SARS-CoV2 at the Alveolar Epithelial-Endothelial Interface – A Hypothesis for the Pathogenesis of COVID-19

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Abstract

Severe COVID-19 is associated with viraemia and multiple organ disease. Similar clinicopathological features have been previously seen in SARS and MERS. Clinically, the severity of SARS, MERS and COVID-19 has been associated with the presence of SARS-CoV, MERS-CoV or SARS-CoV2 viraemia in affected patients. *In vitro* work has looked at the pattern of viral entry and release from polarised epithelial cells infected by coronaviruses. This work has demonstrated a correlation between the severity of a coronavirus infection and the ability of the virus to reach and infect the basal surface of host cells. It has been postulated that this ability helps the virus invade the bloodstream of the host, resulting in a systemic infection with multiple organ involvement. Here we propose that basal surface release and entry of COVID-19 into and out of cells at epithelial-endothelial interface plays a key pathogenic role in severe COVID-19 disease.

Background

The breach of the epithelial-endothelial barrier at the alveoli appears to be a critical step for the development of severe COVID-19 infection. It has been previously suggested that immune and endothelial dysfunction may play an important role in this process. It has been postulated that the breach of the epithelial-endothelial barrier begins with inflammation and the enrolment immune cells into the alveolar cavity. From there, it is hypothesised, that SARS-CoV2 infected immune cells invade the bloodstream through a leaky endothelium (1,2). Thus, providing a pathway through which viraemia and systemic disease may occur in severe COVID-19.

However, little has been said about the pattern of SARS-CoV2 entry and release from infected cells at alveolar epithelial-endothelial interface. Here, based on clinical, pathological, cellular and molecular evidence we suggest that in severe COVID-19 disease critical pathogenic events may occur at the alveolar supportive tissue where epithelium and endothelium meet.

Viraemia and multiple organ involvement are associated with severe SARS, MERS and COVID-19

Previously, the human coronaviruses SARS-CoV and MERS-CoV have caused the international SARS and MERS epidemics, respectively (3,4). Clinically COVID-19 resembles SARS and MERS, with most cases of these infections showing a self-limiting respiratory infection and a minority of cases showing severe multi-organ disease (3–6). Like COVID-19, SARS and MERS are associated with viraemia (7–10).

Interestingly, viraemia in SARS, MERS and COVID-19 correlates with poorer clinical outcomes. The extent of SARS-CoV2 RNAaemia is closely correlated with level of the proinflammatory cytokine IL-6, a marker of COVID-19 disease, and poorer prognosis (11). Similarly, SARS-CoV RNAaemia was previously found to be associated with prolonged illness (12) and admission to an intensive care unit (9). Furthermore, MERS-CoV RNAaemia has been correlated with markedly increased risk of death (8). It is important to note, that MERS infection is associated with a greater degree of mortality and viraemia compared to COVID-19. Thus, While SARS-CoV2 RNAaemia was found in 15% of hospitalised COVID-19 patients (11), MERS-CoV2 RNAaemia was reported in 30% of cases (8).

Thus, evidence from SARS, MERS and Covid-19 clinical research suggests that viraemia may play an important pathogenic role in severe disease.

Histology of the alveolar wall facilitates the infection of different cell types

The alveolar wall consists of three elements: surface epithelium, supporting tissue and blood vessels. Surface epithethilium is made up of type I and II alveolar epithelial cells. The supporting tissue is formed by the basement membrane (fine reticular, collagenous and elastic fibres) and occasional fibroblasts. Blood vessels are mainly capillaries made up of endothelial cells (13).

The alveolar walls are defended locally by alveolar macrophages that reside in the alveolar cavity. Blood born dendritic cells also play a role in detecting antigens in the alveolar cavity but to do this they extend processes from the supporting tissue layer where they can temporarily reside (14). In addition, neutrophils, macrophages and lymphocytes can be recruited to the alveolar wall through the vasculature during infection (2).

The supporting tissue in the alveolar walls forms an attenuated layer beneath the epithelium and surrounding blood vessels. In most of the alveolar wall, the basement membrane which supports the capillary endothelium is directly applied to the basement membrane supporting the alveolar epithelium (13). At these points, only 100nm separates the basal surface of epithelial cells and endothelial cells in the alveoli (15).

Post-mortem studies of SARS cases looking at the cellular distribution of SARS-CoV infection have shown that the main target of the virus is alveolar epithelial cells (16,17). Type II alveolar epithelial cells appear to be preferentially affected compared to type I (16). However, other cell types, including alveolar macrophages, lymphocytes and fibroblast, also demonstrate evidence of SARS-CoV replication within them. Importantly, endothelial cells are positive for intracellular SARS-CoV RNA demonstrating that, despite not been in direct contact with the air rich alveolar cavity, they have been infected by the virus (7). Interestingly, although there is post-mortem evidence that SARSC-CoV2 is primarily infects in alveolar epithelial cells (18), a recent study has also demonstrated evidence of SARS-CoV2 RNA in the endothelial cells in the capillary beds of multiple organs of COVID-19 cases (19).

Therefore, the histology of the alveolar wall facilitates the infection of different cell types.

Pattern of SARS-CoV, MERS-CoV and SARS-CoV2 receptor expression is consistent with multiple organ infection

The human coronaviruses (CoVs), including SARS-CoV, SARS-CoV2 and MERS-CoV, have a common basic structure. CoV particles are made up of their positive sense RNA genome and the structural proteins coded by it. Structural proteins include spike protein (S), envelope protein (E), membrane protein (M) and nucleocapsid protein (N). The S-protein is the dominant surface protein of CoV and it mediates virus attachment to the host cell membrane during infection (20).

The S-proteins in CoVs bind to specific cell surface receptors in target cells to initiate infection. SARS-CoV and SARS-CoV2 bind the angiotensin converting enzyme (ACE2) (21,22), which is found expressed in type I and II alveolar epithelial cells, as well as endothelial cells in the alveoli. Interestingly, ACE2 is also expressed in multiple organs, including intestine, liver, kidney and brain (23–25). MERS-CoV binds dipeptidyl peptidase 4 (DDP4) to cause infection (26). Like ACE2, DDP4 is found in alveolar pneumocytes and endothelium (26) as well as in multiple organs (27).

The pattern of ACE2 and DPP4 expression is consistent with the potential for COVID-19, SARS and MERS to produce multiple organ pathology. However, systemic involvement is restricted to a minority of cases infected by the viruses. Furthermore, MERS demonstrates a

greater degree of systemic involvement compared to SARS and COVID-19 (28). Thus, multiple organ pathology may not be fully explained simply by the pattern of expression of ACE2 and DPP4 at the tissue level.

The pattern of viral entry and release into and from polarised epithelial cells correlates with the severity of coronavirus infection

In vivo, alveolar epithelial and endothelial cells are polarised cells. They have their basal cell surfaces attached to a basement membrane, while their apical surfaces interact with either the alveolar cavity or bloodstream, respectively (15).

In vitro work has been carried out for more than 25 years looking at the pattern of coronavirus entry and release into and from polarised epithelial cells (29). This work uses a cell culture method that aims to model the polarised nature of epithelial cells *in vivo* (30). Studies using this method suggest that there may be a correlation between the severity of a coronavirus infection and the ability of the virus to reach and infect the basal surface of host cells (31). It has been postulated that this ability helps the virus invade the bloodstream of the host, resulting in a systemic infection with multiple organ involvement (29). Evidence of this hypothesis comes from studies of both animal and human coronaviruses.

The entry and release of some animal CoVs occurs preferentially at the apical surface of polarised epithelial cells. CoVs such as transmissible gastroenteritis coronavirus (TGEV), bovine CoV (BCoV) and porcine epidemic diarrhoea virus (PEDV), which cause localised gastrointestinal infections in animals, predominantly infect polarised epithelial cells at their apical domain (30,32–34). After replication, these CoVs, which cause illness without systemic spread, are also mostly released from the apical domain of infected polarised cells. Thus, CoVs that produce localised infections may be associated with an apical pattern of entry to and release from target cells.

Although some animal CoVs demonstrate predominantly apical entry and release, there are others that show a preference for basal release. CoVs that cause severe systemic illness, such mouse hepatitis virus (MHV), feline coronavirus (FCoV) and canine coronavirus (CCoV), mainly infect polarised epithelial cells at their apical domain (31,35,36). After replication, these CoVs, which invade the blood to cause disease in multiple organs, are mostly released from the basal domain. Therefore, basal release may be associated with systemic infections.

Human CoVs are preferentially released from the apical surface of infected cells. CoVs that cause mild localised respiratory illnesses in humans, CoV-229E and CoV-HKU1, as well as those that can cause disease in multiple organs, SARS-CoV and MERS-CoV, are mostly released from the apical domain of polarised human epithelial cells (37–42). Consequently, a

preference for apical viral release appears to be a common feature in human CoVs, irrespective of whether they cause local or systemic disease.

Although human CoVs involved in systemic disease mostly exit from the apical domain, basal release is also evident. Tao et al. (2013) studying MERS- and SARS-CoV demonstrated that about a third of all virus left polarised epithelial cells via the basal surface. Although clinically, MERs causes more severe disease progression than SARS-CoV, there was no difference in extent of release at the basal domain of epithelial cells between both viruses (40). Thus, the potential for systemic invasion of a human CoV may not depend solely on basal release of viral particles in humans.

SARS- and MERS-CoV differ in their ability to enter the basal surface of epithelial cells. Tao et al. (2013) demonstrated that while SARS-CoV could only infect polarised epithelial cells via the apical surface, MERS-CoV could infect both the apical and basal domains of these cells. In fact, MERS-CoV infection through the basal surface produced a higher viral titre than apical infection (40). Therefore, difference in systemic invasion may depend on the ability of CoV to infect polarised by entering their basal surface.

The pattern of entry and release of CoVs from epithelial cells and their association with disease is complex. However, there is evidence that apical entry and release of CoVs from infected polarised cells may be associated with localised infections only. In contrast, basal entry and release of CoVs from infected polarised cells may be associated with systemic disease and multiple organ involvement.

Conclusion

If the pattern of SARS-CoV2 entry and release into and from infected epithelial cells *in vivo* resembles that seen in polarised epithelial cell culture experiments with other coronavirus, then a pathogenic mechanism for COVID-19 may be derived.

Here we propose that epithelial cells infected in COVID-19, release SARS-CoV2 from both their apical and basal surface. Apical viral release propagates infection primarily to the alveolar cavities and from there to the outside. In contrast, basal release spreads infection internally into the basement membrane and associated alveolar supportive tissue. At the alveolar supportive tissue, SARS-CoV2 might enter fibroblasts, dendritic cells, neutrophils and T-cells. Importantly, endothelial cells might also directly become infected by SARS-CoV2 released from the basal surface of epithelial cells. In this way, viraemia may occur as a direct consequence of SARS-CoV2 endothelial infection and may precede or may occur simultaneously as the infection of blood-born immune cells in COVID-19.

Future Research

According to the *in vitro* evidence described above the extent that SARS-CoV2 spreads internally into the basement membrane and alveolar supportive tissue may depend on how much virus gets released from the basal surface of infected epithelial cells. However, it may also depend on the susceptibility of polarised epithelial or endothelial cells to be infected through the basal surface. Research looking at SARS-CoV2 infection of polarised endothelial cells *in vitro* might help to elucidate the mechanism proposed here further (43).

Understanding the pattern of expression of SARS-CoV2 receptors in the basal surface of epithelial and endothelial cells may shed more light on the processes driving SARS-CoV2 endothelial infection and viraemia. In this vein, it is important to know that receptors other than ACE2, such as GRP78 (44), DPP4 (45) and CD147 (46), have been suggested to be targets of SARS-CoV2. Research on the pattern of expression of these receptors and their role in COVID-19 may be fruitful (43).

In addition, studying the intracellular mechanism regulating the basal surface release of SARS-CoV2 from polarised epithelial cells might clarify what drives severe COVID-19 pathology. In this vein, recent work has suggested that the non-structural protein nsp7 interacts with Rab proteins, a family of intracellular transport regulators, in SARS-CoV2 infected cells (47). Targeting therapies to nsp7 may be a novel avenue of treatment.

Finally, focusing research on the interface between epithelial and endothelial may draw our attention to therapies that target the basement membrane and supportive tissue in the alveoli such as those used for pulmonary fibrosis (48). Targeting pharmacological therapies to the critical areas of pathology may result in more effective treatment for COVID-19.

Contributors

ADAS carried out the literature search and drafted the paper. ADAS and FCAS reviewed the evidence and formed the hypothesis. FCAS revised the manuscript. ADAS and FCAS have reviewed the paper prior to submission. This manuscript has not been currently accepted or published elsewhere.

Declaration of interests

We declare no competing interests.

Acknowledgments

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