

# Research Progress on the Mechanism of Sepsis Induced Myocardial Injury

Cheng-Fei Bi<sup>1-3,\*</sup>, Jia Liu<sup>2,4,\*</sup>, Li-Shan Yang<sup>1</sup>, Jun-Fei Zhang<sup>1-3</sup>

<sup>1</sup>Department of Emergency Medical, General Hospital of Ningxia Medical University, Yinchuan, People's Republic of China; <sup>2</sup>School of Clinical Medicine, Ningxia Medical University, Yinchuan, People's Republic of China; <sup>3</sup>Key Laboratory of Hui Ethnic Medicine Modernization, Ministry of Education, Ningxia Medical University, Yinchuan, People's Republic of China; <sup>4</sup>Medical Experimental Center, General Hospital of Ningxia Medical University, Yinchuan, People's Republic of China

\*These authors contributed equally to this work

Correspondence: Li-Shan Yang; Jun-Fei Zhang, Email [nfyfys@126.com](mailto:nfyfys@126.com); [zhangjunfei007@126.com](mailto:zhangjunfei007@126.com)

**Abstract:** Sepsis is an abnormal condition with multiple organ dysfunctions caused by the uncontrolled infection response and one of the major diseases that seriously hang over global human health. Besides, sepsis is characterized by high morbidity and mortality, especially in intensive care unit (ICU). Among the numerous subsequent organ injuries of sepsis, myocardial injury is one of the most common complications and the main cause of death in septic patients. To better manage septic inpatients, it is necessary to understand the specific mechanisms of sepsis induced myocardial injury (SIMI). Therefore, this review will elucidate the pathophysiology of SIMI from the following certain mechanisms: apoptosis, mitochondrial damage, autophagy, excessive inflammatory response, oxidative stress and pyroptosis, and outline current therapeutic strategies and potential approaches in SIMI.

**Keywords:** sepsis induced myocardial injury, mechanism, signaling pathway

## Introduction

Sepsis is an abnormal compound condition of life-threatening organ dysfunction caused by maladjustment of infection response and one of the major diseases that seriously hang over global human health. The third international consensus contends that septic shock is a subset of sepsis and its identification in adult adhere to clinical hypotension criteria, defines sepsis as an uncontrolled response of the host to infection.<sup>1</sup> Some scholars confirmed the higher effectiveness of the third version consensus in predicting septic shock through analysis of the ICU database in England.<sup>2</sup> Septic patients' mortality in ICU decreased from 35.0% in 2000 to 18.4% in 2012.<sup>3</sup> Although the in-hospital mortality of sepsis has decreased significantly worldwide, the survival rate after discharge is still low due to secondary organ damage.<sup>4</sup> A meta-analysis of 13 international electronic databases showed that sepsis is characterized by high morbidity and mortality, and these data are dominated by high-income countries.<sup>5</sup> However, current surveillance data on sepsis in low- and middle-income countries are still scarce.<sup>6</sup> It can be seen that we still have an onerous task to study sepsis. In particular, certain groups of people (such as pregnant women, infants, the elderly, and those with immune deficiency) are at higher risk of sepsis because of their immune function is relatively weak.<sup>7,8</sup> In recent years, despite significant advances in anti-infective therapy and organ function support technologies, infection still remains the leading cause of death worldwide.<sup>9</sup> Sepsis is also a common cause of death in patients in ICU. Due to under-reporting of information, the real situation of high septic mortality is greatly inconsistent with the reported status quo.<sup>10</sup> Then the diagnosis and treatment of sepsis are complicated due to its characteristics of multiple etiologies.<sup>11</sup> So it is particularly important to study the mechanism of sepsis, which lays the solid foundation for the therapeutic prospect of sepsis in our country.

The early manifestation of sepsis is systemic inflammatory response syndrome (SIRS), which can be cured by supportive therapy.<sup>12</sup> When severe sepsis develops, however, multiple organ damages occur and may still result in death after proper treatment.<sup>12</sup> As the major organ regularly compromised by sepsis and always damaged by septic shock, the heart and its injury during sepsis have been studied in clinical and basic study over the years.<sup>13</sup> Cardiac dysfunction, one of the common

complications of sepsis, has attracted more and more attention in the field of ICU's management in recent years.<sup>14</sup> Sepsis induced multiple organ dysfunction is the main reason for the high incidence and fatality of sepsis in ICU.<sup>15</sup> So, it can be seen that some septic patients may die in large part from the secondary cardiac dysfunction. The identification, diagnosis, treatment, and prognosis of infectious cardiomyopathy, a common complication of sepsis, remain the huge challenge for physicians in ICU.<sup>16</sup> The significantly reduced cardiac function induced by sepsis is closely related to excessive inflammatory response, oxidative stress, apoptosis and limited autophagy.<sup>17</sup> Obviously, the autophagy-oxidative stress-inflammation-cell death process provides a potential therapeutic strategy for cardio-protection in sepsis.<sup>18</sup> Based on this, the summary of basic research progress on SIMI will be conducive to the improvement of its therapeutic strategy.

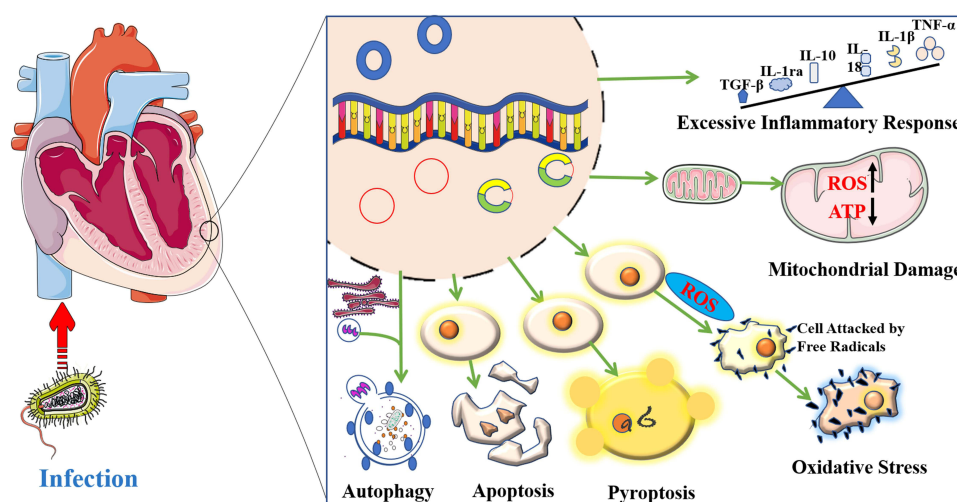
At present, accumulating studies on the mechanism of SIMI treatment have involved foregoing aspects.<sup>19</sup> However, these research directions are relatively fragmented and scattered, and we need to sort out and summarize them so as to conduct further research on SIMI in the future. In addition, previous researches on the mechanism of SIMI are mainly based on a single omics technology, and there is no similar systematic review on the research progress of SIMI. In summary, this paper of the mechanism of SIMI will take up the following aspects: apoptosis, mitochondrial damage, autophagy, excessive inflammatory response, oxidative stress and pyroptosis (Figure 1). The objective of this present review is to sum up some mechanisms of SIMI, to summary the most commonly discussed and researched underlying signaling pathways of myocardial depression in sepsis, and to concisely generalize prevalent therapeutic strategies and potential targets.

## Apoptosis of SIMI

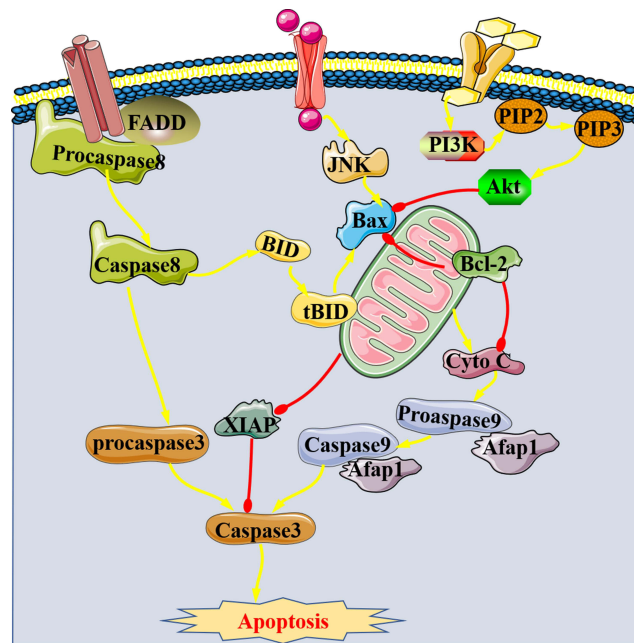
In the pathophysiological process of sepsis, apoptosis is an inevitable result, which may induce cell death to some extent.<sup>20</sup> Studies on the pathophysiology of sepsis suggest that apoptosis occurs in parenchymal cells and one of the adverse effects of parenchymal apoptosis is the multiple organ dysfunctions.<sup>21</sup> However, the specific causes are still unclear and need to be explored. Apoptosis is a widely discussed molecular mechanism of myocardial depression in sepsis.<sup>22</sup> This review will summarize the apoptosis of SIMI from the following three aspects.

## Apoptosis-Related Proteins of SIMI

In recent years, there are more and more studies focus on apoptosis-related proteins (Figure 2), which involve Bcl-2 as well as Bax and caspase-3. The first is an anti-apoptotic protein, while the latter two belong to pro-apoptotic proteins.<sup>23</sup> The present review divided the mechanisms of apoptosis-related proteins in SIMI into two parts: promoting and inhibiting of apoptosis. On the one hand, there are two cases regarding the promotion of apoptosis. Firstly, pro-apoptotic proteins are activated by some signals. For example, high expression of pro-apoptotic signaling pathway



**Figure 1** Mechanisms of myocardial injury induced by sepsis.



**Figure 2** Apoptosis-related proteins of SIMI.

(TNF- $\alpha$ /Bax) induced by extracellular histone promotes myocardial apoptosis in sepsis.<sup>24</sup> Then, the activation of caspase-3 plays a vital role in myocardial apoptosis during sepsis.<sup>25,26</sup> It has been reported that the activation of Caspase-3 is the final result of endogenous and exogenous apoptotic pathways, which further promotes the formation of apoptotic bodies by regulating DNA<sup>27</sup> and trigger cell death. Inflammatory cytokines which were produced during sepsis also induce myocardial apoptosis by activating caspase. Secondly, the inhibition of anti-apoptotic protein, such as miR-21 promotes apoptosis of SIMI by inhibiting Bcl-2 expression.<sup>28</sup> Therefore, the above studies indicate that the onset of SIMI may be related to the activation of Bax and caspase-3 and the inhibition of Bcl-2, which induce the apoptosis of cardiomyocytes during sepsis.

On the other hand, the inhibition of apoptosis was just the opposite, examples are as follows. JNK/Bax, the pro-apoptotic signaling pathway, ameliorates SIMI when it is inhibited.<sup>29</sup> JNK is one of the five characteristic signaling pathways of MAPK, and its phosphorylation promotes apoptosis. Studies have confirmed to be able to inhibit apoptosis of cardiomyocytes by increasing protein expression of Bcl-2 and decreasing the expression of Bid, t-Bid and caspase-9 in mice with SIMI, further confirmed that the pathogenesis of SIMI includes Bcl-2 mediated endogenous anti-apoptosis pathway and caspase-8/Bid/ t-bid/Caspase-9 exogenous pro-apoptosis pathway and the imbalance between the two ways.<sup>30</sup> Bid, one of the pro-apoptotic proteins, is cleaved by activated Caspase-8 into t-bid (the active form of Bid), which promotes apoptosis after it enters the mitochondria. Therefore, Bcl-2 is expected to be a potential therapeutic target for SIMI. X-linked apoptosis inhibitor protein (XIAP) is the strongest apoptosis inhibitor in IAP family, which can directly inhibit Caspases and regulate cell apoptosis in multiple ways. MiR-181a-5p/XIAP signaling pathway was found to be involved in oxidative stress and inflammatory responses in LPS-induced H9c2 cells.<sup>31</sup> It is conceivable that the regulation of apoptotic pathways also affects the progression of oxidation and inflammation during sepsis.

At present, the studies on apoptosis-related proteins in SIMI mainly focus on the above mentioned. There are other types of apoptosis-related proteins, such as other members of the Bcl-2 family (Bak, Bcl-XL, et al),<sup>32</sup> but whether they are expressed in cardiomyocytes remains unknown. Therefore, we still need to pay a lot of efforts to explore the mechanism of apoptosis in SIMI.

## Classical Signaling Pathway of Apoptosis in SIMI

Current studies on the mechanism of apoptosis following with SIMI mainly focus on MAPK and PI3K/AKT/mTOR signaling pathways and come up with those two inhibited ways can attenuate cardiac depression.<sup>33</sup> Recently, gene expression profiles suggest the high-expression of angiotensin II type 1 receptor (AT1R) and initiation of the MAPK signaling pathway in SIMI models.<sup>34</sup> Evidence suggests that miR-101-3p up-regulates and inhibits its specific target dual specificity phosphatase-1 (DUSP1) in LPS-induced myocardial injury mice, further activates MAPK and NF- $\kappa$ B signaling pathways to induce apoptosis.<sup>35</sup> It is verified properly that activation of the MAPK pathway is demonstrated by its phosphorylation.<sup>36</sup> Then, the TNF- $\alpha$ /P38-MAPK/caspase-3 signaling pathway was activated in SIMI to induce apoptosis of cardiomyocytes, which can stand the test of experiment.<sup>37</sup> Going back 20 years, many studies had been conducted to validate the regulation of TNF- $\alpha$  against SIMI's treatment and TNF- $\alpha$  has been confirmed to possess the ability of depressing myocardial contractility.<sup>38</sup> In brief, the signaling pathways related to TNF- $\alpha$  and MAPK participate in the apoptosis during SIMI.

It is noteworthy that the PI3K/AKT/mTOR signaling pathway negatively regulates myocardial cell apoptosis in SIMI.<sup>39</sup> As a pro-apoptotic protein, PTEN is the primary phosphatase which negatively regulates PI3K/Akt pathway.<sup>40</sup> Therefore, the activation of PI3K/Akt pathway leads to the inhibition of apoptosis and mitigates SIMI.<sup>41,42</sup>

This review will also introduce other pathways about the apoptosis mechanism of SIMI from genomic and proteomics perspectives: p53 and NF- $\kappa$ B. In SIMI, splenic reservoir CD11b<sup>+</sup>Gr-1<sup>+</sup> cells rapidly migrated into circulation and the heart, further inducing myocardial cell apoptosis via promoting the high expression of P53 mediated by the inhibition of mTOR.<sup>43</sup> It has been found that myocardial apoptosis in sepsis caused by TRAF6-mediated phosphorylation of NF- $\kappa$ B<sup>44</sup> and ubiquitination of Akt.<sup>45</sup> Increased glycolytic metabolism induced by sepsis produces large amounts of lactate, which leads to SIMI by activating the TLR4-mediated NF- $\kappa$ B signaling pathway relating to apoptosis.<sup>46</sup> Similarly, some scholars researched the TLR2/NF- $\kappa$ B signaling pathway at the gene level and found that inhibition of this pathway can alleviate SIMI.<sup>47</sup> Therefore, I believe that TLR2/NF- $\kappa$ B signaling pathway may be involved in myocardial apoptosis. In addition, miR-208-5p overexpression activates the NF- $\kappa$ B/HIF-1 $\alpha$  signaling pathway during sepsis, resulting in increased HIF-1 $\alpha$  expression in T cells and inducing myocardial apoptosis in SIMI.<sup>48</sup> However, miR-146a mitigated SIMI by targeting regulation of ErbB4 to inhibit NF- $\kappa$ B signaling.<sup>49</sup> Other scholars also studied the myocardial protection effects of some extracts in sepsis from the NF- $\kappa$ B signaling pathway and obtained beneficial results.<sup>50-52</sup> The aforementioned studies suggested that activation of NF- $\kappa$ B signaling pathway involves sepsis-induced apoptosis of cardiomyocytes, and also provided a target for sepsis treatment.

The researches of classical signaling pathway of SIMI always attract our attention in the past, present and future. Therefore, based on this review, our research direction will be more closely related to clinical practice, which will provide potential strategies for the treatment of septic patients.

## Other Aspects of Apoptosis in SIMI

Notch pathway is mainly composed of four parts: Notch receptor, Notch ligand, CSL/DNA binding protein and downstream target gene. Notch receptor signaling between adjacent cells regulates cell differentiation, proliferation and apoptosis. Notch signaling pathway is involved in apoptosis of SIMI.<sup>53</sup> In addition, the study of Li et al found that interferon gene stimulator (STING) led to SIMI by activating NLRP3 mediated inflammation and apoptosis, and proposed a hypothesis on the mechanism of STING-IRF3 promoting myocardial cell inflammation and apoptosis in SIMI.<sup>54</sup> Silent information regulator 1 (SIRT1) regulates the expression of DNA as well as apoptosis and autophagy by deacetylation of substrate proteins, especially proteins of cardio-protection. Some articles have proposed a reliable theory that the activation of SIRT1 improves SIMI by promoting autophagy and inhibiting apoptosis.<sup>55</sup> However, the absence of SIRT1 signaling exacerbated SIMI via weakening its inhibition of the NF- $\kappa$ B signaling pathway.<sup>56</sup> This is the result of proteomics. From genomic perspective, the binding of LncRNA ZFAS1 and miR-34b-5p in sepsis contributes to the over-expression of SIRT1, further improving apoptosis of cardiomyocytes.<sup>57</sup> Similarly, LncRNA CRNDE also attenuates SIMI through miR-29a/SIRT1 signaling pathway.<sup>58</sup>

More and more studies have shown that long non-coding RNAs regulate apoptosis pathways by binding to target genes and affect proliferation differentiation of cells, thus leading to disease. For example, LncRNA HOTAIR highly

binds to PDCD4 mediated by Lin28 to trigger inflammatory storms and apoptosis in sepsis, thereby promoting to SIMI.<sup>59</sup> In sepsis, miR-194 activates its downstream signaling pathway of Wnt/ $\beta$ -catenin, which mediates apoptosis and induces SIMI.<sup>60</sup> Then, some studies have shown that miR-642a inhibits apoptosis of LPS-induced H9C2 cells by promoting cell viability and migration, which was the result of the absence of LncRNA LUCAT1.<sup>61</sup> Last but not least, ROS-mediated endoplasmic reticulum (ER) stress can also lead to apoptosis of septic cardiomyocytes.<sup>62</sup> So, whether oxidative stress also plays an irreplaceable role in the pathophysiology of SIMI? The answer is yes.

Mitochondria are the first barrier of apoptosis, and the specific mechanism of inducing apoptosis in SIMI has not been clarified. The details of ER, another pathway of apoptosis, are still obscure in triggering SIMI. In short, in the process of studying the clinical treatment and management of SIMI, we still have a huge difficulty in pathogenesis to overcome.

## Mitochondrial Injury of SIMI

Mitochondrial injury is a key link in the process from cellular injury to the initiation of sepsis.<sup>63</sup> The degree of mitochondrial damage is closely related to the severity of SIMI, and the relationship is directly proportional.<sup>64</sup>

## Pathophysiology and Improvement of Damaged Mitochondria in SIMI

Some scholars observed mitochondrial damage in cardiomyocytes of septic patients through immunohistochemistry.<sup>65</sup> Electron microscopic analysis also observed large numbers of swollen mitochondria in cardiomyocytes in rats exposed to LPS.<sup>66</sup> Mitochondrial dysfunction is the primary prerequisite for the pathophysiological process of SIMI, which consist of ATP production, Ca<sup>2+</sup> homeostasis, mitochondrial permeability transition pore (MPTP) and over-produced oxygen-free radicals.<sup>67</sup> First, sepsis induces the accumulation of calpain-1 in mitochondria, which impedes ATP synthesis and leads to mitochondrial damage.<sup>68</sup> Second, it is confirmed that the activation of the PINK1/PKA/NCLX signaling pathway maintain mitochondrial calcium homeostasis in cardiomyocytes during sepsis.<sup>69</sup> Similarly, activation of the Akt/GSK-3 $\beta$  signaling pathway mediated by p2X7 maintains mitochondrial calcium homeostasis, which ameliorates myocardial depression induced by sepsis.<sup>70</sup> Most notably, MPTP is significantly opening during sepsis and its closures improve SIMI.<sup>71</sup> Some basic studies that can improve the over-opening of MPTP should be put on the agenda to provide a reference for the clinical treatment of SIMI.

Certain pathways are also involved in the mechanism of mitochondrial damage, although they cannot be explained by the phenomenon described above. TLR2, a member of the Toll-like receptors (TLRs) family, monitors and recognizes a variety of disease-associated molecular patterns (PAMP) and is the body's first barrier against infectious diseases. TLR2-mediated mitochondrial dysfunction, one of the mechanisms of SIMI, was negatively correlated with the expression of miR-410-3p.<sup>72</sup> In the process of studying the mechanism of mitochondrial damage in SIMI, some scholars proposed the concept of Mst1/Drp1/mitochondrial fission/F-actin signaling pathway and believed that this pathway is involved in mitochondrial dysfunction.<sup>73</sup>

Mitochondrial dysfunction has become a hot topic in the pathophysiology of SIMI,<sup>74</sup> and its repairs will be a potential molecular mechanism of ameliorating apoptosis.<sup>75</sup> Previous studies have observed swelling and destruction of mitochondrial structures in LPS-induced sepsis mice. When studying the protective mechanism of mitochondrial damage in SIMI, it was found that NaHS improves mitochondrial function by activating the PGC-1 $\alpha$ /Nrf2 signaling pathway.<sup>76</sup>

## Mitophagy in SIMI

Damaged mitochondria remove selectively broken proteins and organelles and maintain the stability of the intracellular environment via autophagy, which is known as mitochondrial autophagy. Mitochondrial damage is common in the development of sepsis. Therefore, mitophagy in SIMI has become a novel therapy. Mitochondrial dysfunction has been reported to play a fundamental role in SIMI. In sepsis, UPR<sup>mt</sup> activation precedes mitochondrial autophagy, with UPR<sup>mt</sup> repairing mitochondrial proteins and mitochondrial autophagy repairing mitochondrial numbers.<sup>77</sup> In the absence of UPR<sup>mt</sup>, the myocardial protection of mitochondrial autophagy was blocked; therefore, it is hypothesized that UPR<sup>mt</sup> is suppressed in SIMI and thus interrupts the cardio-protective effect of mitochondrial autophagy. However, specific mechanisms have been slow to be discovered. The recovery of mitochondrial damage in sepsis is a reversible process, which is inseparable from the enhancement of PARK2/Parkin-mediated mitophagy.<sup>78</sup> Then the enhanced mitophagy of

SIMI is also regulated by the PINK1/Parkin,<sup>79,80</sup> TFEB<sup>66</sup> and Akt/mTOR<sup>81</sup> signaling pathway. Uncoupling protein 2 (UCP2) protects mitochondria from sepsis by promoting AMPK-activated autophagy during SIMI.<sup>82</sup>

## Autophagy of SIMI

Autophagy plays an important role in maintaining the homeostasis of cardiovascular cells.<sup>83</sup> More and more studies concentrating on autophagy had shown that the activation of autophagy can improve cardiac dysfunction induced by sepsis.<sup>84,85</sup> It is conceivable that the inhibition of autophagy pathway plays a crucial role in the induction of SIMI. But recent papers put forward an opposite view: inhibition of the autophagy pathway ameliorates sepsis-induced cardiac systolic dysfunction.<sup>86,87</sup> Of course, the general trend in basic research still holds that defects in autophagy in healthy cells are a prerequisite for diseases.<sup>88,89</sup> In addition, inhibition of autophagy is a prerequisite for apoptosis. In other words, treatment based on the activation of autophagy improved apoptosis in SIMI. Previous basic studies on the autophagy of SIMI are mainly focused on the regulation of pathways, and this review will elucidate it from the following specific pathways.

There are negative regulation pathways PI3K/Akt, mTOR and positive regulation pathway AMPK relating to autophagy (Figure 3).<sup>90</sup> For example, some scholars hold that cell damage is associated with inhibition of autophagy by activation of the PI3K/Akt/Bcl-2 signaling pathway during sepsis.<sup>91</sup> However, other scholars believe that the activation of autophagy mediated by the activated PI3K/Akt signaling pathway can attenuate SIMI.<sup>92</sup> Then, mTOR (Target of rapamycin) is a serine/threonine kinase. The mTOR signaling pathway promotes substance metabolism, participates in the regulation of apoptosis and autophagy. Suppressing of mTOR signaling pathway can also enhance autophagy in sepsis and thus improve cardiac dysfunction.<sup>93</sup> Platelet-derived exosomes promote neutrophil extracellular trap (NETs) production in sepsis by activating autophagy-related Akt/mTOR signaling pathway, which precipitate myocardial depression induced by sepsis.<sup>94</sup> NETs are the defense mechanism of neutrophils against infectious diseases and play an important role in the process of tissue damage induced by sepsis.<sup>95</sup> Clearly, there is a positive correlation between the number of NETs and the severity of disease. When sepsis-induced cardiomyopathy occurs, the cardiac autophagy pathway is inhibited.<sup>96</sup> Of note, the mechanism of inhibition of autophagy in SIMI is related to restricted phosphorylation of AMPK.<sup>82</sup> The present studies show that the attenuation of SIMI is achieved through autophagy, which is activated by phosphorylated AMPK.<sup>97,98</sup> As an autophagy-initiating kinase, the activating of ULK1 by AMPK through phosphorylating Ser 317 and Ser 777 may ensure that autophagy is initiated. Of course, due to the negative feedback loop formed between ULK1 and AMPK, ULK1 is involved in not only the activation but also the termination of

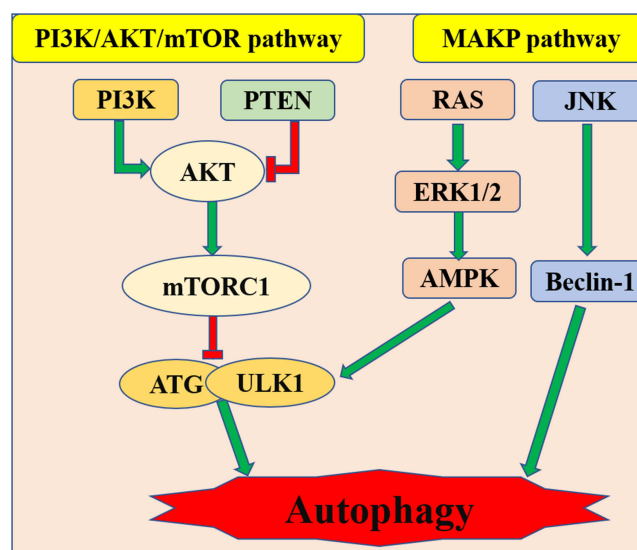


Figure 3 PI3K/Akt/mTOR and AMPK pathway relating to autophagy in SIMI.

autophagy.<sup>99</sup> It had been confirmed that the mechanism of autophagy reaction in SIMI may be related to the phosphorylation of ULK1 based on the activation of AMPK and the suppression of the mTOR.<sup>100,101</sup>

In addition, several momentous but uncommon targets for autophagy have been identified and contributed to the clinical treatment of SIMI. Studies have demonstrated protection of sepsis-induced myocardial damage by regulating JNK signaling pathway-dependent autophagy.<sup>102</sup> Sirtuin6 (SIRT6), a member of the Sirtuin family of NAD<sup>+</sup>-dependent enzymes,<sup>103</sup> has a specific role of improving SIMI via activating autophagy.<sup>104</sup> However, we still have a lot of room for improvement in the treatment of SIMI regarding the regulation of autophagy, especially in epigenetics.

## Over-Inflammation in SIMI

Moderate inflammation is good for the body, while its excessive response is bad. The real causes of cardiac dysfunction induced by sepsis are closely related to excessive inflammatory response.<sup>22</sup>

### The Role of Pro-Inflammatory Cytokines in Over-Inflammation

Some pro-inflammatory cytokines have previously been reported to inhibit myocardial function,<sup>105</sup> and this involves mechanisms of increased apoptosis and activated inflammation.<sup>106</sup> In addition, inflammatory cytokines can also inhibit the contractility of cardiac myocytes.<sup>107</sup> When sepsis occurs, the body can produce a large number of pro-inflammation factors (such as TNF- $\alpha$ , interleukin-6 (IL-6), IL-1 $\beta$ , etc.) and angiotensin II and lead to the damage of macrophages,<sup>108</sup> clearly, the activation of inflammatory storms is a key to SIMI. IL-18 plays a decisive role in the mechanism of sepsis induced cardiac inflammation, which is positively correlated with the inhibition of PLN and Akt phosphorylation mediated by increased PP2A activity.<sup>109</sup> Activation of phosphorylated Akt also provides a promising research basis for the treatment of SIMI.<sup>110</sup> There is a study demonstrated that the NLRP3 inflammasomes were activated in SIMI, and TXNIP<sup>111</sup> as well as GSDMD<sup>112</sup> mediated the activation of NLRP3 inflammasomes. However, the activation of NLRP3 inflammasomes depends on the production of reactive oxygen species (ROS).<sup>112</sup> Proteomic studies have also shown that inflammatory responses in sepsis are induced by activation of the TLR4/NLRP3 signaling pathway.<sup>113</sup> Therefore, therapeutic strategies based on the inhibition of NLRP3 inflammasome will be the key to our study of SIMI.<sup>114,115</sup>

### The Role of Macrophages in Over-Inflammation

The explosive inflammatory response during sepsis is also driven by macrophage infiltration.<sup>116</sup> In SIMI, up-regulation of 5-LOx expression stimulates LTB4 overexpression and activates the BLT1/IL-12P35 signaling pathway, leading to polarization of M1 macrophages and inducing excessive inflammatory responses.<sup>117</sup>

### The Role of Signaling Pathways in Over-Inflammation

On the one hand, activation of pro-inflammatory signaling pathways is the key to the pathophysiology of SIMI, such as JAK2/STAT3,<sup>118</sup> IGF-1/PI3K/Akt/GSK-3 $\beta$ <sup>119</sup> and Fas/FasL<sup>120</sup> signaling pathway.

On the other hand, the mechanisms of RAS during sepsis consist of MAPK, NF- $\kappa$ B and TLR4 signaling pathways, which all mediate inflammation response through the connection of the three of them.<sup>121</sup> Excessive inflammatory responses mediated by NF- $\kappa$ Bp65 signaling have been reported extensively.<sup>122,123</sup> It is also confirmed that TLR4/NF- $\kappa$ B is a key inflammatory storm-induced signaling pathway<sup>124,125</sup> and subsequently triggers TNF- $\alpha$  and IL-18 expression<sup>126</sup> in SIMI, but its negative regulation by miR-146a improves cardiac function.<sup>127</sup> Activation of TLR4 during sepsis promotes nuclear NF- $\kappa$ B translocation, which accelerates cytokine secretion by cardiomyocytes. In addition, TLR4/JNK signaling pathway plays a critical role in regulating myocardial dysfunction during sepsis.<sup>128</sup> Previous studies have shown that inhibition of MAPK/NF- $\kappa$ Bp65 signaling reduces inflammatory storms and ameliorates myocardial injury in SIMI.<sup>129,130</sup> In fact, activation of the MAPK/NF- $\kappa$ B pathway will eventually induce large amounts of TNF, which is produced by cardiomyocytes.<sup>131</sup> MiR-23b<sup>132</sup> and miR-29a<sup>133</sup> mitigated inflammatory responses in SIMI by inhibiting the NF- $\kappa$ B signaling pathway. Similarly, miR-23a suppressed sepsis-induced inflammatory responses by inhibiting the SIRT1/NF- $\kappa$ B signaling pathway as well.<sup>134</sup> The inflammatory storm of cardiomyocytes in sepsis may be also caused by inhibition of phosphorylation of AMPK signaling pathway.<sup>135</sup>

## The Role of Genomics in Over-Inflammation

In the past five years, a large number of experiments have explored novel treatment strategies for SIMI from the perspectives of genomics and epigenetics and provided theoretical basis for the clinical management of patients with SIMI. Upregulation of miR-21 stimulated the production of a large number of pro-inflammatory factors in SIMI.<sup>136</sup> Study has shown that miR-29a was overexpressed in the cell and animal models of sepsis.<sup>137</sup> Of note, overexpression of miR-29a increased LPS-induced inflammation and injury in H9c2 cells. LncRNA PVT1 induces polarization of M1 macrophages and deteriorates myocardial injury in SIMI by activating miR-29a/HMGB1 signaling pathway.<sup>138</sup> Other pathways that PVT1 leading to SIMI are mediated by PVT1/miR-24/KLF6<sup>139</sup> and MAPK/NF- $\kappa$ B,<sup>140</sup> which activate inflammation. LncRNA PTENP1 triggers inflammatory storms in sepsis by regulating the expression of miR-106b-5p and causes myocardial injury.<sup>141</sup> Similarly, LncRNA H19 with low expression plays a pro-inflammatory role in sepsis by promoting the expression of miR-874.<sup>142</sup>

However, different microRNAs have different regulatory effects on inflammation in sepsis. For example, miR-181b mitigated the inflammatory response on SIMI via down-regulating the targeted gene HMGB1.<sup>143</sup> MiR-494-3p, a potential therapy of SIMI, can inhibit PTEN-mediated inflammatory response.<sup>144</sup> In addition, miR-215-5p,<sup>145</sup> miR-141<sup>146</sup> and so on play the anti-inflammatory role in the treatment of SIMI by acting with their respective target genes. Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) ameliorate myocardial depression during sepsis through activating the cholinergic anti-inflammatory pathway (CAP) mediated by  $\alpha$ 7-nicotinic acetylcholine receptors ( $\alpha$ 7nAChRs).<sup>147</sup> The MSC-mediated anti-inflammatory effect of SIMI is largely dependent on the regulation of exosomal miR-223.<sup>148</sup>

## Oxidative Stress in SIMI

Septic patients are often in a state of oxidative stress.<sup>149</sup> Oxidative damage of cardiomyocytes with dysfunction has been documented in abundant literatures on the pathophysiology of sepsis.<sup>150</sup> Then, the oxidative stress that occurs in sepsis is inseparable from mitochondrial dysfunction.<sup>151</sup> Treatment with mitochondrial antioxidants has been reported to alleviate SIMI.<sup>152</sup> Some studies assessed oxidative stress in SIMI by measuring the expression levels of superoxide dismutase (SOD) and malondialdehyde (MDA) through proteomics.<sup>153,154</sup> The former reflects the body's antioxidant potential, while the latter reflects the body's oxidative stress ability. During researching the pathogenesis of SIMI, nuclear factor erythroid-2 related factor 2 (Nrf2) signaling pathway has been confirmed to be involved in the regulation of oxidative stress.<sup>155</sup> Nrf2, an anti-oxidative stress signaling pathway factor, is at the level of low expression during SIMI<sup>156</sup> and inhibits sepsis-induced ROS generation.<sup>157</sup> Oxidative stress, the result of an imbalance between ROS production and antioxidant defense systems, is characterized by an overproduction of ROS.

In previous studies, the mechanism of oxidative stress in SIMI has been elucidated from epigenetic and specific signaling pathways. For example, miR-124-3p has been tested to alleviate SIMI by inhibiting oxidative stress,<sup>116</sup> the activation of PKC $\beta$ 2 signal triggers sepsis-induced oxidative damage in cardiomyocytes, which is the result of activating autophagy,<sup>158</sup> and the inhibition of NF- $\kappa$ B signaling pathway also ameliorates sepsis induced myocardial oxidative damage.<sup>159</sup> Obviously, research on antioxidant therapy for sepsis is still a potential prospect at present.

## Pyroptosis in SIMI

Pyroptosis is affected by oxidative stress, apoptosis and inflammation, and its controlled condition influences the progression of sepsis. Some cytokines, inflammasomes, caspase family, interleukin and GSDMD, are involved in the molecular mechanism of pyroptosis.<sup>160</sup> Interference with these aforementioned molecules has been reported to improve the development of cardiovascular disease.<sup>161</sup> Studies on the pathophysiology of apoptosis in sepsis have largely concentrated on exploring signaling pathways mediated by GSDMD and NLRP3.<sup>162</sup>

Accordingly, the mechanism of pyroptosis on SIMI is mediated by ER/SIRT1/NLRP3/GSDMD signaling pathway, which is the most complete pathway discovered so far.<sup>163</sup> Of note, GSDMD plays an integral role in apoptosis,<sup>164</sup> and some certain activated Caspases (e.g. caspase-4, 5, and caspase-11) cleave it and further trigger pyroptosis. The same is true in sepsis. In addition, pyroptosis is a kind of cell death containing an inflammatory response, which is mediated by GSDMD.<sup>165</sup> So, NLRP3 inflammasome is an important signal molecule of pyroptosis in SIMI.<sup>166</sup> Some scholars have



confirmed that activation of NLRP3 inflammasome induces cardiomyocyte's pyroptosis in sepsis by studying the cardio-protective effect of emodin, and the indirect regulation of pyroptosis by NLRP3 inflammasome is mediated by caspase-1,<sup>167</sup> ROS and NF- $\kappa$ B signaling pathway.<sup>161</sup> Then, C1q/tumor necrosis factor-related protein 1 (CTRP1) is a promoter that inhibits pyroptosis of cell, its inhibition effect of pyroptosis is triggered by binding to overexpressed Nrf2. Nrf2, an important regulator of cellular defense against stress response, can protect against cytotoxic injury by regulating the expression of many cellular protective genes. When sepsis occurs, low expression of Nrf2 leads to non-activation of CTRP1 binding sites, thus inducing pyroptosis of cardiomyocytes.<sup>168</sup>

Previous studies have researched the mechanism of pyroptosis from genomics and laid a foundation for the treatment of SIMI. LncRNA x-inactive specific transcript (XIST) contributes to the treatment of SIMI by affecting pyroptosis mediated by miR-150-5p/c-Fos axis.<sup>169</sup> LncRNA ZFAS1/miR-138-5p/SES2 signaling pathway also improved SIMI by inhibiting pyroptosis.<sup>170</sup> Exosomes in the blood of septic patients promote myocardial pyroptosis by activating NF- $\kappa$ B-dependent miR-885-5p/HMBOX1 signaling pathway.<sup>171</sup> Therefore, some LncRNAs serve as the competing endogenous RNA (ceRNA) of its specific target genes (microRNA) to up-regulate the expression of cell-stress-related proteins, thereby alleviating sepsis-induced myocardial pyroptosis.

Recently, other emerging pathways of pyroptosis have being studied during sepsis, and whether they work in SIMI is still not clear.

## Prospects for Therapeutic Strategies in SIMI

Current therapeutic strategies of SIMI are based on the above six pathophysiological mechanisms. For example, on the one hand, Melatonin et al<sup>98</sup> take the role of improving SIMI through activating AMPK-mediated autophagy; on the other hand, Helium<sup>126</sup> and Berberine<sup>124</sup> et al exert their effect on SIMI by inhibiting inflammation after acting on the TLR4/NF- $\kappa$ B signaling pathway (see Table 1 for details). These basic literatures listed in Table 1 also indicates that the treatment of SIMI under the same mechanism includes both Traditional Chinese medicines and Western medicines, and

**Table 1** Confirmed Therapeutic Strategies Based on 6 Types of Mechanisms in SIMI

Mechanisms	Treatment	Target or Signaling Pathway	Effect	Reference
Apoptosis	H <sub>2</sub> S Melatonin	PI3K/Akt $\uparrow$	Inhibition	[41]
	Resveratrol	PI3K/AKT/mTOR $\uparrow$	Inhibition	[39]
	Oleuropein	GSK-3 $\beta$ /NF- $\kappa$ B $\downarrow$	Inhibition	[50]
	Dehydrocorydaline	TRAF6 $\uparrow$ NF- $\kappa$ B $\downarrow$	Inhibition	[44]
	Tannic acid	ROS $\downarrow$	Inhibition	[62]
	Melatonin	SIRT1 $\uparrow$	Inhibition	[98]
	Xuefu Zhuyu Decoction	Caspase-3 $\downarrow$	Inhibition	[26]
	Shenfu	Bcl-2 Bid t-Bid caspase-9 $\uparrow$	Inhibition	[30]
	Naringin	Bcl-2 $\uparrow$ BAX $\downarrow$	Inhibition	[153]
	Hesperetin	JNK/Bax $\downarrow$	Inhibition	[29]
	Astaxanthin	MAPK $\downarrow$	Inhibition	[33]
	Astaxanthin	PI3K/AKT/mTOR $\downarrow$	Inhibition	[33]
	Oxymatrine	TNF- $\alpha$ /P38-MAPK /caspase-3 $\downarrow$	Inhibition	[37]
	Mitochondrial dysfunction	HuMSC-exo	PINK1/PKA/NCLX $\uparrow$	Inhibition
Ginsenoside-Rg1		P2X7 /Akt/GSK-3 $\beta$ $\uparrow$	Inhibition	[70]
NaHS		PGC-1 $\alpha$ /Nrf2 $\uparrow$	Inhibition	[76]
Autophagy	Melatonin	AMPK $\uparrow$	Activation	[98]
	Luteolin	AMPK $\uparrow$	Activation	[97]
	UCP2	AMPK $\uparrow$	Activation	[82]
	Narciclasine	JNK $\uparrow$	Activation	[102]
	Dexmedetomidine	PI3K/Akt $\uparrow$	Activation	[92]
	Capsaicin	14-3-3 $\gamma$ $\uparrow$ mTOR $\downarrow$	Activation	[93]

(Continued)

Table 1 (Continued).

Mechanisms	Treatment	Target or Signaling Pathway	Effect	Reference
Excessive inflammatory response	Hyperoside	miR-21↓	Inhibition	[136]
	MSC-derived exosomes	miR-223↑	Inhibition	[69]
	WJ-MSCs	$\alpha$ 7nAChRs↑ CAP↑	Inhibition	[147]
	BM-MSC-derived exosomes	miR-141↑ PTEN↓/β-catenin↑	Inhibition	[146]
	Matrine	LncRNA PTENP1↓ miR-106b-5p↓	Inhibition	[141]
	Myricetin	NF-κB↓	Inhibition	[122]
	Astragalus polysaccharide nanoparticles	TLR4/NF-κB↓	Inhibition	[125]
	Helium	TLR4/NF-κB↓	Inhibition	[126]
	Berberine	TLR4/NF-κB↓	Inhibition	[124]
	Resolvin E1	MAPK/NF-κB↓	Inhibition	[130]
	Zerumin A	MAPK/NF-κB↓	Inhibition	[129]
	Astragaloside IV	NF-κB↓ PI3K/Akt ↑	Inhibition	[110]
	Salidroside	IGF-1/PI3K/Akt/GSK-3β↓	Inhibition	[119]
	Disulfiram	NLRP3↓	Inhibition	[115]
	Shikonin	NLRP3↓ SIRT1↑	Inhibition	[114]
	Salidroside	IGF-1/PI3K/Akt/GSK-3β↓	Inhibition	[119]
	Oxymatrine	JAK2/STAT3↓	Inhibition	[118]
	Butyrate	TNF-α, IL-6 LTB4↓	Inhibition	[154]
	Neuregulin-1	TNF-α, IL-1β IL-6↓	Inhibition	[108]
	Naringin	TNF-α, IL-1β IL-6↓	Inhibition	[153]
Oxidative stress	Resveratrol	Nrf2↑	Inhibition	[157]
	Maresin 1	Nrf2↑	Inhibition	[156]
	Naringin	SOD ↑ MDA↓	Inhibition	[153]
	Butyrate	SOD ↑ MDA↓	Inhibition	[154]
	Apigenin	NF-κB ↓	Inhibition	[159]
	Remifentanyl	PKCβ2↓	Inhibition	[158]
pyroptosis	Syringaresinol	ER/SIRT1/NLRP3/GSDMD ↓	Inhibition	[163]
	Irisin	NLRP3 ↓	Inhibition	[166]
	Emodin	Caspase-1↓ NLRP3 ↓	Inhibition	[167]

Notes: ↑: the expression of signaling pathways is enhanced; ↓: the expression of signaling pathways is inhibited.

one drug can ameliorate SIMI by acting on different mechanisms. Based on this, this review proposes whether the combined treatment of Chinese and Western drugs can enhance the treatment effect of SIMI. Then, the molecular mechanisms involved in SIMI are not independent of each other, as the signaling pathways that mediate each mechanism are interlinked. Therefore, the research on multi-targeted monotherapy of SIMI may become the next hot topic.

## Conclusion

There are some signaling pathways that induce both apoptosis and autophagy: p53, Death-associated protein kinase (DAPK), Bcl-2 family and JNK.<sup>172</sup> In most of the cell stress stages, however, autophagy is activated at the early stage and apoptosis is activated at the late stage both by the above four signals, so there is a mutually negative regulatory relationship between autophagy and apoptosis.<sup>173</sup> Some researchers have studied the interaction mechanism between autophagy and apoptosis in cancer and summarized some LncRNAs, ROS and Beclin-1 also participated in it.<sup>174</sup> To sum up, whether the interaction between autophagy and apoptosis also exists in SIMI and which regulatory factors are involved will be the focus of our subsequent study.

In the same way, there are the common signaling pathways between apoptosis and inflammatory response, such as the TLR4/NF-κB.<sup>175</sup> It has been confirmed that apoptosis is the trigger of inflammation and this cascade reaction can be inhibited by RIPK1.<sup>176</sup> Activation of some autophagy-related signaling pathways can protect cells from inflammation response,<sup>177</sup> therefore, autophagy is the key to anti-inflammation. Autophagy is activated by inflammatory

responses found in the early stages of myocardial stress,<sup>178</sup> which may exacerbate myocardial tissue damage. Therefore, whether early application of anti-inflammatory therapy in clinical patients of SIMI is reasonable deserves further investigation.

Oxidative stress is often thought to be the cause of chronic inflammatory disease.<sup>179</sup> In addition, there is a mutual promotion between inflammation and oxidative stress,<sup>180</sup> both mediated by the common signaling pathway: NF- $\kappa$ B.<sup>181</sup> Mitochondrial dysfunction is closely related to oxidative stress because of the excessive production of ROS in mitochondria.<sup>182</sup> Collectively, mitochondrial dysfunction appears to be the mediation between inflammation and oxidative stress. In fact, the essence of pyroptosis is inflammation.<sup>183</sup> Then, caspases<sup>184</sup> and NLRP3<sup>54</sup> trigger the activation of pyroptosis, inflammation and apoptosis. In view of this, we aim to find the monotherapy strategy of multitarget for patients with SIMI that may improve the prognosis of them by reducing the side effects of multidrug use.

In the past 20 years, the mechanisms of SIMI have been studied in a wide range of fields, including proteomics and genomics. In addition, the purposes of research based on SIMI mechanism is also different, some are to explore the treatment of SIMI, while others are just to explore the specific pathway leading to SIMI. However, the ultimate goal of all basic research is better clinical treatment and management. Although studies on the mechanism of SIMI have become mature, none of the six mechanisms mentioned above, including apoptosis, mitochondrial damage, autophagy, excessive inflammatory response, oxidative stress and pyroptosis, has a specific and complete signaling pathway that can explain how SIMI occurs. There are still many signaling molecules lacking in the studied pathway, and also many signaling pathways related to sepsis are not reflected in the studies of SIMI; so it is imperative that we continue to explore and refine the existing mechanisms of SIMI.

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## Disclosure

The authors declare that there is no conflicts of interest in this work.

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