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Insight into the Pathophysiology of Myocardial Infarction

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ABSTRACT

Myocardial infarction is classified as the irreversible myocardial cell death following ischemia. Ischemia could be initiated as a result of atherosclerotic or variable non-atherosclerotic causes. Consequent effects of ischemia are primarily caused due to oxidative stress which is the main precursor of cell death. Myocardial cell death is triggered through intrinsic or extrinsic pathways. In both pathways, apoptosis has been clearly explained through different studies but recently, necroptosis was determined to be involved. The heart has negligible ability for regeneration, thus infarcted regions are healed by replacing dead cells with scar formation. Infarct healing is triggered through an inflammatory cascade, induced by alarmins released from dying cells. Clearance of dead cells by immune cells is followed with the activation of fibroblasts to promote deposition of extracellular matrix proteins. This review discusses the events involved following ischemia including the mechanistic signalling during injury, inflammation, and repair of the infarcted heart. Moreover, the possible complications are mentioned along with the established treatment strategies and some new therapeutic approaches for myocardial infarction.

Keywords: *Apoptosis, Inflammatory response, Ischemia, Myocardial infarction, Necroptosis.*

INTRODUCTION

Ischemic heart disease

Ischemia is a well-known condition of imbalance between myocardial oxygen supply and demand. The heart being an aerobic organ is very sensitive to interruption in oxygen balance. The causes of ischemia could be divided to: a) atherosclerotic; mainly known as type 1 myocardial ischemia and b) non-atherosclerotic; known as type 2 myocardial ischemia[1].

Type 1 myocardial ischemia (atherosclerotic)

Type 1 is mainly associated with acute coronary syndrome resulting from atherosclerotic plaque rupture with subsequent platelet aggregation and developed thrombus leading to occlusion of the coronary artery. Plaque rupture could be initiated depending on several factors including intrinsic stability of the atherosclerotic lesion which could be influenced by internal process causing its weakness or if the plaque has thin fibrous cap to be easily ruptured[2]. Other factors playing role in

plaque rupture involve physical stress represented by high blood pressure, heart rate and force of contraction. In addition, activation of sympathetic nervous system could induce atherosclerotic lesion[3].

Type 2 myocardial ischemia (non-atherosclerotic)

Myocardial oxygen demand and supply imbalance in this type is unrelated to atherosclerosis and could be induced by several factors including endothelial dysfunction as decreased release of endothelial vasodilators leading to abnormal vascular tone. In addition, continuous activation of sympathetic nervous system led to increased contractility resulting in imbalance between myocardial blood supply and demand to act as a common cause for type 1 and type 2 myocardial infarction[3]. A summary of other non-atherosclerotic causes of ischemia are mentioned in **Figure 1**. However, as reported in several studies, the majority of cases develop myocardial infarction resulting from coronary atherosclerotic diseases[4].

Pathophysiology of ischemia and structural changes in heart

Despite the cause of ischemia, the pathophysiological consequences are similar. The severity and duration of oxygen imbalance could range the myocardial dysfunction from rapid and fully reversible stage to prolonged contractility defect with reversible recovery stage termed as myocardial stunning and finally, irreversible necrotic stage termed as myocardial infarction[5].

Reversible stage

Within few minutes following ischemic initiation, decreased tissue oxygen level enforced anaerobic respiration associated with decreased ATP production and reduction in pH through lactate accumulation[6]. Moreover, reactive oxygen species (ROS) from electron transport chain are generated during early stages and may oxidize contractile proteins[7]. At this stage, the common ultrastructural change in cardiomyocytes is observed include the depletion of cytoplasmic glycogen granules as glycogen was increasingly consumed to replace decreased ATP production[8, 9]. Further changes reported was distortion of the transverse tubular system and mitochondrial swelling resulted from intracellular Ca^{+2} overload[10]. Up to this stage, full recovery is possible but limited to restoration of oxygen balance. If oxygen is rapidly restored within 15-20 min full recovery of myocardial function is familiar[11].

Myocardial stunning stage

Unfortunately, ROS as well as acidosis and depleted ATP levels for longer durations result in further impairment in contractile function and distortion of cardiomyocytes and ends with systolic dysfunction leading to delayed myocardial recovery as observed in myocardial stunning stage[12, 13]. The ATP-dependent Na-K-ATPase transporter is also impaired, thus normal electrolyte balance between Na^+ and K^+ was not achieved leading to edema and possible arrhythmias[10].

Myocardial infarction stage

Furtherly, excessive production of ROS in prolonged untreated ischemia (time interval above 30 min) leads to increased intracellular Ca^{+2} levels initiating irreversible myocardial necrosis (infarction) and followed by acute inflammatory response. During myocardial infarction, irreversible changes in heart are marked by sarcolemmal disruption along with mitochondrial permeability transition pores. Moreover, wavy fibres with interstitial edema are commonly observed possibly resulting from forceful systolic tugs by viable fibres or from marked increase in hydrostatic pressure caused by interstitial edema[14]. Necrotic cells urge the release of danger signals that amplify an inflammatory response to characterize the infarcted region with the presence of inflammatory infiltrates. Consequently, the infarcted tissues are replaced by fibrotic scar which lead to further depression of myocardial contractile force and thus promote remodelling of the myocardium with a variety of complications come into existence[5].

The extent of tissue damage in the course of myocardial infarction depends on various determinants including the oxygen demand of the affected region, adequacy of blood supply from adjacent coronary vessels, ratio between occluded vessel and the mass of myocardium supplied by it, duration of oxygen imbalance and degree of tissue response to the ischemic process[11].

Mechanistic pathway of Myocardial infarction

The normal physiology of the heart depends on aerobic respiration. In ischemia, decrease in oxygen levels switches the metabolism to anaerobic respiration associated with deposition of lactate, ATP depletion, Na^+ and Ca^{+2} overload along with inhibition of myocardial contractile function[15]. Moreover, ROS emitted from electron transport chain induces opening in mitochondrial transition pores and lipid peroxidation of cell membrane. Oxidative stress is immediately associated with inflammatory response enhanced by cytokines and complements[16].

Oxidative stress

The ROS-derived free radicals in cardiac myocytes originate from several sources during ischemia. Mainly, through leakage of electrons from disrupted mitochondrial electron transport chain

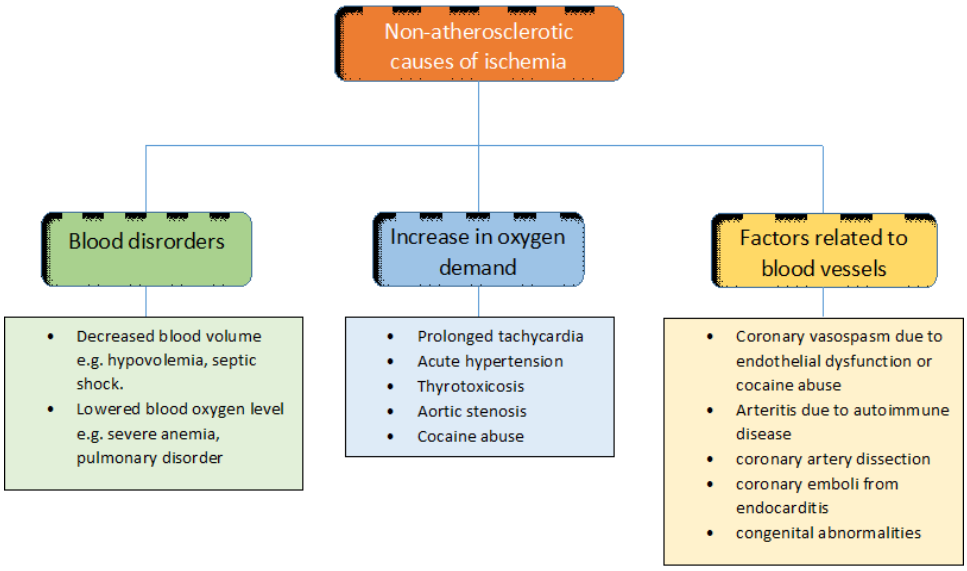

Figure 1. Schematic diagram of different non-atherosclerotic causes of ischemia

Moreover, ATP depletion and increased Ca^{+2} concentration during ischemia was involved in activation of Ca^{+2}-dependant proteases which convert xanthine dehydrogenase enzyme by selective proteolysis to the oxidase form thus using molecular oxygen as an electron acceptor to produce superoxide radicals[17]. Additional sources could be nitric oxide synthase (NOS), lipoxygenase (LOX)/cyclooxygenase (COX) pathways or auto-oxidation of various substances, particularly catecholamines[18]. Diverse forms of ROS are produced including superoxide ($O_2^{\cdot-}$), hydroxyl radical ($OH^{\cdot}$) or hydrogen peroxide (H_2O_2)[19]. Furthermore, O_2 combine with nitric oxide (NO) to generate cytotoxic peroxynitrite ($^{\cdot}ONOO$) thus losing the physiologic benefit of NO which had a role in regulation of cardiac function through coronary vasodilation, inhibition of platelet and neutrophil adhesion as well as modulation of cardiac contractile function[20].

Hereafter, the defence systems in the body are activated to scavenge and degrade ROS. Intracellular antioxidants involve superoxide dismutase (SOD), glutathione peroxidase (GSHPx) and catalase with the superiority to GSHPx due to its higher affinity to H_2O_2 and its outcome is excluded of toxic $^{\cdot}OH$[21]. Oxidative stress is resulted from overproduction of ROS that exceed the scavenging ability of antioxidants resulting in subsequent cell injury[22].

In ischemia, ROS was proved to induce cardiac cellular damage through several mechanisms. Primarily, ROS directly interact with cellular lipids (including cell membrane), proteins, mitochondria and DNA causing their damage and cell death. In mitochondria, lipid peroxidation also decreased Mitochondrial DNA (mtDNA) copy number associated with decreased Mitochondrila RNA (mtRNA) transcripts thus affecting mitochondrial function accompanying further decrease of ATP production[23, 24].

Simultaneously, as a response to oxidative stress-induced cell death, myocardial growth and matrix remodelling are stimulated with consequent activation of several downstream signalling pathways. First, hypertrophy signalling kinases including mitogen-activated protein kinases (MAPK) and Jun-nuclear kinase (JNK) to induce apoptosis[25]. Second, DNA strands destruction by ROS activate the nuclear enzyme poly (ADP-ribose) polymer (PARP-1) and therefore express inflammatory mediators which enhance the progression of cardiac remodelling. Third, ROS also stimulate transcription of nuclear factor-κB (NF-κB) and activator protein-1 to stimulate matrix metalloproteinases (MMPs) expression which plays a role in remodelling processes[26].

Certainly, these cumulative effects of ROS influence the contractile function of heart. Studies reported that malondialdehyde, a settled marker of lipid peroxidation, is inversely correlated with left ventricular (LV) ejection fraction. Alternatively, ROS was found to affect endothelial function via vascular cells damage which initiates the development of atherosclerosis and worsen the hypoxia of cardiac cells[27].

Finally, it could be concluded that oxidative stress plays a major role in initiation of inflammatory mediators as well as cell death[28]. Recently, different modes of cell death in cardiac myocytes was discussed.

Among them, apoptosis and programmed necrosis (known as necroptosis) occupy the main role in ischemic-induced cell death[29, 30].

Different cell death pathways in myocardial infarction

During stress events in ischemic conditions, cell death could be introduced through activation of: 1) intrinsic pathway initiating from the mitochondria and 2) extrinsic pathway mediated through different cell death receptors activated by cell death ligands[31].

In both previous pathways, cell death occurs mainly through two morphologically different modes; apoptosis and necrosis. Recently, necrosis was determined being programmed with different types existing, of which necroptosis is the most common in myocardial infarction. Primarily, apoptosis and necroptosis could share common signalling pathways, however, several factors could enforce the switch between both modes[31,32]. Of these factors, ROS play an important role along with ATP deficiency. Presence of limited levels of free radicals along with moderate ATP levels allow apoptosis to be superior as apoptosis requires ATP. While, as ROS level are enhanced along with depleted ATP leads to shift from apoptosis to necroptosis[33, 34].

Morphologically, apoptosis is characterized by shrinkage of the cells associated with condensation of chromatin, fragmentation of the nucleus followed by splitting into apoptotic bodies and vacuoles filled with cytoplasm and intact organelles to be cleared by phagocytes without inducing inflammatory reaction as pictured in **Figure 2**[32]. Once necroptosis occur, the cells die in a different behaviour. Necroptotic cell death is represented by cell swelling including organelles, as endoplasmic reticulum and mitochondria ending up with rupture of plasma membrane and cell lysis. The rupture of cells enhances the release of danger signals that trigger intense inflammatory response that exacerbate myocardial damage as characterized in infarcted cardiomyocytes[32, 35].

Intrinsic pathway of cell death involved in myocardial infarction

An interplay between several factors could induce apoptosis or necroptosis through the mitochondrial pathway[36]. Initially, apoptosis could be stimulated by p53 protein which act as an important sensor to a range of stress signals including ischemia, oxidative stress and DNA damage. During stress events, an abundance of cytoplasmic p53 transfer to the mitochondrial surface to physically interact with membrane bound anti- and pro-apoptotic Bcl-2 family members. The balance between anti- and pro-apoptotic Bcl-2 members would determine the induction of mitochondrial outer membrane permeability (MOMP) and apoptosis or not[37].

The Bcl-2 protein family are divided according to their function into: first, anti-apoptotic members including Bcl-X_L, Bcl-2, Bcl-W and Mcl-1. These members are responsible to negatively control the pro-apoptotic proteins to maintain survival[38]. The second class of members are pro-apoptotic proteins including Bax and Bak which plays a pivotal role in inducing pores in the outer mitochondrial membrane to initiate its permeabilization and release of cell death-promoting proteins[39]. The third group enclose proteins that only have a short BH3 domain (such as Bad, Bnip3, Nix, Bid, and Puma). BH3-only members may interact between anti- and pro-apoptotic members to activate Bax proteins and thus apoptosis either by inducing conformational changes to the binding site or via displacing anti-apoptotic members. Hence, the activated Bak and Bax (pro-apoptotic members) are now able to induce MOMP through formation of channels in the outer membrane[39].

In addition, the inner mitochondrial membrane (IMM) permeability consistency is critical for oxidative phosphorylation and ATP production[40]. However, activated Bax and Bak could influence the IMM permeability through the binding of cyclophilin D, a regulator of the mitochondrial permeability transition pore (MPTP) complex, resulting in the opening of MPTP and the free passage of protons into the mitochondrial matrix and disrupt the oxidative phosphorylation[30, 41]. At this stage, release of pro-apoptotic factors into the cytosol occurs including cytochrome c (Cyt c), apoptosis inducing factor (AIF), endonuclease G (endo G) and second mitochondria-derived activator of caspases/direct inhibitor of apoptosis (IAP)-binding protein with low pl (Smac/Diablo)[40].

Once in the cytosol, Cyt c enhance the formation of apoptosome complex which comprehend apoptosis activating factor-1 (Apaf-1), procaspase-9 and dATP. Procaspase-9 is auto-activated in this complex and activate a series of executor caspases as caspase-3, 6, and 7. Smac/Diablo also played role in activation of caspases through binding and altering the function of inhibitor of apoptosis proteins (IAP) which are caspase inhibitors[38, 42].

Another factor that could play role in apoptosis is the mitochondrial Ca^{2+} pool. Normally, the mitochondria require low pools of Ca^{2+} which stimulate Ca^{2+}-sensitive matrix dehydrogenases to provide NADPH that is essential in the oxidative phosphorylation and ATP production process. Under pathological conditions, mitochondria uptake high levels of Ca^{2+} supplied by the endoplasmic reticulum through a Ca^{2+} uniporter. Although Ca^{2+} is important for normal mitochondrial function, high levels could initiate the binding of cyclophilin D (Cyp D) to the MPTP complex enhancing the opening of the IMM to produce similar events as produced by Bax and Bak[30, 42].

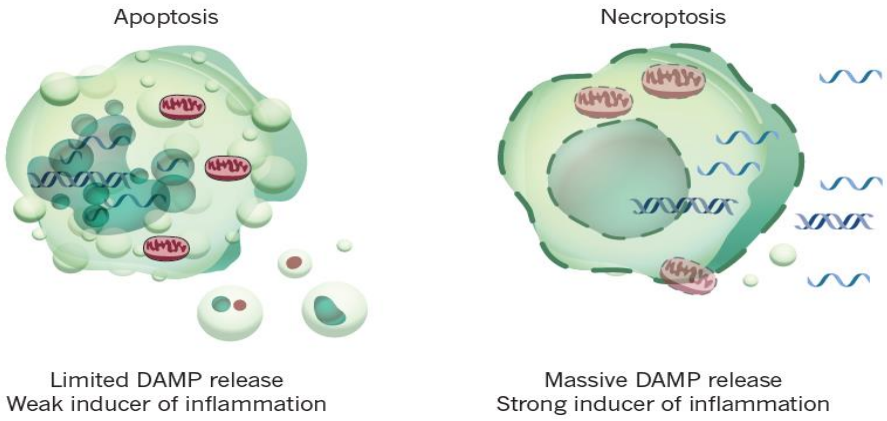

Figure 2. Morphological features of apoptosis and necroptosis.

The long-standing paradigm had been that p53 and Bcl-2 family play role in apoptosis but isn't involved in necroptosis. Recently, studies provide compelling evidence that p53 initiate necroptotic cell death through activation of Cyp D which in turn led to opening of the MPTP in the IMM. Alteration of IMM permeability allow molecules passage into the matrix leading to osmotic swelling followed by rupture of mitochondria and the cell to die in a necrotic behaviour[43, 44]. This phenomenon was proved in independent strains, Cyp D null mice was shown to be resistant to ischemia-induced necrosis in myocardial infarction and Ca^{2+}- Cyp D-deficient mitochondria and cells are resistant to H_2O_2-induced necrotic cell death. Hence, studies reported that p53 action could be inhibited by the specific Cyp D inhibitor CsA, and by genetic Cyp D deletion or knockdown[45].

Similarly, recent studies on different models revealed the involvement of Bcl-2 in necroptosis. Some of these studies include models of insulin-dependent diabetes mellitus which clearly demonstrated that necroptosis was involved in early stages induced by various cytokines and cell death could be prevented by Bcl-2 overexpression[46]. Moreover, models using N-methyl-N-nitro-N-nitrosoguanidine https://pubchem.ncbi.nlm.nih.gov/compound/N-Methyl-N-nitro-N_-nitrosoguanidine, a standard necroptotic inducer in high doses showed that Bax activation was involved in mitochondrial rupture while overexpression of Bcl-X_L was protective[40]. Furthermore, Bcl-2 overexpression was proved to protect neuronal[47] and non-neuronal cells[48] from necrotic cell death.

Extrinsic pathway of cell death involved in myocardial infarction

Extrinsic cell death is facilitated through death receptors (DRs) located at the plasma membrane[49]. Death receptors includes Fas, TNFR1 or TRAIL receptors and each contain an intracellular death domain (DD). The binding of a specific ligand to each DR is essential for the receptors trimerization to enhance the recruitment of the DD to the intracellular surface of the receptor and form death-inducing signalling complex (DISC)[50]. Different studies reported that formation of DISC complex could directly initiate apoptosis through activation of caspase 8 and subsequent cleavage of caspase 3 which occurs in 1 type of cells. While indirectly DISC complex could trigger the mitochondrial apoptosis in a second type of cells by cleavage of BH3-only protein Bid to be transformed to truncated Bid (t-Bid). After wise, t-Bid translocate to the outer mitochondrial membrane (OMM) to activate Bax leading to MOMP and enhance apoptosis in a similar way as intrinsic pathway of apoptosis[51].

It has been reported that Fas and TRAIL receptors follow the former pathway as Fas Ligand (Fas L) bind to Fas receptors and enhance the recruitment of FADD adaptor molecule to produce the DISC complex and initiate apoptosis either according to type 1 cells or type II cells pathway[52]. Similarly, TRAIL-R1 or R2 receptors mediate apoptosis but instead activated by the death ligand TRAIL as represented in **Figure 3**[38, 53].

The downstream signalling pathway enhanced by activation of TNFR1 is slightly different. Once TNF-α ligand bind to TNFR1, receptor trimerization would

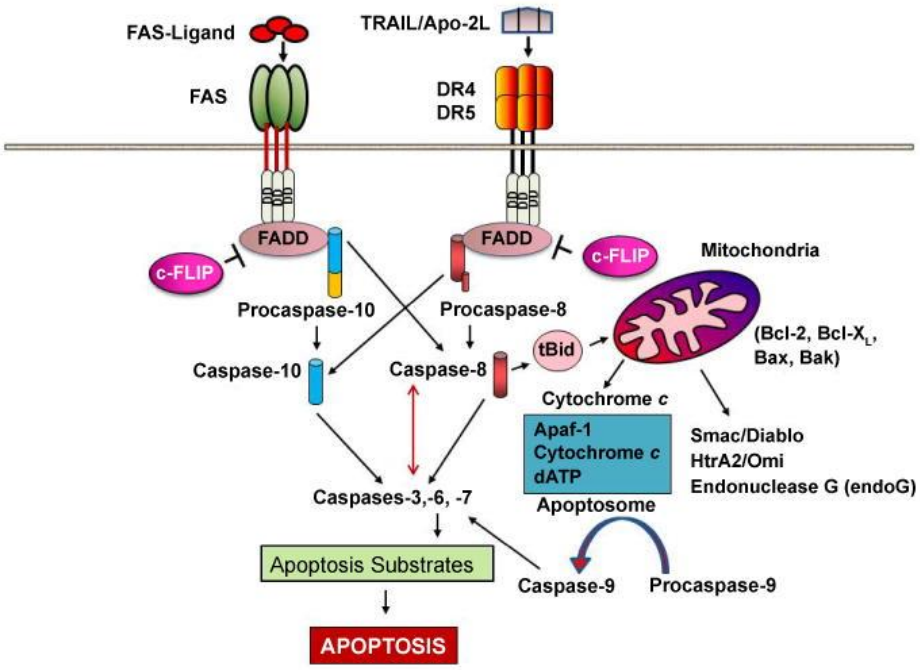

Figure. 3 Apoptosis signaling pathways and roles of c-FLIP in preventing apoptosis. Through FADD-dependent autocatalytic activation of caspases-8 and -10 and Bid cleavage to truncated Bid, TRAIL interaction with its receptors DR4 and DR5 or binding of Fas ligand to Fas receptor initiates the death receptor (extrinsic) and subsequently mitochondrial apoptosis signalling pathways. c-FLIP isoforms suppress caspase-8 and -10 activation, preventing the downstream apoptosis cascade.

induce the recruitment of TNF-R associated adaptor protein with death domain (TRADD) to its surface. This complex is able to promote cell survival or cell death depending on the factors involved[50].

Primarily, TRADD is bound to polyubiquitinated RIPK1 and TRAF 2/5 along with cellular inhibitors of apoptosis 1 and 2 (cIAP 1/2) to develop complex I which enhance cell survival through the transcription of NF-κB[45, 54]. This in turn activate the inflammatory response via release of i-NOS, MCP-1 and IL-6 cytokines and upregulate antioxidants, anti-apoptotic proteins such as Bcl-Xl, X-linked inhibitor of apoptosis (XIAP) and cFLIP[55, 56]. cFLIP is a key regulator of apoptosis and it obtains the same structure as caspase 8 but lacks a catalytic cysteine. Caspase 8 has higher affinity to be in heterodimer with cFLIP which act as a competitive inhibitor[57].

Increased stress factors may initiate inhibition of cIAPs resulting in RIPK1 deubiquitination and autophosphorylation which in turn favour the formation of complex II (DISC complex) along with RIPK3, TRADD, FADD and caspase 8[58]. In the presence of low levels of cFLIP, caspase 8 would be activated by FADD and p-RIPK1. Active caspase 8 now modulate the proteolytic cleavage of P-RIPK1/RIPK3 and initiate the pro-apoptotic caspase activation cascade to promote apoptosis either directly or through t-Bid-mediated mitochondrial pathway[59]. In contrast, higher concentrations of cFLIP, as a result of increased levels of ROS[60], would favour the inhibition of apoptotic process through the prevention of the assembly of FADD/ caspase 8 homodimer[51].

Instead, p-RIPK1 in complex II initiate the phosphorylation of RIPK3 and the formation of necrosome complex to which an interacting partner MLKL is recruited and phosphorylated by p-RIPK3[61, 62]. Polymerization of p-MLKL by intracellular HSP 70 protein[63] is immediately processed to mediate the necrotic action of p-MLKL through its translocation to the cell membrane and enhance formation of pores within the membrane to disrupt its integrity[61]. Consequently, electrolytes including Na^+ and Ca^{2+} flow intracellularly to drive osmotic swelling and rupture of cells to die in a necrotic manner. Recent studies confirmed that RIPK1-mediated cell death could also be initiated following activation of Fas receptors[64, 65].

Briefly, cFLIP is a key regulator that determine the fate of the cell to survive or die as well as control the mode of cell death initiated. cFLIP could prevent the binding of FADD and caspase 8 to prevent apoptosis and maintain cell survival. However, at the same time if cell death is initiated through RIPK1 deubiquitination (in case of inhibition of cIAP 1/2), it's the cFLIP concentration that would determine if cell died by

apoptosis or necroptosis[51, 66]. Moreover, upregulation of Bcl-2 or Bcl-X_L could express protective effect in type II cells only. While interestingly, cFLIP could affect apoptosis and necroptosis in type I and II cells due to its direct action on the DISC complex, **Figure 4** [67].

Another factor that affect the interplay between apoptosis and necroptosis is the intracellular ATP level and mitochondria being responsible for the central role of energy is considered the key organelle. As previously mentioned, ROS produced through mitochondria enhance DNA-damage associated with release of inflammatory cytokines including TNF-α, the most expressed necrosis-inducing ligand[34, 68]. TNF-α in turn activate PARP1, a nuclear enzyme in charge of DNA repair and transcriptional regulation. Since PARP1 consume NAD^+ during DNA repair, thus exceeded upregulation of PARP1 by TNF-α would result in massive ATP depletion. Accordingly, it could be suggested that ROS and TNF-α could affect the molecular switch between apoptosis and necroptosis via management of ATP levels intracellularly[54].

Inflammatory response and repair following cell death in myocardial infarction

Myocardial infarction result in abundant loss of cardiomyocytes which lack the opportunity of regeneration. Hence, the body responds by initiating cardiac repair through enhancement of inflammatory and immune response. The inflammatory phase could be stimulated by different but overlapping pathways; danger signals, once released from dead cells enhance the recruitment of leukocytes for removal of the dead cells. Moreover, TNFR-induced NF-KB activation which in turn boost the transcription of various cytokines and chemokines along with the innate immune system for healing of the infarcted area[69].

Inflammatory response

For several years, it had been stated that apoptosis doesn't induce inflammation[70]. This property refer to its ability to preserve intracellular contents including proinflammatory signals and the cell is divided into apoptotic blebs to be quickly and easily ingested by phagocytes. Moreover, other studies suggested that apoptotic cells stimulate macrophages which in turn release mediators such as IL-10 and TGF-β that has inhibitory effect on inflammation[71]. In contrast, other studies implied that apoptosis could be followed by inflammatory response which is more characteristic to the necrotic cell death. The possible explanation of the induction of inflammatory response following apoptosis could be related to the rate of clearance of apoptotic cells which if elongated could then undergo a secondary necrosis releasing inflammatory mediators[72].

The mechanistic explanation is related to the presence of ROS. The ROS has direct oxidative action on NF-κB resulting in upregulation of cytokines and chemokines accompanied with leukocyte chemotaxis enhanced by complement cascade[73]. The ROS generation has important role in cardiac repair as long as they are counterbalanced by antioxidants. In myocardial infarction, increased levels of ROS would overcome the balance of antioxidants and high levels of apoptotic cells could not be quickly cleared initiating secondary necrosis and thus inflammation.

Necrotic cell death is defined and diagnosed with the release of inflammatory signals known as danger signals or alarmins which are variable including High mobility group box 1 protein (HMGB1), heat shock proteins (HSP), DNA chromatin complexes, and various purines such as adenosine, ATP and several others[74,75]. HMGB1 and HSP70, the most common alarmins are primarily present as endogenous molecules where HMGB1 act as a regulator of gene transcription while HSP70 has a role in intracellular repair processes and function as chaperones in protein folding and translocation; however, upon injury HMGB1 and HSPs can function as danger signals[63, 76].

Collectively, they are passively released following necrotic cell death which then stimulate monocytes to produce inflammatory mediator NF-κB[77]. Consequently, NF-κB induce transcription of several inflammatory cytokines including TNF-α, IL-1, IL-6, IL-8, and macrophage inflammatory protein (MIP)[78, 79]. In addition, studies highlighted the role of HMGB1and HSP70 in stimulating an innate immune response through initiation of T cells. This process mainly occurs when dendritic cells are directed toward the signals and hydrolyse these antigens into peptides which are expressed on their outer surface. Thus, T cells are activated once they recognize their specific antigenic peptide bound to dendritic cells[79, 80].

The alarmin, HMGB1, although it is an endogenous molecule but only released after necrotic and not apoptotic cell death. This has been referred to the role of caspase activity in the modification of HMGB1 into non-immunogenic oxidized form. Moreover, caspase-dependent condensation of chromatin traps HMGB1 which explains why inflammatory response is not commonly enhanced following apoptosis[74, 81].

Additional source of alarmins are the extracellular matrix proteins in the heart. These proteins as well as being source of support they also act as a source of inflammatory cytokines[82]. During infarction, the matrix proteins are degraded by activation of interstitial MMP which enhance collagenolysis in the infarcted area[83]. The low molecular weight fragments then act as a signal that attract proinflammatory mediators. MMP could regulate the processing of cytokines as TNF-α and its release from the cell surface as well as chemokines such as IL-1 and TGF-β[84].

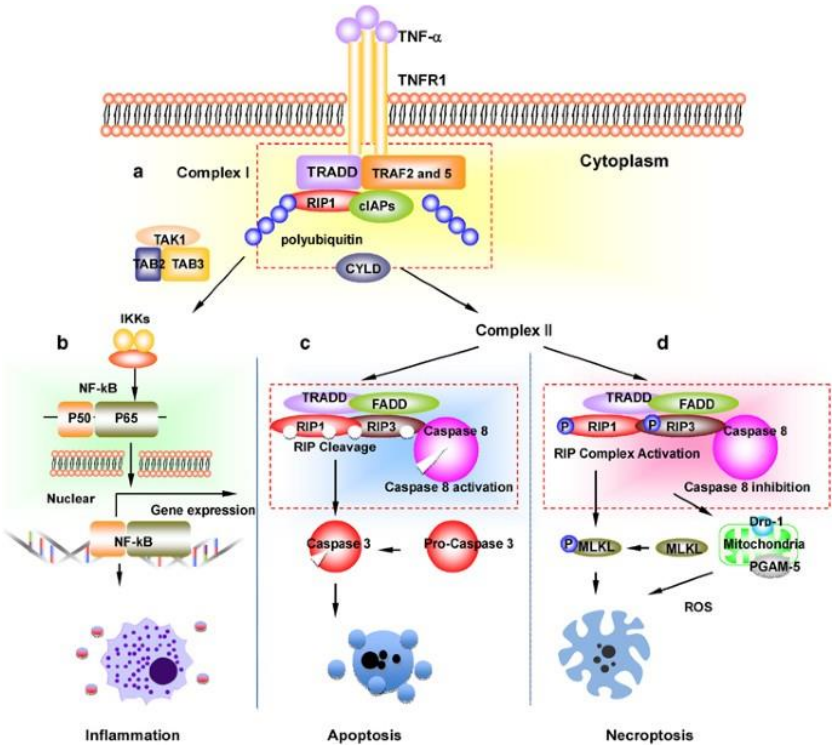

Figure. 4. Signalling pathways after stimulation of the TNFR1. TNF- is abundantly released when there is inflammation. (a) TNF receptor 1 recruits TRADD, TRAF2 and 5, RIP-1, cIAPs, and other molecules to form complex I upon binding to TNF receptor 1. (b) TNFR1-signaling activates NF-kB in response to polyubiquitinated RIP-1, which causes the production of proinflammatory cytokines. The development of complex II is triggered by the deubiquitination of RIPK1. (c) Caspase-8 activation in complex II reduces the induction of necroptosis and prevents RIPK1/RIPK3 activation, which prevents necroptosis. (d) During the construction of the necrosome, RIPK1, RIPK3, and MLKL are phosphorylated and activated as a result of Caspase-8 inactivation through cFLIP in complex II. Abbreviation: TNF, tumor necrosis factor; TRADD, TNFRSF1A-associated via death domain; TRAF, TNF receptor associated factors; cIAPs, cellular inhibitor of apoptosis protein; MLKL, mediator mixed-lineage kinase domain like; RIP, receptor-interacting protein kinase **[107].**

proinflammatory mediators. MMP could regulate the processing of cytokines as TNF-α and its release from the cell surface as well as chemokines such as IL-1 and TGF-β[84].

Once released, alarmins signal for the innate immune system to detect their presence through the surface receptors pattern recognition receptors (PRRs). PRRs include receptor for advanced glycation end-products (RAGE) and toll- like receptors (TLRs). RAGE receptors commonly found on the surface of monocytes, immature dendritic cells and vascular smooth muscles with being stimulated by HMGB1and S100 family alarmins. Stimulation of RAGE receptors is associated with the activation of NF-κB signalling pathway[75]. Moreover, TLRs mainly TLR2 and TLR4 are also involved in the production of NF-κB in macrophages when stimulated by HMGB1 and HSP70 signals[85]. Previous study clarified the role of PRRs in the aggravation of ischemic injury as TLR2 knockout mice showed decreased inflammation and infarct size[74].

Repair phase in myocardial infarction

Once the innate immune response has enhanced the inflammatory leukocytes clear the dead cells allowing the heart to be ready for repairing. Repairing process is organized by several factors including monocytes/macrophages, cardiac extracellular matrix along with the platelets[11].

Monocytes/macrophages and extracellular matrix have a master role in induction of repair through the activation of fibroblasts and endothelial cells for the formation of scar and replacing the damaged matrix proteins[86].

In response to the infarct, monocytes undergoes maturation into macrophages which in turn stimulate upregulation of growth factors such as macrophage-colony stimulating factor (M-CSF) which exhibit proliferative activity[87]. Thus macrophages have different roles: phagocytosis; to clear the dead cells, inflammatory; through release of cytokines and regenerative; via upregulation of growth factors,

fibroblasts and neovessel formation and maturation[88]. Moreover, the degradation of extracellular matrix proteins enhance the deposition of new fibrin matrix network through the recruitment of fibrinogen and plasma fibronectin[89].

In addition, Platelets being hemostatic cells, they aggregate at the site of infarction. However, their role also includes modulating secreting chemokines and growth factors along with the formation of fibrin network which might promote recruitment of reparative cells [89, 90].

Complications and clinical symptoms of myocardial infarction

Necrosis followed by inflammatory response during myocardial infarction result in several complications according to the degree of damage of tissues. Primarily, infarcted tissues are removed by macrophages to be replaced by fibrotic tissue. According to the mass of replaced myocardial tissue depends on the weakness of ventricular wall and susceptibility to myocardial wall rupture. Responsively, ventricular remodelling is enhanced with further impairment in systolic contractile function. Unfortunately, non-infarcted tissue also subjected to increased stress to compensate the increased cardiac output required which can eventually predispose to arrhythmia and heart failure[91, 92]. **Figure 5**, illustrates several myocardial infarction-related consequences.

On the clinical spectrum, several symptoms characterize MI including intense chest pain radiating into the neck, jaw or arms, difficulty in breathing, fatigue, tachycardia and arrhythmia, sweating, sleeplessness, hypertension or hypotension (depending on stage of cardiac damage). The mentioned symptoms may vary between men and women. Men are more exposed to chest pain and female might possess weakness, fatigue and dyspnea[93].

Treatment approaches to treating myocardial infarction

Post-ischemic therapeutic strategies including restoring coronary blood flow or prevention of thrombus formation has great impact in prophylaxis from infarction. Treatment as early as possible would decrease the cardiac necrotic events and preserve the contractile function of the heart with the least complications after acute ischemia.

Until now, the most classes of drugs used in the treatment of myocardial ischemia include: Angiotensin converting enzyme (ACE) inhibitors and Angiotensin receptor blocker (ARBs) and considered as 1st line treatment in ischemia. Studies suggested ACE inhibition may reverse remodelling of heart and reduce interstitial fibrosis. In addition, ACE inhibition was found to be correlated with anti-arrhythmic effect and prevention of sudden cardiac death. ACE inhibitors also exert antiapoptotic and anti-inflammatory action through reduction of angiotensin II[11, 94].

Secondly, β-blockers, mainly used to reduce the heart rate and contractility to modulate the heart demand of blood. Moreover, studies reflected the antiapoptotic, anti-inflammatory and anti-fibrotic action of β-blockers. Other studies suggested the possible prevention of remodeling by β-blockers to conserve its importance as a treatment in myocardial ischemia or infarction. Third, statins proved its effectiveness in reducing mortality through its anti-inflammatory effect, modulation of fibrinolytic system along with its lipid lowering effect. The protective effect of statins can be enhanced through its ability to attenuate MMP expression thus reducing inflammation[11, 93].

Other important classes commonly used in treatment of ischemic events are vasodilators such as nitro dilators and antiarrhythmic drugs. Moreover, anti-thrombotic drugs to prevent thrombus formation or thrombolytics such as plasminogen activators are essential treatment. Analgesics are beneficial to reduce pain and morphine have additional vasodilatory effect [93].

Recent strategies of treatment not clinically applied include antioxidants, attenuation of calcium overload, cyclosporine, and antiapoptotic effect. However, all these strategies are under trials but still not proved to be clinically effective[95, 96]. Cyclosporine, suggested by some studies to be able to inhibit the opening of mitochondrial permeable membrane thus prevent cell death[97]. Another approach under examination is to decrease inflammatory mediators which eventually could modulate cell death. Clinical studies targeting the complement cascade and β2 integrin in myocardial infarction didn't show promising results[98]. However, other clinical studies showed positive results while using anti-IL I which enhanced cardiac dilation following infarction[99].

Additional studies focusing on the inhibition of MMP to prevent degradation of extracellular matrix proteins was facing challenges. The study showed promising results during the short term inhibition of MMP while prolonged inhibition was detrimental[100]. Visionary goals in treatment of myocardial infarction included targeting the regeneration of myocardium. Several trials were done such as using skeletal myoblasts or bone marrow derived cells but the disappointing results of clinical trials that these cells can transdifferentiate into cardiomyocytes reduced enthusiasm about the approach[101-103].

A recent study used the novel antioxidant and anti-inflammatory ethyl pyruvate drug as a prophylactic treatment to prevent infarction following an ischemic event. The study showed that ethyl pyruvate exerted anti-inflammatory, antiapoptotic and antinecroptotic effect[104]. Other agents as zingiberene also exerted

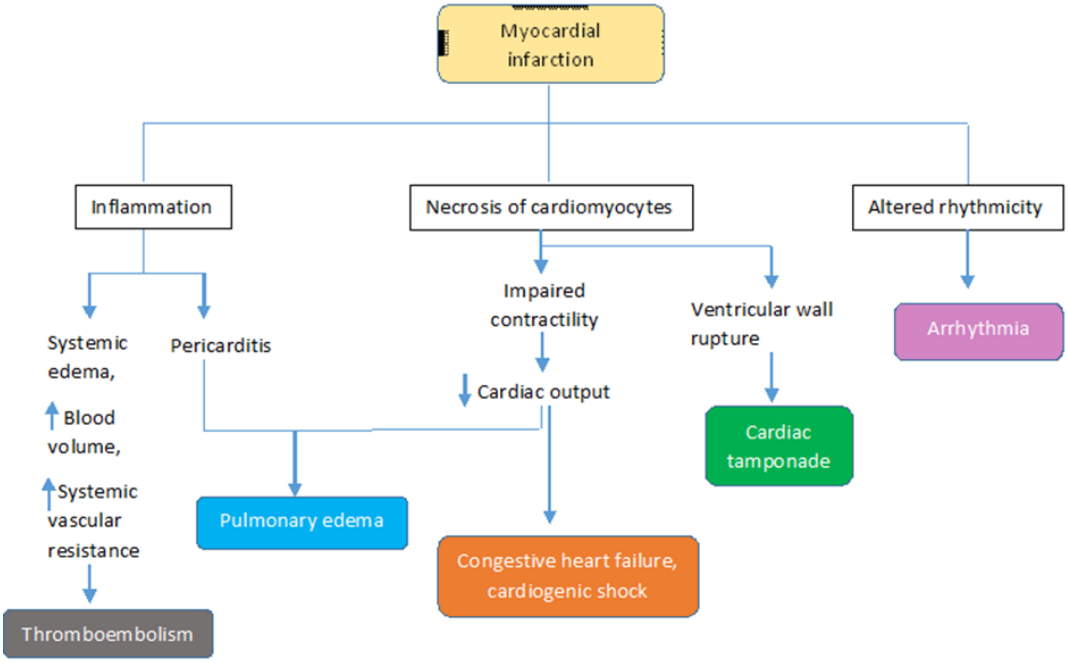

Figure 5. A list of early and late complications associated with myocardial infarction.

anti-inflammatory and antiapoptotic effect in a study of myocardial infarction[105]. Moreover, a traditional Chinese alkaloid, Huperzine A, was evaluated for treatment in a model of acute myocardial infarction. The cardioprotective effect of Huperzine A is associated with its antioxidant, anti-apoptotic and anti-inflammatory properties in acute myocardial infarction in rats[106].

CONCLUSION

Myocardial infarction remains to be a worldwide disease associated with morbidity and mortality. Studying the causes of ischemia and the consequences associated is of critical significance. The desire to understand the molecular signals involved in cell death, inflammation and cardiac repair is of concern to investigate different treatment approaches.

According to the pathophysiology of MI, the injury is caused by oxidative stress, which is then followed by a cascade of inflammatory responses that result in the death of the myocardial cells through apoptosis. Unfortunately, under oxidative stress, apoptosis eventually changes to necroptotic cell death, which greatly increases subsequent inflammation and worsens the injury. From this vantage point, antioxidants might be suggested as a reasonable treatment; however, despite positive results from experimental studies (primarily utilising animal models), clinical settings have not yet profited from these advantages.

Anti-inflammatory medication may also be helpful, which would enhance the subsequent reparative phase rather than hinder the acute phase in ischemia. The onset and progression of MI may be controlled by anti-inflammatory and antioxidant therapy. Interestingly, inhibiting c-FLIP might also be a therapy goal for acute MI. By inhibiting c-FLIP, cell death will result in apoptosis and limit the damage and MI size by avoiding the inflammatory response's exaggeration from necroptosis.

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Conflict of interest

The author declares that there isn't any conflict of interest regarding the publication of this paper.

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