Cardiomyocyte death in sepsis: Mechanisms and regulation (Review)

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Abstract. Sepsis-induced cardiac dysfunction is one of the most common types of organ dysfunction in sepsis; its pathogenesis is highly complex and not yet fully understood. Cardiomyocytes serve a key role in the pathophysiology of cardiac function; due to the limited ability of cardiomyocytes to regenerate, their loss contributes to decreased cardiac function. The activation of inflammatory signalling pathways affects cardiomyocyte function and modes of cardiomyocyte death in sepsis. Prevention of cardiomyocyte death is an important therapeutic strategy for sepsis-induced cardiac dysfunction. Thus, understanding the signalling pathways that activate cardiomyocyte death and cross-regulation between death modes are key to finding therapeutic targets. The present review focused on advances in understanding of sepsis-induced cardiomyocyte death pathways, including apoptosis, necroptosis, mitochondria-mediated necrosis, pyroptosis, ferroptosis and autophagy. The present review summarizes the effect of inflammatory activation on cardiomyocyte death mechanisms, the diversity of regulatory mechanisms and cross-regulation between death modes and the effect on cardiac function in sepsis to provide a theoretical basis for treatment of sepsis-induced cardiac dysfunction.

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1. Introduction

Sepsis is a severe life-threatening form of organ dysfunction caused by dysregulated host response to infection (1) and it has high morbidity and mortality rates, Fleischmann *et al* (2) searched 15 international citation databases to estimate population-level sepsis morbidity and mortality in adult populations, the global estimator of hospital-treated sepsis morbidity from 2003 to 2015 was 437 sepsis cases per 100,000 person-years, hospital mortality was 17%. The heart is essential for maintenance of adequate organ perfusion and is one of the major organs affected during sepsis. Therefore, cardiac dysfunction is a common complication of sepsis that has a poor prognostic outcome (2). The pathological mechanism of sepsis-induced cardiac dysfunction is complex and multifactorial. Numerous factors, such as hemodynamic and myocardial energy metabolism disorder, oxygen free radicals, myocardial inhibitors and cardiomyocyte death, are involved in cardiac dysfunction, of which cardiomyocyte death is one of the primary elements that cause myocardial dysfunction. To the best of our knowledge, however, its mechanism is not yet fully understood.

A certain number of cardiomyocytes is needed for maintenance of normal heart function. Cell death in the heart is detrimental because the majority of adult cardiomyocytes are terminally differentiated and non-regenerative cells with a limited capacity to perform key functions (3). According to the Nomenclature Committee on Cell Death, there are multiple modes of cell death (4). Cardiomyocyte death modality exhibits tissue specificity and key cardiomyocyte death modalities include apoptosis, necroptosis, mitochondrial-mediated necrosis, pyroptosis, ferroptosis and autophagic cell death (5). Cell membrane remains intact when cells die via apoptosis, ferroptosis and autophagy. On the other hand, death by necroptosis, mitochondrial-mediated necrosis and pyroptosis leads to disruption of the cell membrane (5). Multiple types of cell death can occur simultaneously or in succession during disease progression (4).

Sepsis is characterized by acute release of multiple inflammatory mediators (such as TNF-α, IL-6 and IL-1β); excessive release of inflammatory mediators damage tissue and organs. There is increasing evidence that inflammation is associated with cell death (6-8); cells with a certain number and proper function are important for maintaining normal organ function,

which play a crucial role in fighting against microbial infection. Inflammation and cell death can occur simultaneously (9) or in sequence. Different types of cell death do not act independently but interact with each other (10). Mechanisms of cellular death are associated with organ function, therefore, targeting the mechanism of cardiomyocyte death in sepsis may identify potential options for treatment of sepsis-induced myocardial dysfunction. The present review aimed to summarize the effects of inflammatory activation on cardiomyocyte death and the association between modes of cell death modes to identify potential targets for novel therapeutic strategies based on pathogenesis.

2. Inflammation and cardiomyocyte death in sepsis

Cardiac cell apoptosis in sepsis. Apoptosis is a regulated cell death program and is the most common type of cell death (11). It is morphologically characterized by cellular shrinkage, chromatin condensation, nuclear fragmentation and formation of apoptotic bodies (12). Apoptosis is highly regulated in normal healthy tissue but is activated under certain pathological conditions, such as when cells are damaged by disease or a toxic agent (13). Intracellular cysteine-dependent aspartate-specific proteases (caspases) are effector proteins associated with activation of apoptotic signaling (14,15). Numerous studies have shown that apoptosis typically exerts a beneficial effect in anti-inflammatory and immunosuppressive processes (16,17). However, this programmed cell death may have different roles in different tissues, moreover, insufficient or excessive apoptosis promotes organ dysfunction (18).

Apoptosis serves a crucial role in cardiovascular disease, apoptosis of myocytes is among those processes that have been extensively studied *in vitro* (19). Sepsis notably increases cardiomyocyte apoptosis (20); this negatively impacts cardiac function, as apoptosis serves a major role in the loss of cardiomyocytes (21). Adult cardiomyocytes are terminally differentiated and loss of cardiomyocytes through apoptosis has been recognized as the underlying mechanism in the development of cardiac dysfunction following sepsis (22). *In vitro* and *in vivo* experiments have shown that a high levels of cardiomyocyte apoptosis result in decreased cardiac function (23,24). As shown by numerous studies, the pathological changes of the myocardium in sepsis are associated with inflammation and cardiomyocyte apoptosis, which may impair myocardial function directly (25,26). Wencker *et al* (27) demonstrated that very low levels of myocyte apoptosis (23 compared with 1.5 myocytes per 105 nuclei in controls) cause life-threatening dilated cardiomyopathy. Cardiomyocyte apoptosis induced by lipopolysaccharide (LPS) is completely prevented by treatment with broad-spectrum caspase inhibitor z-Val-Ala-Asp-fluoromethylketone (28). MicroRNAs (miRNAs or miRs) are a class of small non-coding RNA involved in numerous types of disease, including cardiovascular disease. It is reported that >30 miRNAs are involved in sepsis-induced cardiac dysfunction; among these, >10 miRNAs have been implicated in regulating sepsis-induced cardiac apoptosis (29-31). Certain miRNAs (such as miR-155, -24 and miR-192-5p) activate cell apoptosis but others (such as miR-214, -25, -93-3p, -23b, -146a, -98 and -150-5p) inhibit cell apoptosis (29).

Cardiac cell necroptosis in sepsis. Necroptosis is an important form of cell death that leads to the disruption of cellular membranes and leakage of cellular substances, which causes inflammation (32). Necroptosis, also named programmed necrosis (33), is a pro-inflammatory form of cell death with features of both necrosis and apoptosis (34). Necroptosis is similar to necrosis in morphological features, but, like apoptosis, is strictly regulated by multiple signalling pathways. Necroptosis is a caspase-independent mode of programmed cell death and is negatively regulated by caspases (33,35). Necroptosis is regulated by signalling molecules receptor-interacting protein kinase-1 (RIPK1) and RIPK3 in a kinase-dependent manner (36-38), resulting in activation of mixed lineage kinase domain-like (MLKL) and rapid loss of plasma membrane integrity (39). The necroptosis and apoptosis pathways affect each other (40). In the absence of apoptotic caspase activation, cells undergo necroptosis via alternative routes (38).

Numerous studies have shown that necroptosis serves an important role in the regulation of inflammatory conditions and the course of infectious disease (33,41). Sepsis is characterized by inflammatory response imbalance and excessive production of pro-inflammatory cytokines, such as TNF-α and IL-1β, in a cytokine storm (42). TNF activation can trigger two signalling pathways associated with cell death, namely apoptosis and necroptosis (43,44). RIPK1, RIPK3 and MLKL are three key proteins involved in TNF-induced necroptosis (45,46). Necroptosis is regulated by the RIPK1/RIPK3/MLKL pathway and is associated with organ injury (47,48). Necrostatin-1 (Nec-1) prevents necroptosis by blocking RIPK1 kinase activity in various injury models (49,50). Schenck *et al* (51) reported that RIPK3, a marker of necroptosis, is positively correlated with mortality and organ dysfunction in sepsis. However, *in vivo*, necroptosis promotes *Staphylococcus aureus* clearance by limiting excessive inflammation to improve prognosis in a mouse model of sepsis (52). These findings indicate that necroptosis may be associated with different pathological effects and mechanisms in sepsis caused by different etiologies and different stages of sepsis development.

Similar to the pathology of apoptosis in cardiomyocytes, cardiomyocyte loss through necroptosis serves a key role in the pathogenesis of cardiac dysfunction (53). To investigate the importance of necroptosis in cardiomyocyte death and heart injury in sepsis, a number of studies both *in vivo* and *in vitro* have been performed (53,54). Beno *et al* (55) reported that cardiomyocyte death and heart damage are necroptosis-dependent in a *Streptococcus pneumoniae* mouse model in which necroptosis inhibition attenuated myocardial injury. The promotive effects of necroptosis on sepsis-associated myocardial damage have been confirmed by cell experiments (56,57). *In vivo* and *vitro* study reported that necroptosis caused by doxorubicin in cardiomyocytes is inhibited by potent necroptosis inhibitor Nec-1 (58).

Experimental studies have shown that peroxisome proliferator-activated receptor γ, a protein receptor with cardioprotective effects, decreases cardiac inflammation and alleviates sepsis-associated cardiomyopathy by inhibiting apoptosis and necroptosis (54,59). *In vitro* experiments have confirmed that heparan sulfate fragments (a class of

danger/damage-associated molecular patterns) induce apoptosis in cardiomyocytes and RIP3-mediated necroptosis occurs over time, indicating that necroptosis is associated with sepsis-associated cardiomyopathy (56,60). Another study by Fu *et al* (61) suggested that necroptosis is activated by LPS in cardiomyocytes via the RIPK3/PGam5 signalling pathway.

Mitochondria-mediated cardiac necrosis in sepsis. In addition to apoptosis, necrosis is a key cell death modality (62). Mitochondria are essential intracellular organelles involved in energy metabolism. In cardiac myocytes, mitochondria comprise ~30% of cell volume (63) and cardiomyocyte function is associated with mitochondria. Cell stress induces intracellular calcium overload (64), reactive oxygen species (ROS) production, adenine nucleotide depletion and excessive calcium (Ca^{2+}) in mitochondria, resulting in a long-lasting opening of the mitochondrial permeability transition pore (mPTP), which leads to mitochondrial permeability transition (MPT) (65). As a consequence of MPT, mitochondrial swelling and rupture occur, followed by MPT-dependent necrosis, which is also known as mitochondria-mediated necrosis (66). MPT is key for mitochondria-mediated necrosis (67), which manifests as a necrotic morphotype (68). mPTP opening causes mitochondrial dysfunction, cell death and irreversible tissue damage (69). As cardiomyocytes are not able to regenerate following necrosis, loss of cardiomyocytes via necrosis leads to fibrosis and cardiac dysfunction (70). In an *in vitro* experiment, increased opening of mPTP and cardiac mitochondrial dysfunction have been observed in a cecal ligation and puncture-induced septic heart, while sepsis-induced myocardial dysfunction is prevented by inhibiting mPTP (70). Hence, selective mPTP modulators may serve as an effective pharmaceutical tool to treat mPTP-related diseases by preventing channel formation (71-73). Zhou *et al* (74) found that decreased expression of PTEN-induced kinase 1 (PINK1) in the myocardium of sepsis mice leads to cardiomyocyte mitochondrial Ca^{2+} efflux disorder and mitochondrial calcium overload, PINK1 contained in exosomes isolated from human umbilical cord mesenchymal stem cells (huMSC-exo) prevents cardiomyocyte mitochondrial calcium efflux; thus, PINK1 may be a therapeutic target to protect cardiomyocyte mitochondria, and the application of huMSC-exo is a promising strategy against sepsis-induced heart dysfunction.

Cardiac cell pyroptosis in sepsis. Pyroptosis is a caspase-dependent inflammatory form of programmed cell death in response to diverse pathogen- and host-derived danger signals (75,76). Its morphological features differ from apoptosis in that they involve cell swelling and lysis (77). Pyroptosis is a key host innate immune defense mechanism against pathogens (78). However, excess pyroptosis results in excessive inflammation and multiple organ dysfunction. Pyroptosis occurs via two pathways: Classical caspase-1 (caspase-1-mediated) and non-classical caspase-4/5/11 pathways (caspase-4/5/11-mediated, human homologs caspase-4- and caspase-5-mediated and murine caspase-11-mediated) (79,80). In the classical caspase-1 pathway, NLRP3 inflammasome activation occurs via caspase-1 (81,82). Studies (4,80) have shown, non-classical pathways, intracellular LPS directly binds with caspase-4, -5, and -11 with high affinity, resulting in caspase-4, -5, and -11 self-assembly and triggering cell pyroptosis. Activating caspase-4, -5, and -11 indirectly promotes cleavage of pro-inflammatory factor precursors (pro-IL-1β and pro-IL-18) by activating NLRP3 inflammasome and caspase-1 (83).

Pyroptosis has been described as inflammatory death and is directly associated with inflammatory response (84,85). Therefore, studying the molecular mechanism of pyroptosis is key for elucidation of the pathological mechanism of sepsis. Kang *et al* (86) established a sepsis model using glutathione peroxidase 4 (GPX4) $Mye^{-/-}$ mice and showed that caspase-11-dependent pyroptosis mediates septic death. NLRP3 inflammasome is activated in sepsis, while NLRP3 inflammasome-mediated caspase-1 activation induces cell death via pyroptosis (81,87). Extracellular LPS activates toll-like receptor (TLR)4 on the cell surface, thereby indirectly activating caspase-11, which is also activated by directly binding to intracellular LPS (88). Cheng *et al* (89) studied caspase-$1^{-/-}$ and -$11^{-/-}$ gene knockout mice; double inflammatory caspase gene-deficient mice exhibited a 90% survival rate, while mice lacking caspase-1 but expressing caspase-11 exhibited 0% survival within 72 h, indicating that caspase-11 serves a greater role in the mechanism of endotoxemia-induced death in mice. Sphingosine-1-phosphate is a biomarker of sepsis severity (90); sphingosine-1-phosphate receptor increases macrophage caspase-11 activity and promotes macrophage pyroptosis during sepsis (91).

Pyroptosis promotes cell swelling, membrane pore formation and plasma membrane rupture in sepsis, resulting in leakage of inflammatory factors from the cell and inducing cell death (92-94). Studies have modulated NLRP3 inflammasome activation to affect pyroptosis (95,96). Chu *et al* (97) inhibited activation of atypical macrophage inflammasomes using oxidized phospholipids, which decreased the inflammatory response in septic mice. Lee *et al* (98) demonstrated that phospholipase D1 inhibitor VU0155069 has antibacterial activity and inhibits formation of inflammasomes, thus exerting an anti-pyroptosis effect. Li *et al* (99) found that normal saline containing methane decreases release of inflammatory mediators TNF-α and IL-β, ROS production and NLRP3-mediated pyroptosis in sepsis.

Pyroptosis in septic response occurs in cardiomyocytes within the myocardium (100). Inflammation and cardiomyocyte pyroptosis contribute to sepsis-induced cardiomyopathy (100). Furthermore, inhibition of NLRP3-mediated pyroptosis exerts a cardioprotective effect against sepsis-induced myocardial dysfunction (101). Carvedilol, a neurohumoral antagonist, protects mitochondria and cell lysosomes from damage during the immune response, which inhibits the classical activation pathway of pyroptosis by decreasing production of NLRP3 inflammasomes, ultimately inhibiting pyroptosis and improving cardiac function (102). The potential role of miRNA in the regulation of pyroptosis has been reported previously: Inhibition of miR-15 downregulates expression of NLRP3 and caspase-1, which decreases pyroptosis (103). Chen *et al* (104) reported that trimetazidine decreases LPS-induced cardiomyocyte pyroptosis via neutrophils. To the best of our knowledge, there have been relatively few studies on pyroptosis in septic myocardial damage and the role of the atypical pyroptosis pathway in septic myocardial damage has

not yet been systematically analyzed. As a result, the detailed mechanism of pyroptosis and myocardial damage in sepsis needs further investigation in future.

Cardiac cell ferroptosis in sepsis. Iron is one of the trace elements necessary for the human body. It participates in the mitochondrial respiratory chain, nucleic acid replication and repair and metabolism (105). Iron is also a key biological element in microbial life (106). It has been shown that iron promotes bacterial growth and enhance the virulence of bacteria (107-109). In order to improve anti-infection ability, it is necessary to enhance uptake of iron by the host, but prevent uptake of iron by bacteria (110). However, intracellular iron overload induces ferroptosis and causes organ dysfunction (111). Therefore, how to maintain this balance needs more research.

Ferroptosis is a ROS- and iron-dependent form of non-autophagic and non-apoptotic programmed cell death (112). Ferroptosis is activated by iron oxidation, which differs from other modes of cell death on morphological, biochemical and genetic levels (113). The mechanism of ferroptosis primarily involves two pathways: Consumption of glutathione (GSH) and reduction of GPX4 activity (GSH/GPX4) pathway (3,112) and reduction of ferroptosis suppressor protein 1 (FSP1) activity and consumption of co-enzyme Q10 (FSP1/CoQ/NADPH) pathway (3). Ferroptosis causes notable iron accumulation and lipid peroxidation during cell death. It is distinct from apoptosis or necroptosis because it is inhibited by iron chelators and lipophilic antioxidants but is not inhibited by caspase or RIPK1 inhibitors (114). Genes and pathways involved in iron, lipid and amino-acid metabolism have been found to modulate ferroptosis (115-120).

It is hypothesized that ferroptosis is associated with cancer suppression and neurodegenerative disease (121-126). Sepsis is often accompanied by increased ROS generation, which induces ferroptosis in cells (127). GPX4 decreases ROS production, thereby inhibiting ferroptosis (118). Previous reports have suggested that ferroptosis modulated by GPX4 may be a novel pathophysiological mechanism (112,128) that leads to organ dysfunction in sepsis.

The morphological hallmarks of ferroptosis include mitochondrial shrinkage and condensation with a decreased number of mitochondrial ridges (122,129). As myocardial tissue containing abundant mitochondria, ferroptosis studies have primarily focused on myocardial injury in sepsis compared with kidney, brain and other organs (130,131). Fang *et al* (132) found that high-iron diet in mice lacking ferritin H in cardiomyocytes caused severe cardiac injury and hypertrophic cardiomyopathy with morphological features of ferroptosis, decreased GSH levels and increased lipid peroxidation; ferrostatin-1 (Fer-1), a specific inhibitor of ferroptosis, reversed these effects (132). This suggested that inhibition of ferroptotic cell death via iron metabolism interference improves cardiac function. By affecting lipid composition, Acyl-CoA thioesterase 1 prevents doxorubicin-induced ferroptosis in cardiomyocytes and offers a potential therapeutic approach to the treatment of myocardial injury and prevention of heart failure (133). Additional studies have demonstrated that inhibition of ferroptosis-induced cardiomyocyte death protects against myocardial ischemia-reperfusion injury (134,135). Moreover, an experiment in cardiomyocytes confirmed that GPX4 overexpression protects against palmitic acid-induced ferroptosis, whereas GPX4 knockdown reverses the anti-ferroptotic effect (136). The aforementioned studies demonstrated that ferroptosis plays a pathophysiological role in the heart. Li *et al* (137) studied sepsis models *in vivo* and *in vitro* and demonstrated that iron-dependent ferroptosis serves a crucial role in sepsis-induced cardiomyopathy. Fer-1 and deferoxamine decrease levels of ferroptosis in cardiomyocytes and improve cardiac function and survival rate in septic mice (137). GSH release and expression of GPX4 are significantly decreased in sepsis-induced myocardial injury in mice and dexmedetomidine decreases ferroptosis by decreasing iron concentration and hemeoxygenase-1 protein expression, as well as increasing expression of GPX4 pathway molecules to exert cardioprotective effects (138,139). The aforementioned results confirm the cardioprotective effect of dexmedetomidine, supporting the hypothesis that ferroptosis serves a key role in the pathogenesis of myocardial injury induced by sepsis (139).

Autophagic cardiac cell death in sepsis. Autophagy is necessary for cellular metabolism and homeostasis (140). Autophagy is classified as chaperone-mediated autophagy, microautophagy or macroautophagy depending on physiological functions and delivery routes, macroautophagy is the most well-studied form of autophagy, and, usually, the term 'autophagy' refers to macroautophagy (141). In this review, 'autophagy' refers to macro-autophagy. The primary physiological role of autophagy is a survival mechanism allowing the reuse of cytosolic constituents under cell stress (142). Autophagy is type II programmed death (62) and serves a crucial function in disease development and progression. To a certain extent, autophagy activation degrades cellular components, proteins and damaged organelles in a lysosome-dependent manner, thus preventing spread of biomolecules and damaged organelles (143). However, under certain conditions, autophagy is inappropriately activated; excessive activation of autophagy induces cell death, which is known as 'autophagic cell death' (144). The present review focused on pathological autophagy (autophagic cell death in sepsis) rather than physiological autophagy.

The precise role of autophagic cell death in sepsis is controversial. Certain studies have suggested that the activation of autophagy alleviates multiple organ dysfunction caused by sepsis (145-148); the primary mechanism may be associated with suppression of inflammation by regulating activation of macrophages and inhibiting release of inflammatory factors (149). By eliminating damaged organelles, autophagy can maintain cellular homeostasis and cell viability. Another study confirmed that the viability of T cells in cellular immunity is decreased following autophagy inhibition (150). One study revealed that autophagy activation aggravates lung injury and respiratory muscle dysfunction in sepsis, increases aggregation of granulocytes and other inflammatory cells and decreases the ability of macrophages and granulocytes to phagocytose pathogenic bacteria. Conversely, inhibition of mitochondrial autophagy of macrophages promotes macrophage activation and enhances host antibacterial activity (151). Autophagy activation decreases the

viability of immunosuppressive T cells ($CD4^+$, $CD25^+$ and T regulatory cells) and increases the immune response in septic patients (152-154). However, a prior clinical study has shown that autophagy level of neutrophils is positively correlated with survival rate in septic patients (155). The aforementioned studies demonstrate that inhibiting autophagy is typically harmful. Although increasing autophagy has shown certain beneficial results in experimental research, the potential use of autophagy activators in the clinic requires further investigation.

The pathogenesis of sepsis is characterized by excessive inflammatory response and secondary immune dysfunction (156). The role of autophagy in response to sepsis is a dynamic process and autophagy serves different roles in different stages of disease (157). Therefore, effects of autophagy in different stages of sepsis are key for treatment and protection of vital organs during sepsis.

Levels of mitochondria are higher in myocardium compared with other tissue (63). Mitophagy refers to the process by which cells selectively remove damaged and aging mitochondria via autophagy (158). TLR4 induces release of mitochondrial DNA and activates mitochondrial autophagy via TLR9, removes damaged mitochondria and promotes mitochondrial self-repair (159). Normal mitochondrial structure and function are associated with function of cardiomyocytes (160). Therefore, the effect of mitochondrial autophagy on cardiac function is a key research topic. ROS are produced by cardiac mitochondria when mitochondria become dysfunctional during inflammation (161). Autophagy is a biological process and its occurrence, development and outcome are associated with chemical processes, such as ROS production in the body, abnormal lipid metabolism, ubiquitination and protein phosphorylation (162,163). Studies have shown that production of ROS in cardiomyocytes contribute to the development of autophagy (164,165). In addition, cardiomyocyte autophagy decreases ROS production (166). ROS activation of autophagy may exert a protective effect, but excessive autophagy causes irreversible deterioration of cardiac function (167,168). Additionaly, numerous studies on myocardial tissue support the hypothesis that autophagy enhancement to a certain extent contributes to repair and production of new mitochondria and improves cardiac function (169-172).

Autophagy has become a focus of research and a potential therapeutic target to protect cardiomyocytes from damage. Studies confirmed that autophagy plays a protective role in sepsis-induced cardiac dysfunction by inhibiting the mTOR pathway associated with autophagy activation (173,174). Similarly, Hsieh *et al* (175) used rapamycin to induce autophagy in myocardial cells of septic mice to improve cardiac function. Numerous studies have revealed that activation of cardiac autophagy attenuates myocardial damage induced by sepsis (176-178). The effect of miRNAs on autophagy was studied by inducing or suppressing autophagy, certain miRNAs (such as miR-1, miR-22, miR-145 and -144) activate cell apoptosis but others (such as miR-20b-5p, miR-21, miR-34a, -101, miR-30a and -122) inhibit apoptosis (179). Up to date, the current research on cardiac autophagy in sepsis is still only at the basic research level, further basic and clinical studies of how autophagy affects myocardial function in sepsis are required.

3. Interplay of cardiomyocyte death signalling pathways in sepsis

Cell death pathways involve complex interactions in cardiomyocyte death signalling during sepsis (180,181). In different stages, activation of multiple cell death pathways may co-occur and affect each other during the development of sepsis-induced myocardial injury and crosstalk between signalling cascades has been observed in cardiomyocyte death pathways (Fig. 1) (180-182).

Apoptosis and necroptosis are key forms of regulated cell death (183). The occurrence of apoptosis and necroptosis is associated with cell damage and activation of inflammatory factors (184). Apoptosis may precede necrosis/necroptosis (185). If apoptotic cells are not phagocytosed quickly, they undergo secondary necrosis, the membrane ruptures and cellular components are released (186). RIP kinases are key decision makers in cell death, the interaction of signalling pathways is the activation of RIP kinases (187). RIPK1 is a kinase that regulates necroptosis and induces apoptosis under oxidative stress and inflammation (188). Therefore, apoptosis is associated with necroptosis and cell death processes that cannot be explained by apoptosis may be explained by the mechanism of necroptosis (189).

Autophagy and necroptosis may occur at the same time in some disease models (190). Autophagy also mediates ferroptosis and causes disease (191). Moreover, NF-κB activates autophagy and is associated with apoptosis (43). Beclin-1 serves an important role in autophagy and apoptosis during infection (192). MPT is involved in the mitochondria-mediated necrosis pathway (66,67). The anti-apoptotic protein Bcl-2 regulates the integrity of the mitochondrial outer membrane and cytochrome C release (193), while MPT regulates inner membrane permeabilization. As a secondary messenger, intracellular calcium ions are implicated in regulating diverse pathways leading to cell death (194). The mitochondrial calcium uniporter (MCU) complex transports Ca^{2+} into mitochondria. MCU are key transporters of iron in iron-overload conditions. The level of intracellular calcium ions and function of MCU and iron transporters are associated with occurrence of mitochondria-mediated necrosis and ferroptosis (65,195).

In experimental myocardial injury models, inhibition of Beclin-1 haplotype inhibits ferroptosis and mitochondrial damage, as well as myocardial remodeling and systolic dysfunction (196,197). Experiments have confirmed that there is an overlap between the substrates of caspase-1 and -3, key effectors of cell apoptosis (198,199). Therefore, there may be a connection between pyroptosis and apoptosis. Dysfunctional autophagy promotes NLRP3 inflammasome assembly and leads to pyroptotic cell death (94). Pyroptosis and apoptosis share common reaction substrates (198), caspase-8, which promotes apoptosis, and caspase-11, which mediates pyroptosis, that are not dependent on RIPK1 and RIPK3 and cause inflammation by activating TNF (200). GPX4 is a key factor that inhibits lipid peroxidation, ferroptosis and pyroptosis (201). During sepsis, mitochondrial damage and release large amounts of ROS to trigger apoptosis, pyroptosis, autophagy and ferroptosis. Following cell death, release of inflammatory mediators and excessive production of ROS induce other types of cell death, which interact with each other (202,203). Inflammatory mediators released during apoptosis and necroptosis induce pyroptosis via NLRP3 and caspase-1 activation, which activate marker of pyroptosis gasdermin D (61).

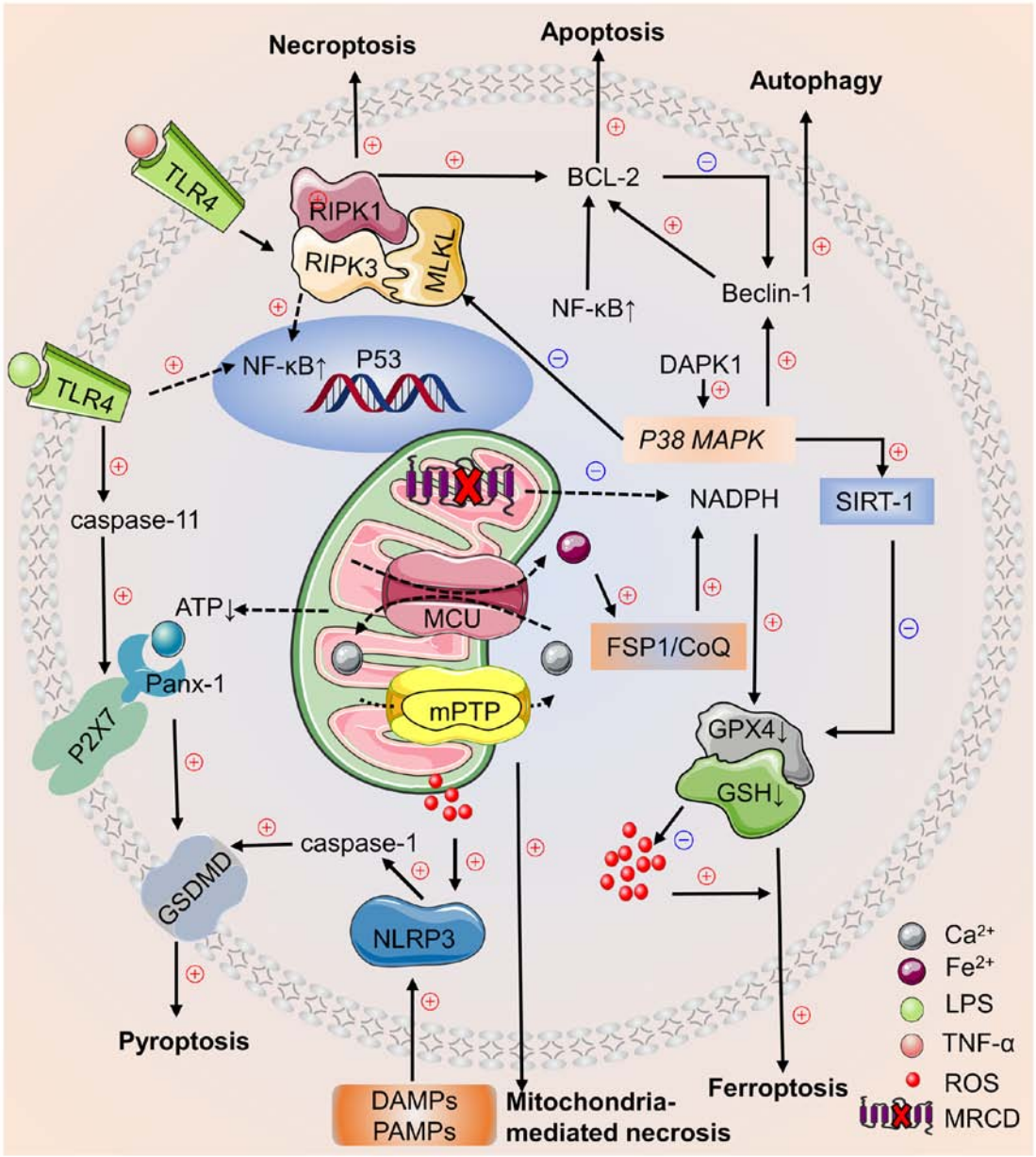

Figure 1. Interplay of cardiomyocyte death signalling pathways in sepsis. PAMPs and DAMPs activate pyroptosis via classical NLRP3 inflammasome pathways. TLR4 involves pyroptosis, apoptosis and necroptosis. Decreased ATP production following mitochondrial damage increases TLR4-mediated atypical pyroptosis activation pathway. Activation of RIPK1 regulates necroptosis and induces apoptosis under oxidative stress and inflammatory processes. Level of intracellular calcium ions, function of MCU, and iron transporters are associated with occurrence of mitochondria-mediated pyroptosis and ferroptosis. Beclin-1 regulates autophagy and apoptosis during infection. DAPK1 regulates necroptosis, apoptosis, autophagy and ferroptosis, inhibits necroptosis by activating P38 MAPK pathway and regulates mitochondrial autophagy by promoting expression of SIRT1. FSP1/CoQ/NADPH pathway regulates ferroptosis. PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; TLR4, Toll-like receptor 4; RIPK, receptor-interacting protein kinase; MLKL, mixed lineage kinase domain-like; GSH, glutathione; GPX4, glutathione peroxidase 4; FSP1, ferroptosis suppressor protein 1; CoQ, coenzyme Q; Panx-1, pannexin-1; Fer-1, ferrostatin-1; DAPK1, death-related protein kinase 1; ROS, reactive oxygen species; MCU, mitochondrial calcium uniporter; MPT, mitochondrial permeability transition; MRCD, mitochondrial respiratory chain disorder; SIRT1, Sirtuin 1; GSDMD, gasdermin D.

Death-related protein kinase 1 inhibits necroptosis by activating *P38 MAPK* pathway and regulates mitochondrial autophagy by promoting expression of NAD-dependent protein deacetylase Sirtuin 1, which simultaneously decreases ferroptosis via solute carrier family 7 member 11 (132,134).

4. Conclusion

The present review discusses the mechanisms of sepsis-induced cardiomyocyte death and interaction of pathways, as well as current experimental treatment strategies in sepsis-induced myocardial injury and prospects for the future. It is unclear which mode of cell death occurs first and which mode of cell death is most important during sepsis-induced cardiac injury. It remains to be determined whether cardiomyocytes exhibit different characteristics from other types of cell during sepsis-induced cell death. Determining the role of cell death in sepsis-induced cardiac dysfunction requires further studies to identify the underlying mechanisms. Increased knowledge of cardiomyocyte death in sepsis and the molecular mechanisms

may facilitate development targeted therapy options for sepsis-induced myocardial injury in future.

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Authors' contributions

GZ and YZ conceived and designed the review. YZ drafted and edited the manuscript. GZ, DD, XW and YZ reviewed the manuscript and contributed to the discussion. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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