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RESEARCH HIGHLIGHT

SARS-CoV-2-induced lung pathology: AHR as a candidate therapeutic target

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The aryl hydrocarbon receptor (AHR) is activated by multiple viruses to evade the host immune response, a strategy exploited in pre-clinical models to limit the replication of Zika and Influenza A. In a recent study, Liu et al. report that AHR drives the hypersecretion of lung mucins after SARS-CoV-2 infection, suggesting a role for AHR in respiratory failure and highlighting its potential therapeutic value.

COVID-19 shows a wide spectrum of clinical severity, ranging from asymptomatic or mild infection (~80% of cases) to severe and critical life-threatening forms of the disease (~5%–15%). The primary cause of death in severe COVID-19 patients is progressive respiratory failure. Since respiratory symptoms in these patients usually worsen a week after disease onset, it has been suggested that they result from a dysregulated pro-inflammatory response, which eventually damages lung epithelial and endothelial cells, impairing the exchange of O_2 and CO_2.[1] An imbalanced inflammatory response, however, does not explain hypoxia in all COVID-19 patients. Indeed, severe hypoxia has also been reported at early stages of COVID-19, before an excessive inflammatory response is established. Intriguingly, despite presenting low blood O_2 levels, some of these patients show minimal symptoms and apparent distress, a condition referred to as 'silent hypoxia'.[2] The mechanism responsible for the development of silent hypoxia is still lacking. In a recent work published in *Cell Research*, Liu et al. report that SARS-CoV-2-triggered IFN signaling induces mucin overproduction by lung epithelial cells, thickening the blood–air barrier and hindering O_2 diffusion, leading to hypoxia.[3] Moreover, they show that mucin expression is driven by the transcription factor aryl hydrocarbon receptor (AHR), identifying AHR as a potential target for the treatment of hypoxia in COVID-19 patients.

Liu et al. first detected increased expression of mucins in bronchoalveolar lavage (BALF) samples taken from COVID-19 patients and macaques infected with SARS-CoV-2, in agreement with independent scRNA-Seq studies[4] and the detection of increased mucin expression and mucus production in COVID-19 autopsy samples.[5] Mucus hypersecretion in COVID-19 patients has been associated with airflow obstruction and respiratory distress, hence the mechanisms that control it are considered therapeutic targets of interest. Through a combination of in vitro and in vivo experiments, Liu et al. found that IFN-β and IFN-γ upregulate mucin production in lung epithelial cells. IFNs are known to activate AHR signaling, e.g., by inducing the expression of the enzymes IDO1/TDO2 which catalyze the generation of the AHR agonist Kynurenine (Kyn).[6,7] Indeed, the authors found that an IFN-IDO-Kyn-AHR axis drives mucin expression in lung epithelial cells. Finally, the authors used a murine model to evaluate the translational implications of their work. Using human ACE2 transgenic mice, they found that SARS-CoV-2 induced the upregulation of lung mucin expression and decrease in O_2 levels in peripheral blood, which was reverted by the administration of an AHR antagonist, identifying AHR as a candidate target to treat SARS-CoV-2-induced lung pathology.

AHR signaling has been shown to play a physiological role in the regulation of the host anti-viral response.[8–10] Type I IFN (IFN-I), the central regulator of the anti-viral response, induces AHR expression, but AHR can suppress the expression of IFN-I, most likely as part of a negative feedback loop.[6–9] Moreover, AHR has also been shown to inhibit NF-κB, an additional key effector molecule in the host anti-viral and inflammatory response.[6,7,9] Previous studies using AHR antagonists and gene knockdown have shown that AHR inactivation reduces Influenza A, Zika and Dengue virus replication.[8,9] These findings led to the hypothesis that AHR is a pro-viral host factor targeted by multiple viruses to limit IFN-I/NF-κB-driven host anti-viral immunity and promote virus replication (Fig. 1). The identification of AHR as a pro-viral host factor also has important therapeutic implications. Indeed, in mice infected with Influenza A virus, AHR antagonism increased IFN-β levels, reduced BALF viral titers and increased survival.[8] AHR antagonism also reduced Zika virus replication in fetuses and ameliorated congenital Zika virus syndrome in a pre-clinical mouse model.[9]

It was recently reported that infection with human coronaviruses, including SARS-CoV-2, activated AHR signaling, as determined by the RNA-seq analysis of lung epithelial cells.[10] This finding triggered the question of whether AHR also plays a role as a pro-viral host factor in the replication of coronaviruses and, consequently, can be a candidate therapeutic target against SARS-CoV-2. The work by Liu et al. uncovers an additional benefit of targeting AHR during SARS-CoV-2 infection; pharmacologic inhibition of AHR may not only boost anti-viral immunity, but also directly suppress mechanisms of lung pathology (Fig. 1). However, since the effects of AHR inhibition on lung SARS-CoV-2 replication were not assessed, Liu et al. cannot rule out the possibility that the reduction in virus-induced lung pathology results from the suppression of SARS-CoV-2 replication. AHR antagonists likely ameliorate lung pathology by both boosting anti-viral immunity and limiting virus replication, and also by suppressing excessive mucus production.

Independently of the specific mechanisms involved in the therapeutic effects of AHR antagonists on SARS-CoV-2 infection, the last few years have seen an increasing number of reports

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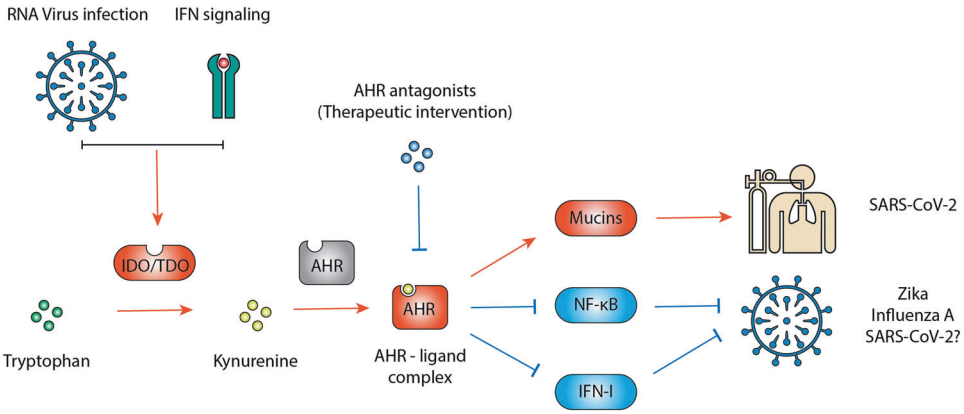

Fig. 1 AHR is a candidate therapeutic target for viral infection. AHR activation during viral infection results in the upregulation of IDO/TDO, which convert tryptophan to Kynurenine (Kyn). Kyn activates AHR, leading to formation of an AHR–ligand complex that limits host anti-viral responses mediated by IFN-I and NF-κB, thus promoting viral replication. AHR signaling also induces mucin expression in lung epithelial cells, thickening the blood–air barrier, impairing O_2 diffusion and causing hypoxia. AHR antagonists limit AHR activation, boosting the host anti-viral response and consequently reducing viral replication. AHR antagonism also reduces the expression of mucins, limiting lung pathology during SARS-CoV-2 infection.

identifying AHR as a candidate target for novel anti-viral therapies. The work by Liu et al. highlights the need to characterize the role of AHR in virus-induced pathology and the mechanisms involved, to guide the development of AHR-targeted therapies for virus-induced diseases.

ADDITIONAL INFORMATION

Competing interests: F.J.Q. is a member of the Scientific Advisory Board of Kyn Therapeutics.

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