Cell Death in Cardiovascular Disease

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Cell death has been recognized in the cardiovascular system for centuries. In Virchow’s 1858 lectures, he described atherosclerosis as producing new tissue, followed by cell death: “Thus, we have here an active process which really produces new tissues, but then hurries on to destruction in consequence of its own development.” Degraded and dying cells are found in both myocardial infarction and in atherosclerosis, and until the last 20 years were classified as necrosis. Death was considered a passive phenomenon due to ischemic or other insult, resulting in cell membrane dissolution and leakage of proinflammatory contents. The consequences of cell death resulted from loss of the function of the live cells and subsequent inflammation.

This scenario changed with the description of apoptosis in the 1970s, and the subsequent detailed description of the mechanisms underlying this form of ‘programmed cell death.’ The presence of apoptosis in atherosclerotic plaques has been confirmed by a number of studies. Apoptotic indices are low in early lesions (Stary grades I–III) but seen with increasing frequency as lesions develop, in both the necrotic core and fibrous cap. Apoptosis is predominantly restricted to macrophages and vascular smooth muscle cells (VSMCs), although all cell types within the vessel wall can undergo apoptosis. Plaque rupture occurs most commonly in the shoulder area of the plaque, a region characterized by reduced VSMC and increased macrophages. This suggests that VSMC apoptosis, perhaps induced by macrophages, may be a central event in plaque rupture and its subsequent sequelae.

VSMC apoptosis in the fibrous cap of mouse lesions leads to multiple features of plaque vulnerability, including medial degeneration, and plaque calcification, and it accelerates both atherogenesis and progression of advanced lesions. In contrast, medial VSMC apoptosis has been identified when vessels remodel, eg the physiological remodeling after birth or after surgically-induced flow changes, suggesting that VSMC apoptosis may regulate vessel structure following changes in vessel caliber. Macrophage apoptosis has been implicated in formation of the necrotic core and endothelial cell apoptosis in atherogenesis and thrombosis.

The role of cardiomyocyte apoptosis in the heart in a variety of disease entities has also been elucidated over the last 10 years. Cardiomyocyte apoptosis occurs in end-stage heart failure due to both ischemic and dilated cardiomyopathy, in ageing, during transplantation, and in the transition from compensated to decompensated hypertrophy. High levels of apoptosis are also seen in some congenital heart disease, for example in arrhythmogenic right ventricular dysplasia, a condition characterized by myocardial replacement with fibrofatty material. There is also increasing evidence that toxic cardiomyopathies, such as that induced by doxorubicin (adriamycin), are associated with cardiomyocyte apoptosis. Although the evidence that apoptosis promotes heart failure is persuasive, the extent of cell death is controversial. Vastly different rates of apoptosis have been reported in both human and animal heart failure, with rates of up to 35.5%. More realistic rates of <0.5% cell death have been reported in end-stage heart failure, but animal studies have demonstrated that low levels can still result in heart failure.

Although cardiovascular scientists have focused on the role and mechanisms of apoptosis in disease, recent discoveries of other forms of cell death, many intimately coupled with inflammation, have shown the complexity of regulation of death. Thus, cell death and inflammation are coupled through activation of inflammasomes, multiprotein complexes that regulate inflammatory cytokine release. Inflammasomes are intrinsically linked to both proinflammatory responses and to apoptosis with proinflammatory aspects. Apoptosis is traditionally thought to be “silent” to the immune system. In contrast, inflammasome-induced forms of apoptosis—pyroptosis and pyronecrosis—are inflammatory and share features with necrosis.

Finally, autophagy has also been observed in the cardiovascular system during injury, particularly in the heart (reviewed in) but also in the vasculature. Autophagy is
involved in the degradation and recycling of the building blocks of organelles, proteins, and other components of the cytoplasm important for cellular homeostasis. Despite the fact that autophagy can lead to cell survival, recent studies indicate that apoptosis and autophagy involve complementary pathways and that autophagic degeneration may be a part of apoptosis, at least in some cell types.

This review series in ATVB on “Cell Death in the Cardiovascular System” is therefore very timely. The reviews cover the relationship between cell death and inflammation, particularly covering the innate immune system (Zheng et al), the evidence for and role of autophagy in vascular disease (Schijvers et al), and how ER stress and the unfolded protein response regulates apoptosis (Scull and Tabas). Importantly, the reviews demonstrate that we are moving beyond simple descriptions of cell death in disease. The elucidation of mechanisms underlying cell death has allowed the causal role of cell death to be elucidated in disease. These studies show that very little cell death (as measured) can result in profound consequences for the tissue, and that prevention of cell death is both part of the mechanism of action of established drugs, and a fertile ground for new therapeutics.

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