CORRESPONDENCE

Apoptosis and pericyte loss in alveolar capillaries in COVID-19 infection: choice of markers matters. Author's reply

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Dear Editor,

We thank Jain et al. for their comments and agree about the difficulties to identify pericytes because of a lack of specific markers [1]. α -SMA is one of the common proteins expressed by pericytes, along with PDGFR β and NG2 [2]. Contrary to the affirmation of the authors, quiescent pericytes in the alveolar septa in human lungs express α -SMA, forming a delicate α -SMA network along the capillaries as observed in our control case [3–5]. Importantly, most descriptions have been made in mice, which are not reliable models for lung capillaries pericytes. Indeed, pericytes are known to be rare or absent in lung capillaries of small mammals, whereas pericytes are present in human lung capillaries [4, 5]. We additionally performed a NG2 immunolabelling in our control case, showing the same distribution compared to the α -SMA staining and confirming the presence of pericytes along lung capillaries (Fig. 1a).

The distinction with myofibroblast which may also express α -SMA, may be challenging. Proliferation of myofibroblasts is notably induced by injuries. For this reason, to avoid the confusion with such cells, we focused our observation in lung territories distant from inflammatory areas. In the former, the alveolar walls were devoid of either pericytes or myofibroblasts, whereas inflammatory territories were enriched in α -SMA-positive myofibroblasts. We agree that α -SMA expression is increased in case of lung injury. The authors suggest that in our control case (pneumothorax), α -SMA

expression may be increased because of inflammation and oxidative stress. In such a hypothesis, we would

Fig. 1 NG2 and α -SMA immunolabelling in normal lungs ($\times 400$). **a** NG2 immunolabelling in the control lung used in Cardot-Leccia et al. [5]. The alveolar capillaries are lined by NG2 expressing cells demonstrating the presence of pericytes around the capillaries. **b** α -SMA immunolabelling in a second lung control (autopsy from a 64-year-old woman died from a non-pulmonary etiology, i.e. necrotizing fasciitis) showing a delicate α -SMA positive network along the capillaries, corresponding to normal pericytes

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also expect a higher α -SMA expression in our COVID-19 patient because of a patent inflammation and diffuse alveolar damages, whereas most lung capillaries were α -SMA negative [3]. To further verify this point, we analyzed an additional control case without any lung affection, and we found the same α -SMA delicate network (Fig. 1b), arguing against a fallacious increase of α -SMA.

The mechanism of pericyte loss in lung capillaries of COVID-19 patients is not elucidated. Pericytes in brain and heart have been shown to highly express ACE2 suggesting a possible direct infection of the pericytes by the virus. Expression of ACE2 in lung pericytes is not increased in mice but remains unknown in humans [6]. Thus, a specific apoptosis of lung pericytes induced by the SARS-CoV-2 cannot be ruled out. However, as rightfully suggested by the authors, other mechanisms may also be involved in pericyte apoptosis in the lung of SARS-CoV-2-infected patients. Nevertheless, the result is a profound loss of pericytes in lung that could play a key role in the micro-vasculopathy which appears to be one of the hallmarks of COVID-19 infection.

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Compliance with ethical standards

Conflict of interest

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