

# A Focus on the Mechanisms of Alteration in Host Lymphocyte Level Following Severe Fever with Thrombocytopenia Syndrome Virus (SFTSV) Infection

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**Abstract:** Nowadays, severe fever with thrombocytopenia syndrome (SFTS), featuring clinical manifestation of fever with leukopenia, thrombocytopenia and multiple organ function impairment, has been paid more and more attention. It has become the pandemic for a few years and a quantity of people died of it. Severe fever with thrombocytopenia syndrome virus (SFTSV) infection may lead to the development of SFTS, which is characterized by decreased counts of lymphocyte subsets, especially T cells, B cells and natural killer cells, and disruptive release of cytokines, chemokines and growth factors. However, the deeper mechanism of this disease remains unidentified. To excavate the mechanisms of lymphopenia in SFTSV infection and to introduce the potential therapeutics, this paper focuses on lymphopenia as well as reviews the mechanisms and effects of lymphopenia caused by SFTSV infection, mainly through making analogies with other similar viruses to explain the details of programmed cell death. Other factors such as IL-6, IL-10, TNF- $\alpha$  and some vital immunocytes also play significant roles in eliciting lymphopenia. Eventually, the probable clinical implications have been discussed, mentioning that lymphopenia induced by multiple pathways in SFTSV infection may be associated with the severity of viral disease and opportunistic infection.

**Keywords:** lymphopenia, SFTSV, cytokines, chemokines, infection, immune response

## Introduction

Lymphocytes are significant players in the immune response and are divided into T cells, B cells and natural killer (NK) cells according to their origin, morphological structure, surface markers and immune function. Lymphopenia refers to an absolute reduction of lymphocytes in the peripheral blood<sup>1</sup> and thus we can diagnose it through the abnormally lower total level of lymphocytes than normal due to viral infection,<sup>2</sup> chemotherapy, radiotherapy,<sup>3</sup> autoimmune diseases,<sup>4</sup> cancer<sup>5</sup> and other severe injuries.<sup>6</sup> Most viral infections cause relative or absolute lymphocyte depletion, or even severe lymphopenia.

Severe fever with thrombocytopenia syndrome virus (SFTSV) leads to severe fever with thrombocytopenia syndrome (SFTS). A small number of SFTSV infected patients are serious and develop rapidly, with a fatality rate of 5%-30%.<sup>7</sup> As of 2018, according to a report, the total number of SFTS cases in 25 provinces in China was about 12,000.<sup>8</sup> Additionally,

it is reported that cases of SFTS have been recorded in South Korea, Japan, Vietnam and other countries,<sup>9–11</sup> among which more than 300 cases have been recorded in Japan and nearly 800 cases in South Korea. SFTSV has a wide spread risk, and its main vector is ticks,<sup>12</sup> although it may also be transmitted through air, contact, etc. Nowadays, specific antiviral therapy is being needed to overcome this disease, with mostly broad-spectrum antiviral drugs, such as Ribavirin, Favipiravir, and IFN- $\gamma$  being clinically used to inhibit viral replication for empirical treatment. However, the therapeutic effect is often poor partly because of the lack of the appropriate treatment response in the late stages of the viral infectious disease. Therefore, it is of immense significance to consider drugs with different mechanisms of action for combined therapy.

SFTSV and the host immune system interact in a complicated way, which is the main cause of SFTS. Previous studies have indicated that SFTSV infection induces a decrease in the count of T cells, B cells and NK cell subsets,<sup>13,14</sup> while during the convalescence stage of the disease, the amount of lymphocytes gradually rises. Moreover, a research has shown that patients with a higher SFTSV viral load frequently exhibit increasing numbers of the cytokines IL-6 and IL-10, indicating a correlation between these cytokines and both viral load and disease severity.<sup>15</sup> It is suggested that SFTSV infection may lead to peripheral lymphopenia, accompanied by excessive immunosuppression and extravagant inflammatory responses due to the disorder of cytokines and chemokines, however, the deeper mechanism of this disease is still unclear. This paper examines how viral infections cause lymphopenia, focusing specifically on the possible underlying mechanisms of lymphopenia in SFTSV infection. The aim of this paper is to give a thorough understanding of this intricate pathogenic process mainly focusing on programmed cell death, involvement of cytokines and chemokines and other sorts of immunocytes, as well as identifying potential new treatments.

## Mechanisms and Effect of Lymphopenia Associated with SFTSV Infection

All kinds of viruses, such as SARS-CoV-2 and HIV, are demonstrated in a quantity of studies that they reduce lymphocyte counts in patients' peripheral blood. The dramatic decline of lymphocytes is closely related to disease severity and may even lead to fatal outcomes. This underscores of virus-induced lymphocyte reduction in the progression of diseases. Interestingly, it has been shown that SFTSV infection may cause a decreased counts of lymphocytes like T cells, B cells, NK cells and other lymphocyte subsets in patients' peripheral blood. However, the potential mechanism of lymphopenia caused by viral infection is complex and remains unclear, especially for SFTSV. This section summarizes the mechanism and effect of viral induced lymphopenia, especially in SFTSV infection.

## Programmed Cell Death

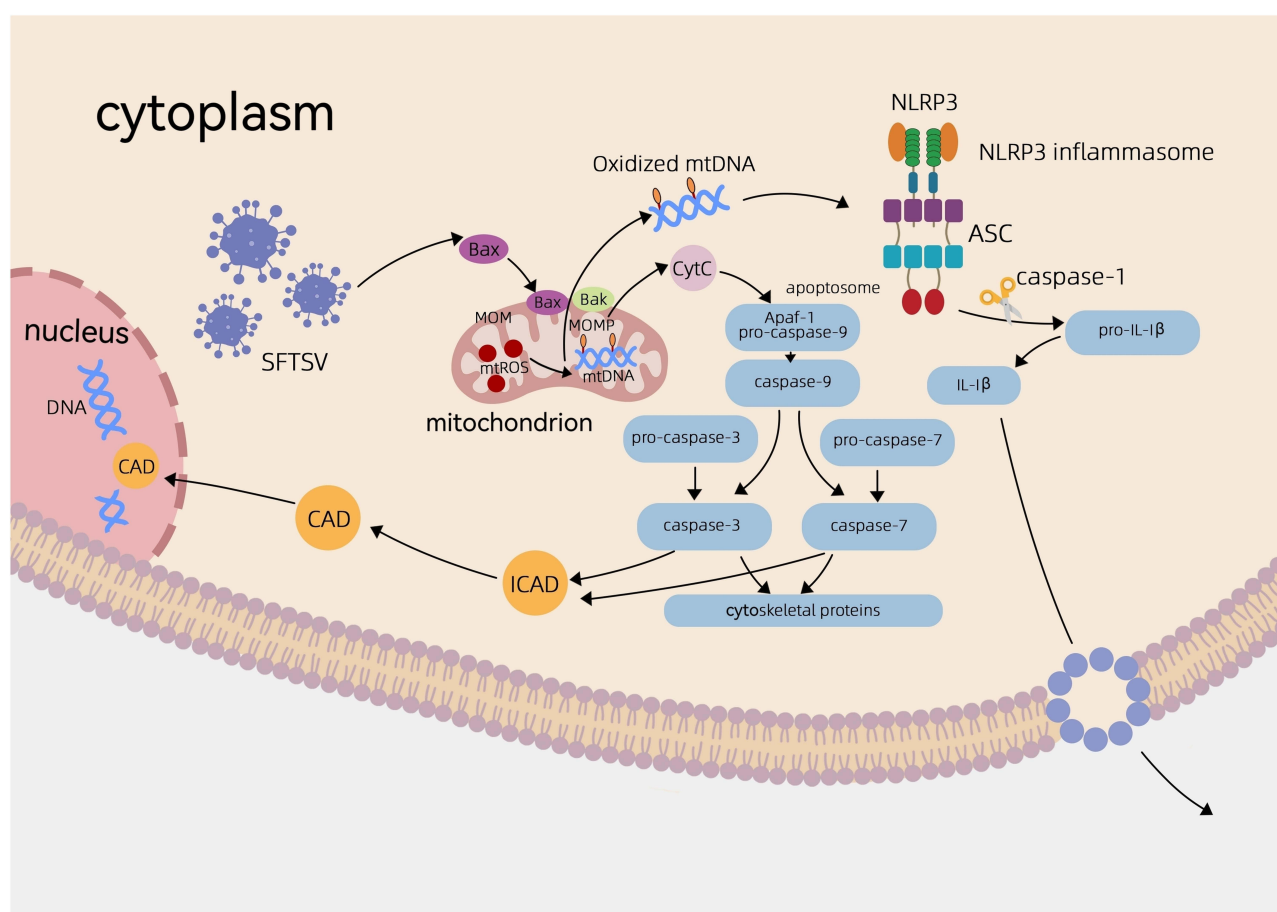
Cell death may occur due to metabolic arrest, structural destruction or loss of cellular functions. Programmed cell death (PCD) is a regulated and fundamental form of cell death, which is strictly controlled during immune responses. It is essential in fighting viruses that hide within host cells. The most common and well known types of PCD are apoptosis, autophagy, pyroptosis and cell necrosis. Studies have shown that in order to clear a virus infection, PCD is essential in killing infected cells to prevent viruses from invading other host cells.<sup>16</sup> At the same time, it mediates lymphocyte death, which leads to the lymphopenia caused by viral infections, such as HIV<sup>17</sup> and COVID-19,<sup>18</sup> among which apoptosis is the main pathway. Consequently, it can be inferred that PCD is also linked to SFTSV infection. The detailed information associated with PCD and SFTSV is discussed in this section. The treatments aiming at PCD associated molecules are promising.

## Apoptosis Induced by SFTSV

According to the existing studies, the apoptosis of lymphocytes caused by viral infection can be both directly induced and indirectly induced. HIV, MERS-CoV and other viruses are known to directly induce lymphocyte apoptosis.<sup>17,19</sup> Currently for indirect induction, it is generally believed that bystander lymphocytes that are adjacent to virus-infected cells are induced to apoptose. This mechanism may be associated with the enhancement of particular receptor binding to lymphocytes (Fas/FasL), activation of apoptosis-related proteins, intrinsic pathways (caspase), and activation of cytokines (TNF- $\alpha$ ) caused by viral infection.<sup>20,21</sup> Apoptosis is a crucial initial step in the reduction of lymphocyte numbers, and it can impact the body's immune capability by altering the counts of various T lymphocyte subsets.

Similarly, in the peripheral blood, there is a widespread apoptosis process regarding T cells after SFTSV infection, which may be related to the elevated amount of the apoptotic markers, referring to annexin V and CD95.<sup>14</sup> In addition, a study on the proteasome inhibitor, PS-341, in the treatment of SFTSV virus infection revealed that targeting apoptosis in dormant infected cells may help cure SFTSV virus infection.<sup>22</sup> These studies suggest that SFTSV infection is closely related to lymphocyte apoptosis.

Apoptosis is mainly controlled by the death receptor activation pathway, mitochondrial pathway and endoplasmic reticulum pathway, among which the mitochondrial pathway plays the biggest role in the apoptosis process. Mitochondria are dynamic organelles that constantly move, fuse and divide to form dynamic equilibrium according to the needs of cells. There is increasing evidence that this mitochondrial homeostasis has important effects on the innate immunity and T cell function.<sup>23</sup> Apoptosis can be caused by a significant disorder, mitochondrial dysfunction, during SFTSV infection.<sup>24</sup> BCL2 antagonist/killer 1 (BAK) is a pro-apoptotic regulator that participates in various cellular activities and is a key protein in maintaining mitochondrial function.<sup>25,26</sup> BAK and BAK/BCL2-associated X (BAX) are up-regulated and activated during SFTSV infection, resulting in mitochondrial DNA (mtDNA) being damaged by ROS and triggering activation of procaspases. IL-1 $\beta$  is released in abundance subsequently.<sup>27</sup> This eventually leads to lymphocyte apoptosis (Figure 1).



**Figure 1** The effect of mitochondrial outer membrane permeabilization facilitated by SFTSV. SFTSV infection leads to the upregulation of two critical pro-apoptotic proteins, Bax and Bak. This increase in Bax levels results in its insertion into the mitochondrial outer membrane (MOM). Once at the MOM, both Bax and Bak become activated and oligomerize, which facilitates a process known as mitochondrial outer membrane permeabilization (MOMP). As a consequence of MOMP, cytochrome C is released from the mitochondria into the cytoplasm. In the cytoplasm, cytochrome C interacts with Apoptotic protease activating factor-1 (Apaf-1) and pro-caspase-9, forming a complex known as the apoptosome. The activation of caspase-9 occurs within this complex, and it subsequently activates caspase-3 and caspase-7. These activated caspases play a crucial role in the apoptosis process by cleaving various substrates, including essential cytoskeletal proteins. Additionally, caspase-3 and caspase-7 induce proteolytic attack on ICAD (inhibitor-CAD), allowing CAD (caspase-activated DNase) to activate and then to enter the nucleus to degrade chromosomal DNA, which eventually initiates apoptosis. Meanwhile, Mitochondrial DNA (mtDNA) is oxidized by ROS and released into the cytoplasm through MOMP. Cytoplasmic mtDNA plays a critical role in activating the NLRP3 inflammasome, an important component of the innate immune response. The NLRP3 inflammasome is composed of three main elements: the receptor protein NLRP3, the adapter protein ASC, and the inflammatory protease caspase-1. When cytoplasmic mtDNA is detected, it triggers the assembly and activation of the NLRP3 inflammasome. Once activated, caspase-1 undergoes a conformational change that allows it to facilitate the maturation and release of IL-1 $\beta$ , a key pro-inflammatory cytokine that contributes to the immune response and inflammation.

## Pyroptosis Induced by SFTSV

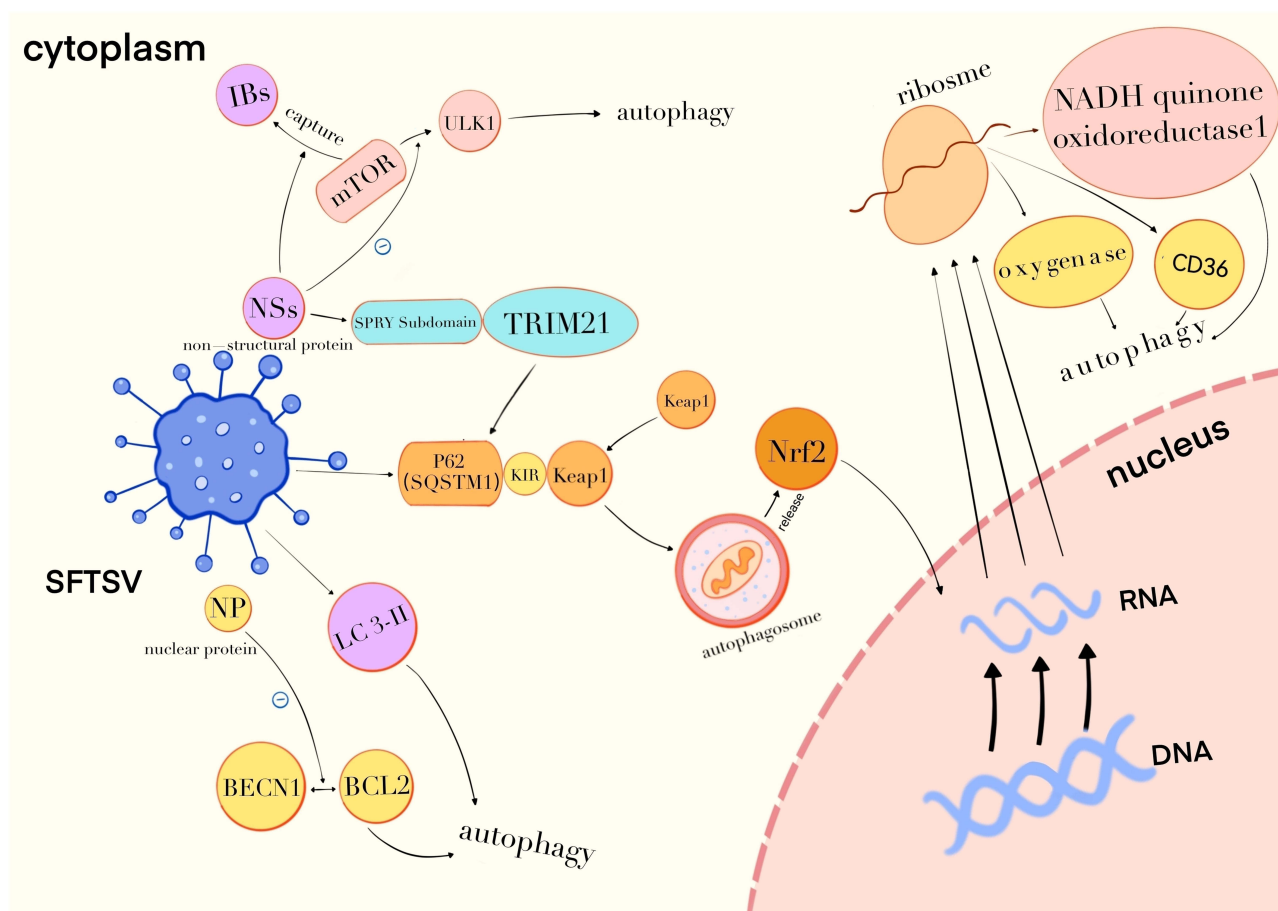
Pyroptosis is a kind of programmed cell death featuring highly pro-inflammatory, which is also able to elicit lymphopenia. In viral induced pyroptosis, intracytoplasmic pattern recognition receptors of the host cell recognize the virus and form inflammasomes that recruit and activate caspase-1, which leads to a scorched-death of the cell. Pyroptosis results in the release of substantial amounts of inflammatory factors, such as IL-1 $\beta$ , along with cellular contents, which is a vital way to induce lymphopenia. This process can trigger widespread inflammation within the body.<sup>28</sup> During infections with the influenza A virus, the NOD-like receptor family protein 3 (NLRP3) inflammasome is specifically activated in response to viral RNA, which eventually results in the lymphocyte pyroptosis by initiating the activation of caspase-1 as well as increasing the level of IL-1 $\beta$  and IL-18.<sup>29</sup> In conclusion, pyroptosis is an important pathological event related to virus infection, lymphocyte death and inflammation, which further raises the incidence of opportunistic infections among patients.

The similar phenomenon has been observed in SFTSV infection. In the innate immune system, the inflammasome induced proinflammatory response is important for the resistance to pathogens. The activation of inflammasomes involves several signaling pathways. First, through the RLRs, TLRs and NF- $\kappa$ B signaling pathways, the up-regulated level of pro-IL-1 $\beta$  and pro-IL-18 occurs. Next, the assembly of inflammasomes is activated through NLRP3, which promotes the maturation and subsequent release of pro-IL-1 $\beta$  and pro-IL-18 that also promotes pyroptosis.<sup>30,31</sup> This is particularly evident in patients with SFTS and in infected animal models, where elevated levels of IL-1 $\beta$  are observed. Additionally, there is significant activation of caspase-1, which is accompanied by cell death and the processing of gasdermin D in human peripheral blood mononuclear cells (PBMCs) infected with SFTSV. Additionally, Nod-like receptor (NLR) knockdown experiments showed that NLRP3 inflammasomes lead to the activation of caspase-1 and the release of IL-1 $\beta$  in the process of SFTSV infection, and the activation of NLRP3 inflammasomes is responsible for pyroptosis in SFTSV-infected cells.<sup>24,31</sup> The mechanisms above result in lymphocyte reduction.

## Autophagy Caused by SFTSV

Autophagy is a crucial defense pattern of cells which transport viral particles parasitizing in host cells to lysosomes. However, excessive autophagy induces cell death, which leads to lymphopenia. The initiation of autophagy depends on the deacetylation of light chain 3 (LC3), which is a microtubule-related protein and also has great effects on the extension and maturation of autophagosome membranes. Studies have found that silencing LC3 inhibits coronavirus (CoV) replication.<sup>32</sup> What's more, the endoplasmic reticulum (ER) stress-related signaling pathway was found to be activated to induce T cell autophagy during Ebola virus disease (EVD).<sup>33</sup>

Similarly, it has been demonstrated that autophagy can be induced by SFTSV, using the autophagy pathway for virus assembly and release and then causing lymphopenia.<sup>34</sup> When examining autophagy, several markers are used. LC3 is used as a general marker of autophagy,<sup>35</sup> SQSTM1 (Sequestosome 1) indicates of autophagy degradation, especially a selective one,<sup>36</sup> and p62 is a multifunctional binding protein that regulates autophagy.<sup>37</sup> One study<sup>35</sup> found that SFTSV could lead to the rise of LC3-II levels and spot aggregation of endogenous LC3, resulting in increased expression of SQSTM1. In addition, it has also been found that SFTSV infection activates the P62 pathway to induce autophagy in somatic cells.<sup>38</sup> However, the mechanisms of interaction between SFTSV infection and autophagy are relatively complex. In terms of the structure of the SFTSV, studies have found that the mutation of key amino acids of the Gn protein of SFTSV can lead to increased expression amount of autophagy-associated proteins p62 and LC3, at the same time, multiple mechanisms have evolved in Gn protein of SFTSV to evade host cell autophagy.<sup>39</sup> It has also been found that through disturbing BECN1-BCL2 binding, the SFTSV nuclear protein (NP) induces autophagy that depends on BECN1.<sup>40</sup> Recently, a study indicates that SFTSV non-structural proteins (NSs) disrupt mTOR's inhibition of mTOR-mediated UnC-51-like kinase 1 (ULK1) activity by targeting ULK1 phosphorylation, thus promoting autophagy induction.<sup>41</sup> In summary, autophagy can be induced through many pathways, eventually leading to lymphocyte death. These studies suggest that autophagy inhibition may develop new therapeutics for SFTSV infection (Figure 2).



**Figure 2** SFTSV induces some signal pathways to regulate autophagy. The non-structural proteins (NSs) of the SFTSV play a crucial role in manipulating cellular processes by interacting with the mechanistic target of rapamycin (mTOR). This interaction results in the trapping of mTOR within viral inclusion bodies (IBs), thereby inhibiting its ability to phosphorylate UNC-51-like kinase 1 (ULK1). The inhibition of ULK1 phosphorylation disrupts mTOR's regulatory control, promoting autophagy. P62 ubiquitination mediated by tripartite motif-containing (TRIM) 21 eliminated oligomerization and sequestration activities of p62, and disrupted the antioxidant response mediated by Keap1-Nrf2 pathway. The NS proteins bind specifically to the SPRY subdomain of TRIM21, which enhances the stability and oligomerization of p62. Moreover, Keap1 interacts with the Keap1-interacting region (KIR) of P62. Through this interaction, p62 facilitates the degradation of Keap1 in autophagosomes. As Keap1 is degraded, Nrf2 is released from its inhibitory complex, allowing for its stabilization and activation. The activated Nrf2 ultimately translocates to the nucleus, where it drives the transcription of various antioxidant genes, such as NAD(P)H quinone oxidoreductase 1 (NQO1) and oxygenase. Simultaneously the increased expression level of CD36 has also been seen. What's more, SFTSV is capable of contributing to accumulation of endogenous LC3-II levels and spot aggregation, resulting in mounting SQSTM1 expression. Additionally, nucleoprotein (NP) of SFTSV is able to facilitate autophagy by negatively regulating the BECN1-BCL2 binding.

## Other Sorts of Cell Death Caused by Viral Infections

Apart from the common forms of cell death that are able to induce lymphocyte, there are some other categories such as activation induced cell death (AICD) and antibody-dependent cell-mediated cytotoxicity (ADCC). Their effect to reduce the amount of lymphocytes has been shown in several viruses. However, the AICD and ADCC leading to lymphopenia in SFTSV infection remain ambiguous and need to be excavated.

**Activation induced cell death (AICD):** During infection, viral components expressed on the membrane of host cells are presented to T lymphocytes as endogenous antigens to induce AICD. The mechanism of lymphocyte AICD is connected with the activation of the Fas ligand. AICD causes apoptosis of autoreactive T or B cells through Fas/FasL binding between T-cells.<sup>42,43</sup> Fas induces T cell apoptosis during HIV and hepatitis C virus (HCV) infection. With infections with SARS-CoV-2 and RSV, Fas upregulation has been observed, and upregulation of Fas expression levels significantly decrease CD4<sup>+</sup> T lymphocytes level in the blood.<sup>44,45</sup>

**Antibody-dependent cell-mediated cytotoxicity (ADCC):** Infected effector lymphocytes undergo ADCC via the binding of their Fc receptors to the Fc fragments of antibody-antigen coated target cells. NK cells are the primary effector lymphocytes mediating ADCC. The ADCC effect is mediated by Fas and FAS-L pathway, perforin and

granzyme pathway, and reactive oxygen intermediates (ROI/ROS) pathway.<sup>46</sup> It has been indicated that ADCC has an outstanding effect on the body's resistance to HIV-1, HCV, EVD, SARS-CoV-2 and other viruses.<sup>47-50</sup>

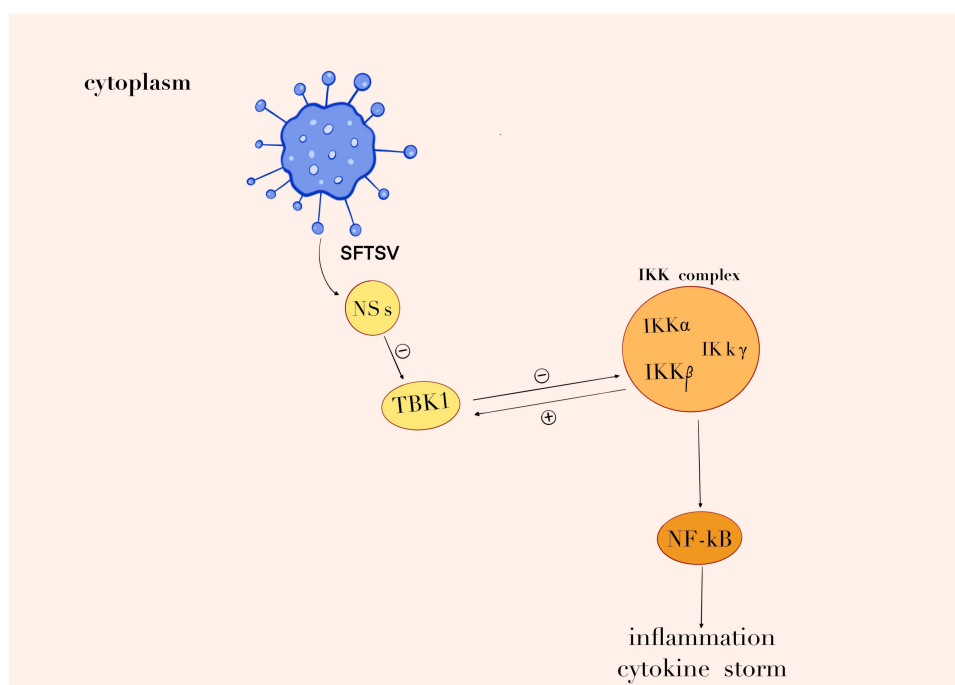
## Process Induced by Cytokines, Chemokines And Growth Factors

Cytokines, chemokines and growth factors are important molecules in the process of resisting foreign body invasion and promoting immune responses. They have a central effect on the pathological progression of many inflammatory diseases. Viral infection causes host lymphopenia, universally accompanied by accumulation of cytokines, chemokines, and growth factors, involving Interleukin-2 (IL-2), Interleukin-6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), Interferon- $\gamma$  (INF- $\gamma$ ), CCL2/MCP-1, CXCL10/IP-10, etc. SARS-CoV is capable of causing MODS involving liver dysfunction by inducing the cytokine storm and thus the terrible prognosis occurs.<sup>51</sup> Different viral infections positively regulate different categories of the three types of factors. For example, SARS-CoV,<sup>52</sup> HIV,<sup>53</sup> EBOV,<sup>54</sup> CSFV<sup>55</sup> and other viral infections can cause a significant increase of IL-6. HIV,<sup>56</sup> MERS-CoV<sup>57</sup> and SARS-CoV<sup>58</sup> may cause increased IFN secretion. The mechanisms of the three types of factors in immune response are pretty complicated, including all kinds of cells and multiple signaling pathways. In addition, they often function in a synergistic, antagonistic, and networked interaction. Moreover, cytokines, chemokines and growth factors also make a big difference in the control of proliferation and survival of lymphocytes.

IL-6 is a cytokine which has a transient proinflammatory effect through the adaptive immune response, which occurs after lymphocyte extravasation into the inflammatory site. IL-6 affects lymphocyte proliferation and survival by mediating STAT3 activation or directly damaging hematopoietic stem cells. IL-10 has been shown to promote sustained anti-inflammatory effects.<sup>59</sup> As a pro-inflammatory factor TNF- $\alpha$  is manufactured by activated macrophages and monocytes. Recent studies have found that being inversely associated with serum IL-6, IL-10 and TNF- $\alpha$ , the amount of T cells is negatively related to the severity of the disease during COVID-19 infection.<sup>60,61</sup> It is suggested that COVID-19 does not directly attack T cells, but promotes T cell depletion and inhibition by eliciting the secretion of cytokines involving IL-6, IL-10 and TNF- $\alpha$ ,<sup>62</sup> which exhibits that lymphopenia in peripheral blood is related to the upregulated level of the three kinds of cytokines.

TNF- $\alpha$  promotes inflammatory responses and simultaneously induces apoptosis. Studies indicate that TNF- $\alpha$  inhibits the maturation of T cells resulting in the downward number of CD4+T cells and even exhaustion.<sup>63</sup> During ASFV infection, it has been observed that concurrent with apoptosis in T lymphocytes, the expression level of TNF- $\alpha$  highly rises.<sup>64</sup> Moreover, during viral infection, TNF- $\alpha$  directly induces apoptosis in T lymphocytes.<sup>65</sup> IFNs is a multipotent cytokine with antiviral, antitumor and immunomodulatory properties, featuring a crucial coordinating factor of the immune response.<sup>66</sup> Additionally, in the peripheral blood, IFNs regulates recruitment of leukocytes and reduce lymphocyte levels. During SARS-CoV-2 infection, there was significant lymphopenia in COVID-19 patients, but the amount of IFN- $\gamma$  and other inflammatory cytokines was significantly increased in the peripheral blood.<sup>67,68</sup> Similarly, levels of type IIFNs were upregulated in IAV-infected organisms.<sup>69</sup> In addition, there is evidence that IFN- $\gamma$  leads to lymphopenia through promoting T lymphocyte apoptosis.<sup>70</sup>

The significant impact of cytokines, chemokines, and growth factors in SFTSV infection has been explained. Phagocytes are activated when they recognize invading viruses through various receptors, which are expressed on their cell membranes. Large quantities of cytokines and chemokines are then released by the activated phagocytes, which leads to lymphocyte depletion and adaptive immunity suppression. Studies<sup>71,72</sup> have found that SFTSV manipulates the level of miRNA-146b in macrophages elicited by non-structural proteins (NSs) of the virus or IL-10, which affects the macrophage differentiation through inhibiting STAT1. Additionally, IL-10 is able to activate STAT3, transferring to nuclear and promoting the expression of miRNA-146b. The function of M1 phenotype is pro-inflammatory but that of M2 phenotype is anti-inflammatory. During SFTSV infection, macrophages differentiate into the M1 phenotype and the secretion amount of co-stimulatory molecules and inflammatory factors are increased in the early stage. However, with the extension of infection time, macrophages gradually show a M2 phenotype, and the amplification of T cells is interrupted by suppressing antigen presenting and co-stimulatory molecules. In addition, studies have shown that the number of cytokines and chemokines is much higher in people with SFTS than those with milder disease, such as TNF- $\alpha$ , IFN- $\gamma$ , interferon-inducible protein (IP) -10, IL-10, IL-6, and IL-8.<sup>73,74</sup> In addition, He et al<sup>75</sup> also indicated that severe



**Figure 3** The interaction between TBK1 and IKK complex. IKK $\beta$  phosphorylates TBK1 and then the activated TBK1 inhibits the IKK complex. NS activates the NF- $\kappa$ B-dependent cytokine storm by inhibiting TBK1's interaction with the IKK complex to release NF- $\kappa$ B.

patients have more cytokines such as IL-6, IL-10, IP-10 and macrophage chemoattractant protein-1 in their peripheral blood by contrast to mild ones. Park et al<sup>13</sup> simultaneously detected 76 cytokines in the peripheral blood of patients infected by SFTSV to show that the expression levels of TNF- $\alpha$ , C-C chemokine ligand 20, CX3 chemokine ligand 1 and other cytokines in dead patients were extraordinarily higher compared to those in surviving ones. They all elucidate the correlation between cytokine level and disease severity. Animal experiments have further confirmed that SFTSV infection leads to increased secretion number of inflammatory factors in the peripheral blood, spleen and liver, which is capable of inducing lymphopenia and multiple organ dysfunction syndrome (MODS).<sup>76,77</sup> SFTSV infection promotes the release of IL-1 $\beta$ , a pro-inflammatory factor, by activating NLRP3 inflammasome that increases the level of active caspase-1.<sup>78</sup> IL-1 $\beta$  induces lymphocyte apoptosis and pyroptosis mentioned above. Recent research indicates that SFTSV interacts with the TBK1 kinase that inhibits the I $\kappa$ B kinase (IKK) complex activating transcription factor NF- $\kappa$ B via its NSs, resulting in a reduction of its inhibitory impact on NF- $\kappa$ B. This interaction causes a rise of it, which translocates into the nucleus contributing to the growth of a cytokine storm<sup>79</sup> (Figure 3). It elicits decreased amount of lymphocytes and MODS. In conclusion, the secretion of cytokines, chemokines and growth factors play a vital role in eliciting lymphopenia. The therapy of SFTS patients targeted the suppression of mi-RNA146b, NF- $\kappa$ B and some cytokines mentioned may effective and needs to be explored.

## Involvement of Vital Immunocytes

The body's immune response to viral infections containing SFTSV involves activation of specialized immune cells, which reduces the number of lymphocytes. The participation of immune cells like CD8<sup>+</sup> cytotoxic T lymphocytes (CTLs) enables the immune system to fully harness its antiviral capabilities, however, this also causes lymphopenia. The antiviral effects of B cells and dendritic cells (DCs) are decreased during viral infections, which is manifested as severe disruption of the humoral immunity and dysfunction of antigen-presentation by DCs. Consequently, some molecules involved in these vital immunocytes can also be therapeutic targets of SFTS.

## Role of CD8+CTL in SFTS

Virus-specific CTL dependent killing: Cytotoxic T lymphocytes (CTLs), which express coreceptor CD8 molecules on their surface, are important effector cells that mediate cellular immune responses as a form of adaptive immune responses to fight against viral infection. By activation of antigen recognition receptor, CD8+T cells differentiate into CTLs to perform antiviral immune responses after viral infection. With viral clearance, 90%-95% of CTLs die of apoptosis, and only 5%-10% of CTLs survive and are subsequently transformed into memory T cells. CTLs have been observed in killing lymphocytes infected with various viruses including MERS-CoV, HIV, HBV and HCV.<sup>80,81</sup> The characteristics of CD8+CTLs to eliminate virus by cytotoxic mechanisms are as follows: (1) the killing effect of CD8+CTL is antigen-specific and restricted by MHC-I molecules; (2) CTLs can continuously kill target cells with high killing efficiency; for example one CTL cell can kill dozens of target cells within a few hours.

CD8+T cells are the most crucial effector cells of cellular immunity. Studies have found that the effects of CD8 +T cells to fight against viruses in the PBMCs of SFTS patients are significantly enhanced with greater proliferation than healthy controls.<sup>82</sup> These T cells have increased CD69, CD25 and PD-1 expression amount and high IFN- $\gamma$  and granzyme release. The effects above boost effector lymphocyte cell death.

## Role of B Cells in SFTS

During virus infections, B cells produce antigen-specific antibodies to effectively inhibit viral transmission and replication. However, the immunological characteristics of SFTSV infection remain largely unknown. There has been limited research on the dynamics and immune response patterns of specific antibodies IgM and IgG during SFTSV infection. Notably, patients with impaired immune systems or high initial viral loads exhibit severe immune system damage, a sharp decline in lymphocyte subsets, and insufficient production of IgM and IgG antibodies.<sup>13,83</sup> This suggests that SFTSV can manipulate and attack cells that initiate antiviral responses, such as T lymphocytes and B lymphocytes, thereby weakening the host immune response and suppressing cellular as well as humoral immunity. The mechanism that is similar to SFTSV has been observed as a common pathogenicity of other viral hemorrhagic fever (VHF) agents, involving Marburg,<sup>84</sup> Ebola,<sup>85</sup> and Rift Valley fever viruses.

## Role of DCs in SFTS

Lymphopenia can be induced through involvement of DCs during virus infection. The research about the associated mechanisms are abundant.

Dendritic Cell (DC)-Mediated Killing of Lymphocytes: Dendritic cells, as professional cells that present antigens, are capable of effectively activating immature CD4+ T lymphocytes as well as CD8+ T lymphocytes *in vivo*, having a significant effect on initiating, manipulating, and driving immune responses against viruses. Herpes simplex virus I (HSV - 1) infects DCs, strongly disturbing their antigen-presenting ability and inhibits dendritic cell-mediated T cell proliferation, which leads to the degeneration of CD4+T and CD8+T cell responses.<sup>86</sup> Furthermore, in H2N2 influenza virus infection, upregulated Fas can bind to FasL in plasmacytoid dendritic cells (pDCs) and facilitate apoptosis of T cells.<sup>87,88</sup> After HIV infection of DCs, the interaction between TNF related apoptosis-inducing ligand (TRAIL) and T cell death receptors on DCs activates the caspase pathway to promote T cell apoptosis.<sup>89</sup>

We have summarized above that DC-dependent killing of lymphocytes is one of the mechanisms of lymphopenia caused by virus infection including SFTSV. Thus, ensuring the normal function of DCs is essential. During SFTSV infection, there are special mechanisms demonstrated. Song et al<sup>73</sup> studied the changes of pDCs and myeloid DCs (mDCs) in people infected by SFTSV, indicating that deceased patients have much higher proportion of mDCs than survivors and healthy controls in the first week after the onset. Also, the proportion of mDCs in deceased patients gradually decreased at two and three weeks after the onset. However, the proportion of mDCs in the surviving patients gradually increased in the second and third weeks, and the surviving patients have significantly higher proportion of mDCs compared to the deceased ones at the third week. Song et al<sup>83</sup> found that the apoptotic level of monocytes in dead patients was significantly more than that in surviving ones and healthy controls. The level of mDCs in deceased patients remained consistently low after the onset of symptoms, whereas the mDC levels in surviving patients showed a significant increase after onset. Deceased patients had lower number of costimulatory molecules CD80 and CD86 on

mDCs than surviving ones at 3 weeks after onset. Functionally, mDCs failed to elicit T cell proliferation and cytokine secretion as SFTSV infection inhibited this ability of mDCs. Retaining the normal level of mDCs is probably vital for recovery of SFTS.

## Clinical Implications of Lymphopenia During SFTSV Infection

### Relation of Lymphopenia to Viral Disease Severity

T cells and NK cells are essential players in both natural and adaptive immune responses, whereas B cells play a primary role in humoral immune response as a form of adaptive immune response. The decrease of these three types of lymphocytes may impair the host's capability to elicit an immune response against viruses effectively. Studies have found that during SFTSV, patients have a significantly decreased count of NK cells in the peripheral blood, and the count of NK cells quickly increased with the recovery of the disease.<sup>90</sup> In addition, the study has also found that the peripheral blood B cell count level of SFTSV infected patients decreased significantly within 1 week after the onset of infection, gradually returning to ordinary with the recovery of the disease.<sup>90</sup> At the same time, the composition of B-cell subsets showed significant alterations in the peripheral blood of people with SFTS. Compared with surviving patients, the percentage of naive B cells in deceased ones was outstandingly lowered, while the amount of plasmablasts was highly increased.<sup>83,91</sup> Another study indicated that in patients' peripheral blood, SFTSV infection could reduce the number of T lymphocytes, particularly the number of CD4+ T lymphocytes, which is linked to a worsening of their disease conditions.<sup>92</sup> In addition, the depletion of CD8+ T cells as well as natural killer T (NKT) cells during SFTSV infection is correlated with a worsening disease condition.<sup>93</sup> Studies also found that the plasma blasts of the deceased patients produce lower levels of IgG antibodies, which are protective and persist for a long time. In addition, there are a large number of plasma blasts that do not express IgG, IgM, IgD and IgA antibodies in the deceased patients.<sup>83</sup> In summary, SFTSV-infected patients experience a significant reduction in lymphocyte count, indicating notable damage to cellular immune function. This damage is more severe in patients with more critical conditions, suggesting a possible correlation between disease severity and lymphocyte count. During SFTSV infection, cytokines and chemokines released by phagocytes progress the lymphocyte depletion and adaptive immunity impairment. Notably, their level is positively correlated with disease severity. In addition, lymphopenia has been reported as a clinical indicator of severity grading in patients with immunodeficiency induced by infection of viruses, including immune impairment (eg SARS-CoV-2, HIV, tuberculosis).<sup>94,95</sup> However, there is currently no conclusive evidence that lymphopenia can serve as a trustworthy marker for assessing the severity of SFTS in patients, which indicates a potential area for future research and follow-up studies.

### Increases in Opportunistic Infection

Opportunistic infection refers to microorganisms with limited or no disease-causing ability in hosts with normal immune systems. Although, after an immunosuppressive mechanism is enabled by diseases (such as AIDS) or therapeutic factors, the host is more vulnerable to pathogen attack. On the one hand, viral infections cause lymphocyte depletion or damage, resulting in poor cellular immune function. On the other hand, the application of glucocorticoids, corticosteroids and immunosuppressants severely suppress the immunity of patients, so the opportunistic infection rate increases significantly. One study has indicated that corticosteroids tend to postpone the clearance of SARS-CoV-2 in surviving patients by influencing the host's adaptive immune response.<sup>96</sup> Opportunistic infections tend to be more frequent and more severe than pre-existing diseases.<sup>97,98</sup> A study has demonstrated that a sharp decline in CD4+T cell level in HIV patients marks the progressive deterioration of HIV-1 AIDS, which is significantly associated with the incidence of opportunistic infections.<sup>99</sup> The level of CD4+T cells not only affects the probability of opportunistic infections, but also affects the number of infection sites involved and the types of pathogens. The same phenomenon occurs in patients with COVID-19.<sup>100</sup> SFTSV infection may inhibit lymphocyte activity and also the SFTSV-induced cytokine storm, which is related to cyclophilin A, may cause organ dysfunction.<sup>101</sup> Organ dysfunction increases the chance of opportunistic infections. Co-infections during SFTSV infection can cause or aggravate MODS, such as pulmonary infections, which can cause pneumonia. *K. pneumoniae* is the most common microorganism detected in secondary bacterial infections.<sup>102</sup> However,

to our knowledge, opportunistic infections have rarely been reported in SFTSV infectious diseases with lymphopenia. Therefore, the relationship between opportunistic infection and lymphopenia during SFTSV infection needs to be further studied.

## Conclusions

Viral infection and the host immune response interact complicatedly and this interaction is at the core of the disease prognosis mechanism. During viral infections, a compromised function or reduced count of lymphocytes can lead to the host's immune response, influencing clinical progression. Lymphocytes have a great effect on the early diagnosis and monitoring of infectious diseases, immune deficiency disorders, and certain cancers. In this review, we examined the underlying mechanisms of lymphopenia, which include various categories of cell death (especially PCD) and the process induced by cytokines, chemokines and other factors. We also delved into the involvement of some types of vital immunocytes in SFTSV infection. At last, the potential clinical implication is demonstrated that lymphopenia induced by SFTSV infection leads to immunodeficiency, and then driving the disease severity and raising the incidence of opportunistic infection. More exploration of the lymphopenia as a clinical indicator of severity grading in SFTS patients as well as the deeper relationship between lymphopenia and opportunistic infection is expected. In general, diverse viruses can induce lymphopenia through a variety of mechanisms. The process by which SFTSV leads to lymphopenia is relatively intricate; it might be due to a single mechanism or the combined effect of several mechanisms. This has not been fully elucidated and requires additional research such as the clear mechanisms of the reduction of B cells. Specific medications or other therapies can be exploited targeting mechanisms of lymphopenia and bring more hope to SFTS patients.

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## References

- Mitrovic Z, Perry AM, Suzumiya J, et al. The prognostic significance of lymphopenia in peripheral T-cell and natural killer/T-cell lymphomas: a study of 826 cases from the international peripheral t-cell lymphoma project. *Am J Hematol*. 2012;87:790–794. doi:10.1002/ajh.23205
- Zhang -J-J, Cao -Y-Y, Tan G, et al. Clinical, radiological, and laboratory characteristics and risk factors for severity and mortality of 289 hospitalized COVID-19 patients. *Allergy*. 2021;76:533–550. doi:10.1111/all.14496
- Lin AJ, Rao YJ, Chin R-I, et al. Post-operative radiation effects on lymphopenia, neutrophil to lymphocyte ratio, and clinical outcomes in palatine tonsil cancers. *Oral Oncol*. 2018;86:1–7. doi:10.1016/j.oraloncology.2018.08.008
- Merayo-Chalico J, Rajme-López S, Barrera-Vargas A, Alcocer-Varela J, Díaz-Zamudio M, Gómez-Martín D. Lymphopenia and autoimmunity: a double-edged sword. *Hum Immunol*. 2016;77:921–929. doi:10.1016/j.humimm.2016.06.016
- Ménétrier-Caux C, Ray-Coquard I, Blay J-Y, Caux C. Lymphopenia in cancer patients and its effects on response to immunotherapy: an opportunity for combination with cytokines? *J Immunother Cancer*. 2019;7:85. doi:10.1186/s40425-019-0549-5
- Girardot T, Rimmelé T, Venet F, Monneret G. Apoptosis-induced lymphopenia in sepsis and other severe injuries. *Apoptosis*. 2017;22:295–305. doi:10.1007/s10495-016-1325-3
- Yu X-J, Liang M-F, Zhang S-Y, et al. Fever with thrombocytopenia associated with a novel bunyavirus in China. *N Engl J Med*. 2011;364:1523–1532. doi:10.1056/NEJMoa1010095
- Miao D, Liu M-J, Wang Y-X, et al. Epidemiology and ecology of severe fever with thrombocytopenia syndrome in China, 2010–2018. *Clin Infect Dis*. 2021;73:e3851–8. doi:10.1093/cid/ciaa1561
- Tran XC, Yun Y, Van AL, et al. Endemic severe fever with thrombocytopenia syndrome, Vietnam. *Emerg Infect Dis*. 2019;25:1029–1031. doi:10.3201/eid2505.181463
- Sharma D, Kamthania M. A new emerging pandemic of severe fever with thrombocytopenia syndrome (SFTS). *Virusdisease*. 2021;32:220–227. doi:10.1007/s13337-021-00656-9

11. Li J, Li S, Yang L, Cao P, Lu J. Severe fever with thrombocytopenia syndrome virus: a highly lethal bunyavirus. *Crit Rev Microbiol.* **2021**;47:112–125. doi:10.1080/1040841X.2020.1847037
12. Luo L-M, Zhao L, Wen H-L, et al. Haemaphysalis longicornis ticks as reservoir and vector of severe fever with thrombocytopenia syndrome virus in China. *Emerg Infect Dis.* **2015**;21:1770–1776. doi:10.3201/eid2110.150126
13. Park A, Park S-J, Jung KL, et al. molecular signatures of inflammatory profile and b-cell function in patients with severe fever with thrombocytopenia syndrome. *mBio.* **2021**;12:e02583–20. doi:10.1128/mBio.02583-20
14. Li -M-M, Zhang W-J, Liu J, et al. Dynamic changes in the immunological characteristics of T lymphocytes in surviving patients with severe fever with thrombocytopenia syndrome (SFTS). *Int J Infect Dis.* **2018**;70:72–80. doi:10.1016/j.ijid.2018.03.010
15. Fujikawa K, Koga T, Honda T, et al. Serial analysis of cytokine and chemokine profiles and viral load in severe fever with thrombocytopenia syndrome: case report and review of literature. *Medicine.* **2019**;98:e17571. doi:10.1097/MD.00000000000017571
16. Wu X, Nagy LE, Gautheron J. Mediators of necroptosis: from cell death to metabolic regulation. *EMBO Mol Med.* **2024**;16:219–237. doi:10.1038/s44321-023-00011-z
17. Garg H, Mohl J, Joshi A. HIV-1 induced bystander apoptosis. *Viruses.* **2012**;4:3020–3043. doi:10.3390/v4113020
18. Cizmecioglu A, Akay CH, Mh G, et al. Apoptosis-induced T-cell lymphopenia is related to COVID-19 severity. *J Med Virol.* **2021**;93:2867–2874. doi:10.1002/jmv.26742
19. Liang Y, Wang M-L, Chien C-S, et al. Highlight of immune pathogenic response and hematopathologic effect in SARS-CoV, MERS-CoV, and SARS-Cov-2 Infection. *Front Immunol.* **2020**;11:1022. doi:10.3389/fimmu.2020.01022
20. Garg H, Joshi A. Host and viral factors in HIV-mediated bystander apoptosis. *Viruses.* **2017**;9:237. doi:10.3390/v9080237
21. Brenner D, Blaser H, Mak TW. Regulation of tumour necrosis factor signalling: live or let die. *Nat Rev Immunol.* **2015**;15:362–374. doi:10.1038/nri3834
22. Liu S, Liu H, Zhang K, et al. Proteasome Inhibitor PS-341 effectively blocks infection by the severe fever with thrombocytopenia syndrome virus. *Virol Sin.* **2019**;34:572–582. doi:10.1007/s12250-019-00162-9
23. Kim IS, Silwal P, Jo E-K. Mitofusin 2, a key coordinator between mitochondrial dynamics and innate immunity. *Virulence.* **2021**;12:2273–2284. doi:10.1080/21505594.2021.1965829
24. Zhou C-M, Yu X-J. Unraveling the underlying interaction mechanism between dabie bandavirus and innate immune response. *Front Immunol.* **2021**;12:676861. doi:10.3389/fimmu.2021.676861
25. Peña-Blanco A, Bax G-SAJ. Bak and beyond - mitochondrial performance in apoptosis. *FEBS J.* **2018**;285:416–431. doi:10.1111/febs.14186
26. Song J, Zhang F, Wang Y, et al. Bak interacts with AKT and is involved in TNF $\alpha$ /CHX-induced apoptosis. *Mol Cell Biochem.* **2022**;477:939–949. doi:10.1007/s11010-021-04348-2
27. Li S, Li H, Zhang Y-L, et al. SFTSV Infection Induces BAK/BAX-Dependent Mitochondrial DNA release to trigger nlrp3 inflammasome activation. *Cell Rep.* **2020**;30:4370–4385.e7. doi:10.1016/j.celrep.2020.02.105
28. Zhang C, Song J-W, Huang -H-H, et al. NLRP3 inflammasome induces CD4+ T cell loss in chronically HIV-1-infected patients. *J Clin Invest.* **2021**;131:e138861,138861. doi:10.1172/JCI138861
29. Pandey KP, Zhou Y. Influenza A virus infection activates NLRP3 inflammasome through trans-golgi network dispersion. *Viruses.* **2022**;14:88. doi:10.3390/v14010088
30. Gao C, Yu Y, Wen C, et al. nonstructural protein nss activates inflammasome and pyroptosis through interaction with NLRP3 in human microglial cells infected with severe fever with thrombocytopenia syndrome bandavirus. *J Virol.* **2022**;96:e0016722. doi:10.1128/jvi.00167-22
31. Li Z, Hu J, Bao C, et al. Activation of the NLRP3 inflammasome and elevation of interleukin-1 $\beta$  secretion in infection by severe fever with thrombocytopenia syndrome virus. *Sci Rep.* **2022**;12:2573. doi:10.1038/s41598-022-06229-0
32. Bernasconi R, Noack J, Molinari M. Unconventional roles of nonlipidated LC3 in ERAD tuning and coronavirus infection. *Autophagy.* **2012**;8:1534–1536. doi:10.4161/auto.21229
33. Younan P, Santos RI, Ramanathan P, et al. Ebola virus-mediated T-lymphocyte depletion is the result of an abortive infection. *PLoS Pathog.* **2019**;15:e1008068. doi:10.1371/journal.ppat.1008068
34. Liu S, Su Y, Lu Z, et al. The SFTSV nonstructural proteins induce autophagy to promote viral replication via interaction with vimentin. *J Virol.* **2023**;97:e0030223. doi:10.1128/jvi.00302-23
35. Sun Y, Liu -M-M, Lei X-Y, Yu X-J. SFTS phlebovirus promotes LC3-II accumulation and nonstructural protein of SFTS phlebovirus co-localizes with autophagy proteins. *Sci Rep.* **2018**;8:5287. doi:10.1038/s41598-018-23610-0
36. Lee DH, Park JS, Lee YS, et al. SQSTM1/p62 activates NFE2L2/NRF2 via ULK1-mediated autophagic KEAP1 degradation and protects mouse liver from lipotoxicity. *Autophagy.* **2020**;16:1949–1973. doi:10.1080/15548627.2020.1712108
37. Miyakawa K, Nishi M, Ogawa M, et al. Galectin-9 restricts hepatitis B virus replication via p62/SQSTM1-mediated selective autophagy of viral core proteins. *Nat Commun.* **2022**;13:531. doi:10.1038/s41467-022-28171-5
38. Choi Y, Jiang Z, Shin W-J, Jung JU. Severe fever with thrombocytopenia syndrome virus NSs Interacts with TRIM21 To Activate the p62-Keap1-Nrf2 pathway. *J Virol.* **2020**;94:e01684–19. doi:10.1128/JVI.01684-19
39. Wang C, Gong L, Zeng Z, et al. Genome-based analysis of SFTSV causing severe encephalitis with brain lesions. *J Neurovirol.* **2020**;26:181–187. doi:10.1007/s13365-019-00816-0
40. Yan J-M, Zhang W-K, Yan L-N, Jiao Y-J, Zhou C-M, Yu X-J. Bunyavirus SFTSV exploits autophagic flux for viral assembly and egress. *Autophagy.* **2022**;18:1599–1612. doi:10.1080/15548627.2021.1994296
41. Feng K, Zhang H, Jiang Z, et al. SFTS bunyavirus NSs protein sequesters mTOR into inclusion bodies and deregulates mTOR-ULK1 signaling, provoking pro-viral autophagy. *J Med Virol.* **2023**;95:e28371. doi:10.1002/jmv.28371
42. Green DR, Droin N, Pinkoski M. Activation-induced cell death in T cells. *Immunol Rev.* **2003**;193:70–81. doi:10.1034/j.1600-065X.2003.00051.x
43. Sikora E. Activation-induced and damage-induced cell death in aging human T cells. *Mech Ageing Dev.* **2015**;151:85–92. doi:10.1016/j.mad.2015.03.011
44. Zhu L, Yang P, Zhao Y, et al. Single-cell sequencing of peripheral mononuclear cells reveals distinct immune response landscapes of COVID-19 and influenza patients. *Immunity.* **2020**;53:685–696.e3. doi:10.1016/j.immuni.2020.07.009

45. Roe MFE, Bloxham DM, White DK, Ross-Russell RI, Tasker RTC, O'Donnell DR. Lymphocyte apoptosis in acute respiratory syncytial virus bronchiolitis. *Clin Exp Immunol.* 2004;137:139–145. doi:10.1111/j.1365-2249.2004.02512.x
46. Chin DS, Lim CSY, Nordin F, Arifin N, Jun TG. Antibody-dependent cell-mediated cytotoxicity through Natural Killer (NK) cells: unlocking NK cells for future immunotherapy. *Curr Pharm Biotechnol.* 2022;23:552–578. doi:10.2174/1389201022666210820093608
47. Singh K, Marasini B, Chen X, Spearman P. A novel Ebola virus antibody-dependent cell-mediated cytotoxicity (Ebola ADCC) assay. *J Immunol Methods.* 2018;460:10–16. doi:10.1016/j.jim.2018.06.002
48. Mele D, Oliviero B, Mantovani S, et al. Adaptive natural killer cell functional recovery in hepatitis c virus cured patients. *Hepatology.* 2021;73:79–90. doi:10.1002/hep.31273
49. Xie Z, Zheng J, Wang Y, et al. Deficient IL-2 Produced by Activated CD56+ T Cells Contributes to Impaired NK Cell-Mediated ADCC Function in Chronic HIV-1 Infection. *Front Immunol.* 2019;10:1647. doi:10.3389/fimmu.2019.01647
50. Ma Y, Wang Y, Dong C, et al. SARS-CoV-2 spike stem protein nanoparticles elicited broad ADCC and robust neutralization against variants in mice. *Small.* 2022;18:e2200836. doi:10.1002/smll.202200836
51. Lu F, Chen R, Xu K, et al. Liver dysfunction on admission worsens clinical manifestations and outcomes of coronavirus disease 2019. *Chin Med J Pulm Crit Care Med.* 2023;1:181–187. doi:10.1016/j.pccm.2023.08.004
52. Yao Z, Zheng Z, Wu K, Junhua Z. Immune environment modulation in pneumonia patients caused by coronavirus: SARS-CoV, MERS-CoV and SARS-CoV-2. *Aging.* 2020;12:7639–7651. doi:10.18632/aging.103101
53. Peng X, Tao R, Chen Y, Su J, Huang Y, Zhu B. Transient HIV reservoirs and interleukin-6 increase after anti-programmed death-1 antibody infusion in HIV patients with lung cancer. *J Inflamm Res.* 2022;15:199–204. doi:10.2147/JIR.S349099
54. Alsamman AM, Zayed H. The transcriptomic profiling of SARS-CoV-2 compared to SARS, MERS, EBOV, and H1N1. *PLoS One.* 2020;15:e0243270. doi:10.1371/journal.pone.0243270
55. Lv H, Dong W, Cao Z, et al. TRAF6 is a novel NS3-interacting protein that inhibits classical swine fever virus replication. *Sci Rep.* 2017;7:6737. doi:10.1038/s41598-017-06934-1
56. Da Silva Prates G, Fm M, de Toledo Gonçalves F, et al. AIDS incidence and survival in a hospital-based cohort of HIV-positive patients from São Paulo, Brazil: the role of IFN- $\lambda$ 4 polymorphisms. *J Med Virol.* 2021;93:3601–3606. doi:10.1002/jmv.26054
57. Te N, Rodon J, Ballester M, et al. Type I and III IFNs produced by the nasal epithelia and dimmed inflammation are features of alpacas resolving MERS-CoV infection. *PLoS Pathog.* 2021;17:e1009229. doi:10.1371/journal.ppat.1009229
58. Shuai H, Chu H, Hou Y, et al. Differential immune activation profile of SARS-CoV-2 and SARS-CoV infection in human lung and intestinal cells: implications for treatment with IFN- $\beta$  and IFN inducer. *J Infect.* 2020;81:e1–10. doi:10.1016/j.jinf.2020.07.016
59. Saraiva M, Vieira P, O'Garra A. Biology and therapeutic potential of interleukin-10. *J Exp Med.* 2020;217:e20190418. doi:10.1084/jem.20190418
60. Zanza C, Romenskaya T, Ac M, et al. Cytokine Storm in COVID-19: immunopathogenesis and Therapy. *Medicina.* 2022;58:144. doi:10.3390/medicina58020144
61. Diao B, Wang C, Tan Y, et al. Reduction and functional exhaustion of t cells in patients with coronavirus disease 2019 (COVID-19). *Front Immunol.* 2020;11:827. doi:10.3389/fimmu.2020.00827
62. Toor SM, Saleh R, Sasidharan Nair V, Taha RZ, Elkord E. T-cell responses and therapies against SARS-CoV-2 infection. *Immunology.* 2021;162:30–43. doi:10.1111/imm.13262
63. Krammer PH, Arnold R, Lavrik IN. Life and death in peripheral T cells. *Nat Rev Immunol.* 2007;7:532–542. doi:10.1038/nri2115
64. Gómez Del Moral M, Ortuño E, Fernández-Zapatero P, et al. African swine fever virus infection induces tumor necrosis factor alpha production: implications in pathogenesis. *J Virol.* 1999;73:2173–2180.
65. Takano T, Hohdatsu T, Hashida Y, Kaneko Y, Tanabe M, Koyama H. A 'possible' involvement of TNF-alpha in apoptosis induction in peripheral blood lymphocytes of cats with feline infectious peritonitis. *Vet Microbiol.* 2007;119:121–131. doi:10.1016/j.vetmic.2006.08.033
66. Teijaro JR. Type I interferons in viral control and immune regulation. *Curr Opin Virol.* 2016;16:31–40. doi:10.1016/j.coviro.2016.01.001
67. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest.* 2020;130:2620–2629. doi:10.1172/JCI137244
68. Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *EBioMedicine.* 2020;55:102763. doi:10.1016/j.ebiom.2020.102763
69. Wu W, Metcalf JP. The role of type I ifns in influenza: antiviral superheroes or immunopathogenic villains? *J Innate Immun.* 2020;12:437–447. doi:10.1159/000508379
70. Bixler SL, Goff AJ. The Role of Cytokines and Chemokines in Filovirus Infection. *Viruses.* 2015;7:5489–5507. doi:10.3390/v7102892
71. Zhang L, Fu Y, Wang H, et al. Severe fever with thrombocytopenia syndrome virus-induced macrophage differentiation is regulated by miR-146. *Front Immunol.* 2019;10:1095. doi:10.3389/fimmu.2019.01095
72. Yunna C, Mengru H, Lei W, Weidong C. Macrophage M1/M2 polarization. *Eur J Pharmacol.* 2020;877:173090. doi:10.1016/j.ejphar.2020.173090
73. Song P, Zheng N, Zhang L, et al. Downregulation of Interferon- $\beta$  and Inhibition of TLR3 Expression are associated with fatal outcome of severe fever with thrombocytopenia syndrome. *Sci Rep.* 2017;7:6532. doi:10.1038/s41598-017-06921-6
74. Sun Y, Jin C, Zhan F, et al. Host cytokine storm is associated with disease severity of severe fever with thrombocytopenia syndrome. *J Infect Dis.* 2012;206:1085–1094. doi:10.1093/infdis/jis452
75. He Z, Wang B, Li Y, et al. Changes in peripheral blood cytokines in patients with severe fever with thrombocytopenia syndrome. *J Med Virol.* 2021;93:4704–4713. doi:10.1002/jmv.26877
76. Westover JB, Hickerson BT, Van WAJ, et al. Vascular leak and hypercytokinemia associated with severe fever with thrombocytopenia syndrome virus infection in mice. *Pathogens.* 2019;8:158. doi:10.3390/pathogens8040158
77. Xu S, Jiang N, Nawaz W, et al. Infection of humanized mice with a novel phlebovirus presented pathogenic features of severe fever with thrombocytopenia syndrome. *PLoS Pathog.* 2021;17:e1009587. doi:10.1371/journal.ppat.1009587
78. Liu J-W, Chu M, Jiao Y-J, Zhou C-M, Qi R, Yu X-J. SFTSV Infection Induced Interleukin-1 $\beta$  Secretion Through NLRP3 Inflammasome Activation. *Front Immunol.* 2021;12:595140. doi:10.3389/fimmu.2021.595140

79. Khalil J, Yamada S, Tsukamoto Y, et al. The nonstructural protein nss of severe fever with thrombocytopenia syndrome virus causes a cytokine storm through the hyperactivation of NF- $\kappa$ B. *Mol Cell Biol.* 2021;41:e0054220. doi:10.1128/MCB.00542-20
80. Keyoumu T, Guo K, Ma W, Keyoumu T, Guo K, Ma W. Periodic oscillation for a class of in-host MERS-CoV infection model with CTL immune response. *MBE.* 2022;19:12247–12259. doi:10.3934/mbe.2022570
81. Njagarah JBH, Nyabadza F, Kgosimore M, Hui C. Significance of antiviral therapy and CTL-mediated immune response in containing hepatitis B and C virus infection. *Appl Math Comput.* 2021;397:125926. doi:10.1016/j.amc.2020.125926
82. Zong L, Yang F, Liu S, et al. CD8+ T cells mediate antiviral response in severe fever with thrombocytopenia syndrome. *FASEB J.* 2023;37:e22722. doi:10.1096/fj.202201343RR
83. Song P, Zheng N, Liu Y, et al. Deficient humoral responses and disrupted B-cell immunity are associated with fatal SFTSV infection. *Nat Commun.* 2018;9:3328. doi:10.1038/s41467-018-05746-9
84. Geisbert TW, Hensley LE, Gibb TR, Steele KE, Jaax NK, Jahrling PB. Apoptosis induced in vitro and in vivo during infection by Ebola and Marburg viruses. *Lab Invest.* 2000;80:171–186. doi:10.1038/labinvest.3780021
85. Feldmann H, Jones S, Klenk H-D, Schnittler H-J. Ebola virus: from discovery to vaccine. *Nat Rev Immunol.* 2003;3:677–685. doi:10.1038/nri1154
86. Gao Y, Cheng J, Xu X, et al. HSV-1 infection of epithelial dendritic cells is a critical strategy for interfering with antiviral immunity. *Viruses.* 2022;14:1046. doi:10.3390/v14051046
87. Legge KL, Braciale TJ. Lymph node dendritic cells control CD8+ T cell responses through regulated FasL expression. *Immunity.* 2005;23:649–659. doi:10.1016/j.immuni.2005.11.006
88. Langlois RA, Legge KL. Plasmacytoid dendritic cells enhance mortality during lethal influenza infections by eliminating virus-specific CD8 T cells. *J Immunol.* 2010;184:4440–4446. doi:10.4049/jimmunol.0902984
89. Majumder B, Venkatachari NJ, Schafer EA, Janket ML, Ayyavoo V. Dendritic cells infected with vpr-positive human immunodeficiency virus type 1 induce CD8+ T-cell apoptosis via upregulation of tumor necrosis factor alpha. *J Virol.* 2007;81:7388–7399. doi:10.1128/JVI.00893-06
90. Lu Q-B, Cui N, Hu J-G, et al. Characterization of immunological responses in patients with severe fever with thrombocytopenia syndrome: a cohort study in China. *Vaccine.* 2015;33:1250–1255. doi:10.1016/j.vaccine.2015.01.051
91. Takahashi T, Sano K, Suzuki T, et al. Virus-infected peripheral blood plasmablasts in a patient with severe fever with thrombocytopenia syndrome. *Int J Hematol.* 2021;113:436–440. doi:10.1007/s12185-020-03040-3
92. Sun L, Hu Y, Niyonsaba A, et al. Detection and evaluation of immunofunction of patients with severe fever with thrombocytopenia syndrome. *Clin Exp Med.* 2014;14:389–395. doi:10.1007/s10238-013-0259-0
93. Li H, Li X, Lv S, et al. Single-cell landscape of peripheral immune responses to fatal SFTS. *Cell Rep.* 2021;37:110039. doi:10.1016/j.celrep.2021.110039
94. Henry B, Cheruiyot I, Vikse J, et al. Lymphopenia and neutrophilia at admission predicts severity and mortality in patients with COVID-19: a meta-analysis. *Acta Biomed.* 2020;91:e2020008. doi:10.23750/abm.v91i3.10217
95. du Bruyn E, Stek C, Daroowala R, et al. Effects of tuberculosis and/or HIV-1 infection on COVID-19 presentation and immune response in Africa. *Nat Commun.* 2023;14:188. doi:10.1038/s41467-022-35689-1
96. Wang Y, Guo L, Fan G, et al. Impact of corticosteroids on initiation and half-year durability of humoral response in COVID-19 survivors. *Chin Med J Pulm Crit Care Med.* 2024;2:48–55. doi:10.1016/j.pccm.2024.02.005
97. Ranganathan K, Umadevi KMR. Common oral opportunistic infections in Human Immunodeficiency Virus infection/Acquired Immunodeficiency Syndrome: changing epidemiology; diagnostic criteria and methods; management protocols. *Periodontol 2000.* 2019;80:177–188. doi:10.1111/prd.12274
98. Masur H. Recurring and emerging questions related to management of HIV-related opportunistic infections. *Top Antivir Med.* 2018;26:79–84.
99. Imoto S, Suzukawa M, Takeda K, et al. Evaluation of cytokine levels in response to mitogen among HIV-1-infected blood cells and their relationships to the number of T cells. *Cytokine.* 2022;153:155840. doi:10.1016/j.cyto.2022.155840
100. Pasero D, Sanna S, Liperi C, et al. A challenging complication following SARS-CoV-2 infection: a case of pulmonary mucormycosis. *Infection.* 2021;49:1055–1060. doi:10.1007/s15010-020-01561-x
101. Huang H, Jin K, Ouyang K, et al. Cyclophilin A causes severe fever with thrombocytopenia syndrome virus-induced cytokine storm by regulating mitogen-activated protein kinase pathway. *Front Microbiol.* 2022;13:1046176. doi:10.3389/fmicb.2022.1046176
102. Zhang Y, Huang Y, Xu Y. Associated microbiota and treatment of severe fever with thrombocytopenia syndrome complicated with infections. *J Med Virol.* 2022;94:5916–5921. doi:10.1002/jmv.28059

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