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Review Article

Roles of autophagy in sepsis-induced myocardial dysfunction: a comprehensive review

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Abstract: Sepsis-induced myocardial dysfunction (SIMD) is a worldwide health issue. Regarding malignant cardiac dysfunction and mortality, the fatality rate of SIMD accounts for 70-90%. The molecular mechanisms that underlie the inflammatory effects and cardiac function of SIMD appear to be intricate. A crucial cellular process associated with cardiomyopathy is the death of cardiomyocytes. In the review, we have summarized the present evidence on the role of autophagy in the pathomechanism of SIMD. The included studies suggest that cardiomyocyte death induced by SIMD might be partially regulated by autophagy and its associated genes and pathways, including but not limited to Unc-51 like-autophagy-activating kinase 1 (ULK1), Zinc finger antisense 1 (ZFAS1), miR-590-3p, miR-214-3p, miR-21-3p, Silent information regulator 1 (SIRT1), SH3 domain-containing protein 2 (SORBS2), AMP-activated protein kinase (AMPK), Mammalian target of rapamycin (mTOR), TLR4/ERK1/2/NF-κB, TFEB-CLEAR, and Tensin homolog deleted on chromosome 10/Protein kinase B (PTEN/AKT) pathway. The crosstalk among autophagy and its associated genes it might be one of the pivotal molecular and cellular mechanisms for SIMD. In addition, some interventions for treating SIMD, e.g. exogenous fibroblast growth factor 21, melatonin, urolithin A, and minocycline, were reported to be associated with their effects on the regulation of autophagy. However, due to limited research, the potential molecular mechanism underlying autophagy in regulating SIMD is unclear and requires further exploration through in vitro and in vivo experiments. Overall, a deeper understanding of SIMD pathogenesis may facilitate new prospects of therapeutic applications targeted to autophagy.

Keywords: Sepsis-induced myocardial dysfunction, autophagy, mechanisms, cardiomyopathy, treatment

Introduction

Sepsis, characterized as a severe systemic inflammatory response syndrome, is frequently induced by the infiltration of pathogenic microorganisms and their metabolites into normally sterile tissues [1]. Despite significant advancements in intensive care and supportive technologies over the past century, sepsis remains among the top ten causes of death and is the leading cause of mortality among critically ill patients [2]. Statistics indicate that there are over 48.9 million sepsis cases globally, resulting in more than 11 million deaths, underscoring sepsis as a persistent clinical challenge and a global healthcare issue [3, 4]. The heart is one of the potentially affected organs during sepsis, but multiple organ dysfunction (e.g., lung, kidney) is more common and critical in determining outcomes [5]. The heart is the organ most severely affected during sepsis. Epidemiological studies have shown that approximately 64% of sepsis patients experience myocardial injury or cardiac dysfunction. More frustrating, the fatality rate of sepsis-induced myocardial dysfunction (SIMD) is up to 70-90% [6]. However, current therapeutic strategies for sepsis-induced myocardial dysfunction (SIMD) primarily focus on supportive care, including the administration of vasoactive medications, fluid resuscitation, and empiric antibiotics. Moreover, there is a notable absence of targeted interventions specifically addressing myocardial dysfunction in sepsis. Therefore, intensive research into the mechanisms underlying SIMD and the development of novel pharmacological and therapeutic approaches are of paramount importance.

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SIMD is characterized by both systolic and diastolic dysfunction. Despite extensive surveys into the pathophysiology of SIMD, the underlying mechanisms are still controversial. Numerous factors (e.g., inflammation, apoptosis and pyroptosis, autophagy), play crucial roles in pathological process of SIMD. The regulation of SIMD is complex and involves many pathways of the septic inflammatory response mediated by damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) [7]. Toll-like receptors, belonging to the PAMPs and DAMPs, activate pattern-recognition receptors expressed on cardiomyocytes [7]. Toll-like receptors trigger multiple intracellular cascades, i.e., mitogen-activated protein kinases (MAPKs) and nuclear factor-κB (NF-κB) [7]. Furthermore, Toll-like receptors effect cardiomyocyte contractility by increasing cytokine production [8]. High-mobility group protein B1 is also a pro-inflammatory DAMP and has an important role in mediating the pathophysiology of SIMD [9]. Li et al. [10] reported that stimulator of interferon genes (STING), could enhance SIMD by inducing apoptosis and pyroptosis through activating NOD-like receptor family pyrin domain containing 3 (NLRP3). Accumulating studies had proved that autophagy, a programmed cell death other than apoptosis and pyroptosis, plays an essential effect in the molecular pathophysiology of SIMD. One popular opinion is that autophagy may enhance SIMD [11, 12]. However, alternate research holds that autophagy significantly inhibits the progression of SIMD [13, 14]. Therefore, this present study collected all of the literature related to this topic to describe the pivotal role of autophagy in SIMD and better assess the association between autophagy and SIMD.

Overview of autophagy

Mammalian autophagy is characterized by "self-digestion", which is a fundamental biological process toward maintaining energy requirements contributing to cellular metabolism [15]. At present, autophagy is classified into 3 main subsets known as macroautophagy, microautophagy, and chaperone-associated autophagy [16]. Among these, the most commonly studied is macroautophagy. Autophagy is initiated with the formation of isolation membrane or cup-shaped phagophores, also known as the precursor of the autophagosome [17]. Autophagy-related protein 8/microtubule associated protein 1 light chain 3 (ATG8/LC3) changes from LC3-I form to LC3-II through conjugating with a phosphoethanolamine during autophagy, ensuring elongation and expansion of autophagy [18]. Cellular components then get engulfed with phagophore and form a double-membrane vesicle, named the autophagosome [19]. Autophagosome can fuse with acidic lysosomal membranes to form autolysosomes, where autophagic cargo is degraded [20].

It is reported that autophagy is negatively regulated by mechanistic target of rapamycin (mTOR) under basal conditions [21]. mTOR forms two structurally distinct complexes, mTORC1 and mTORC2, which are composed of discrete protein binding partners to modulate cell growth, migration, and metabolism [22]. The primary function of mTORC1 is to modulate cell growth through phosphorylating ribosomal protein S6K1 [22]. Infection, oxidative stress and electron reduction regulate the availability of glucose to inhibit mTOR, but also activate Unc-51 Like Autophagy Activating Kinase 1 (ULK1) complex (consisting of ULK1, Autophagy Related 13 [ATG13], FAK Family Interacting Protein of 200 kDa [FIP200], and Autophagy Related 101 [ATG101]), which induces autophagy by phosphorylating ATG13 and FIP200 [23, 24]. mTOR inhibition promotes autophagy through the upregulation of autophagy markers such as autophagy-related 3 (ATG3), and autophagy-related 5 (ATG5), and microtubule-associated protein 1A/1B-light chain 3-II (LC3-II) as well as the downregulation of p62 [25]. There is an interesting and complex interaction between AMP-activated Protein Kinase (AMPK) and mammalian Target of Rapamycin Complex 1 (mTORC1). The activation of AMPK has been reported to trigger various catabolic processes including autophagy by inhibiting the mTORC1 pathway through the phosphorylation of Tuberous Sclerosis Complex 2 (TSC2) (an upstream regulator of the pathway) [26]. In addition, ULK1 is phosphorylated by activated AMPK, which reverses mTORC1-mediated inhibition of autophagy [27]. As a negative feedback mechanism, ULK1 inhibits mTORC1 activity by phosphorylating Raptor, as shown in multiple sites [28]. Additionally, autophagy is also regulated by other pathways and mole-

cules, such as thioredoxin-1 (Trx1), heat shock protein 70 (Hsp70) and TLR4/ERK1 etc [29-31].

In recent years, autophagy is thought to be a key mediator in the signal cascade of programmed cell death caused by sepsis [32]. Autophagy is an important process that has beneficial or pathogenic effects related to a variety of cardiac disorders [33]. Accumulation of autophagosomes has been reported in isolated stressed cardiomyocytes and cardiac biopsies in subjects with cardiac diseases [34]. Autophagy has recently received significant attention as a cell protective mechanism in the ischemic myocardium [35]. Autophagy's impact on cell death can be advantageous or harmful, contingent on the insult's duration and intensity [36]. Likewise, autophagy plays a dual role in SIMD [37, 38]. However, there has been no review on the association between autophagy and SIMD.

The roles of autophagy in SIMD

The activation of AMPK attenuated SIMD by inducing autophagy through inhibiting mTOR

Beclin-1, one of the earliest detected mammalian autophagy effectors, is widely expressed in multiple tissues [39]. Beclin-1 plays a crucial role in the initiation of autophagy via its communication with PtdIns (3)-kinase (Vps34). mTOR is an important regulatory point inhibiting Beclin-1-dependent autophagic activity. As is well known, administration of lipopolysaccharide (LPS) to animals has been used to mimic SIMD. Recently, Sun et al. [40] found that the expression level of LC3-II was upregulated compared to shams in LPS-challenged animals. Interestingly, LC3-II was increased relative to shams at low doses, but gradually decreased in high doses [40]. Further study demonstrated that the level of LC3-II was significantly increased in in the hearts of Beclin-1-overexpression mice, but was much weaker in Beclin-1-low-expression mice [40]. Furthermore, a high expression of Beclin-1 dramatically blunted the activation of mTOR [40]. The suppression of the mTOR/S6K1 cascade was observed in SIMD rats, which exerted cardioprotective effects via inducing autophagy during sepsis caused by cecal ligation and puncture (CLP) [41, 42]. The AMPK/ULK1 cascade is activated by the overexpression of Beclin-1 in LPS-challenged animals [40]. Importantly, the researchers found that Beclin-1 overexpression protected the myocardium from fibrotic injury by inducing autophagy in LPS-challenged animals [40]. Wu et al. [43] showed that inhibiting the AMPK pathway could significantly reduce the level of LC3-II and Beclin-1 and enhance the expression of p62. Furthermore, ULK1 expression has been reported to be suppressed by AMPK inhibitors and autophagy inhibitors [43]. Tang et al. [44] also revealed that the expression level of LC3-II, Beclin-1, p-AMPK and p-ULK1 were significantly upregulated in animal model of SIMD. Moreover, an autophagy inhibitor aggravated cardiac dysfunction and inhibited the expression level of p-AMPK and p-ULK1 [44]. Zhang et al. [45] found that pharmacological activation of AMPK dramatically improved cardiac function by upregulating autophagy through the inhibition of p-mTOR in LPS-challenged mice. Liu et al. [46] demonstrated that zinc finger antisense 1 (ZFAS1) aggravated septic cardiac dysfunction by inhibiting autophagy of cardiomyocytes through targeting the signal axis of miR-590-3p/AMPK/mTOR. The aforementioned studies suggested that the inhibition of AMPK/mTOR could attenuated SIMD by increasing autophagy.

Melatonin improved SIMD by inducing autophagy through activating the SIRT1/Beclin-1 pathway

The silent information regulator sirtuin 1 (SIRT1) molecule belongs to the group of the class III histone deacetylases (HDAC III) [47]. SIRT1 is the first member of the SIRT family identified in mammals [47]. As reported, SIRT1 protein exerts an essential role on enhancing longevity [48]. SIRT1-driven histones and non-histone protein deacetylation occurs in an NAD+-dependent fashion [49]. SIRT1-mediated deacetylation regulates multiple biological processes, including autophagy, apoptosis, oxidative stress, cellular senescence and inflammation [50-52]. It was reported that SIRT1 could deacetylate Beclin-1 by suppressing histone deacetylase (HDAC) classes I, II, and IV [53]. Yang et al. [54] indicated that exogenous Fibroblast growth factor 21 (FGF21) therapy significantly enhanced the expression level of LC3-II and Beclin-1 proteins, which alleviated the severity of acute liver injury. Importantly, SIRT1 knockdown reversed the protective role

of FGF21 on acute liver injury by inhibiting autophagy through suppressing Beclin-1 expression [54]. However, whether SIRT1 is involved in the regulation of SIMD by modulating autophagy is unclear. Previous research reported that melatonin dramatically relieved SIMD by inhibiting both inflammation and pyroptosis in myocardial cells [55]. Recently, Pi et al. [56] showed that the expression of SIRT1 and Beclin-1 were decreased in in septic hearts. Furthermore, melatonin dramatically promoted Beclin-1 deacetylation and increased autophagy flux in septic hearts, which improved cardiac function [56]. Also, the expression of SIRT1 was increased [56]. However, the protective effects of melatonin on both cardiac function and Beclin-1 were negated when SIRT1 activity was suppressed [56]. Consist with the abovementioned result, Zhang et al. [57] further revealed that melatonin's cardioprotective properties were linked to the inhibition of autophagy via suppressing apoptosis, mediated by the upregulation of SIRT1 and Beclin-1 expression in septic mice. These studies revealed that melatonin associated autophagy, by activating Beclin-1 deacetylation and promoting SIRT1, resulted in improved sepsis-associated cardiac function. Melatonin may serve as a potential candidate drug for effectively treating SIMD.

Apelin might ameliorate SIMD by suppressing autophagy through the inhibition of the TLR4/ERK1/2/NF-κB pathway

As is well known, the initiation of autophagy is closely associated to inflammation. Autophagy can be rapidly upregulated by inflammatory signals in response to bacterial infection or excessive oxidative stress [58]. Oxidative stress has been reported to be modulated by multiple signaling pathways including TLR4/NF-κB, MAPK/ERK and TNF-α/ERK1/2/Bax signaling pathways [59-61]. It was reported that NF-κB was a key molecular switch for oxidative stress in cells [62]. NF-κB, existing in the form of dimer, has been found to participate in the development of various human diseases associated with inflammation and apoptosis, such as myocardial infarction [63]. Also, NF-κB plays a pivotal role in the development and progression of SIMD. Luo et al. [64] found that ginsenoside Rg1 restored impaired cardiac function induced by LPS, by attenuating inflammation and apoptosis through blocking the TLR4/NF-κB/NLRP3 pathway both in neonatal rat cardiomyocytes and septic mice. In addition, the activation of the NF-κB associated pathway could induce autophagy. Li et al. [65] reported that death-associated protein kinase 1 (Dapk1) significantly improved LPS-associated acute lung injury (ALI) by suppressing autophagy and oxidative stress, by inhibiting the p38MAPK/NF-κB pathway. He et al. [66] demonstrated that Qiang-Xin 1 (QX1), a traditional Chinese medicine formula, significantly ameliorated cardiac tissue damage in septic mice by controlling the cytokine storm through suppressing the activity of MAPK (P38, ERK1/2, and JNK) and TLR4/NF-κB signaling cascades. However, whether NF-κB is participating in the progression of SIMD by regulating autophagy remains unknown. According to Hu et al.'s study [67], LPS administration resulted in a significant elevation of inflammatory cytokine concentrations in the bloodstream and heart tissue. In the meantime, the expression of LC3-II, Beclin-1, nuclear factor κBp65, TLR and ERK1/2 were increased in the myocardium after LPS injection [67]. Apelin, an angiotensin like G protein coupled receptor, had a protective effect against SIMD [68]. Furthermore, apelin intervention significantly reduced the apoptosis rate, increased LC3-II, Beclin-1 expression, and inhibited nuclear factor κBp65, TLR and ERK1/2 in the LPS group; while F13A, an inhibitor of apelin, remarkably suppressed this trend [67]. These results indicated that exogenous administration of apelin might improve SIMD by inhibiting autophagy and inflammatory actions via the TLR4/ERK1/2/NF-κB pathway. However, no related study was conducted on different time nodes, which might affect the judgment of research results.

TFEB-CLEAR ameliorated SIMD related to aging by promoting autophagy

It is reported that elderly patients are more susceptible to suffering from SIMD than young patients [69]. As reported, enhanced autophagy flux is associated with the aging process, while a reduction in autophagosome formation contributes to the deceleration of aging [70] Autophagy is important for maintaining homeostasis in the heart. Additionally, the decline in autophagy is correlated with cardiac aging [71]. Transcription factor EB (TFEB) is one of the important regulators of autophagy [72]. The

translocation of TFEB into the nucleus enables it to regulate the CLEAR network, which consists of hundreds of genes responsible for coordinated lysosomal expression and regulation [73]. The genes within the CLEAR network are involved in processes such as the formation and elongation of autophagosomes, the creation of vesicles, and the recognition and breakdown of cellular cargo [73]. Map1lc3 and Vps11 are involved in autophagosome formation and vesicle formation and elongation, and they are well-known targets of TFEB [74]. Zhang et al. [75] suggested that the spliced X-box binding protein 1 (sXBP1), may induce the adaptive UPR, significantly ameliorating glucose intolerance and steatosis by enhancing autophagy through promoting TFEB transcription. Wang et al. [76] reported that the expression levels of TFEB, Beclin-1 and Vps11 decreased significantly following kidney ischemia reperfusion injury when compared to controls. Moreover, pretreatment with urolithin A attenuated renal injury by promoting autophagy through activating the TFEB-CLEAR pathway [76]. However, the role of TFEB-CLEAR-mediated autophagy in septic cardiomyopathy related to aging is not yet clearly understood. Li et al. [77] showed that DNA fragmentation induced by LPS increased by more than 412% and 654% in young and aged mice, respectively, which indicates that aged mice are more likely to develop cardiac dysfunction. Additionally, the level of LC-II expression is significantly higher in young mice than in aged mice following LPS treatment [77]. It was further noted by the authors that LPS-induced TFEB nuclear localization was significantly elevated in young mice, while it was undetectable in older mice [77]. LPS-induced Map1lc3 and Vps11 expression was absent in old mice whereas induction was significant in young mice [77]. Therefore, the TFEB-CLEAR pathway and its target LC3-II, improved septic cardiomyopathy of aging by inducing autophagy.

miR-214-3p overexpression improved SIMD by suppressing autophagy by targeting PTEN/AKT/mTOR signaling cascade

mTOR, an autophagy effector, significantly influences cellular and physiological functions at the organism level [78]. PRAS40, a component of mTORC1, has been demonstrated to be a downstream target of AKT [79]. The serine/threonine protein kinase subfamily comprising AKT isoforms 1, 2, and 3 regulates multiple biological functions essential for developmental processes and maintenance of tissue equilibrium [80]. According to research by Shin and colleagues [81], the bioactive ginsenoside derivative compound K demonstrated anti-tumor effects in liver cancer cells by triggering programmed cell death via suppression of the AKT/mTOR cascade in hepatocellular carcinoma models. Zhang et al. [82] showed that minocycline significantly prevented myocardial apoptosis and injury induced by sepsis and increased the LC3II/LC3I ratio and decreased the expression of p62 compared with normal saline-treated septic mice. Furthermore, an autophagy inhibitor markedly reversed cell survival induced by minocycline [82]. The tumor suppressor gene PTEN (Phosphatase and tensin homolog) was initially discovered during investigations of the 10q23 chromosomal region in 1997 [83]. As a broadly distributed tumor suppressor protein, PTEN frequently undergoes functional loss across multiple cancer types [84]. Extensive research has established PTEN as a critical inhibitory modulator of the PI3K/AKT/mTOR cascade, an essential signaling network that governs fundamental biological functions such as cellular proliferation, viability maintenance, and metabolic regulation [85]. Sang et al. [86] demonstrated that miR-214 inhibited autophagy by activating the AKT/mTOR pathway through suppressing the expression of PTEN in the kidney tissues of septic mice. Furthermore, miR-214 dramatically ameliorated sepsis-induced acute kidney injury (AKI) by suppressing autophagy via modulating the PTEN/AKT/mTOR cascade [86]. However, the role of the PTEN/AKT/mTOR signaling pathway in SIMD is not well understood. Sang et al. [87] found that overexpression of miR-214-3p attenuated myocardial dysfunction and myocardial injuries. Additionally, increased miR-214-3p expression declined the fluorescence intensity of LC3 and decreased the number of p62 in cardiac tissues, which indicated that miR-214-3p overexpression remarkably suppressed autophagy [87]. Furthermore, CLP significantly increased the expression of PTEN, but significantly declined p-AKT and p-mTOR levels [87]. Interestingly, miR-214-3p overexpression increased p-AKT and p-mTOR levels whilst decreasing the PTEN levels. More importantly, suppression of miR-214-3p expression

demonstrated an inverse correlation with the previously mentioned parameters [87]. These studies suggested that miR-214-3p inhibited autophagy by activating the AKT/mTOR signaling cascade via inhibition of PTEN in cardiac tissues, which improved SIMD. Similar to the aforementioned studies, Shiroorkar et al. [88] also showed that tangeretin, a flavonoid which has widespread pharmacological activities, attenuated SIMD by suppressing myocardial autophagy via the PTEN/AKT/mTOR pathway.

miR-21-3p induced SIMD by promoting autophagy through the inhibition of SORBS2

The pathogenesis of SIMD involves numerous contributing elements, with microRNAs serving as crucial regulatory components [89]. As a class of non-coding RNA molecules, microRNAs regulate gene expression at the post-transcriptional level by binding to complementary sequences on target mRNAs [90]. Numerous studies have demonstrated the involvement of microRNAs in the pathophysiological mechanisms underlying sepsis, including its associated organ dysfunction and metabolic disturbances [91, 92]. Shan et al. [93] demonstrated that increased-expression of miR-93-5p remarkably induced apoptosis and decreased the expression of the SH3 domain containing 2 (SORBS2) in LPS-treated cardiomyocytes. In contrast, inhibition of miR-93-5p exhibited opposing effects on both LPS-induced apoptotic processes and SORBS2 expression levels [93]. Extensive research has identified SORBS2 as a tumor-suppressing protein that plays significant roles in the development and progression of various cancer types [93]. Additionally, SORBS2 is involved in the development and progression of infarcted myocardium and left ventricular noncompaction cardiomyopathy [94, 95]. Also, SORBS2 could be modulated by miR-21-3p as a target gene. Bang et al. [96] reported that miR-21-3p regulated the progress of Ang II-induced cardiac hypertrophy by targeting SORBS2. Furthermore, miR-21-3p protected against sepsis and associated acute kidney injury by activating the AKT/CDK2-FOXO1 signal cascade [97]. Whether miR-21-3p is involved in the development of SIMD by targeting SORBS2 is unrevealed. Wang et al. [98] reported that miR-21-3p expression was dramatically elevated and SORBS2 was repressed in heart tissue samples treated with LPS. Notably, significantly elevated levels of plasma miR-21-3p were observed in sepsis patients exhibiting cardiac impairment when compared to those maintaining normal cardiac function [98]. Remarkably, administration of miR-21-3p antagomir effectively maintained cardiac contractility parameters (EF and FS) and suppressed autophagic activity in LPS-challenged mice, whereas miR-21-3p agomir administration exacerbated these pathological alterations [98]. Moreover, miR-21-3p antagomir increased the survival rates of mice treated with LPS [98]. Simultaneously, an inverse correlation was observed between miR-21-3p and the expression level of SORBS2 in the hearts of mice. This finding implies that SORBS2 serves as a crucial target gene of miR-21-3p [98]. Collectively, the inhibition of miR-21-3p improved SIMD by suppressing autophagy through activating SORBS2 expression.

The characteristics of the eligible studies were listed in **Table 1**. **Figure 1** summarized the above underlying molecular mechanisms of the roles of autophagy in the development and progression of SIMD.

The temporal and contextual dual role of autophagy in SIMD

Based on several relevant studies, induced-autophagy might act as a protective mechanism during the initial hyper-inflammatory phase. This includes clearing damaged organelles (e.g., mitochondria via mitophagy), eliminating intracellular pathogens, and providing energy substrates to counteract metabolic stress. Some pivotal signaling cascades (e.g., AMPK activation, mild oxidative stress) might partially drive this adaptive autophagy and its cardioprotective effects. Nevertheless, the autophagic flux might shift from protection to damage of the targeted cells. A recent study developed by Gao et al. [99] showed that the autophagic flux was changed according to different stages of myocardial sepsis. This study indicated that mitochondrial autophagy progressed with dynamic changes in the LPS-induced SIMD model, with an increase in activity during the early stage, followed by suppression in the later stage as the intervention extends. Another recent study also implied that Narciclasine alleviated SIMD by inhibiting ferroptosis and maintaining mitochondrial integrity via BNIP3-mediated mitophagy [100]. Based on the evi-

Table 1. The characteristics of the eligible studies reporting the roles of autophagy in SIMD

Study/ Reference	Research subject	Associated genes/pathways	Measurements	Main findings
Sun et al. 2018	Mouse	AMPK/mTOR/ULK1	ELISA, Western blot	The autophagy improved cardiac function by attenuating cardiac inflammation and fibrosis.
Wu et al. 2020	Mice	AMPK/ULK1	ELISA	Luteolin attenuated SIMD by increasing autophagy through AMPK activation.
Tian et al. 2022	Mice	NA	qRT-PCR	TRPC1 induced septic cardiac dysfunction by inhibiting autophagy and activating myocardial apoptosis.
Liu et al. 2020	Mice	miR-590-3p/ AMPK/mTOR	qRT-PCR	ZFAS1 aggravated septic cardiac dysfunction by inhibiting autophagy and inducing pyroptosis of cardiomyocytes through targeting miR-590-3p/AMPK/mTOR signaling pathway.
Zhang et al. 2019	Mice	SIRT1/Beclin-1	Transmission electron microscopy, Western blot	Melatonin attenuated SIMD by inhibiting cardiomyocyte apoptosis and increasing cardiac autophagy via activating SIRT1.
Wang et al. 2021	Mice	NA	qRT-PCR	Mitophagy sustained mitochondrial performance and improved SIMD.
Wang et al. 2022	Rat	NA	qRT-PCR	Clemastine attenuated SIMD by promoting autophagy.
Sang et al. 2020	Mouse	PTEN/AKT/mTOR	qRT-PCR	miR-214-3p alleviated SIMD by suppressing autophagy through PTEN/AKT/mTOR pathway.
Wang et al. 2018	Rat	mTORC1/S6K1	qRT-PCR, situ hybridization, and hematoxylin and eosin (H&E) staining	Autophagy in the myocardium was increased in CLP rats, which was strongly related to the inhibition of the mTORC1/S6K1 pathway.
Zhang et al. 2019	Mice	AKT/mTOR	qRT-PCR and situ hybridization	Minocycline alleviated SIMD by enhancing autophagy through upregulating AKT phosphorylation and inhibiting mTORC1 expression.
Pi et al. 2021	Rat	SIRT1/Beclin-1	qRT-PCR	Melatonin improved SIMD by inducing autophagy through the activation of SIRT1/Beclin-1 pathway.
Shiroorkar et al. 2020	Rat	PTEN/AKT/mTOR	qRT-PCR and Droplet digital PCR	Flavone tangeretin (TG) attenuated SIMD by inhibiting myocardial autophagy through PTEN/AKT/mTOR pathway.
Zhao et al. 2020	Mice	NA	qRT-PCR	Ulinastatin protected against SIMD through its antiinflammatory activity and the inhibition of autophagy.
Li et al. 2018	Mice	NA	Fluorescence In situ hybridisation (FISH) and immunohistochemistry	Alamandine attenuated SIMD by inhibiting autophagy.
Wang et al. 2021	Mice	NA	qRT-PCR	Hsp70 improved SIMD by attenuating sepsis-induced autophagy.
Ji et al. 2021	Rat	PINK1/Parkin	qRT-PCR	ALDH2 attenuated SIMD by inhibiting PINK1/Parkin-dependent mitophagy.
Tang et al. 2019	Mice	AMPK/ULK1	Echocardiography, qRT-PCR	UCP2 promoted SIMD by inhibiting autophagy through suppressing AMPK/ULK1 signaling pathway.
Zhang et al. 2017	Mice	AMPK/mTOR	Echocardiography, Western blot	The activation of AMPK improved SIMD by enhancing autophagy via inhibiting mTOR.
Hu et al. 2021	Mice	TLR4/ERK1/2/ NF-κB	Cardiac echocardiography, ELISA	Apelin had protective effect on SIMD by increasing autophagy through TLR4/ERK1/2/NF-κB pathway.
Sánchez-Villamil et al. 2016	Mice	NA	qRT-PCR	Trx1 overexpression improved SIMD by activating autophagy.
Hsieh et al. 2011	Mice	NA	Echocardiography, Western Blot	Rapamycin reversed SIMD by inducing complete activation of autophagy.
Li et al. 2016	Mice	TFEB-CLEAR	Echocardiography, Western Blot, qRT-PCR	TFEB improved SIMD by inducing autophagy through activating Map1lc3 and Vps11.
Wang et al. 2016	Mice and patient	miR-21-3p/SORBS2	Electron microscopy, Western Blot, qRT-PCR	miR-21-3p promoted SIMD by inducing autophagy via inhibiting the expression of SORBS2.
Kim et al. 2022	Mice	NA	Echocardiography, Western Blot	TB-peptide, a Beclin-1 activating peptide, improved SIMD by boosting autophagy.
Han et al. 2018	Rat	mTOR/pS6K1	Transmission Electron Microscopy, echocardiography examination, Western Blot, qRT-PCR	The inhibition of mTOR/pS6K1 signaling pathway attenuated SIMD by inducing autophagy.

Note: mTOR = Mammalian target of rapamycin; AMPK = AMP-activated protein kinase; ULK1 = Unc-51 like- autophagy-activating kinase 1; SIMD = Sepsis-induced cardiac dysfunction; TRPC1 = Transient receptor potential canonical channel; ZFAS1 = Zinc finger antisense 1; SIRT1 = Silent information regulator 1; PTEN = Tensin homolog deleted on chromosome 10; AKT = Protein kinase B; S6K1 = Phosphorylation of S6 kinase-1; Hsp70 = Heat shock protein 70; ALDH2 = aldehyde dehydrogenase 2; UCP2 = Uncoupling protein 2; TLR4 = Toll-like receptor 4; ERK1/2 = Extracellular signal-related kinases 1 and 2; NF-κB = Nuclear factor-kappaB; Trx1 = Thioredoxin-1; TFEB = Transcription factor EB; SORBS2 = SH3 domain-containing protein 2.

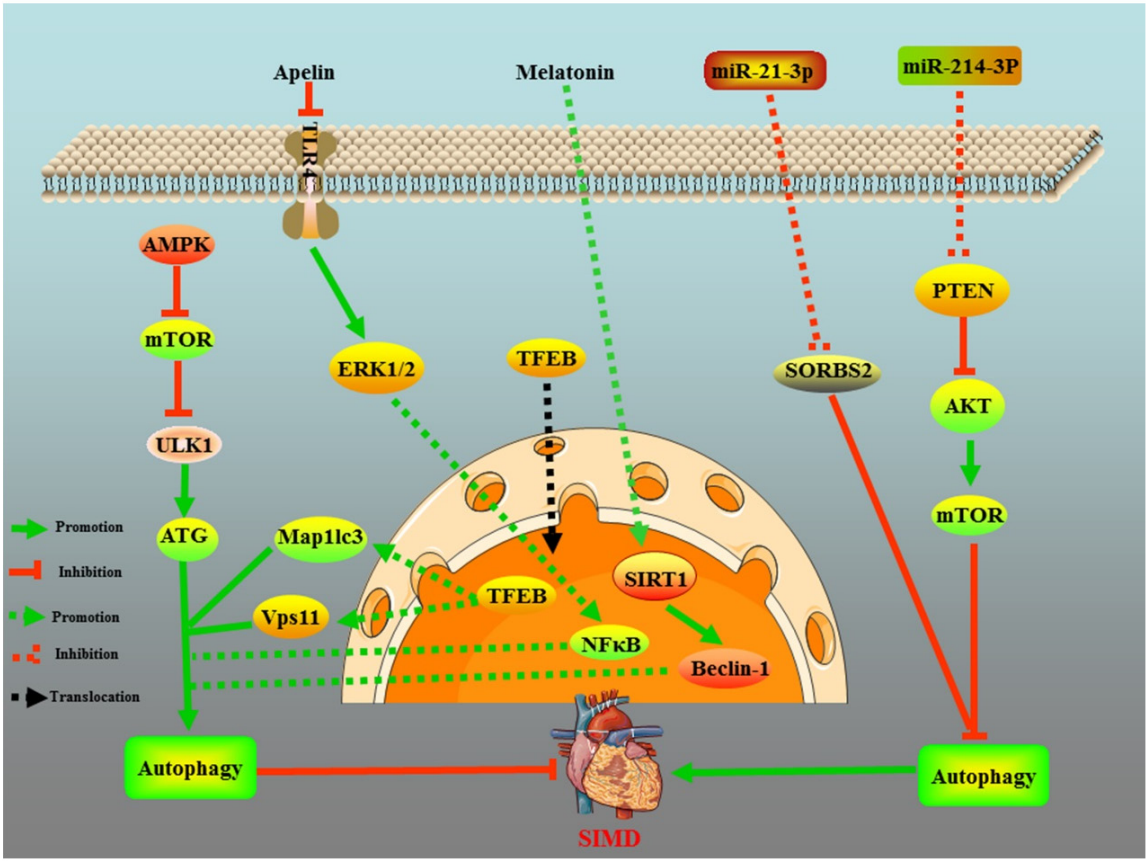

Figure 1. The molecular mechanisms underlying the action of autophagy in the development and progression of SIMD.

dence from the above two relevant studies, it was demonstrated that reduced mitochondrial autophagy might play a protective role on cardioprotective function in SIMD. In a clinical trial, a retrospective cohort analysis suggested that dapagliflozin dramatically improved cardiac outcomes in SIMD by enhancing autophagy and regulating metabolic pathways. However, this study did not show the information in the early or later stage of sepsis-induced cardiomyopathy [101]. Taken together, the changes of autophagic flux during different stages of SIMD are still controversial among the current relevant studies, which is waiting for more well-designed studies to validate the exact role of autophagy in the development, progression, and treatment of SIMD.

Conclusion

SIMD has come to the forefront as a significant public health issue on account of its elevated morbidity and mortality figures. Based on the above evidence, autophagy has been recognized as a crucial element in the development of the disease mechanism of SIMD. However, the association between autophagy and the treatment of SIMD has not been fully investigated. Targeting autophagy as a therapeutic strategy for SIMD requires a nuanced approach. Pharmacological agents that enhance autophagy (e.g., rapamycin) or inhibit excessive autophagy (e.g., 3-methyladenine) have shown promise in preclinical models of sepsis. However, further research is needed to determine the optimal timing, dosage, and specific molecular targets for modulating autophagy in SIMD. Additionally, due to limited research, the exact way autophagy regulates SIMD remains uncertain. A deeper understanding of the molecular pathways regulating autophagy in SIMD, such as the AMPK/mTOR, TLR4/NF-κB, and TFEB-CLEAR pathways, may provide novel therapeutic opportunities to improve outcomes in septic patients. Further investigations via both in vitro

and in vivo experiments are needed to delve deeper into this underlying mechanism. Overall, a better understanding of SIMD pathogenesis is critical to develop therapeutic strategies targeted to autophagy.

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Disclosure of conflict of interest

None.

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