EI-COV20-002 - Molekulares Verständnis der COVID-19-Pathogenese in menschlichen Blutgefäß-Organoiden

Abstract

We have previously provided the first genetic evidence that Angiotensin converting enzyme 2 (ACE2) is the critical receptor for SARS-CoV and that ACE2 protects multiple tissues from organ damage (Imai et al., Nature 2005; Kuba et al., Nature 2005). ACE2 has also been identified as the main receptor for SARS-CoV-2 infection and it has been proposed that inhibiting this interaction might be used for treating patients with COVID-19. The primary site of SARS-CoV-2 infection is the lung, which then becomes a source for viral spread to other tissues such as the heart, kidney and intestine (Ling et al., Chin Med J 2020; Young et al., JAMA 2020). Based on size constraints, it seems that the SARS-CoV-2 virus must directly infect blood vessel cells to spread to secondary tissues. Studying the molecular mechanisms of SARS-CoV-2 infection in blood vessels is therefore important for the understanding of disease pathogenesis, patient care, and virus transmission - critical information required for the containment of this pandemic. We have previously developed vascular organoids from human induced pluripotent stem cells (Wimmer et al., Nature 2019; Wimmer et al., Nature Protocols 2019); and our recent study shows that human recombinant soluble ACE2 (hrsACE2, APN01) significantly reduced SARS-CoV-2 infections of human organ-like tissues (Monteil et al., Cell 2020). Together with an international network of tissue engineers, SMEs (e.g. Apeiron developing ACE2 for therapy), and virologists we dissected, at the single cell level, the pathogenesis of SARS-CoV-2 infections in human vascular organoids. We also treated these organoids with hrsACE2, which is undergoing clinical testing for COVID-19 patients. Since diabetic patients belong to a particular vulnerable COVID-19 risk group, we compared diabetic blood vessels to their healthy counterparts in terms of viral infection and ACE2 expression. We could show that a diabetic environment can exacerbate the inflammatory phenotypes and indeed enhances SARS-CoV-2 replication even in engineered human blood vessel organoids.

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Further links to the persons involved and to the project can be found under
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