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Review

Oxidative stress and left ventricular remodelling after myocardial infarction

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In acute myocardial infarction (MI), reactive oxygen species (ROS) are generated in the ischaemic myocardium especially after reperfusion. ROS directly injure the cell membrane and cause cell death. However, ROS also stimulate signal transduction to elaborate inflammatory cytokines, e.g. tumour necrosis factor-α (TNF-α), interleukin (IL)-1β and -6, in the ischaemic region and surrounding myocardium as a host reaction. Inflammatory cytokines also regulate cell survival and cell death in the chain reaction with ROS. Both ROS and inflammatory cytokines are cardiodepressant mainly due to impairment of intracellular Ca^{2+} homeostasis. Inflammatory cytokines stimulate apoptosis through a TNF-α receptor/caspase pathway, whereas Ca^{2+} overload induced by extensive ROS generation causes necrosis through enhanced permeability of the mitochondrial membrane (mitochondrial permeability transition). Apoptosis signal-regulating kinase-1 (ASK1) is an ROS-sensitive, mitogen-activated protein kinase kinase kinase that is activated by many stress signals and can activate nuclear factor κB and other transcription factors. ASK1-deficient mice demonstrate that the ROS/ASK1 pathway is involved in necrotic as well as apoptotic cell death, indicating that ASK1 may be a therapeutic target to reduce left ventricular (LV) remodelling after MI. ROS and inflammatory cytokines activate matrix metalloproteinases which degrade extracellular matrix, causing a slippage of myofibrils and hence LV dilatation. Consequently, collagen deposition is increased and tissue repair is enhanced with myocardial fibrosis and angiogenesis. Since the extent of LV remodelling is a major predictor of prognosis of the patients with MI, the therapeutic approach to attenuating LV remodelling is critically important.

1. Introduction

The most important structural event after myocardial infarction (MI) is left ventricular (LV) remodelling.[1,2] Remodelling of the heart is derived from intra- and extracellular structural changes of the myocardium and elicits structural changes of the LV wall. Further mechanical load on the LV wall causes LV dilatation. Thus, the extent of LV remodelling could be a predictive factor for mortality and morbidity of the patient with MI.[3]

The underlying mechanism of LV remodelling is multifactorial; many biological reactions are involved in the time course of remodelling after an ischaemic episode: (i) local ischaemia and myocardial cell death, (ii) oxidative stress and inflammatory reactions in injured myocardium,[4] (iii) cardiodepressive reactions due to the production of reactive oxygen species (ROS) and inflammatory cytokines,[5,6] (iv) changes in extracellular matrix following activations of matrix metalloproteinases (MMPs),[7,8] (v) structural changes of myocardium in response to mechanical stress, and (vi) synthesis of collagens and myocardial fibrosis.[9] These reactive processes are related each other and proceed from acute reactions to chronic changes. LV remodelling ultimately elicits LV dilatation usually with LV dysfunction and thus could be one of the most important determinant of prognosis of the patients with MI.

MI is usually initiated by myocardial ischaemia due to coronary artery obstruction. In the ischaemic myocardium, ROS are generated, especially after reperfusion.[10,11] The major sources of ROS in the ischaemic-reperfused myocardium are mitochondria, xanthine oxidase, and phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.[12–14] ROS directly injure the tissue as key molecules for inducing cell death. Detrimental effects of ROS are clearly demonstrated by the findings that in the transgenic mice in which an antioxidant protein, superoxide dismutase (SOD) is overexpressed, infarct size is markedly reduced.[15,16]

In the ischaemic region and surrounding myocardium, inflammatory cytokines, e.g. tumour necrosis factor-α

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(TNF-α), IL-1β, and IL-6 are produced as a host reaction.[17] The inflammatory cytokines regulate cell survival and cell death, and could be a trigger of another inflammatory reaction.[18] ROS stimulate the production of inflammatory cytokines and inversely, inflammatory cytokines stimulate ROS formation.[19] In chronic stage, ROS and inflammatory cytokines activate the MMPs and collagen deposit which contribute to the structural changes and tissue repair of injured myocardium.[20,21] Activations of MMPs elicit degradation of collagens which may cause a slippage in myofibrillar alignment causing LV dilatation.[22] During tissue repair, the cytokines activate angiogenesis and mobilization of stem cells and hereby contribute to late remodelling.

2. Cardiodepression and remodelling through oxidative stress and inflammatory cytokines

Myocardial ischaemia either with or without reperfusion induces ROS and inflammatory cytokines. It is of note that these reactive molecules are cardiodepressant through impairment of Ca^{2+} homeostasis. ROS can induce intracellular Ca^{2+} overload during oxidative stress.[12,23] ROS cause extracellular Ca^{2+} influx mediated by increased membrane lipid peroxidation and the opening of voltage-sensitive Ca^{2+} channels or Na^{+}/Ca^{2+} exchanger.[24] ROS also cause a release of Ca^{2+} from intracellular stores and attenuate Ca^{2+} uptake by sarcoplasmic reticulum Ca^{2+}ATPase.[24]

Inflammatory cytokines, e.g. TNF-α and IL-6 also cause dysregulation of intracellular Ca^{2+}; TNF-α decreases Ca^{2+} sensitivity of myofibrils through nitric oxide as well as neutral sphingomyelinase; sustained induction of TNF-α inhibits expression of SERCA2a and elicits persistent depression of Ca^{2+} pump of sarcoplasmic reticulum.[25] These detrimental effects of inflammatory cytokines could be partially inhibited by radical scavengers indicating that detrimental effects of the inflammatory cytokines are partially mediated with ROS.[26]

After MI, MMPs and tissue inhibitors of MMPs (TIMPs) play an important role in cardiac repair and LV remodelling. A key process in LV enlargement is activation of MMPs in the extracelluar matrix;[27] collagenases (MMP-1, -8, and -13), gelatinases (MMP-2 and -9), stromelysins (MMP-3, -10, and -11), and membrane-type MMPs. TIMPs regulate MMP activities by their inhibiting actions. Thus, degradation of collagen is regulated by the balance of these competitive protein activities. It is also reported that inflammatory cytokines and ROS mediate MMP induction or stimulation and decrease TIMP levels and collagen synthesis;[8] structural changes of myocardial tissue are elaborated by sustained induction of inflammatory cytokines.

In transgenic mice with cardiac overexpression of TNF-α, the heart is enlarged and dilated with marked inflammatory cell infiltration and myocardial fibrosis.[28,29] In this transgenic mice, MMP activations are observed by gelatin zymography.[29] TNF-α blocking protein prevents MMPs induction and myocardial remodelling in the dog pacing-induced heart failure (HF) model, suggesting that TNF-α blocking protein prevents the local induction of MMPs.[30] In transgenic mice with cardiac overexpression of TNF-α, it is also reported that further collagen synthesis, deposition and denaturation are prevented and LV diastolic function is improved, when MMP-2 and MMP-9 expressions are attenuated by inhibition of TNF-α with adenovirus infection expressing soluble TNF-α receptor type I, suggesting that the extracellular matrix changes regulate diastolic function of the heart.[31] In an *in vivo* mouse model of MI, a hydroxyl radical scavenger attenuates the increased myocardial MMP-2 activity and LV remodelling.[32] A clinical study has also demonstrated a positive correlation between a specific marker of oxidative stress and relative level of MMP-2 and MMP-9 in patients with coronary artery disease.[33] These reports strongly suggest that oxidative stress plays an important role in MMP regulation and hence, LV remodelling.

Indeed, the activated MMPs degrade the extracellular matrix, disrupting the fibrillar collagen network and allowing inflammatory cells to migrate into the infarct tissue to remove necrotic myocytes.[34] In the mouse MI model, MMP-9 is mainly expressed in infiltrating neutrophils and macrophages of the infarcted area. Subsequently, MMP-9 activity further increases. Thereafter, MMP-2 activity starts to increase, whereas MMP-9 gradually decreases. During early remodelling phase, the necrotic tissue in infarcted area is replaced by granulation tissue with a collagen-rich matrix. In the remote area, cytokines are activated if the infarct size is large, or if there are other ongoing myocardial stress factors. Also, during late remodelling phase, MMPs and TIMPs continue to play an important role in the remodelling process in the infarcted and remote areas.[34]

3. Reactive oxygen species as intracellular signalling molecules

ROS are major initiators of myocardial damage during ischaemia/reperfusion.[13] It is reported that the development of infarction following myocardial ischaemia/reperfusion is associated with the population of apoptotic cells in peri-necrotic area.[35] Treatments with antioxidant agents or upregulation of endogenous antioxidant enzymes could protect against reperfusion injury.[36–38] Neutrophils are the primary source of ROS during reperfusion.[13] Endothelial cells and cardiomyocytes can also generate ROS. ROS are produced from xanthine oxidase in endothelial cells, mitochondrial electron transport chain reactions in cardiomyocytes, and NADPH oxidase in inflammatory cells.[12–14] A burst of ROS from endothelial cells and cardiomyocytes can amplify local inflammatory response and influence nearby neutrophils, leading to a chain reaction of ROS generation.[39]

In contrast to the direct actions of ROS on cellular injury, ROS play an important role in cell protection as intracellular signalling molecules mediated by the activation and expression of antioxidant enzymes. The low-level oxidant production may be a trigger for ischaemic preconditioning.[40] The delayed pre-conditioning is also tightly related to the production of ROS and the synthesis of antioxidant enzyme, manganese-SOD, after initial ischaemic stress.[41] ROS can activate an ROS-sensitive mitogen-activated protein (MAP) kinase kinase kinase, apoptosis signal-regulating kinase 1 (ASK1), which activates the downstream MAP kinases, p38, and c-Jun N-terminal kinase (JNK).[42] ROS activate nuclear factor κB (NF-κB) mediated through ASK1.[43] The activation of NF-κB can produce TNF-α, leading to activation of extrinsic apoptotic pathway mediated by death receptors[44] as well as activation

of hypertrophic response.[45] It is of interest that TNF-α can also generate ROS which can further activate NF-κB.[45] ROS also stimulate other transcription factors such as Ets and activator protein-1 (AP-1) mediated through Akt and protein kinase C pathways.[46] Oxidative stress-induced activation of transcription factors leads to synthesis of anti-oxidant enzymes such as manganese-SOD and endothelial nitric-oxide synthase.[47] Thus, ROS are key players for cell protection as well as cell injury in response to oxidative stress.

4. Molecular mechanism of cardiomyocyte death mediated by oxidative stress and inflammatory cytokines

Oxidative stress and cytokines play a key role in both apoptotic and necrotic cardiomyocyte death. In apoptotic cardiomyocyte death, there are two major apoptotic signalling pathways i.e. intrinsic pathway via mitochondria and extrinsic pathway via Fas ligand or TNF-α.[44] In the intrinsic pathway, the pro-apoptotic Bcl-2 family e.g. Bax and Bak enhances the permeability of the mitochondrial outer membrane, leading to protein release such as cytochrome c from the intermembrane space to the cytoplasm (*Figure 1*).[48] In contrast, the extrinsic pathway is activated when death ligands, e.g. Fas ligand or TNF-α, bind to cognate receptors on the plasma membrane.[49] These receptors contain an intracellular death domain, which can recruit and activate caspase 8 via adaptor FADD (Fas-associated protein with the death domain), inducing cell death.[50,51]

Necrosis is classically characterized by early plasma membrane rupture and swelling of cytoplasmic organelles, in particular mitochondria.[52,53] Necrosis is often defined in a negative manner, as cell death lacking the characteristics of programmed cell death and thus accidental and uncontrolled.[54] Mitochondrial permeability transition (MPT), also known as mitochondrial depolarization, is defined as the loss of transmembrane potential of the mitochondrial inner membrane and is a Ca^{2+}-dependent increase in the permeability of the mitochondrial membrane, causing the loss of the proton gradient and the shutdown of ATP generation through oxidative phosphorylation (*Figure 1*). Consequently, this results in mitochondrial swelling and rupture of the outer membrane.[55,56] MPT is thought to occur after opening of a putative channel complex termed 'permeability transition pore' composed of the voltage-dependent anion channel, adenine nucleotide translocator, cyclophilin D (CypD), and other molecules.[57,58] MPT pores open in the mitochondrial inner membrane in response to stimuli such as increased intracellular Ca^{2+}, inorganic phosphate, alkaline pH, and ROS. Although the MPT pathway may induce apoptotic cell death under some condition, the MPT pore opening is recognized to be a major cause of the necrotic cell death.[59] CypD-deficient mice show a high level of resistance to ischaemia/reperfusion-induced cardiac necrosis,[60] indicating that ROS is involved in necrotic cardiomyocyte death through MPT pore opening. Thus, ROS could cause both apoptosis and necrosis although precise regulating mechanisms are not elucidated yet.

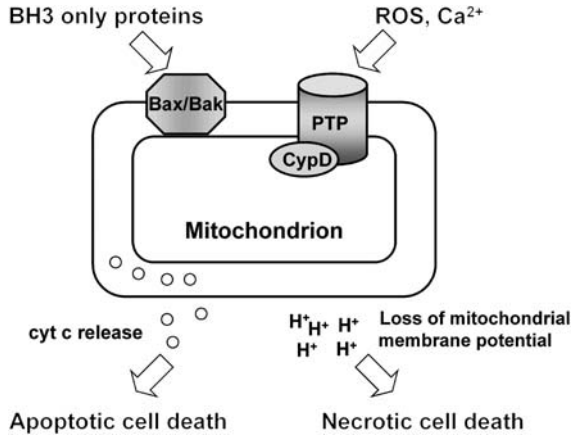

Figure 1 The mechanisms of apoptotic or necrotic cell death mediated through mitochondria. In intrinsic pathway of apoptosis, BH3-only proteins are activated by apoptotic stimuli. Active BH3-only proteins activate Bax and Bak. Once activated, Bax and Bak promote cytochrome c (cyt c) release from the intermembrane space to the cytoplasm, leading to apoptotic cell death. In contrast, Ca^{2+} overload induced by extensive ROS generation could enhance the permeability of the mitochondrial membrane mediated through opening of a putative channel complex, permeability transition pore (PTP), and lead to MPT, which is defined as the loss of transmembrane potential of the mitochondrial inner membrane, and then necrotic cell death. CypD is a component of PTP and a key molecule of cellular necrosis.

5. Apoptosis signal-regulating kinase-1 as a key player in oxidative stress

ASK1, a 160 kDa serine/threonine protein kinase is an ROS-sensitive MAP kinase kinase kinase and activates both p38 and JNK pathways.[42] ASK1 is ubiquitously expressed in most mammalian cells and the kinase activity of ASK1 is activated by many stress signals and proinflammatory cytokines, including H_2O_2, TNF-α, endoplasmic reticulum stress, and serum withdrawal. Thioredoxin 1 binds directly to the N-terminal regulatory domain of ASK1 and inhibits ASK1 activation of this kinase. Upon ROS generation, oxidized thioredoxin 1 is dissociated from ASK1, leading to a robust autophosphorylation of Thr845 in the homo-oligomer.[61] Under modest stressed conditions, activated ASK1 is involved in cardiac hypertrophy, cell protection, and stress responses e.g. cytokine release mediated through the downstream MAP kinase pathways and transcription factors (*Figure 2*).[46,62] We have reported that G-protein-coupled receptor agonists e.g. norepinephrine, angiotensin II, and endothelin rapidly and transiently activate ASK1 via ROS generation and ASK1 is involved in G-protein-coupled receptor agonist-induced NF-κB activation and cardiomyocyte hypertrophy.[43] We have also reported that the ROS–ASK1–JNK pathway plays an important role in apoptosis in the heart under severely stressed conditions.[63] Overexpression of a constitutively active mutant of ASK1 induces apoptosis in isolated rat neonatal cardiomyocytes, whereas neonatal ASK1-deficient cardiomyocytes are resistant to H_2O_2-induced apoptosis. ASK1 is activated in post-infarcted wild-type mouse hearts. Four week after left coronary artery ligation, wild-type hearts had become obviously enlarged compared with ASK1-deficient hearts. The number of apoptotic myocytes after MI is decreased in ASK1-deficient mice.[63] Chronic inhibition of ASK1 activation by transcoronary gene transfer using recombinant adeno-associated virus can attenuate the

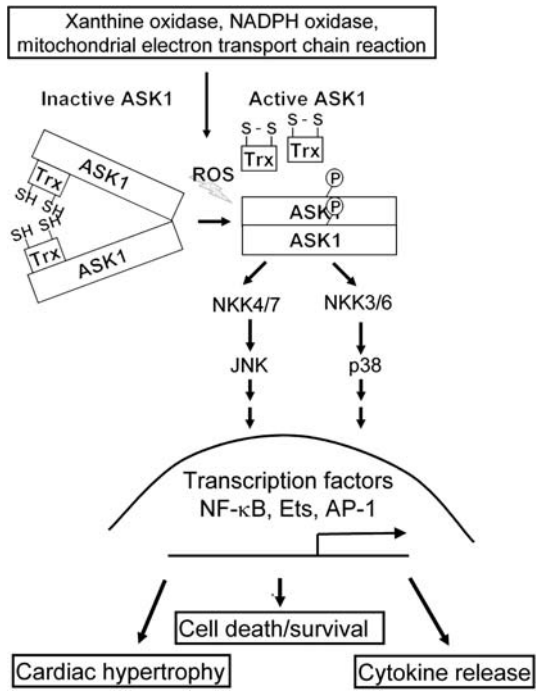

Figure 2 The roles of reactive oxygen species (ROS) and apoptosis signal-regulating kinase-1(ASK1) in oxidative stress. The major sources of ROS in oxidative stress are mitochondria, xanthine oxidase, and NADPH oxidase. The N-terminal regulatory domain of ASK1 interacts with thioredoxin 1 (Trx) in the inactive complex. ROS activate ASK1 mediated by oxidization of Trx and its dissociation from ASK1. Activated ASK1 is involved in cardiac hypertrophy, control of cell fate, and stress responses e.g. cytokine release mediated through the downstream MAP kinase pathways and transcription factors.

progression of cardiac remodelling in TO-2 cardiomyopathic hamsters.[64] In this hamster, inhibition of ASK1 selectively attenuates JNK activation and reduces the number of apoptotic cells. These suggest that the ASK1–JNK pathway may play a pivotal role in regulating LV remodelling by promoting apoptosis.

ASK1–JNK/p38 pathways are also involved in both cell survival and apoptosis. Although the mechanisms have not been clearly understood, the extent and/or duration of activation of JNK/p38 may contribute to determination of cell fate. Sustained activation of JNK/p38 by excessive stimuli may be responsible for apoptosis.[62] In contrast to this hypothesis, we have observed that p38 plays a critical role in the cardiomyocyte survival pathway in cardiac-specific p38α-deficient mice.[65] Although further studies are necessary to clarify the roles of p38 MAP kinase pathways in response to oxidative stresses, it is of interest that the infarct area after ischaemia/reperfusion is dramatically reduced in ASK1-deficient hearts, suggesting that ROS–ASK1 pathway is also involved in necrotic cell death as well as apoptotic cell death.[66] Since ASK1 may be involved in both apoptosis and necrosis, this molecule may be a target of treatment to reduce LV remodelling after MI.

6. Progression of left ventricular remodelling

LV remodelling following MI may promote thinning of the infarcted area and reactive hypertrophic responses of remote myocardium, resulting in progressive enlargement of the LV.[1,67,68] The structure of LV chamber changes from ellipsoidal to spherical shape, i.e. a ratio of long to short axis is decreased. This dilatation is often associated with mitral regurgitation which further deteriorates LV function.[69] Previous studies have also demonstrated that the extent of LV remodelling correlates with prognosis in patients with MI.[3] This is because enlargement of LV chamber is associated with the incidence of cardiac sudden death as well as the chronic HF (CHF).[2]

The thinning of the ventricular wall and chamber dilatation increases the mechanical stress of the ventricular wall and subsequently cause a slippage of the myofibrils. Increased mechanical stress also causes subendocardial ischaemia. Extracellular matrix response to mechanical overload elicits the increase in collagen synthesis which makes the ventricular wall stiffer and thus, increases LV diastolic pressure. There is a large body of clinical evidence that angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, and β-blockers improve the prognosis of the patients. It should be noted that all these drugs attenuate the progression of LV remodelling and even reverse it.[70–72] Surgical repair of mitral regurgitation could also reverse LV remodelling and improve prognosis.[69,73] Furthermore, surgical volume reduction treatment is performed to improve the symptoms as well as prognosis in CHF.[74,75] Myocardial hibernation or severe myocardial ischaemia by coronary artery narrowings also leads to regional contractile dysfunction, resulting in LV remodelling. This is confirmed by the fact that revascularization to the hibernating or ischaemic myocardium can improve LV function and prevent LV remodelling in patients with post-MI.[76] In contrast to systolic HF, however, diastolic HF is not associated with LV dilatation.[77] In this type of HF, LV wall is often thickened and systolic function is preserved within normal range. This abnormality is frequently observed in elderly people especially associated with hypertension or its history.[78] It is speculated that an increase in myocardial fibrosis and/or myofibrillar stiffening due to myofibrillar hypertrophy may be a major cause of an increase in LV diastolic pressure and thus, pulmonary congestion. There are several reports that oxidative stress is also enhanced in diastolic HF and hypertensive heart disease.[79–81] Thus, oxidative stress may play a pivotal role not only in LV remodelling after MI but also in non-ischaemic LV remodelling due to mechanical overload.

7. Antioxidant and anti-inflammatory therapy for reverse remodelling

Antioxidant and anti-inflammatory treatment may be a promising approach for reverse remodelling. In the transgenic mice of oxidant scavenger SOD, the infarct size following ischaemia/reperfusion is markedly reduced.[15,16] The antioxidant agent, mercaptopropionyl glycine,[82] or edaravone[83] also inhibits cardiac hypertrophy by pressure overload in mice. There has been a plenty of evidence that antioxidant agents attenuate the LV remodelling following MI. Probucol, a potent antioxidant exerts a favourable effect on post-infarction HF in rats,[84,85] adriamycin-induced HF,[86] and tachycardia-induced HF in mongrel dogs.[87] However, not a few experimental studies do not support this hypothesis. Administration of probucol after ligation of coronary artery in rats minimally attenuates interstitial collagen content and does not improve

the prognosis.[88] However, the timing of administration of the antioxidant may be important since another report suggested that the infarct size after ischaemia-reperfusion is significantly influenced by the timing of administration of probucol in Watanabe heritable hyperlipidaemic rabbits.[89]

The dose of the agent may also be critical for antioxidant effect. A small dose of aspirin does not attenuate the inflammatory cytokines. However, a large dose of aspirin exerts an inhibitory effect of inflammatory cytokines although aspirin may not attenuate collagen accumulation and hence, LV remodelling.[90] Collagen synthesis and accumulation may be regulated not only by ROS and inflammatory cytokines but also by other factors, e.g. transforming growth factor-β.[91] Thus, the limited effect of antioxidant may minimally inhibit LV remodelling depending upon the underlying conditions of the heart.

Clinically, vitamin C and E supplementation did not influence cytokine levels, functional indexes, quality of life, or neurohumoral status in patients with advanced CHF.[92–94] HMG-CoA reductase inhibitor, statin, has some pleiotropic effects including antioxidant and anti-inflammatory effects.[95] Although statin can prevent cardiac hypertrophy and apoptotic cell death experimentally, rousvastatin did not improve the prognosis of the patients with CHF in CORONA study[96] and GISSI-HF study.[97] In patients with CHF, plasma levels of inflammatory cytokines are increased.[98] Since the CHF patients with the high levels of cytokines had poor short- and long-term prognosis, anti-TNF therapy using etanercept was evaluated in patients with CHF. However, in RENEWAL study which was combined analysis of medium- and high-dose etanercept vs. placebo, the primary endpoint (death or CHF hospitalization) and the secondary endpoint (death for any cause) were not different between etanercept and placebo.[99] In ATTACH trial, chimeric IgG monoclonal antibody of TNF-α, infliximab did not improve the mortality and morbidity of the patients with CHF. These results suggest that anti-TNF therapy is not effective in treatment of CHF.[100] Etanercept may have an agonistic effect of TNF and infliximab may induce cell lysis by binding of TNF-α–anti TNF-α complex to complements.[101,102] Thus, these anti TNF agents may also have detrimental effects. On the other hand, TNF-α is also an essential molecule for cell survival and thus, it plays a role as a double-edged sword. Anti TNF treatment may be on the critical balance between TNF-α activity and inhibitory potency of anti TNF agents. Dose of drug, timing of administration, and the underlying conditions of the disease may be critically important. Also, underlying conditions of CHF and LV remodelling following MI may not be identical: absence of long-term efficacy of anti-TNF-α treatment may not indicate that anti TNF treatment is ineffective to inhibit LV remodelling after MI. Indeed, etanercept and infliximab are effective in anti-inflammatory action and inhibiting tissue remodelling in rheumatoid arthritis and ankylosing spondylitis.[103–106] To our knowledge, there are no clinical trials of antioxidant drugs combined with anti-cytokine therapy and thus, combined treatment should be tested in future.

The renin–angiotension–aldosterone system (RAAS) has a central role in the pathophysiology of LV remodelling and progression of HF. The pharmacologic inhibition of RAAS attenuates oxidative stress and LV remodelling. Several large trials of angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blocker in patients with LV dysfunction or HF after an acute MI were performed and they all demonstrated that the blockade of RAAS reduces the all-cause mortality.[107–110] In these clinical trials, it is also shown that RAAS inhibition attenuates LV remodelling. In animal models with HF, RAAS inhibition demonstrates an attenuation of oxidative stress.[111]

β-blockers can prevent cardiac events and improve the prognosis in patients with acute MI. Carvedilol is a non-selective β-blocker with antioxidant action.[112,113] Administration of carvedilol decreases the oxidative stress level together with improvements of cardiac function in patients with HF.[114] In CAPRICORN study, carvedilol reduced all-cause mortality or non-fatal recurrent MI in patients with LV dysfunction after acute MI.[115] In the echo substudy, carvedilol showed beneficial effects on ventricular remodelling.[116] In the carvedilol or metoprolol European trial (COMET), carvedilol is shown to be superior to metoprolol, suggesting an importance of antioxidant effect.[117] However, the dose and formulation of metoprolol used in this trial has caused a debate, and it has been questioned whether a comparable β1-blockade is obtained in the two intervention groups.[113] Xanthine oxidase is an important source of oxidizing activity molecules and is extensively expressed in patients with HF. Allopurinol effectively counters oxidative stress and attenuates LV remodelling and dysfunction after experimental MI.[118] In clinical setting, allopurinol improves endothelial dysfunction,[119] mortality, and morbidity[120] in patients with CHF. In the OPT-CHF study, a xanthine oxidase inhibitor, oxypurinol, did not exert clinical improvements in unselected patients with moderate-to-severe HF. However, post-hoc analysis suggests that benefits occur in patients with elevated serum uric acid in a manner correlating with the degree of serum uric acid reduction, although prospective clinical studies are necessary.[121]

Thus, several drugs which have beneficial effects on LV remodelling and prognosis in patients with MI and CHF, have some antioxidant effects. However, there is not definitive evidence that antioxidants are effective in reverse remodelling probably because clinically available antioxidant drugs are insufficient in their potency, the dose of the drug is not optimal or the timing of administration is not appropriate in the previous studies. Further studies are needed to clarify the role of oxidative stress in LV remodelling in patients with MI.

8. Conclusion

In acute MI, ROS generated in the ischaemic myocardium directly injure the cell membrane causing cell death. However, ROS also stimulate signal transduction to elaborate inflammatory cytokines which regulate cell survival and cell death in the chain reaction with ROS. In this signal transduction, ASK1, MAP kinase kinase kinase plays a key role in controlling cell fate either in apoptosis or necrosis, and thus, LV remodelling. Chronically, inflammatory cytokines activate MMPs causing a slippage of myofibrils and hence LV dilatation. Since an extent of LV remodelling is a major predictor of prognosis of the patients with MI, therapeutic approach attenuating LV remodelling is critically important. Antioxidant and anti-inflammatory treatments

may be a promising approach though direct positive evidence has not been obtained yet.

Conflict of interest: none declared.

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