Cellular Pathways of Death and Survival in Acute Myocardial Infarction

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Abstract

During acute myocardial infarction (MI), the cumulative loss of functioning cardiomyocytes (CMs) progresses as an imbrication of necrosis, apoptosis, and autophagy. Coronary artery occlusion and subsequent hypoxia causes some CMs to undergo necrosis with most cellular damage occurring near the area of occlusion. The inflammation that ensues plays a critical role in the reparative process and occurs in parallel as CMs struggle to survive. The release of inflammatory pro-apoptotic cytokines compounded with activation of apoptosis results in the programmed death of ischemic CMs. Concurrently, the level of autophagic flux in border zone CMs will determine whether or not these CMs are able to survive hypoxic cellular conditions. The interplay of these processes and the balance that occurs in the peri-infarct area plays a pivotal role in preserving the functional capacity of CMs, specifically through the upregulation of autophagy and downregulation of apoptosis and inflammation. A detailed understanding of these signaling pathways in acute MI is necessary to develop novel therapeutics to promote CM survival and diminish CM death following MI. This review discusses the cellular processes of necrosis, apoptosis, autophagy, and inflammation that occur during acute MI. Also, the common signaling mediators that each process employs and their relationship to each other are discussed to provide a better understanding of these synergistic effects during MI.

Keywords: Myocardial infarction; Necrosis; Apoptosis; Autophagy; Inflammation; Cell signaling

Introduction

Cardiovascular disease (CVD) is accountable for one in every three deaths that occur in the United States and every year close to 1.5 million Americans will experience a myocardial infarction (MI) [1,2]. Occlusion of the coronary artery due to embolization of an unstable plaque is the most common etiology [3]. The initial cellular changes alter the myocardium and prime both the infarcted and non-infarcted area for progressive ventricular dysfunction that eventually leads to a decline in function and heart failure (HF) [4,5]. Restoration of the vital blood supply to dying cardiomyocytes (CMs) represents the most effective current clinical therapy aimed at improving blood flow to myocardial function following MI [7-11].

Without blood to supply CMs, the loss of functional CMs progresses as an imbrication of necrosis, apoptosis, and autophagy. Inflammatory changes in the cell also occur and this process occurs simultaneously as CMs struggle to survive or die. However, since terminally differentiated CMs have a limited capacity for regeneration and repair they must cope with this ischemic insult and adapt. A detailed understanding of the cellular pathways of death and survival in acute MI are necessary before appropriate therapies can be developed to salvage CMs and preserve CM function (Figure 1). Therefore, this review discusses the cellular processes of necrosis, apoptosis, autophagy, and inflammation that initially occur during acute MI. The common signaling mediators of these processes and their relationship to each other will also be discussed to provide a more detailed understanding of the interplay between these processes during MI (Figure 2).

Cardiomyocyte Fates

Necrosis

During an ischemic event, cell death progresses from the subendocardium toward the epicardium in a transmural manner [12]. Within the first 24 hours of MI, extensive loss of CMs is due to ischemic necrosis and this peaks around 24 hours post-MI [13-15]. Factors that promote cellular necrosis have been shown to propagate through gap junctions as administration of carbenoxyolone, a gap junction blocker, limits necrosis during ischemia [16]. MRI imaging of DNA binding to gadolinium chelate, a marker for necrosis, has shown that necrosis begins as early as 2 hours after the initial ischemic insult and subsides 72 hours post-MI [17].

On the cellular level, hypoxic cells under ischemic conditions result in a transition from aerobic metabolism to anaerobic metabolism in order to maintain ATP levels needed for cell survival. The acidosis that ensues forces the cell to remove excess hydrogen ion through the Na’/H’ exchanger. With movement of H’ out of the cell and Na’ into the cell, excess Na’ accumulates inside the cell. Blockade of Na’/H’ exchange has been shown to reduce infarct size, most likely through a reduction in CM necrosis [18]. Excess Na’ is removed via the Na’/Ca’ exchanger and results in large increases in intracellular Ca’”. This leads to excessive influx of water, resulting in the opening of the mitochondrial permeability transition pore (MPTP) and mitochondrial swelling. Blocking late Na’ channels during MI has been shown to decrease necrosis by preventing the subsequent rise of Ca’” that leads to MPTP opening and organelle and cell fragmentation [19].

Ruptured mitochondria release cellular components that increase apoptosis in addition to cell necrosis. Inhibition of MPTP in a model of ischemia/reperfusion (I/R) showed decreased apoptosis and necrotic cell death, implicating the importance of mitochondrial regulators of...
Apoptosis and necrosis [20]. Interestingly, cyclosporine, a known inhibitor of MPTP opening, was shown to reduce infarct size in a human pilot study (Figure 2) [21]. The mechanisms of apoptosis and necrosis through mitochondrial regulation reflect the delicate overlap that is observed during MI.

CM hyperoxic preconditioning has been shown to prevent MPTP opening and cytochrome c release during I/R, reflecting the importance of the initial hypoxic event that contributes to CM necrosis [22]. Calcium/calmodulin-dependent protein kinase II (CaMKII) inhibition has been shown to decrease necrotic cell death in CMs exposed to I/R, implicating this modulator in the signaling pathway of necrotic cell death [23]. Mice with knockout (KO) or non-functional cyclophilin D, a regulator of MPTP opening, were also less susceptible to cell death during I/R, indicating a role of cyclophilin D in MPTP-mediated necrosis [24,25].

Necrosis plays an important role in CM death during the initial ischemic insult. The processes of apoptosis, autophagy, and inflammation occur simultaneously as cells struggle to survive (Figure 1). Although necrotic cell death may not be a reversible process, apoptosis, autophagy, and inflammation can be manipulated to allow struggling CMs to survive during MI.

Apoptosis

Apoptosis is another major determinant of cell death during ischemia that peaks around 4.5 hours [26]. CM death in the peri-infarct zone is largely due to apoptosis and occurs in response to distinct cellular signals [27]. Apoptosis is mediated by the extrinsic pathway through cell surface signaling and the intrinsic pathway through intracellular stimuli and both pathways converging on the mitochondria. Activation of the extrinsic pathway in the heart has been shown to take place via interaction between Fas-ligand and tumor necrosis factor alpha (TNF-α). Mice deficient of the Fas-ligand gene in a model of I/R had no difference in infarct size compared to control animals suggesting that Fas is not a main contributor of apoptosis activation in CMs [28]. High-mobility group box 1 (HMGB1), a stress protein released by immune cells and CMs during ischemic injury, potentiates the apoptotic effects of TNF-α implicating its role in regulating CM apoptosis [29].

The intrinsic pathway has been found to play a more important role in regulating CM death during ischemic episodes than the extrinsic pathway [30]. Pro-apoptotic Bcl-2-associated-X protein (BAX) and BH3-only proteins, such as BNI1P3, help amplify the apoptotic cascade that result in the destabilization of the outer mitochondrial membrane and release of calcium and other pro-apoptotic molecules such as cytochrome c that activate caspases in the cell [31]. Bcl-2 opposes apoptosis in the ischemic myocardium [32] but this protein has been shown to be down-regulated during ischemia; thus promoting cell death [33]. Interestingly, ischemic preconditioning increases Bcl-2 expression via the JAK-STAT signaling pathway explaining a possible cardioprotective role early in the ischemic process [34]. Also, suppression of BAX and p53 mitogen-activated protein kinase (p38 MAPK) phosphorylation and concurrent increased Akt-Bcl-2 signaling reduce apoptosis in the ischemic myocardium [35]. Infarcted BAX-KO mice had improved cardiac function demonstrating the detrimental role of apoptosis in CMs [36]. Inhibition of Akt phosphorylation allows for Akt activation and reduction of apoptosis during MI [37].

Other important regulators of apoptosis in the ischemic myocardium have also been identified. Reduction in p53 decreases apoptosis and promotes myocardial salvage during ischemia [38]. Deletion of p53 has also been shown to decrease apoptosis in CMs [39]. Mammalian target of rapamycin (mTOR) signaling has also been implicated in the myocardial apoptotic pathway as rapamycin activation of mTOR results in decreased apoptosis (Figure 2) [40]. Nicotinamide phosphoribosyltransferase (Nampt) is responsible for salvaging NAD+ in the cell and upregulation of this enzyme is associated with the downregulation of apoptosis [41]. Endonuclease-G (EndoG), a DNA degradative protein during apoptosis, is involved in DNA degradation during CM apoptosis in isolated CMs exposed to ischemia [42]. Also, inhibiting mitochondrial fission via mitofusion proteins has been shown to reduce infarct size in models of I/R [43].

Both intrinsic and extrinsic pathways converge on caspases that cleave important regulatory proteins that can result in cell death. Caspases-3 and -7 have been shown to be important in ischemic injury [44]. X-chromosome linked inhibitor of apoptosis protein (XIAP) is a pro-survival protein that has been shown to decrease apoptosis and promote CM survival during I/R when delivered via adenovirus vectors through inhibition of caspase-3 [45]. Inhibition of caspase activation reduces infarct size in models of MI showing an important correlation between apoptosis and CM survival during ischemia [46,47].

The process of apoptosis is a programmed mechanism for CM death that can be altered to halt the execution of struggling CMs. Manipulation of autophagic flux to minimize CM injury may further improve cell survival during ischemic events.

Autophagy

Autophagy is a process that occurs in healthy CMs to remove...
intracellular protein aggregates and organelles through a double membrane bound vesicle, the autophagosome, to lysosomes for degradation to maintain energy homeostasis [48]. In cultured CMs, glucose deprivation, a less severe simulation of the hypoxic conditions of ischemia, has also been shown to induce autophagy [49]. Pathological glucose deprivation, a less severe simulation of the hypoxic conditions of ischemia, has also been shown to induce autophagy [49].

Depletion of ATP levels during hypoxic conditions increases the ratio of AMP/ATP resulting in the activation of AMPK and inhibition of mTOR to activate autophagy (Figure 2). Also, the pro-apoptotic protein BNIP3 has been shown to activate autophagy during I/R in addition to regulating the opening of the MPTP [50,52]. Rises in intracellular calcium through depletion of sarcoplasmic reticulum stores and reactive oxygen species (ROS) have been shown to increase levels of autophagy in CMs as well [53,54].

Increased autophagy in CMs when exposed to ischemic conditions has been found to be more important in the acutely stunned myocardium than when exposed to chronic ischemic episodes, suggesting a vital role in the initial injury [55]. Autophagy during the initial ischemic insult has also been shown to be activated through an AMPK mechanism while autophagy during reperfusion was shown to be mainly stimulated through beclin-1 [49,56,57]. Mice exposed to I/R and oxidative stress displayed increases in beclin-1 expression, autophagic flux, and autophagosome formation [58]. The importance of autophagosome clearance by lysosome associated membrane protein-2 (LAMP2) has recently been shown to be due to enhanced cell death during I/R when clearance is impaired [59].

Upregulation of p62, a microtubule associated protein-1 light chain-3 (LC3)-binding protein involved in protein aggregation, and the ratio of LC3-II/I are indicators of autophagy during I/R [60,61]. Beclin-1 is also upregulated in response to ischemia and inhibited by the anti-apoptotic protein Bcl-2. It has been postulated that this interaction may modulate the ratio of cell survival to cell death [62]. Autophagy has been shown to have a role during ischemic episodes as measured by increases in Bcl-2-associated anathogene (BAG-1) and inhibition of autophagy through si-RNA of BAG-1 abolishes the cardioprotection afforded by the elevated autophagy [63]. In addition to enhancing the anti-apoptotic effects of the Bcl-2, it has been shown that the BAG-1 can induce protective autophagy in a model of I/R by linking heat shock proteins (HSP) Hsc70/Hsp70 with the proteasome [63]. In a model of I/R, treatment with rapamycin, a known activator of autophagy, resulted in improved functional recovery and showed that HSP 20 is involved in the blockade of autophagy during myocardial ischemia (Figure 2) [64].

In a permanent coronary artery occlusion model, autophagy was shown to be activated within 30 minutes of ischemia and noted to be strongly activated in the peri-infarct area [65]. Inhibition of mTOR with everolimus resulted in increased LC3 expression in the border zone of infarction, also suggesting autophagic activity is more prominent in the peri-infarct CMs (Figure 2) [66]. The enhanced autophagy in the peri-infarct area most likely explains why numerous studies have shown that autophagy is able to limit the size of infarction in various models of MI [67,68].

Autophagy’s role in the survival of dying CMs has shown to be a valuable player in the life and death of ischemic CMs. This process occurs simultaneously as cells succumb to the fatal events of necrosis and apoptosis unless mediators of these processes are altered to blunt these cellular responses. Inflammation and its mediators also play an important role in these cascades and have the potential to blunt necrosis, apoptosis, and autophagy. As they share many common mediators, the following section discusses the interplay between these processes and inflammation (Figure 2).

**Components of the Inflammatory Response**

The inflammatory response is vital to the healing process post-MI. The vascular endothelial cells, neutrophils, and macrophages become activated by pro-inflammatory mediators released from injured CMs. This response is initiated and amplified by ischemia and hypoxia followed by necrosis at the site of injury [69]. During acute MI, the...
inflammatory response results in the amplification of CM destruction due to vascular dysfunction, release of pro-apoptotic cytokines, recruitment of inflammatory cells, and cell-mediated mechanisms [70-75].

Pro-inflammatory gene transcription and cell activation

Hypoxia-driven mechanisms induce the activation of pro-inflammatory transcription factors and inflammatory cell activation during acute MI. Hypoxia inducible factor-1α (HIF-1α) degradation is driven by ubiquitin proteasomes and elevated levels of this transcription factor during hypoxia result in the expression of many pro-inflammatory proteins [76-80]. Under similar conditions, up-regulation of TNF-α and p38 MAPK also occurs [81]. Hypoxic activation of PKCa and AGEs/RAGE/PKCβII/c-Jun pathways induce early growth response-1 (EGR-1) expression that upregulates inflammatory and prothrombotic genes in endothelial cells [82,83]. EGR-1 has also been implicated in TNF-α gene regulation [84].

Production and release of TNF-α signifies the initial amplification phase in the inflammatory response. TNF-α signaling mediates many cellular pathways resulting in cell damage, apoptosis, and the regulation of inflammatory response genes (Figure 2). TNF-α activates inducible nitric oxide synthase (iNOS), elevating nitric oxide (NO) levels in CMs [85]. NO upregulates p53, BAX, and causes mitochondrial release of cytochrome c, resulting in apoptosis [86]. Furthermore, elevated NO and ROS levels along with activation of hypoxia-induced PKC-dependent signaling leads to nuclear translocation of NF-κB and the upregulation of TNF-α, IL-6, and IL-10 [87,88]. TNF-α has been shown to induce NF-κB translocation in cultured CMs promoting inflammatory gene expression and cytokine cascade activation (Figure 2) [89]. TNF-α-KO mice during MI showed a significant reduction in inflammation, matrix degradation, metalloproteinase activity, and apoptosis [90]. TNF-α and NF-κB reciprocal stimulation signifies a synergistic amplification during MI leading to the upregulation of these genes and signaling pathways that enhance the inflammatory process. Cells adjacent to the site of injury are activated by mechanisms discussed previously or through cellular signaling. Caspase-8, induced by TNF-α, causes ryanodine receptor-2 channel leakage and a rise in intracellular calcium causing CM dysfunction [91].

After the initial hypoxic conditions, interleukins, and cytokines enter the intercellular space. Induction of inflammatory genes occurs in a concentric manner from the site of initial insult [92]. Cell damage is inflicted by ROS through the oxidation of many cellular components. These factors cause CM damage and upregulate pro-inflammatory genes in nearby cells [90,93,94]. Hypoxia induces production of ROS due to depletion of the glutathione reducto pathway, mitochondrial dysfunction, xanthine oxidase, and NADPH oxidase [95-98]. TNF-α downregulates the expression of antioxidant defense mechanisms causing a further increase in ROS damage [94]. The acute phase of the inflammatory response has been shown to be concentrated in the infarct zone while interleukin and TNF-α activation are most heavily concentrated in the peri-infarct zone [92]. Centrally located CMs near the area of insult succumb to death through necrosis, apoptosis, or cell-mediated mechanisms resulting in the expansion of the infarct into the peri-infarct zone [99].

Mast cell activation

HIF-1α transcription activity primes mast cells for degranulation by upregulating histamine production [79]. Purine salvage pathway dysfunction due to hypoxic inhibition of adenosine kinase leads to increased extracellular levels of inosine and adenosine in CMs resulting in the activation of mast cells [73,100,101]. Mast cell activation triggers rapid degranulation releasing pre-formed granules containing TNF-α, histamine, tryptase, and chymase [73,74,102-105]. Inhibition of mast cell degranulation has been shown to decrease oxidative CM injury, reduce plasma histamine levels, and reduce infarct size [106,107]. Histological observations have also shown leukocyte clustering around degranulated mast cells and a tryptase-induced pro-inflammatory response in endothelial cells during MI [108].

Vascular dysfunction

Hypoxia, histamine, typtase, and angiotensin II induce cardiac vascular endothelial cell expression of P-Selectin, ICAM-1, VCAM-1, and VEGF-1; increasing the permeability of the vasculature and allowing leukocyte and lymphocyte infiltration [73,77,78,108-110]. HIF-1α also has been shown to increase expression of the paracrine VEGF-1 in the endothelial cells of cardiac vasculature which is known to be a more potent inducer of vascular permeability than histamine [77,78]. Murine models of MI have demonstrated that hypoxia-induced activation of p38 MAPK has a significant role in the upregulation of adhesion molecules (P-Selectin, ICAM-1) in endothelial cells [109]. Hypoxia also induces shedding of the endothelial glycoalyx membrane and enhances expression of platelet activating factor (PAF) to promote thrombosis [74,111,112].

P-selectin, E-selectin, VCAM, and ICAM play a key role in leukocyte adhesion to the vascular endothelium and subsequent extravasation [110,113,114]. Under hypoxic conditions, histamine-H1 induces exocytosis of pre-packaged P-Selectin to the plasma membrane of endothelial cells [103,115,116]. TNF-α and IL-1 stimulate de-novo synthesis of E-selectin and subsequent expression through NF-κB [117-119]. Angiotensin II has been shown to induce VCAM-1 expression in vascular endothelial cells and promote neutrophil accumulation through the release neutrophil chemotactrants during MI [110,120]. Angiotensin II, in an autocrine manner, participates in the induction of oxidative stress while suppressing antioxidant defenses [121]. ROS induce endothelial expression of monocyte chemotactic protein-1 (MCP-1) through NF-κB [122]. Hypoxia, TNF-α, IL-1β, and LPS have been shown to induce expression of ICAM-1 on the vascular endothelial surface [81,109,123]. VCAM-1 and ICAM-1 interact with alpha-4 integrin (VLA-4) expressed on B-lymphocytes, and beta-2 integrins expressed on neutrophils and monocytes/macrophages resulting in extravasation [124,125].

Intimal endothelial shedding, release of PAF, and increased neutrophil adhesion to the microvasculature leads to a subsequent expansion in infarct size [126]. Activation of endothelial cells causes the release of P-selectin resulting in activation of platelets and thrombus formation [127]. Neutrophil activation and release of tissue factor results in coagulation activation [128]. PAF is induced by the action of thrombin on the endothelial cells and acts as a chemoattractant of neutrophils [129]. I/R models have shown that PAF increases thromboxane and leukotriene levels causing vasoconstriction [130]. Furthermore, angiotensin II has been shown to induce COX-2 expression through the p38 MAPK pathway resulting in counteractive vasodilation [131]. The balance between vascular constriction and dilation plays a critical role in infarct expansion.

Neutrophil infiltration

Chemotaxis and activation of neutrophils is mediated by death associated molecular pattern (DAMP)-toll like receptor (TLR)-4
signaling. C5a, PAF, and IL-8 [111,132-135]. HIF-1α in neutrophils results in the upregulation of chemotactic receptor expression causing increased neutrophil recruitment to the site of injury in acute MI [80]. DAMP activation of TLR-4 signaling results in myeloid differentiation factor 88 (MyD88) activation of NF-κB [136]. MyD88 deficient mice showed improved contractility, decreased neutrophil recruitment, and decreased expression of pro-inflammatory mediators MCP-1 and ICAM-1 [137,138]. Shifting the TLR mediated MyD88-dependent NF-κB pathway to a PI3K/Akt pathway using glucan phosphate in a model of I/R reduced infarct size [136]. Mice deficient in TLR-4 showed a reduction in infarct size, neutrophil accumulation, lipid peroxide, and complement deposition [139]. IL-6 induced-expression of ICAM-1 in CMs targets these cells for neutrophil induced-injury (Figure 2) [140]. Additionally, increasing levels of DAMPs activate constitutively expressed TLR-4 on CMs and increase expression of IL-6 [137,141].

Chemoattractant receptors mediate neutrophil recruitment through the binding of chemokines during MI [142]. Plasma C5a levels have been shown to increase as early as 5 minutes post-MI and progressively increase for 3 to 4.5 hours acting as a chemoattractant for neutrophils [143,144]. MI models of rats treated with C3 inactivator showed decreased levels of leukocyte and neutrophil infiltration [145]. PAF also acts as a chemoattractant of neutrophils to the infarct site by upregulating beta-2 integrin and shedding the neutrophil-endothelial homing mediator, L-selectin [129,146,147]. Induction of neutrophils by PAF also upregulates the production of ROS and subsequently primes neutrophils for respiratory burst-mediated cell death [148]. IL-8 is induced by the action of HIF-1α, PI3K/Akt, and p38 MAPK in the vascular endothelium [149]. Plasma levels of IL-8 have been shown to rise slowly in acute MI, suggesting a second wave of neutrophil recruitment by neutrophils themselves [143,150,151].

Infiltration of the vascular endothelium is mediated through ICAM-1-beta-2 integrin (CD18) extravasation. Blockade of P-Selectin during I/R has shown a decrease in infarct size and neutrophil infiltration [152]. CD18 blockade has also been shown to decrease neutrophil infiltration during I/R [109]. Neutrophil infiltration is rapid and infiltration is faster in models of I/R compared to permanent coronary ligation [75,153]. Furthermore, neutrophil infiltration is directly proportional to infarct size [75].

Lymphocytes

Autoimmunity against cardiac troponin-I (cTnI) has been shown to have a role in the acute immune response through production of anti-cTnI antibodies [154]. B-cell infiltration in acute MI leads to production of auto-heart IgM and activation of the classical complement cascade [155]. Dendritic cell precursors are recruited to the infarct site and begin presenting cardiac autoantigens via major histocompatibility complex (MHC) to infiltrating lymphocytes and releases IL-6, IL-10, IL-12, and TNF-α [156,157]. Activation of CD8+ cytotoxic T-cells initiates a cell-mediated autoimmune response against CMs via MHC-restricted killing and also attacks healthy CMs, leading to further CM dysfunction [158]. The CD4/CD8 ratio is low post-MI indicating a higher activity of cell-mediated killing [159]. Activation of CD4+ T-cells to cardiac autoantigens leads to suppression of the Th1 immune response and upregulation of the Th2 response leading to anti-heart IgG and decreased cell-mediated killing that has been shown to be cardioprotective during MI [160].

The inflammatory response is therefore a multi-cell and multi-factorial process that is regulated by many signaling mediators that are common to the processes of necrosis, apoptosis, and autophagy. The equilibrium between these pathways determines the delicate balance between CM survival and death post-MI (Figure 2).

Conclusion

The initial ischemic insult during acute MI initiates the cellular processes of necrosis, apoptosis, autophagy, and inflammation. The hypoxic environment causes CM necrosis and elicits an inflammatory response with most damage occurring close to the area of coronary occlusion [99]. The inflammatory pro-apoptotic cytokines compounded by activation of the intrinsic apoptotic pathway results in the programmed death of ischemic CMs. During these processes, CMs are able to elicit the cardioprotective process of autophagy to alter the fate of struggling CMs in order to survive the hypoxic cellular conditions and prevent cell death. The interaction between each of these cellular processes with common signaling mediators (Figure 2) will determine the fate of ischemic CMs with the balance that occurs in the peri-infarct area most likely playing a vital role in CM preservation of functional capacity via appropriate autophagic flux and mitigation of apoptosis and inflammation [27,65,92]. With an in-depth understanding of the factors that determine the balance between cellular survival and death of CMs in response to acute MI, novel therapeutics can be developed to promote CM survival during the initial ischemic insult and improve cardiac function following MI.

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