8th EUROPEAN CONGRESS OF VIROLOGY 2023

ABSTRACTS

4–7 May 2023
Gdansk Poland

ECV 2023

www.eusv-congress.eu

ISBN 978-3-948023-30-0

PP 203

Effect of OAS genes on SARS-CoV-2 infection and the induction of innate immune responses

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Severe Acute Respiratory Syndrome 2 (SARS-CoV-2) infections cause different clinical symptoms ranging from asymptomatic patients to patients suffering severe respiratory disease leading to death in some of them. Genetic and functional studies have shown inborn-errors of interferon (IFN)-related genes in severe COVID-19 patients explaining why some young patients devoid of co-morbidities succumbed to infection. In addition, very large genomic studies identified common genetic variants affecting the expression and splicing of IFN-stimulated genes (ISGs) of the 2",5"-oligoadenylate (2-5A) synthetase (OAS) family associated with COVID-19 severity. We have sequenced the whole genome of 274 patients who required hospitalization after SARS-CoV-2 infection, finding ultrarare mutations in OAS1 and OAS3 genes. Upon double-stranded (ds)RNA binding, the OAS1, OAS2, and OAS3 proteins synthetize 2´-5´olygoadenylates which activate the endonuclease RNAseL. This endonuclease degrades viral and cellular RNAs, inhibiting viral replication. We have analyzed the effect of OAS1 and OAS3 genetic variants identified in our patients, and found that some of them impair the RNAseL activation. In addition, by using OAS3 knock-out cells generated in our laboratory and performing overexpression experiments, we have shown that OAS3 negatively modulates pro-inflammatory responses induced by immune challenges, and that the activation of the RNAseL activity seems necessary for this function. In addition, by using OAS3 knock-out mice infected with SARS-CoV-2 or treated with the double-stranded RNA analog poly(I:C), we have shown that OAS3 deficiency leads to a higher mouse susceptibility to SARS-CoV-2 infection and that OAS3 counteracts the induction of innate immune responses in the mouse infected-lungs, leading to a higher inflammatory response in OAS3 knock-out mice, compared to the parental mice. Given the contribution of exacerbated inflammatory responses to COVID-19 disease severity, our results suggest that OAS1/OAS3 could play a role limiting the severity of the clinical symptoms after SARS-CoV-2 infection.