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What makes a dead cell attractive?

John P. Konhilas, Ph.D.

Department of Molecular, Cellular, and Developmental Biology, University of Colorado, Boulder, CO 80309

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 pharmacologic 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 (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 Ca^{2+} 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 phagocytotic 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 this issue of *Journal of Applied Physiology*, Kobara et al demonstrate that apoptotic cells may recruit phagocytotic cells through the release of chemokines, specifically monocyte chemoattractant protein-1 (MCP-1). MCP-1 regulates the recruitment of inflammatory cells into tissue during acute inflammatory events (2). In this study, *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 hours of reperfusion, the

ischemic border region demonstrates significant apoptosis as detected by both 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 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 involve a common inflammatory chemokine, MCP-1. Kobara et al 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

1. Adams KF Jr. New epidemiologic perspectives concerning mild-to-moderate heart failure. *Am J Med* 2001;110(Suppl 7A):6S–13S. [PubMed: 11334770]
2. Castellani ML, Bhattacharya K, Tagen M, Kempuraj D, Perrella A, De Lutiis M, Boucher W, Conti P, Theoharides TC, Cerulli G, Salini V, Neri G. Anti-chemokine therapy for inflammatory diseases. *Int J Immunopathol Pharmacol* 2007;20:447–453. [PubMed: 17880758]
3. Danial NN, Korsmeyer SJ. Cell death: critical control points. *Cell* 2004;116:205–219. [PubMed: 14744432]
4. Foo RS, Mani K, Kitsis RN. Death begets failure in the heart. *J Clin Invest* 2005;115:565–571. [PubMed: 15765138]
5. Hughes J, Liu Y, Van Damme J, Savill J. Human glomerular mesangial cell phagocytosis of apoptotic neutrophils: mediation by a novel CD36-independent vitronectin receptor/thrombospondin recognition mechanism that is uncoupled from chemokine secretion. *J Immunol* 1997;158:4389–4397. [PubMed: 9127003]
6. Hunter JJ, Chien KR. Signaling pathways for cardiac hypertrophy and failure. *N Engl J Med* 1999;341:1276–1283. [PubMed: 10528039]
7. Kajstura J, Cheng W, Sarangarajan R, Li P, Li B, Nitahara JA, Chapnick S, Reiss K, Olivetti G, Anversa P. Necrotic and apoptotic myocyte cell death in the aging heart of Fischer 344 rats. *Am J Physiol* 1996;271:H1215–1228. [PubMed: 8853362]
8. Lefkowitz RJ, Rockman HA, Koch WJ. Catecholamines, cardiac beta-adrenergic receptors, and heart failure. *Circulation* 2000;101:1634–1637. [PubMed: 10758041]
9. Li MO, Sarkisian MR, Mehal WZ, Rakic P, Flavell RA. Phosphatidylserine receptor is required for clearance of apoptotic cells. *Science* 2003;302:1560–1563. [PubMed: 14645847]
10. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D’Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation* 2002;106:3068–3072. [PubMed: 12473553]
11. Maass A, Konhilas JP, Stauffer BL, Leinwand LA. From sarcomeric mutations to heart disease: understanding familial hypertrophic cardiomyopathy. *Cold Spring Harb Symp Quant Biol* 2002;67:409–415. [PubMed: 12858566]
12. Marks AR. Ryanodine receptors, FKBP12, and heart failure. *Front Biosci* 2002;7:d970–977. [PubMed: 11897558]
13. Nakayama H, Chen X, Baines CP, Klevitsky R, Zhang X, Zhang H, Jaleel N, Chua BH, Hewett TE, Robbins J, Houser SR, Molkentin JD. Ca²⁺- and mitochondrial-dependent cardiomyocyte necrosis as a primary mediator of heart failure. *J Clin Invest* 2007;117:2431–2444. [PubMed: 17694179]
14. Platt N, da Silva RP, Gordon S. Recognizing death: the phagocytosis of apoptotic cells. *Trends Cell Biol* 1998;8:365–372. [PubMed: 9728398]

15. Ren G, Dewald O, Frangogiannis NG. Inflammatory mechanisms in myocardial infarction. *Curr Drug Targets Inflamm Allergy* 2003;2:242–256. [PubMed: 14561159]
16. Wang JM, Sica A, Peri G, Walter S, Padura IM, Libby P, Ceska M, Lindley I, Colotta F, Mantovani A. Expression of monocyte chemotactic protein and interleukin-8 by cytokine-activated human vascular smooth muscle cells. *Arterioscler Thromb* 1991;11:1166–1174. [PubMed: 1911703]
17. Witting A, Muller P, Herrmann A, Kettenmann H, Nolte C. Phagocytic clearance of apoptotic neurons by Microglia/Brain macrophages in vitro: involvement of lectin-, integrin-, and phosphatidylserine-mediated recognition. *J Neurochem* 2000;75:1060–1070. [PubMed: 10936187]