Cellular Pathways of Death and Survival in Acute Myocardial Infarction

Wesley T. O'Neal*, William F. Griffin, Susan D. Kent and Jitka A. I. Virag

Department of Physiology, Brody School of Medicine, East Carolina University, Greenville, NC, USA

Abstract

During acute myocardial infarction (MI), the cumulative loss of functioning cardiomyocytes (CM) 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.

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 coronary 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 nonperfused myocardium, yet it neglects the reversal of the cellular responses to ischemic insult [6]. Altering the initial cellular responses to ischemia may enhance CM survival and ultimately preserve 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 carbenoxolone, 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^{2+} exchanger and results in large increases in intracellular Ca^{2+}. 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^{2+} 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

*Corresponding author: Wesley T. O'Neal, Department of Physiology, LSB-235, Brody School of Medicine, East Carolina University, 600 Moye Blvd, Greenville, NC 27834, USA, Tel: +12527441878; Fax: +12527445477; E-mail: onealwe08@ecu.edu
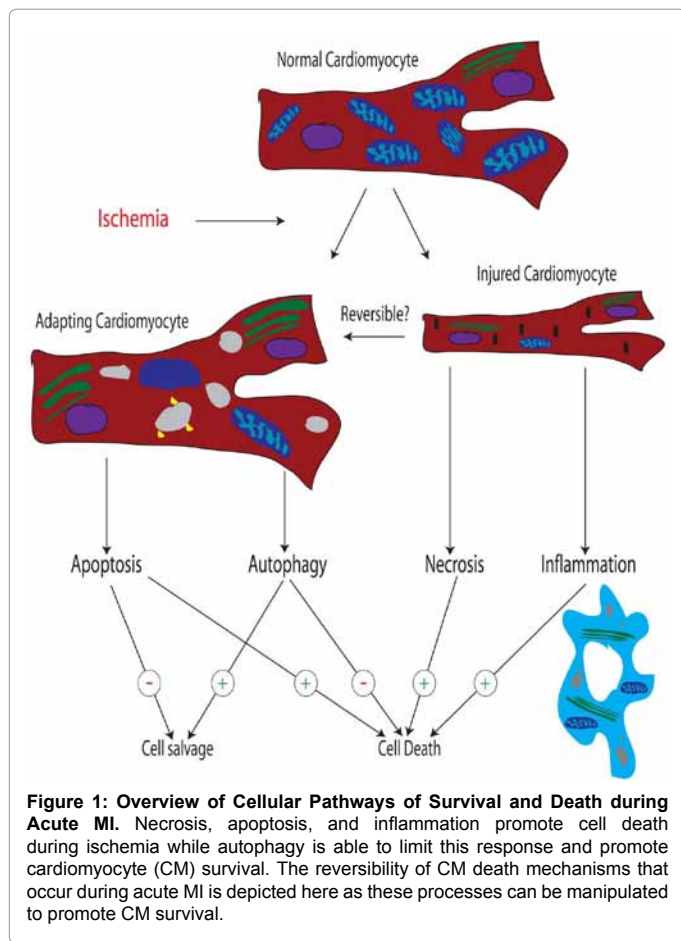
Figure 1: Overview of Cellular Pathways of Survival and Death during Acute MI. Necrosis, apoptosis, and inflammation promote cell death during ischemia while autophagy is able to limit this response and promote cardiomyocyte (CM) survival. The reversibility of CM death mechanisms that occur during acute MI is depicted here as these processes can be manipulated to promote CM survival.

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 BNIP3, 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 p38 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

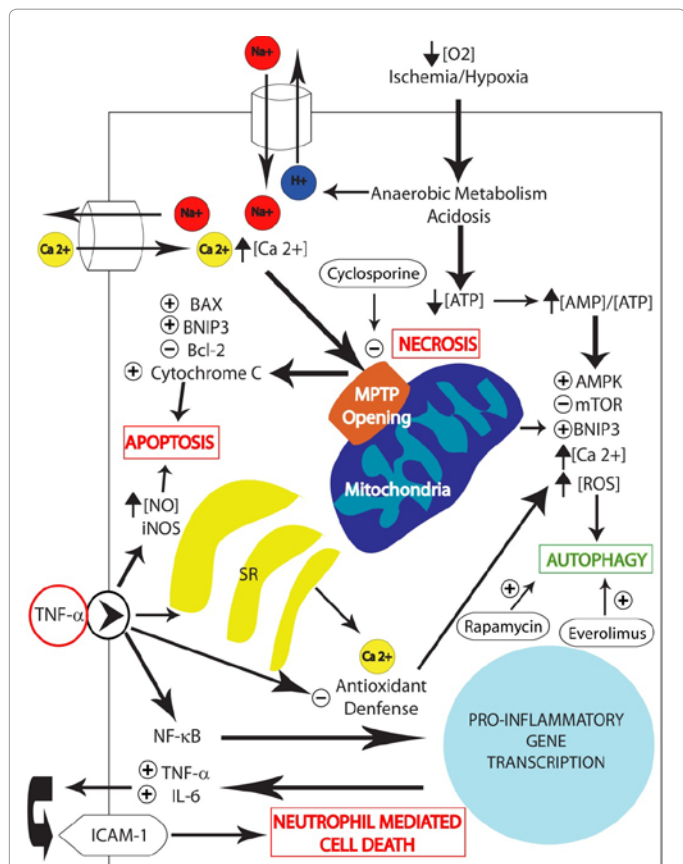Autophagy is a process that occurs in healthy CMs to remove

Figure 2: Common Signaling Pathways of Necrosis, Apoptosis, Autophagy, and Inflammation during Acute MI. Under ischemic conditions, a transition from aerobic metabolism to anaerobic metabolism induces acidosis and depletion of ATP levels. The Na^+/H^+ exchanger removes excess H^+ out of the cell and Na^+ into the cell. Excess Na^+ is removed via the Na^+/Ca^{2+} exchanger causing increases in intracellular Ca^{2+} and opening of the MPTP. Cyclosporine has been shown to reduce infarct size through inhibition of MPTP opening. Mitochondria release intrinsic pro-apoptotic mediators (BAX, BNIP3, and cytochrome c) and decrease the release of anti-apoptotic proteins (Bcl-2) to increase apoptosis and necrosis. Activation of apoptosis mediated by the extrinsic pathway in CMs is through TNF-α induction of iNOS and elevated levels of NO. TNF-α decreases antioxidant defenses causing an increase in ROS. Depletion of ATP levels increases the ratio of AMP/ATP resulting in the activation of AMPK and inhibition of mTOR to activate autophagy. BNIP3, TNF-α-induced rise in intracellular Ca^{2+} through disruption of the sarcoplasmic reticulum (SR), opening of the MPTP, and increased ROS levels also induce autophagy. Rapamycin and everolimus induce autophagy through interaction with mTOR. TNF-α induces NF-κB translocation and the subsequent upregulation of more TNF-α and IL-6. IL-6 induces expression of ICAM-1 in CMs and targets these cells for neutrophil-mediated cell death.

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 events such as ischemia employ this mechanism to remove intracellular waste and recycle substrates for ATP generation to promote cell survival [50,51].

Depletion of ATP levels during hypoxic conditions increases the ratio of AMP/ATP resulting in the activation of AMP activated protein kinase (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 increase during ischemic episodes as measured by increases in Bcl-2-associated athanogene (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 JNK and p38 MAPK also occurs [81]. Hypoxic activation of PKCα 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 redox 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 glycocalyx 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 chemoattractants 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]. My-D88 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-KB 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.

References

1. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, et al. (2010) Executive summary: heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation 121: 948-954.

2. Trogdon JG, Finkelstein EA, Nwaise IA, Tangka FK, Orenstein D (2007) The economic burden of chronic cardiovascular disease for major insurers. Health Promot Pract 8: 234-242.

3. White HD, Chew DP (2008) Acute myocardial infarction. Lancet 372: 570-584.

4. Jugdutt BI (2012) Ischemia/Infarction. Heart Fail Clin 8: 43-51.

5. Frangogiannis NG, Smith CW, Entman ML (2002) The inflammatory response in myocardial infarction. Cardiovasc Res 53: 31-47.

6. Keeley EC, Hillis LD (2007) Primary PCI for myocardial infarction with ST-segment elevation. N Engl J Med 356: 47-54.

7. Kanamori H, Takemura G, Goto K, Maruyama R, Tsujimoto A, et al. (2011) The role of autophagy emerging in postinfarction cardiac remodelling. Cardiovasc Res 91: 330-339.

8. French CJ, Taatjes DJ, Sobel BE (2010) Autophagy in myocardium of murine hearts subjected to ischemia followed by reperfusion. Histochem Cell Biol 134: 519-526.

9. Hamacher-Brady A, Brady NR, Gottlieb RA (2006) Enhancing macroautophagy protects against ischemia/reperfusion injury in cardiac myocytes. J Biol Chem 281: 29776-29787.

10. Shaw J, Kirshenbaum LA (2008) Molecular regulation of autophagy and apoptosis during ischemic and non-ischemic cardiomyopathy. Autophagy 4: 427-434.

11. Kung G, Konstantinidis K, Kitsis RN (2011) Programmed necrosis, not apoptosis, in the heart. Circ Res 108: 1017-1036.

12. Reimer KA, Jennings RB (1979) The "wavefront phenomenon" of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. Lab Invest 40: 633-644.

13. Tavernarakis N (2007) Cardiomyocyte necrosis: alternative mechanisms, effective interventions. Biochim Biophys Acta 1773: 480-482.

14. Golstein P, Kroemer G (2007) Cell death by necrosis: towards a molecular definition. Trends Biochem Sci 32: 37-43.

15. Kajstura J, Cheng W, Reiss K, Clark WA, Sonnenblick EH, et al. (1996) Apoptotic and necrotic myocyte cell deaths are independent contributing variables of infarct size in rats. Lab Invest 74: 86-107.

16. Shintani-Ishida K, Unuma K, Yoshida K (2009) Ischemia enhances translocation of connexin43 and gap junction intercellular communication, thereby propagating contraction band necrosis after reperfusion. Circ J 73: 1661-1668.

17. Huang S, Chen HH, Yuan H, Dai G, Schuhle DT, et al. (2011) Molecular MRI of acute necrosis with a novel DNA-binding gadolinium chelate: kinetics of cell death and clearance in infarcted myocardium. Circ Cardiovasc Imaging 4: 729-737.

18. Yamada K, Matsui K, Ogawa S, Yamamoto S, Mori M, et al. (2005) Reduction of myocardial infarct size by SM-198110, a novel Na+/H+ exchange inhibitor, in rabbits. Naunyn Schmiedebergs Arch Pharmacol 371: 408-419.

19. Hale SL, Leeka JA, Kloner RA (2006) Improved left ventricular function and reduced necrosis after myocardial ischemia/reperfusion in rabbits treated with ranolazine, an inhibitor of the late sodium channel. J Pharmacol Exp Ther 318: 418-423.

20. Bognar Z, Kalai T, Palfi A, Hanto K, Bognar B, et al. (2006) A novel SOD-mimetic permeability transition inhibitor agent protects ischemic heart by inhibiting both apoptotic and necrotic cell death. Free Radic Biol Med 41: 835-848.

21. Piot C, Croisille P, Staat P, Thibault H, Rioufol G, et al. (2008) Effect of cyclosporine on reperfusion injury in acute myocardial infarction. N Engl J Med 359: 473-481.

22. Petrosillo G, Di Venosa N, Moro N, Colantuono G, Paradies V, et al. (2011) In vivo hyperoxic preconditioning protects against rat-heart ischemia/reperfusion injury by inhibiting mitochondrial permeability transition pore opening and cytochrome c release. Free Radic Biol Med 50: 477-483.

23. Vila-Petroff M, Salas MA, Said M, Valverde CA, Sapia L, et al. (2007) CaMKII inhibition protects against necrosis and apoptosis in irreversible ischemia-reperfusion injury. Cardiovasc Res 73: 689-698.

24. Baines CP, Kaiser RA, Purcell NH, Blair NS, Osinska H, et al. (2005) Loss of cyclophilin D reveals a critical role for mitochondrial permeability transition in cell death. Nature 434: 658-662.

25. Nakagawa T, Shimizu S, Watanabe T, Yamaguchi O, Otsu K, et al. (2005) Cyclophilin D-dependent mitochondrial permeability transition regulates some necrotic but not apoptotic cell death. Nature 434: 652-658.

26. Anversa P, Cheng W, Liu Y, Leri A, Redaelli G, et al. (1998) Apoptosis and myocardial infarction. Basic Res Cardiol 93: 8-12.

27. Abbate A, Bussani R, Biondi-Zoccai GG, Santini D, Petrolini A, et al. (2005) Infarct-related artery occlusion, tissue markers of ischaemia, and increased apoptosis in the peri-infarct viable myocardium. Eur Heart J 26: 2039-2045.

28. Tekin D, Xi L, Kukreja RC (2006) Genetic deletion of fas receptors or Fas ligands does not reduce infarct size after acute global ischemia-reperfusion in isolated mouse heart. Cell Biochem Biophys 44: 111-117.

29. Xu H, Yao Y, Su Z, Yang Y, Kao R, et al. (2011) Endogenous HMGB1 contributes to ischemia-reperfusion-induced myocardial apoptosis by potentiating the effect of TNF-α/JNK. Am J Physiol Heart Circ Physiol 300: H913-21.

30. Gomez L, Chavanis N, Argaud L, Chalabreysse L, Gateau-Roesch O, et al. (2005) Fas-independent mitochondrial damage triggers cardiomyocyte death after ischemia-reperfusion. Am J Physiol Heart Circ Physiol 289: H2153-2158.

31. Kubasiak LA, Hernandez OM, Bishopric NH, Webster KA (2002) Hypoxia and acidosis activate cardiac myocyte death through the Bcl-2 family protein BNIP3. Proc Natl Acad Sci U S A 99: 12825-12830.

32. Maulik N, Engelman RM, Rousou JA, Flack JE, 3rd, Deaton D, et al. (1999) Ischemic preconditioning reduces apoptosis by upregulating anti-death gene Bcl-2. Circulation 100: II369-375.

33. Hattori R, Hernandez TE, Zhu L, Maulik N, Otani H, et al. (2001) An essential role of the antioxidant gene Bcl-2 in myocardial adaptation to ischemia: an insight with antisense Bcl-2 therapy. Antioxid Redox Signal 3: 403-413.

34. You L, Li L, Xu Q, Ren J, Zhang F (2011) Postconditioning reduces infarct size and cardiac myocyte apoptosis via the opioid receptor and JAK-STAT signaling pathway. Mol Biol Rep 38: 437-443.

35. Kato K, Yin H, Agata J, Yoshida H, Chao L, et al. (2003) Adrenomedullin gene delivery attenuates myocardial infarction and apoptosis after ischemia and reperfusion. Am J Physiol Heart Circ Physiol 285: H1506-1514.

36. Hochhauser E, Cheporko Y, Yasovich N, Pinchas L, Offen D, et al. (2007) Bax deficiency reduces infarct size and improves long-term function after myocardial infarction. Cell Biochem Biophys 47: 11-20.

37. Sugano M, Tsuchida K, Hata T, Makino N (2005) RNA interference targeting SHP-1 attenuates myocardial infarction in rats. FASEB J 19: 2054-2056.

38. Naito AT, Okada S, Minamino T, Iwanaga K, Liu ML, et al. (2010) Promotion of CHIP-mediated p53 degradation protects the heart from ischemic injury. Circ Res 106: 1692-1702.

39. Matsusaka H, Ide T, Matsushima S, Ikeuchi M, Kubota T, et al. (2006) Targeted deletion of p53 prevents cardiac rupture after myocardial infarction in mice. Cardiovasc Res 70: 457-465.

40. Khan S, Salloum F, Das A, Xi L, Vetrovec GW, et al. (2006) Rapamycin confers preconditioning-like protection against ischemia-reperfusion injury in isolated mouse heart and cardiomyocytes. J Mol Cell Cardiol 41: 256-264.

41. Hsu CP, Oka S, Shao D, Hariharan N, Sadoshima J (2009) Nicotinamide phosphoribosyltransferase regulates cell survival through NAD+ synthesis in cardiac myocytes. Circ Res 105: 481-491.

42. Zhang J, Ye J, Altafaj A, Cardona M, Bahi N, et al. (2011) EndoG links Bnip3-induced mitochondrial damage and caspase-independent DNA fragmentation in ischemic cardiomyocytes. PLoS One 6: e17998.

43. Ong SB, Subrayan S, Lim SY, Yellon DM, Davidson SM, et al. (2010) Inhibiting mitochondrial fission protects the heart against ischemia/reperfusion injury. Circulation 121: 2012-2022.

44. Chapman JG, Magee WP, Stukenbrok HA, Beckius GE, Milici AJ, et al. (2002) A novel nonpeptidic caspase-3/7 inhibitor, (S)-(+)-5-[1-(2-methoxymethylpyrrolidinyl)sulfonyl]isatin reduces myocardial ischemic injury. Eur J Pharmacol 456: 59-68.

45. Kim SJ, Kuklov A, Crystal GJ (2011) In vivo gene delivery of XIAP protects against myocardial apoptosis and infarction following ischemia/reperfusion in conscious rabbits. Life Sci 88: 572-577.

46. Holly TA, Drincic A, Byun Y, Nakamura S, Harris K, et al. (1999) Caspase inhibition reduces myocyte cell death induced by myocardial ischemia and reperfusion in vivo. J Mol Cell Cardiol 31: 1709-1715.

47. Chandrashekhar Y, Sen S, Anway R, Shuros A, Anand I (2004) Long-term caspase inhibition ameliorates apoptosis, reduces myocardial troponin-I cleavage, protects left ventricular function, and attenuates remodeling in rats with myocardial infarction. J Am Coll Cardiol 43: 295-301.

48. Tannous P, Zhu H, Nemchenko A, Berry JM, Johnstone JL, et al. (2008) Intracellular protein aggregation is a proximal trigger of cardiomyocyte autophagy. Circulation 117: 3070-3078.

49. Matsui Y, Takagi H, Qu X, Abdellatif M, Sakoda H, et al. (2007) Distinct roles of autophagy in the heart during ischemia and reperfusion: roles of AMP-activated protein kinase and Beclin 1 in mediating autophagy. Circ Res 100: 914-922.

50. Dong Y, Undyala VV, Gottlieb RA, Mentzer RM, Jr., Przyklenk K (2010) Autophagy: definition, molecular machinery, and potential role in myocardial ischemia-reperfusion injury. J Cardiovasc Pharmacol Ther 15: 220-230.

51. Przyklenk K, Undyala VV, Wider J, Sala-Mercado JA, Gottlieb RA, et al. (2011) Acute induction of autophagy as a novel strategy for cardioprotection: Getting to the heart of the matter. Autophagy 7: 432-433.

52. Hamacher-Brady A, Brady NR, Logue SE, Sayen MR, Jinno M, et al. (2007) Response to myocardial ischemia/reperfusion injury involves Bnip3 and autophagy. Cell Death Differ 14: 146-157.

53. Brady NR, Hamacher-Brady A, Yuan H, Gottlieb RA (2007) The autophagic response to nutrient deprivation in the hl-1 cardiac myocyte is modulated by Bcl-2 and sarco/endoplasmic reticulum calcium stores. FEBS J 274: 3184-3197.

54. Scherz-Shouval R, Shvets E, Fass E, Shorer H, Gil L, et al. (2007) Reactive oxygen species are essential for autophagy and specifically regulate the activity of Atg4. EMBO J 26: 1749-1760.

55. Yan L, Sadoshima J, Vatner DE, Vatner SF (2009) Autophagy in ischemic preconditioning and hibernating myocardium. Autophagy 5: 709-712.

56. Takagi H, Matsui Y, Hirotani S, Sakoda H, Asano T, et al. (2007) AMPK mediates autophagy during myocardial ischemia in vivo. Autophagy 3: 405-407.

57. Ma H, Guo R, Yu L, Zhang Y, Ren J (2011) Aldehyde dehydrogenase 2 (ALDH2) rescues myocardial ischaemia/reperfusion injury: role of autophagy paradox and toxic aldehyde. Eur Heart J 32: 1025-1038.

58. Hariharan N, Zhai P, Sadoshima J (2011) Oxidative stress stimulates autophagic flux during ischemia/reperfusion. Antioxid Redox Signal 14: 2179-2190.

59. Ma X, Liu H, Foyil SR, Godar RJ, Weinheimer CJ, et al. (2012) Impaired Autophagosome Clearance Contributes to Cardiomyocyte Death in Ischemia-Reperfusion Injury. Circulation.

60. Komatsu M, Waguri S, Koike M, Sou YS, Ueno T, et al. (2007) Homeostatic levels of p62 control cytoplasmic inclusion body formation in autophagy-deficient mice. Cell 131: 1149-1163.

61. Xiao J, Zhu X, He B, Zhang Y, Kang B, et al. (2011) MiR-204 regulates cardiomyocyte autophagy induced by ischemia-reperfusion through LC3-II. J Biomed Sci 18: 35.

62. Pattingre S, Tassa A, Qu X, Garuti R, Liang XH, et al. (2005) Bcl-2 antiapoptotic proteins inhibit Beclin 1-dependent autophagy. Cell 122: 927-939.

63. Gurusamy N, Lekli I, Gorbunov NV, Gherghiceanu M, Popescu LM, et al. (2009) Cardioprotection by adaptation to ischaemia augments autophagy in association with BAG-1 protein. J Cell Mol Med 13: 373-387.

64. Qian J, Ren X, Wang X, Zhang P, Jones WK, et al. (2009) Blockade of Hsp20 phosphorylation exacerbates cardiac ischemia/reperfusion injury by suppressed autophagy and increased cell death. Circ Res 105: 1223-1231.

65. Kanamori H, Takemura G, Goto K, Maruyama R, Ono K, et al. (2011) Autophagy limits acute myocardial infarction induced by permanent coronary artery occlusion. Am J Physiol Heart Circ Physiol 300: H2261-2271.

66. Buss SJ, Riffel JH, Katus HA, Hardt SE (2010) Augmentation of autophagy by mTOR-inhibition in myocardial infarction: When size matters. Autophagy 6: 304-306.

67. Huang C, Liu W, Perry CN, Yitzhaki S, Lee Y, et al. (2010) Autophagy and protein kinase C are required for cardioprotection by sulfaphenazole. Am J Physiol Heart Circ Physiol 298: H570-579.

68. Sala-Mercado JA, Wider J, Undyala VV, Jahania S, Yoo W, et al. (2010) Profound cardioprotection with chloramphenicol succinate in the swine model of myocardial ischemia-reperfusion injury. Circulation 122: S179-184.

69. Harris BH, Gelfand JA (1995) The immune response to trauma. Semin Pediatr Surg 4: 77-82.

70. Mezzaroma E, Toldo S, Farkas D, Seropian IM, Van Tassell BW, et al. (2011) The inflammasome promotes adverse cardiac remodeling following acute myocardial infarction in the mouse. Proc Natl Acad Sci U S A 108: 19725-19730.

71. Becker BF, Fischer J, Hartmann H, Chen CC, Sommerhoff CP, et al. (2011) Inosine, not adenosine, initiates endothelial glycocalyx degradation in cardiac ischemia and hypoxia. Nucleosides Nucleotides Nucleic Acids 30: 1161-1167.

72. Khatib SY, Farah H, El-Migdadi F (2001) Allopurinol enhances adenine nucleotide levels and improves myocardial function in isolated hypoxic rat heart. Biochemistry (Mosc) 66: 328-333.

73. Tilley SL, Wagoner VA, Salvatore CA, Jacobson MA, Koller BH (2000) Adenosine and inosine increase cutaneous vasopermeability by activating A(3) receptors on mast cells. J Clin Invest 105: 361-367.

74. Annecke T, Fischer J, Hartmann H, Tschoep J, Rehm M, et al. (2011) Shedding of the coronary endothelial glycocalyx: effects of hypoxia/reoxygenation vs ischaemia/reperfusion. Br J Anaesth 107: 679-686.

75. Smith EF 3rd, Egan JW, Bugelski PJ, Hillegass LM, Hill DE, et al. (1988) Temporal relation between neutrophil accumulation and myocardial reperfusion injury. Am J Physiol 255: H1060-1068.

76. Salceda S, Caro J (1997) Hypoxia-inducible factor 1alpha (HIF-1alpha) protein is rapidly degraded by the ubiquitin-proteasome system under normoxic conditions. Its stabilization by hypoxia depends on redox-induced changes. J Biol Chem 272: 22642-22647.

77. Lee SH, Wolf PL, Escudero R, Deutsch R, Jamieson SW, et al. (2000) Early expression of angiogenesis factors in acute myocardial ischemia and infarction. N Engl J Med 342: 626-633.

78. Roberts WG, Palade GE (1995) Increased microvascular permeability and endothelial fenestration induced by vascular endothelial growth factor. J Cell Sci 108: 2369-2379.

79. Jeong HJ, Moon PD, Kim SJ, Seo JU, Kang TH, et al. (2009) Activation of hypoxia-inducible factor-1 regulates human histidine decarboxylase expression. Cell Mol Life Sci 66: 1309-1319.

80. Dong F, Khalil M, Kiedrowski M, O'Connor C, Petrovic E, et al. (2010) Critical role for leukocyte hypoxia inducible factor-1alpha expression in post-myocardial infarction left ventricular remodeling. Circ Res 106: 601-610.

81. Sun HY, Wang NP, Halkos M, Kerendi F, Kin H, et al. (2006) Postconditioning attenuates cardiomyocyte apoptosis via inhibition of JNK and p38 mitogen-activated protein kinase signaling pathways. Apoptosis 11: 1583-1593.

82. Chang JS, Wendt T, Qu W, Kong L, Zou YS, et al. (2008) Oxygen deprivation triggers upregulation of early growth response-1 by the receptor for advanced glycation end products. Circ Res 102: 905-913.

83. Lo LW, Cheng JJ, Chiu JJ, Wung BS, Liu YC, et al. (2001) Endothelial exposure to hypoxia induces Egr-1 expression involving PKCalpha-mediated Ras/Raf-1/ERK1/2 pathway. J Cell Physiol 188: 304-312.

84. Kramer B, Meichle A, Hensel G, Charnay P, Kronke M (1994) Characterization of an Krox-24/Egr-1-responsive element in the human tumor necrosis factor promoter. Biochim Biophys Acta 1219: 413-421.

85. Song W, Lu X, Feng Q (2000) Tumor necrosis factor-alpha induces apoptosis via inducible nitric oxide synthase in neonatal mouse cardiomyocytes. Cardiovasc Res 45: 595-602.

86. Brune B, von Knethen A, Sandau KB (1999) Nitric oxide (NO): an effector of apoptosis. Cell Death Differ 6: 969-975.

87. Xuan YT, Tang XL, Banerjee S, Takano H, Li RC, et al. (1999) Nuclear factor-kappaB plays an essential role in the late phase of ischemic preconditioning in conscious rabbits. Circ Res 84: 1095-1109.

88. Zingarelli B, Hake PW, Yang Z, O'Connor M, Denenberg A, et al. (2002) Absence of inducible nitric oxide synthase modulates early reperfusion-induced NF-kappaB and AP-1 activation and enhances myocardial damage. FASEB J 16: 327-342.

89. Onai Y, Suzuki J, Kakuta T, Maejima Y, Haraguchi G, et al. (2004) Inhibition of IkappaB phosphorylation in cardiomyocytes attenuates myocardial ischemia/reperfusion injury. Cardiovasc Res 63: 51-59.

90. Sun M, Dawood F, Wen WH, Chen M, Dixon I, et al. (2004) Excessive tumor necrosis factor activation after infarction contributes to susceptibility of myocardial rupture and left ventricular dysfunction. Circulation 110: 3221-3228.

91. Fauconnier J, Meli AC, Thireau J, Roberge S, Shan J, et al. (2011) Ryanodine receptor leak mediated by caspase-8 activation leads to left ventricular injury after myocardial ischemia-reperfusion. Proc Natl Acad Sci U S A 108: 13258-13263.

92. LaFramboise WA, Bombach KL, Dhir RJ, Muha N, Cullen RF, et al. (2005) Molecular dynamics of the compensatory response to myocardial infarct. J Mol Cell Cardiol 38: 103-117.

93. Perrelli MG, Pagliaro P, Penna C (2011) Ischemia/reperfusion injury and cardioprotective mechanisms: Role of mitochondria and reactive oxygen species. World J Cardiol 3: 186-200.

94. Kaur K, Sharma AK, Dhingra S, Singal PK (2006) Interplay of TNF-alpha and IL-10 in regulating oxidative stress in isolated adult cardiac myocytes. J Mol Cell Cardiol 41: 1023-1030.

95. Such L, Alberola A, Gil F, Bendala E, Vina J, et al. (1993) Effect of glutathione on canine myocardial ischaemia without reperfusion. J Pharm Pharmacol 45: 298-302.

96. Waypa GB, Guzy R, Mungai PT, Mack MM, Marks JD, et al. (2006) Increases in mitochondrial reactive oxygen species trigger hypoxia-induced calcium responses in pulmonary artery smooth muscle cells. Circ Res 99: 970-978.

97. Duilio C, Ambrosio G, Kuppusamy P, DiPaula A, Becker LC, et al. (2001) Neutrophils are primary source of O2 radicals during reperfusion after prolonged myocardial ischemia. Am J Physiol Heart Circ Physiol 280: H2649-2657.

98. Scarabelli T, Stephanou A, Rayment N, Pasini E, Comini L, et al. (2001) Apoptosis of endothelial cells precedes myocyte cell apoptosis in ischemia/reperfusion injury. Circulation 104: 253-256.

99. Schaper J (1986) Ultrastructural changes of the myocardium in regional ischaemia and infarction. Eur Heart J 7: 3-9.

100. Bowditch J, Brown AK, Dow JW (1985) Accumulation and salvage of adenosine and inosine by isolated mature cardiac myocytes. Biochim Biophys Acta 844: 119-128.

101. Decking UK, Schlieper G, Kroll K, Schrader J (1997) Hypoxia-induced inhibition of adenosine kinase potentiates cardiac adenosine release. Circ Res 81: 154-164.

102. Frangogiannis NG, Lindsey ML, Michael LH, Youker KA, Bressler RB, et al. (1998) Resident cardiac mast cells degranulate and release preformed TNF-alpha, initiating the cytokine cascade in experimental canine myocardial ischemia/reperfusion. Circulation 98: 699-710.

103. Asako H, Kurose I, Wolf R, DeFrees S, Zheng ZL, et al. (1994) Role of H1 receptors and P-selectin in histamine-induced leukocyte rolling and adhesion in postcapillary venules. J Clin Invest 93: 1508-1515.

104. Wei CC, Hase N, Inoue Y, Bradley EW, Yahiro E, et al. (2010) Mast cell chymase limits the cardiac efficacy of Ang I-converting enzyme inhibitor therapy in rodents. J Clin Invest 120: 1229-1239.

105. Kinoshita M, Okada M, Hara M, Furukawa Y, Matsumori A (2005) Mast cell tryptase in mast cell granules enhances MCP-1 and interleukin-8 production in human endothelial cells. Arterioscler Thromb Vasc Biol 25: 1858-1863.

106. Rork TH, Wallace KL, Kennedy DP, Marshall MA, Lankford AR, et al. (2008) Adenosine A2A receptor activation reduces infarct size in the isolated, perfused mouse heart by inhibiting resident cardiac mast cell degranulation. Am J Physiol Heart Circ Physiol 295: H1825-1833.

107. Nistri S, Cinci L, Perna AM, Masini E, Bani D (2008) Mast cell inhibition and reduced ventricular arrhythmias in a swine model of acute myocardial infarction upon therapeutic administration of relaxin. Inflamm Res 57: S7-8.

108. Somasundaram P, Ren G, Nagar H, Kraemer D, Mendoza L, et al. (2005) Mast cell tryptase may modulate endothelial cell phenotype in healing myocardial infarcts. J Pathol 205: 102-111.

109. Gao F, Yue TL, Shi DW, Christopher TA, Lopez BL, et al. (2002) p38 MAPK inhibition reduces myocardial reperfusion injury via inhibition of endothelial adhesion molecule expression and blockade of PMN accumulation. Cardiovasc Res 53: 414-422.

110. Tummala PE, Chen XL, Sundell CL, Laursen JB, Hammes CP, et al. (1999) Angiotensin II induces vascular cell adhesion molecule-1 expression in rat vasculature: A potential link between the renin-angiotensin system and atherosclerosis. Circulation 100: 1223-1229.

111. Milhoan KA, Lane TA, Bloor CM (1992) Hypoxia induces endothelial cells to increase their adherence for neutrophils: role of PAF. Am J Physiol 263: H956-962.

112. Morgan EN, Boyle EM, Jr., Yun W, Kovacich JC, Canty TG, Jr., et al. (1999) Platelet-activating factor acetylhydrolase prevents myocardial ischemia-reperfusion injury. Circulation 100: II365-368.

113. Jones SP, Trocha SD, Strange MB, Granger DN, Kevil CG, et al. (2000) Leukocyte and endothelial cell adhesion molecules in a chronic murine model of myocardial reperfusion injury. Am J Physiol Heart Circ Physiol 279: H2196-2201.

114. Beekhuizen H, van Furth R (1993) Monocyte adherence to human vascular endothelium. J Leukoc Biol 54: 363-378.

115. Akgur FM, Brown MF, Zibari GB, McDonald JC, Epstein CJ, et al. (2000) Role of superoxide in hemorrhagic shock-induced P-selectin expression. Am J Physiol Heart Circ Physiol 279: H791-797.

116. Yamakuchi M, Greer JJ, Cameron SJ, Matsushita K, Morrell CN, et al. (2005) HMG-CoA reductase inhibitors inhibit endothelial exocytosis and decrease myocardial infarct size. Circ Res 96: 1185-1192.

117. Suefuji H, Ogawa H, Yasue H, Sakamoto T, Miyao Y, et al. (2000) Increased plasma level of soluble E-selectin in acute myocardial infarction. Am Heart J 140: 243-248.

118. Ioculano M, Altavilla D, Squadrito F, Canale P, Squadrito G, et al. (1995) Tumour necrosis factor mediates E-selectin production and leukocyte accumulation in myocardial ischaemia-reperfusion injury. Pharmacol Res 31: 281-288.

119. Turner NA, Das A, O'Regan DJ, Ball SG, Porter KE (2011) Human cardiac fibroblasts express ICAM-1, E-selectin and CXC chemokines in response to proinflammatory cytokine stimulation. Int J Biochem Cell Biol 43: 1450-1458.

120. Nabah YN, Mateo T, Estelles R, Mata M, Zagorski J, et al. (2004) Angiotensin II induces neutrophil accumulation in vivo through generation and release of CXC chemokines. Circulation 110: 3581-3586.

121. Lu L, Quinn MT, Sun Y (2004) Oxidative stress in the infarcted heart: role of de novo angiotensin II production. Biochem Biophys Res Commun 325: 943-951.

122. Lakshminarayanan V, Lewallen M, Frangogiannis NG, Evans AJ, Wedin KE, et al. (2001) Reactive oxygen intermediates induce monocyte chemotactic protein-1 in vascular endothelium after brief ischemia. Am J Pathol 159: 1301-1311.

123. Myers CL, Wertheimer SJ, Schembri-King J, Parks T, Wallace RW (1992) Induction of ICAM-1 by TNF-alpha, IL-1 beta, and LPS in human endothelial cells after downregulation of PKC. Am J Physiol 263: C767-772.

124. Couture P, Paradis-Massie J, Oualha N, Thibault G (2009) Adhesion and transcellular migration of neutrophils and B lymphocytes on fibroblasts. Exp Cell Res 315: 2192-2206.

125. Hillis G, Taggart P, Dalsey W, Mangione A, Ma XL (2001) The expression of the CD18 leucocyte integrin in a rabbit model of acute myocardial infarction: a pilot study of temporal changes and relationship to infarct size. Cardiology 95: 35-39.

126. Barrabes JA, Mirabet M, Agullo L, Figueras J, Pizcueta P, et al. (2007) Platelet deposition in remote cardiac regions after coronary occlusion. Eur J Clin Invest 37: 939-946.

127. Oostingh GJ, Pozgajova M, Ludwig RJ, Krahn T, Boehncke WH, et al. (2007) Diminished thrombus formation and alleviation of myocardial infarction and reperfusion injury through antibody- or small-molecule-mediated inhibition of selectin-dependent platelet functions. Haematologica 92: 502-512.

128. Afshar-Kharghan V, Thiagarajan P (2006) Leukocyte adhesion and thrombosis. Curr Opin Hematol 13: 34-39.

129. Montrucchio G, Alloatti G, Mariano F, Comino A, Cacace G, et al. (1993) Role of platelet-activating factor in polymorphonuclear neutrophil recruitment in reperfused ischemic rabbit heart. Am J Pathol 142: 471-480.

130. Mickelson JK, Simpson PJ, Lucchesi BR (1988) Myocardial dysfunction and coronary vasoconstriction induced by platelet-activating factor in the post-infarcted rabbit isolated heart. J Mol Cell Cardiol 20: 547-561.

131. Scheuren N, Jacobs M, Ertl G, Schorb W (2002) Cyclooxygenase-2 in myocardium stimulation by angiotensin-II in cultured cardiac fibroblasts and role at acute myocardial infarction. J Mol Cell Cardiol 34: 29-37.

132. Sabroe I, Dower SK, Whyte MK (2005) The role of Toll-like receptors in the regulation of neutrophil migration, activation, and apoptosis. Clin Infect Dis 41: S421-426.

133. Abe Y, Kawakami M, Kuroki M, Yamamoto T, Fujii M, et al. (1993) Transient rise in serum interleukin-8 concentration during acute myocardial infarction. Br Heart J 70: 132-134.

134. Amsterdam EA, Stahl GL, Pan HL, Rendig SV, Fletcher MP, et al. (1995) Limitation of reperfusion injury by a monoclonal antibody to C5a during myocardial infarction in pigs. Am J Physiol 268: H448-457.

135. Guillen I, Blanes M, Gomez-Lechon MJ, Castell JV (1995) Cytokine signaling during myocardial infarction: sequential appearance of IL-1 beta and IL-6. Am J Physiol 269: R229-235.

136. Li C, Ha T, Kelley J, Gao X, Qiu Y, et al. (2004) Modulating Toll-like receptor mediated signaling by (1-->3)-beta-D-glucan rapidly induces cardioprotection. Cardiovasc Res 61: 538-547.

137. Boyd JH, Mathur S, Wang Y, Bateman RM, Walley KR (2006) Toll-like receptor stimulation in cardiomyoctes decreases contractility and initiates an NF-kappaB dependent inflammatory response. Cardiovasc Res 72: 384-393.

138. Feng Y, Zhao H, Xu X, Buys ES, Raher MJ, et al. (2008) Innate immune adaptor MyD88 mediates neutrophil recruitment and myocardial injury after ischemia-reperfusion in mice. Am J Physiol Heart Circ Physiol 295: H1311-H1318.

139. Oyama J, Blais C Jr, Liu X, Pu M, Kobzik L, et al. (2004) Reduced myocardial ischemia-reperfusion injury in toll-like receptor 4-deficient mice. Circulation 109: 784-789.

140. Kukielka GL, Smith CW, Manning AM, Youker KA, Michael LH, et al. (1995)

Induction of interleukin-6 synthesis in the myocardium. Potential role in postreperfusion inflammatory injury. Circulation 92: 1866-1875.

141. Piccinini AM, Midwood KS (2010) DAMPening inflammation by modulating TLR signalling. Mediators Inflamm pii: 672395.

142. Montecucco F, Lenglet S, Braunersreuther V, Pelli G, Pellieux C, et al. (2010) Single administration of the CXC chemokine-binding protein Evasin-3 during ischemia prevents myocardial reperfusion injury in mice. Arterioscler Thromb Vasc Biol 30: 1371-1377.

143. Ivey CL, Williams FM, Collins PD, Jose PJ, Williams TJ (1995) Neutrophil chemoattractants generated in two phases during reperfusion of ischemic myocardium in the rabbit. Evidence for a role for C5a and interleukin-8. J Clin Invest 95: 2720-2728.

144. Dreyer WJ, Michael LH, Nguyen T, Smith CW, Anderson DC, et al. (1992) Kinetics of C5a release in cardiac lymph of dogs experiencing coronary artery ischemia-reperfusion injury. Circ Res 71: 1518-1524.

145. Hill JH, Ward PA (1971) The phlogistic role of C3 leukotactic fragments in myocardial infarcts of rats. J Exp Med 133: 885-900.

146. Auchampach JA, Pieper GM, Cavero I, Gross GJ (1998) Effect of the platelet-activating factor antagonist RP 59227 (Tulopafant) on myocardial ischemia/reperfusion injury and neutrophil function. Basic Res Cardiol 93: 361-371.

147. Siminiak T, Egdell RM, O'Gorman DJ, Dye JF, Sheridan DJ (1995) Plasma-mediated neutrophil activation during acute myocardial infarction: role of platelet-activating factor. Clin Sci (Lond) 89: 171-176.

148. Ko W, Hawes AS, Lazenby WD, Calvano SE, Shin YT, et al. (1991) Myocardial reperfusion injury. Platelet-activating factor stimulates polymorphonuclear leukocyte hydrogen peroxide production during myocardial reperfusion. J Thorac Cardiovasc Surg 102: 297-308.

149. Kim KS, Rajagopal V, Gonsalves C, Johnson C, Kalra VK (2006) A novel role of hypoxia-inducible factor in cobalt chloride- and hypoxia-mediated expression of IL-8 chemokine in human endothelial cells. J Immunol 177: 7211-7224.

150. Akasaka Y, Morimoto N, Ishikawa Y, Fujita K, Ito K, et al. (2006) Myocardial apoptosis associated with the expression of proinflammatory cytokines during the course of myocardial infarction. Mod Pathol 19: 588-598.

151. Kilgore KS, Park JL, Tanhehco EJ, Booth EA, Marks RM, et al. (1998) Attenuation of interleukin-8 expression in C6-deficient rabbits after myocardial ischemia/reperfusion. J Mol Cell Cardiol 30: 75-85.

152. Wang K, Zhou X, Zhou Z, Tarakji K, Qin JX, et al. (2002) Recombinant soluble P-selectin glycoprotein ligand-Ig (rPSGL-Ig) attenuates infarct size and myeloperoxidase activity in a canine model of ischemia-reperfusion. Thromb Haemost 88: 149-154.

153. Fishbein MC, Maclean D, Maroko PR (1978) Experimental myocardial infarction in the rat: qualitative and quantitative changes during pathologic evolution. Am J Pathol 90: 57-70.

154. Volz HC, Buss SJ, Li J, Goser S, Andrassy M, et al. (2011) Autoimmunity against cardiac troponin I in ischaemia reperfusion injury. Eur J Heart Fail 13: 1052-1059.

155. Lachtermacher S, Esporcatte BL, Montalvao F, Costa PC, Rodrigues DC, et al. (2010) Cardiac gene expression and systemic cytokine profile are complementary in a murine model of post-ischemic heart failure. Braz J Med Biol Res 43: 377-389.

156. Kretzschmar D, Betge S, Windisch A, Pistulli R, Rohm I, et al. (2012) Recruitment of circulating dendritic cell precursors into the infarcted myocardium and pro-inflammatory response in acute myocardial infarction. Clin Sci (Lond) 123: 387-398.

157. Zhang J, Yu ZX, Fujita S, Yamaguchi ML, Ferrans VJ (1993) Interstitial dendritic cells of the rat heart. Quantitative and ultrastructural changes in experimental myocardial infarction. Circulation 87: 909-920.

158. Varda-Bloom N, Leor J, Ohad DG, Hasin Y, Amar M, et al. (2000) Cytotoxic T lymphocytes are activated following myocardial infarction and can recognize and kill healthy myocytes in vitro. J Mol Cell Cardiol 32: 2141-2149.

159. Syrjala H, Surcel HM, Ilonen J (1991) Low CD4/CD8 T lymphocyte ratio in acute myocardial infarction. Clin Exp Immunol 83: 326-328.

160. Hofmann U, Beyersdorf N, Weirather J, Podolskaya A, Bauersachs J, et al. (2012) Activation of CD4+ T lymphocytes improves wound healing and survival after experimental myocardial infarction in mice. Circulation 125: 1652-1663.