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Review

Cardiomyocyte necrosis: Alternative mechanisms, effective interventions

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Abstract

Necrotic death of cardiac myocytes is a major contributor to heart failure associated with several cardiac pathologies such as ischemia and reperfusion injury. Preventing cardiomyocyte necrosis is an important challenge towards the development of effective strategies, aiming to battle cardiovascular disorders. While, necrotic cell death was traditionally considered a passive and chaotic process, emerging evidence indicates that specific molecular mechanisms underlie cellular destruction during necrosis. Elucidation of these mechanisms will facilitate therapeutic intervention against heart failure.

Keywords: Ischemia; Lipid; Mitochondria; Necrotic cell death; Oxidative stress; Peroxidation; Reperfusion

Three major types of cell death have been described in diverse organisms, apoptosis autophagic vacuolation and necrosis [1–3]. Although necrosis has been associated with extensive cell loss that accompanies many devastating human pathologies such as stroke, heart diseases and several neurodegenerative conditions, the biochemical pathways mediating the necrotic destruction of cells have long remained obscure. One of the main reasons why molecular characterization of necrosis lagged considerably behind that of the other two types of cell death has been the – until recently – prevailing notion that necrosis is a catastrophic type of cell death that is uncontrollable and does not involve any specific mechanisms [4]. Why study necrosis if there is nothing there to find?

However, this concept is being overturned by findings in organisms ranging from the lowly nematode worm *Caenorhabditis elegans* to mammals, which reveal that necrotic death is carried out by conserved cellular processes. Genetic and biochemical dissection of these processes shows that, rather than being a disorganized breakdown of the cell, necrosis is orchestrated and executed by appropriate mechanisms, depending on the death initiating stimulus [5]. What triggers necrotic cell death? Cells suffer necrosis when exposed to excessive stress and adverse environmental conditions such as lack of oxygen or essential nutrients (i.e. in the case of ischemia during a heart attack or following stroke), elevated temperature, toxic or corrosive compounds and excessive mechanical strain (i.e. in the case of trauma). In addition to external predicaments, necrotic cell death can also be inflicted by genetic abnormalities (i.e. deleterious gene mutations in neurodegenerative disorders).

An important corollary of investigating the mechanisms of necrosis, highly relevant to human health, is the emerging potential for prevention or therapeutic intervention. Although, once induced, necrotic cell death was considered inevitable, the recent identification of signaling pathways and genes required for cell demise offers opportunities for the development of educated intervention strategies, designed to counter or ameliorate pathological conditions with a significant necrosis component. The study by Casey, Arthur and Bogoyevitch holds such a promise for heart damage following acute myocardial infarction and ischemia [6]. In this and other cardiac pathologies, ensuing cardiomyocyte cell death is a major contributor to heart dysfunction and failure. Oxidative stress due to accumulation of reactive oxygen species (ROS) has been implicated in triggering cell death [7]. Casey, Arthur and Bogoyevitch show that high hydrogen peroxide (H_2O_2) concentration causes a pattern of late-onset death of neonatal cardiomyocytes in culture. Dying cells exhibit ultrastructural characteristics of necrosis, with delayed leakage of lactate dehydrogenase (LDH), which signifies compromise of plasma

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membrane integrity. Lack of caspase-3 activation, which occurs during apoptosis, further suggests that cardiomyocyte death is not apoptotic.

One of the traditional hallmarks of ROS-initiated cell death is mitochondrial dysfunction and energy depletion [8]. This is manifested by opening of the mitochondrial permeability transition pore (MPTP), the collapse of the mitochondrial membrane potential (MMP) and the concomitant drop in ATP production [9–11]. These events set in motion a battery of cell destruction cascades and at the same time, limit the capacity of the cell for energy production. Intriguingly, Casey, Arthur and Bogoyevitch demonstrate that necrotic death of cardiomyocytes under oxidative stress does not involve opening of MPTP of loss of MMP. Furthermore, cellular ATP content is only transiently reduced upon treatment with H_2O_2 and in fact, it later recovers to close the normal levels. These observations suggest that death is not merely the result of an inescapable energy crisis that undermines cell viability.

What then is killing the cells experiencing oxidative stress induced by H_2O_2? Calcium-activated calpain proteases and lysosomal, acidic aspartyl proteases, which are required for necrotic cell death in *C. elegans* and mammalian neurons [12,13], do not appear to be involved. Rather, alternative mechanisms of cell destruction might be in operation, in this experimental paradigm. Casey, Arthur and Bogoyevitch show that lipid peroxidation is an important contributing factor. First, lipid peroxidation is significantly increased upon exposure of cardiac myocytes to H_2O_2 and second, inhibition of lipid peroxidation by the vitamin E analogue trolox or by the iron chelator dipyridyl prevents cell death (Fig. 1).

What cellular processes could be stimulated or augmented to fortify cells against cell death? Previous studies have shown that two hypertrophic agents, endothelin-1 (ET-1) and leukemia inhibitory factor (LIF) protect cardiomyocytes under oxidative stress from apoptotic death [14,15]. Interestingly, Casey, Arthur and Bogoyevitch have found that peroxiredoxin 3 and alpha-B crystallin are among the proteins with increased abundance after treatment of cardiomyocytes with ET-1, whereas treatment with LIF increases the abundance of Cu/Zn superoxide dismutase and Hsp20 and 60 [16]. Therefore, by provoking such proteomic profile changes, these hypetrophic agents may strengthen antioxidant and stress defenses of cells. Indeed, pretreatment of cardiomyocytes with ET-1 or LIF inhibits necrosis induced by H_2O_2 (Fig. 1).

The totality of these findings highlight the feasibility of formulating effective interventions against necrotic cell death associated with human pathologies. This is a particularly exciting prospect, given that ischemic diseases of the heart, kidney and brain as well as neurodegenerative disorders are among the primary causes of disability, morbidity and mortality. Numerous studies utilizing an assortment of experimental systems converge to the conclusion that necrosis is not simply

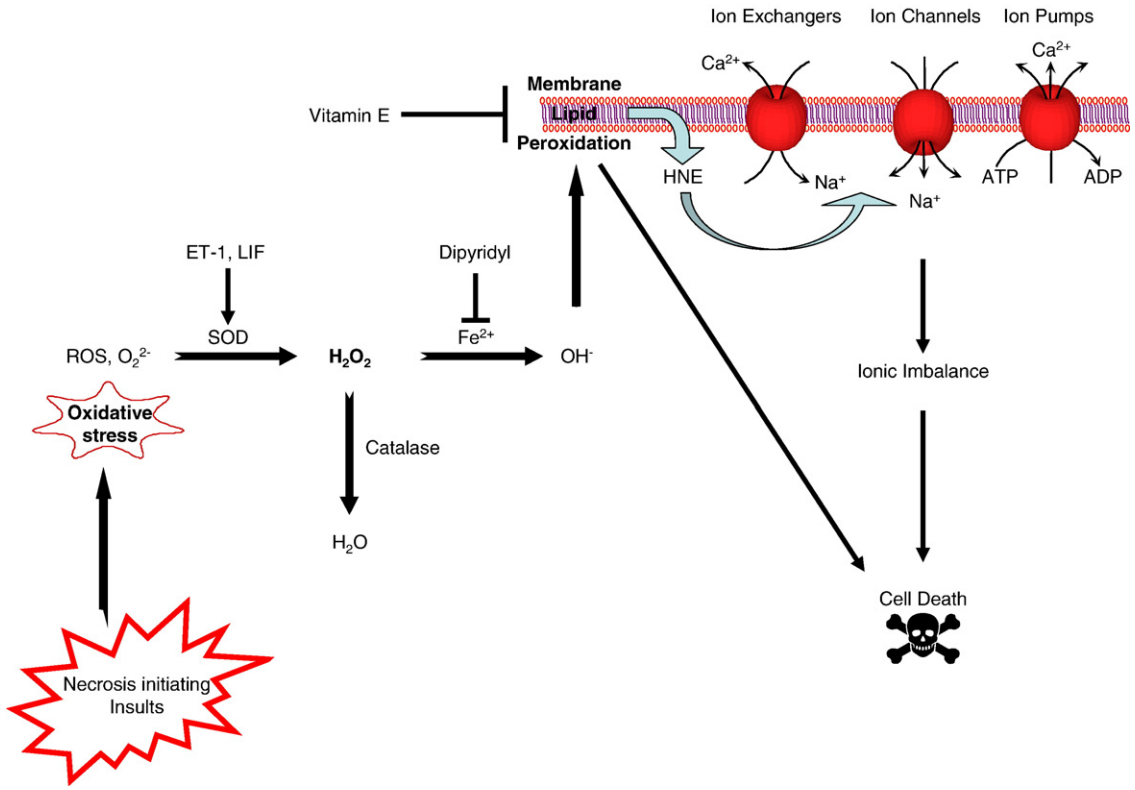

Fig. 1. Membrane lipid peroxidation contributes to oxidative stress-induced cell death. Excessive accumulation of reactive oxygen species (ROS) saturates cellular antioxidant defenses and causes peroxidation of plasma or other membrane lipids. Peroxidation compromises the integrity of these membranes and generates lipid hydroperoxides and aldehyde byproducts such as 4-hydroxynonenal (HNE). In turn, HNE may perturb ion homeostasis by interfering with the function of ion channels transporters and pumps [20,21]. The cumulative effect of such modifications is cell injury and ultimately, death. ET-1: endothelin-1, HNE: 4-hydroxynonenal, LIF: leukemia inhibitory factor, ROS: reactive oxygen species, SOD: superoxide dismutase.

the decadent and inexorable fate of a cell otherwise not meant to die [1,17,18]. Understanding the intricacies of necrosis inflicted by diverse initiators will shed light into the biochemical events that transpire during cell death. The molecules enacting these biochemical events are effectors of necrosis and should, in principle, constitute excellent targets for drug development [19] and other methodologies designed to ameliorate or block pathological cell death.

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