoptotic cells express relatively more MCP-1 than necrotic cells, suggesting that MCP-1 may be playing different roles in these cell types. The differences between these two processes may result from the timing by which the cells are cleared. More studies examining the dynamics of apoptotic and necrotic cell clearance will more clearly elucidate this contention.

REFERENCES


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