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LETTER TO THE EDITOR

Apoptosis induced by SARS-CoV-2: can we target it?

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Abstract
Some viruses are known to be associated with increased apoptosis. Apoptotic cell death triggered by these viruses has a complex role in host antiviral immunity, and might facilitate the viral clearance or act as a mechanism for virus-induced tissue injury and disease progression. The induction of apoptosis is a hallmark of SARS-CoV-2 infection. Accumulating evidence suggests that there is a direct relationship between apoptosis rate and COVID-19 pathogenicity/severity. Targeting virus-induced apoptosis could be a promising strategy in the treatment of SARS-CoV-2 virus infection.

Keywords SARS-CoV · SARS-CoV-2 · Apoptosis · ORF3a

To the Editor,

Viruses interact with the cell death machinery in different ways. For example, infections induced by adenoviruses, baculoviruses, herpesviruses and poxviruses are associated with reduction of apoptosis. Viruses encoding anti-apoptotic proteins could have the opportunity to complete the viral replication cycle before cell destruction and spread of the viruses. In this case, apoptotic cell death has an important role in host defense by inhibiting viral expansion [1].

In contrast, infections induced by influenza or human immunodeficiency viruses are associated with increased rate of apoptosis. Apoptosis may help in viral egress, and the suppression of apoptosis might prevent viral pathogenesis. Therefore, apoptosis triggered by viruses has a complex role in host antiviral immunity, and might facilitate the viral clearance or act as a mechanism for virus-induced tissue injury and disease progression [1–4].

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused a pandemic transmission in the world, causing severe respiratory illness in the patients, called the coronavirus disease 2019 (COVID-19). Coronavirus-encoded accessory proteins have important roles in virus–host interactions and the regulation of host immune responses, thereby contributing to pathogenicity of coronaviruses. Previous studies reported that the SARS-CoV-encoded accessory protein ORF3a can trigger apoptosis in cells [5, 6]. Recent study showed that SARS-CoV-2 ORF3a also can efficiently induce apoptosis in cells [7].

SARS-CoV-2 ORF3a can induce the activation/cleavage of caspase-8 without effect on Bcl-2 expression levels. The activation/cleavage of caspase-8 is known as a hallmark of the extrinsic apoptotic pathway, whereas Bcl-2 has a pivotal role in initiation of the intrinsic pathway [8]. This implies that SARS-CoV-2 ORF3a induces apoptosis via the extrinsic apoptotic pathway [7].

The membrane association is essential for the pro-apoptotic activity of SARS-CoV-2 ORF3a. However, the membrane-association feature is involved in but not mandatory for the pro-apoptotic activity of SARS-CoV ORF3a. Ren and colleagues reported that SARS-CoV ORF3a has higher pro-apoptotic activity than SARS-CoV-2 ORF3a [7]. It is also accepted that SARS-CoV is more virulent than SARS-CoV-2, suggesting that differences in the relative strength of pro-apoptotic activity may contribute to the pathogenicity differences between SARS-CoV and SARS-CoV-2. In accordance to this, severe COVID-19 patients have higher frequency of apoptotic cells, compared to mild patients [9], suggesting that there is a direct correlation between apoptosis rate and pathogenicity/severity of COVID-19.

Recent study reported that SARS-CoV-2 infection could activate caspase-8 to induce apoptosis and inflammatory cytokine processing in the lung epithelial cells, triggering necroptosis pathway [10]. The caspase-8-mediated apoptosis activation and inflammatory responses could induce

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downstream immune pathogenesis in the lung tissue. Accumulating evidence suggests that the virus-induced lung damage and inflammatory cytokine storm directly associated with clinical manifestations of COVID-19, implying that targeting virus-induced apoptosis could be a new hope in the treatment of SARS-CoV-2 virus infection.

The induction of apoptosis is a hallmark of SARS-CoV-2 infection. Failure of apoptosis activation will not only inhibit cell death and tissue damage, but also will result in decreasing SARS-CoV-2 clearance from infected cells. Previous study proposed that caspase inhibitor may be used in SARS-CoV infected cells [11], and we also propose that targeting virus-induced apoptosis could be a promising strategy in treatment of SARS-CoV-2 virus infection.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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