Interferon signaling controls immune complex-mediated hyper-inflammation by alveolar macrophages in severely ill COVID-19 patients

[1] Chen HJ, [2,3] Hoepel W, [2,3] Geyer CE, [1] Griffith GR, [5]de Taeye SW, [5]van Gils MJ, [6]Vidarsson G,[2,3] den Dunnen J, [1]de Winther MPJ

[1]dept. of Medical Biochemistry, [2]dept. of Rheumatology and Clinical Immunology, [3]dept. of Experimental Immunology, [4]dept. of Pulmonary Medicine, [5]dept. of Medical Microbiology, [6]dept. of Experimental Immunohematology

COVID-19 patients often become seriously ill around the time of seroconversion. Previously, we have investigated the role of immune complexes in the pathophysiology of COVID-19, which showed that both high titer and aberrant Fc-tail afucosylation of IgG contribute to hyperinflammation in alveolar macrophages through Fcγ receptor (FcγR) signaling. Here, we provide evidence that interferon (IFN) is a novel and targetable regulator in this process.

While serum-derived afucosylated IgG induces IFN-β and IFN-γ secretion, we observed decreased expression and production of CXCL10, a classic IFN responding chemokine. This suggests a differential regulation of IFN signaling, which is in line with the delayed and dysregulated IFN responses in severe COVID-19 patients. To investigate this, we applied IFNs to human macrophages. Surprisingly, while immune-complexes alone do not trigger proinflammatory cytokine production, the co-stimulation with IFN-β, but not IFN-γ, strongly amplifies IL-6 and TNF secretion, independent of viral stimulus. By blocking IFN-β receptor, we further confirmed that the immune-complex-induced cytokine production was mainly caused by autocrine IFN-β, but less by IFN-γ. Moreover, RNA-sequencing analysis showed that genes involved in IFN pathway are associated with IgG fucosylation levels. As IgG fucosylation changes during disease development, glycosylation may be dynamically altering immune responses at different stages through FcγR and IFN signaling.

Our data show that IFN-β secreted by activated immune cells, together with immune complexes, can result in excessive inflammation in the absence of other viral stimuli leading to uncontrolled inflammation. Our findings open an avenue on new intervention fine-tuning the immune response against COVID-19.