

HYPOTHESES

Is lymphopenia different between SARS and COVID-19 patients?

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Abstract

Lymphopenia is commonly observed in SARS and COVID-19 patients although the lymphocyte count is not always below $0.8 \times 10^9/L$ in all the patients. It is suggested that lymphopenia serves as a useful predictor for prognosis in the patients. It is also hypothesized that lymphopenia is related to glucocorticoids and apoptosis. However, the ordering between lymphopenia and apoptosis appears different between SARS and COVID-19 patients, ie, lymphopenia is prior to apoptosis in SARS patients whereas apoptosis is prior to lymphopenia in COVID-19 patients. This paper attempts to figure out this contradiction through three players, lymphopenia, glucocorticoids, and apoptosis. Although the literature does not provide a solid explanation, the level of glucocorticoids could determine the ordering between lymphopenia and apoptosis because the administration of high doses of glucocorticoids could lead to lymphopenia whereas low doses of glucocorticoids could benefit patients. In the meantime, this paper raises several questions, which need to be answered in order to better understand the whole course of COVID-19.

KEYWORDS

COVID-19, lymphopenia, glucocorticoids, apoptosis, SARS-CoV, SARS-CoV-2

1 | INTRODUCTION

Lymphopenia is commonly observed in COVID-19 patients¹⁻³ and SARS patients^{4,5} although the lymphocyte count is not always below $0.8 \times 10^9/L$ in all the patients.

Most importantly, this clinical measure gives a statistical difference between severe and non-severe groups.^{6,7} Lymphopenia was found as one of the earliest pathological changes, and thus served as a useful predictor for the prognosis of the patients during the SARS epidemic from 2003

Abbreviations: ACE2, angiotensin I-converting enzyme 2; APRIL, a proliferation-inducing ligand; COVID-19, coronavirus disease 2019; Fas, Fas cell surface death receptor; FasL, Fas ligand; HCV, hepatitis C virus; KEGG, Kyoto Encyclopedia of Genes and Genomes; MERS-CoV, Middle East respiratory syndrome coronavirus; MSC, mesenchymal stem cells; NLRs, NOD-like receptors; NOD, nucleotide-binding and oligomerization domain; RIG-I, retinoic-acid inducible gene I; RLRs, RIG-I-like receptors; SARS, Severe Acute Respiratory Syndrome; SARS-CoV, Severe Acute Respiratory Syndrome coronavirus; SARS-CoV-2, Severe Acute Respiratory Syndrome coronavirus 2; ssRNA, single-stranded RNA; TACE, TNF- α -converting enzyme; TLRs, toll-like receptors; TMPRSS2, cellular serine protease; TNF- α , tumor necrosis factor α ; TRAIL, TNF-related apoptosis-inducing ligand; Y2H, yeast-2-hybrid.

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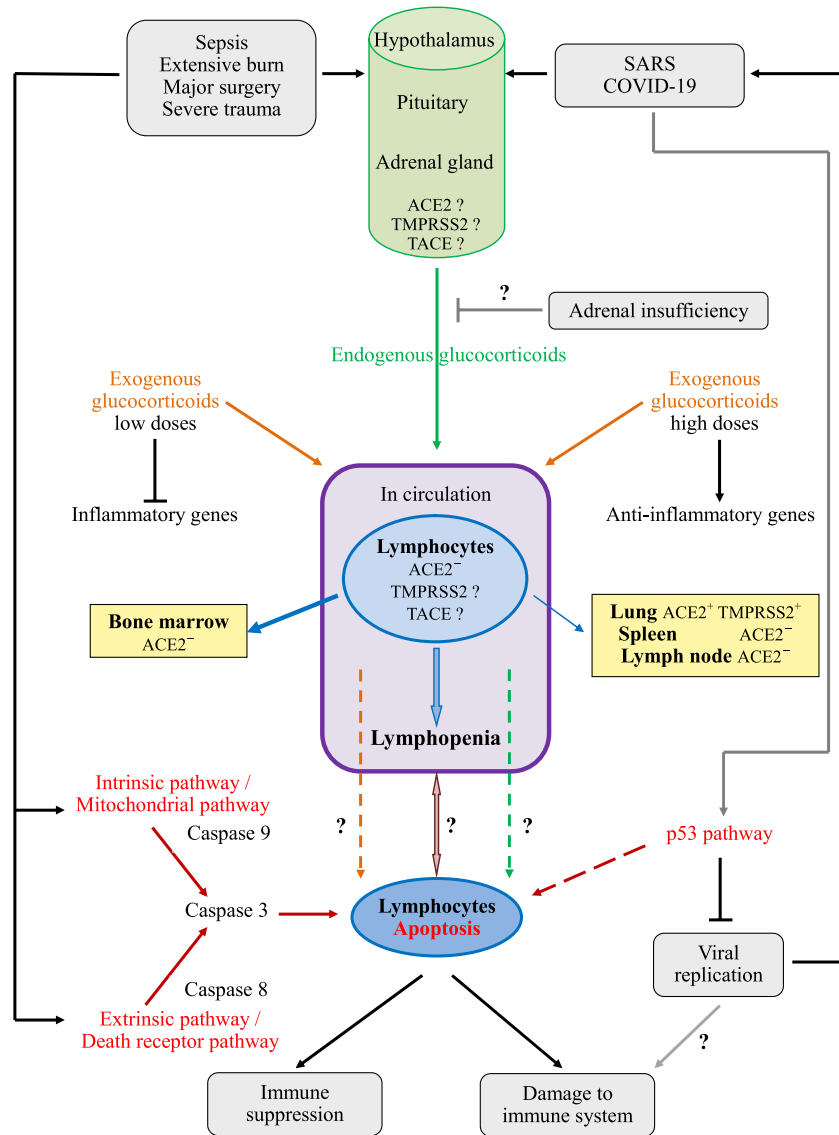


FIGURE 1 Mechanism for lymphopenia in SARS and COVID-19 patients. Decreased amount of lymphocytes in circulation causes lymphopenia (central violet rectangle). This symptom can be found in SARS and COVID-19 patients as well as in the patients with sepsis, severe trauma, extensive burns, major surgery (top part). These circumstances trigger a stress response to stimulate the hypothalamic-pituitary-adrenal axis. Both an excessive amount of endogenous glucocorticoids (green arrows) and exogenous glucocorticoids (orange arrows) cause lymphocytes to move out from the peripheral circulation and apoptosis of lymphocytes (central vertical part). Two signaling pathways induce apoptosis: mitochondrial pathway and death receptor pathway (left-hand lower part). The activation of p53 can inhibit the replication of SARS-CoV and SARS-CoV-2, and also induce apoptosis in lymphocytes (right-hand lower part). Consequently, lymphocyte apoptosis brings about the damage of the immune system and immune suppression (bottom part). ACE2, the angiotensin I-converting enzyme 2; TACE, the TNF- α -converting enzyme; TMPRSS2, the cellular serine protease.

to 2004.^{4,8-11} Now lymphopenia appears again in the current COVID-19 pandemic.¹²⁻¹⁴

As a matter of fact, lymphopenia is not exclusively in SARS and COVID-19 patients (right-hand part in Figure 1), but can be found in many medical conditions, eg, sepsis, severe trauma, extensive burns, and major surgery. Typically lymphopenia is followed by immunosuppression (left-hand part in Figure 1).¹⁵

Lymphopenia in SARS patients is attributed to the endogenous glucocorticoids and apoptosis (central vertical part in

Figure 1). (a) SARS-CoV initially triggers a stress response to stimulate the hypothalamic-pituitary-adrenal axis (the black arrow at the top right-hand part in Figure 1) to generate an excessive amount of endogenous glucocorticoids,¹⁶ which cause lymphocytes to move out from the peripheral circulation.¹⁷ (b) Lymphocytes eventually undergo apoptosis.¹⁸ Consequently, damage occurs to the immune system (right-hand lower part in Figure 1).¹⁹⁻²² For these reasons, it was suggested that a SARS patient without lymphopenia might have adrenal insufficiency (upper right part in Figure 1)²³

although it is not clear whether a corticotropin test was performed.

Lymphopenia is also attributed to the exogenous glucocorticoids, which were given to SARS patients with different dosages, eg, methylprednisolone ≥ 500 mg/day,²⁴ prednisolone 0.5-1 mg/kg/day, hydrocortisone (100 mg every 8 h), methylprednisolone 500 mg/day up to 3000 mg/day.²⁵ Basically, a high dose of glucocorticoids activates the genes, which encode anti-inflammatory proteins (right-hand middle part in Figure 1), whereas a low dose of glucocorticoids suppresses inflammatory genes (left-hand middle part in Figure 1).²⁶

Clinically, lymphopenia (lymphocytopenia) caused by glucocorticosteroids was studied from a very early time. Lymphopenia could be transient from a single administration of corticosteroids but could be sustained with respect to the chronic elevation of plasma corticosteroids.^{27,28}

Corticosteroid mainly leads T lymphocytes to leave from the peripheral circulation and then enter into the bone marrow (left-hand middle part in Figure 1).²⁷ However, lymphocytic infiltration was sparse in lungs, and lymphocytes decreased in spleen and lymph nodes in SARS patients (right-hand middle part in Figure 1).²² Furthermore, T lymphocytes distributed mainly at the periphery of the germinal centers of the splenic white pulp, lymph nodes, and peripheral blood in SARS patients (right-hand middle part in Figure 1).²² These results imply that other types of lymphocytes might not leave from the peripheral circulation except for T lymphocytes.

Thus, it is easy to see that lymphopenia in SARS patients occurs first and then the apoptosis of lymphocytes follows.²⁹ For a different reason, the KEGG pathway analysis in transcriptomic data suggests that lymphocytes probably undergo apoptosis through the p53 signaling pathway,³⁰ which in turn leads to lymphopenia in COVID-19 patients.^{3,30} These findings suggest that the apoptosis of lymphocytes occurs before lymphopenia (lower middle part in Figure 1), ie, the ordering between lymphopenia and lymphocyte apoptosis appears different for SARS patients and COVID-19 patients.

In summary, this section raises two questions. (a) Does a COVID-19 patient with adrenal insufficiency have a better outcome since the amount of glucocorticoids inside circulation may not be sufficient to lead to lymphopenia? (b) Which event is the first between lymphopenia and lymphocyte apoptosis (up-down arrow in lower middle part in Figure 1)?

2 | CAN SARS-COV AND SARS-COV-2 INFECT LYMPHOCYTES?

To infect a host cell, both SARS-CoV and SARS-CoV-2 at first need to recognize the angiotensin I-converting enzyme 2 (ACE2) receptor on the surface of the host cell by its spike protein.³¹⁻³⁴ Meanwhile, it is unknown whether the

spike protein from SARS-CoV-2, like the spike protein from SARS-CoV,³⁵ can down-regulate ACE2 expression. It turns out that several coronaviruses including SARS-CoV-2,³² SARS-CoV,³⁵ and HNL63-CoV^{36,37} enter into the host cell in such a way. In contrast, HCoV-229E uses CD13 as its entering the cellular receptor.³⁸ Together with ACE2, TNF- α -converting enzyme (TACE) is also positively involved in SARS-CoV entry into host cells.³⁹

Therefore, ACE2-positive cells are the prerequisite for cells to be infected by SARS-CoV^{35,40} and SARS-CoV-2.³² The ACE2 receptor widely exists on the surface of human cells, especially in the alveolar type II cells and capillary endothelium in lung,^{22,41,42} the upper respiratory tract,⁴² and other human tissues such as heart, liver, kidney, and digestive organs.^{42,43} Nevertheless, SARS-CoV mainly infects pneumocytes and macrophages in the lung,⁴⁴ subsequently ACE2 plays a particular role in lung injury.^{39,45} Currently, these findings and implications are applicable to SARS-CoV-2 although more studies are in need to expand our knowledge on SARS-CoV-2.

On the other hand, the cells related immune system, ie, bone marrow, lymph nodes, thymus, spleen, T and B lymphocytes, and macrophages, are consistently negative for ACE2 (two yellow rectangles in Figure 1).⁴² In reality, SARS-CoV is unlikely to cause massive infection in lymphocytes because SARS-CoV was found in lymphocytes only in 6 of 22 early stage patients, of which 51.5% of lymphocytes were SARS-CoV positive.²² This low infection rate in lymphocytes should partly result from the absence of ACE2 in lymphocytes. To take a step further, if lymphocytes lack ACE2, then TACE, which works with ACE2 together,³⁹ would not exist in lymphocytes.

The innate immune system has three classes of cytoplasmic pattern recognition receptors to response to virus: toll-like receptors (TLRs), RIG-I-like receptors (RLRs), and NOD-like receptors (NLRs). They recognize the viral RNA, and then arouse a series of anti-viral reactions, including both humoral and cellular immune responses.⁴⁶⁻⁴⁹ It is necessary to know who recognizes whom first, ie, does it first begin with the SARS-CoV and SARS-CoV-2 to recognize host cells via the spike protein toward ACE2 or does it begin with the innate immune system to recognize SARS-CoV and SARS-CoV-2 via TLRs, RLRs, and NLRs?

The second prerequisite for cells to be infected by SARS-CoV and SARS-CoV-2 seems to be that the host cells have the cellular serine protease TMPRSS2 for spike protein priming, which is essential for SARS-CoV-2,⁵⁰ SARS-CoV,⁵¹⁻⁵⁴ and MERS-CoV^{55,56} to enter into host cells. In fact, the alveolar type II cells in lung highly express TMPRSS2.⁵² Oppositely, it is not clear whether lymphocytes have TMPRSS2 or any similar protease, eg, endosomal cysteine proteases cathepsin B and L (CatB/L) because SARS-CoV can use these proteases to enter into host cells⁵⁷ together with TMPRSS2.^{51,58,59}

In a clinical study,⁶ mesenchymal stem cells (MSCs) were given to COVID-19 patients, since MSCs do not have ACE2 and TMPRSS2 but secrete anti-inflammatory factors, which is similar to the high doses of glucocorticoids,²⁶ to prevent the cytokine storm. This result demonstrates the importance of ACE2-negative and TMPRSS2-negative cells. It really matters to ask whether the cells in the hypothalamic-pituitary-adrenal axis are ACE2- and TMPRSS2-positive or negative. This is so not only because SARS-CoV viral particles and genomic sequence were detected in the neurons of the brain²² but also because SARS-CoV initially triggers a stress response to stimulate the hypothalamic-pituitary-adrenal axis (middle-upper part in Figure 1).²⁹ In this way, it is fair to ask whether lymphocytes have TMPRSS2 since SARS-CoV viral particles and genomic sequence were widely detected (circulating lymphocytes, monocytes, and lymphoid tissues, as well as the epithelial cells of the respiratory tract, the mucosa of the intestine, the epithelium of the renal distal tubules, and macrophages in different organs).²²

Factors related to the entrance of SARS-CoV into host cells also include cathepsin L⁶⁰ and a low endosomal pH⁶¹ as the fusion of viral particles and cytoplasmic membranes depends upon them.⁶¹ Naturally, cathepsin L⁵⁷ or Ben-HCl⁶²⁻⁶⁴ is subjected to peptidase inhibitors but they are not the case for HNL63-CoV.⁶⁰ Consequently, it is highly likely that SARS-CoV and SARS-CoV-2 do not infect lymphocytes directly and massively so one may wonder why lymphopenia occurs.

In summary, this section raises two questions. (a) Does it first begin with the SARS-CoV and SARS-CoV-2 to recognize host cells via the spike protein toward ACE2 or does it begin with the innate immune system to recognize SARS-CoV and SARS-CoV-2 via TLRs, RLRs, and NLRs? (b) Are the cells in the hypothalamic-pituitary-adrenal axis ACE2- and TMPRSS2-positive or negative?

3 | HOW DOES APOPTOSIS OCCUR IN LYMPHOCYTES?

No matter whether glucocorticoids or apoptosis bring about lymphopenia, the involvement of apoptosis is certain. Indeed, endogenous glucocorticoids can lead to apoptosis in T lymphocytes⁶⁵ because lymphopenia is often found in patients without the administration of exogenous glucocorticoids.¹⁸ Apoptosis in alveolar epithelial cells and respiratory endothelial cells was found in humans and animals with acute lung injury and acute respiratory distress syndrome.⁶⁶ Additionally, lymphocytes are rapidly dividing cells, whose death can minimize the inflammatory response to host.⁶⁷ Besides, it showed that the low doses of corticosteroids can be useful in terms of apoptosis in lymphocytes.^{68,69}

In general, lymphocytes show an inversely correlated pattern with the cortisol diurnal rhythm.⁷⁰ The function of T lymphocytes is influenced by glucocorticoids, which activate the expression of indoleamine-2,3-dioxygenase. This tryptophan-degrading enzyme regulates T-lymphocyte function via increased secretion of the anti-inflammatory cytokine IL-10,⁷¹ but the adrenal insufficiency would desensitize both α - and β -adrenergic receptors.⁷² And the transcription of the gene of the β 2-adrenergic receptor is increased by glucocorticoids in human lung *in vitro*⁷³ and nasal mucosa *in vivo*.⁷⁴ Collectively, the functions of glucocorticoids are closely relevant to anti-inflammatory and inflammatory genes, which encode cytokines, chemokines, adhesion molecules, inflammatory enzymes, and receptors.⁷⁵

What is the direct link between apoptosis and corticosteroids? What mechanism is for glucocorticoids to initiate apoptosis in lymphocytes (dotted lines in the middle part in Figure 1)? Studies on the immune response to sepsis suggest a biphasic pattern, ie, a hyper-inflammatory response is associated with high levels of pro-inflammatory cytokines, but an immune-paralysis is associated with apoptosis of immune cells, in particular, with apoptosis of lymphocytes,^{76,77} which go through the death receptor (extrinsic) and the mitochondrial (intrinsic) pathways,⁷⁸⁻⁸⁰ converging to a common point, caspase 3 (left-hand lower part in Figure 1).⁶⁷

For COVID-19 patients, apoptosis in lymphocytes is attributed to the activation of the p53 signaling pathway in lymphocytes (right-hand lower part in Figure 1).³⁰ Interestingly, the p53 pathway seems not to be involved in both extrinsic and intrinsic pathways, because the former needs death ligands, eg, FasL, TNF- α , APRIL, TRAIL, whereas the latter needs the intracellular stress, eg, reactive oxygen species, radiation, and chemotherapeutic agents.^{30,67,78} Accordingly, SARS-CoV and SARS-CoV-2 infection should serve as intracellular stress to trigger the intrinsic pathway to apoptosis under the condition that SARS-CoV or SARS-CoV-2 enters into lymphocytes (the black arrow on left-hand part in Figure 1). If this is the case, then the intrinsic pathway would be initiated to lead to apoptosis without the action of the extrinsic pathway although the cross-talk between two pathways exists in hepatocytes rather than in lymphocytes.⁸¹ Furthermore, the extrinsic pathway can trigger BCL-2-regulated apoptotic programs.⁸²

Activation of p53 can inhibit the replication of SARS-CoV in infected HEK293 and HCT116 cells⁸³ but those cells are not lymphocytes and do not come from any immune system. This role of p53 with respect to SARS-CoV was found in the yeast-2-hybrid (Y2H) screen.⁸⁴ Actually, p53 serves as an antiviral factor against positive-sense single-stranded RNA (ssRNA) hepatitis C virus (HCV) and poliovirus as well as negative-sense ssRNA influenza A virus and retrovirus HIV-1.⁸⁵⁻⁸⁸

In summary, this section raises two questions. (1) Does apoptosis of lymphocytes occur inside or outside the circulation? (2) Which is the first between the SARS-CoV triggered

stress response through the hypothalamic-pituitary-adrenal axis to generate glucocorticoids and the immune response to SARS-CoV and SARS-CoV-2?

4 | CONCLUSION

In this paper, we attempt to address the contradiction that lymphopenia is prior to apoptosis in SARS patients whereas apoptosis is prior to lymphopenia in COVID-19 patients because no other pneumonitis produces such a profound lymphopenia as seen in SARS and COVID-19 patients. Although the literature does not provide a solid explanation, the level of glucocorticoids could determine the ordering between lymphopenia and apoptosis because the administration of high doses of glucocorticoids could lead to lymphopenia whereas low doses of glucocorticoids could benefit patients. In the meantime, we raise several questions, which need to be answered in order to better understand the whole course of COVID-19.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

GW designed this review and wrote the first draft. SY composed the figures. Both finalized this manuscript.

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