**Title: Role of SREBP-2 as an inflammatory mediator in response to viral infection**

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**Abstract.**

The modulation of cellular lipid metabolism to interfere with virus multiplication may be an appealing, broadly applicable approach for antiviral therapy. Sterol regulatory-element binding proteins (SREBPs) are a family of transcription factors that regulate lipid metabolism by controlling the expression of enzymes required for endogenous cholesterol, fatty acid (FA), triacylglycerol, and phospholipid synthesis. Using an infectious disease mouse model, inhibitors of SREBP-2 and NF-κB suppressed cytokine storms caused by viral infection and prevented pulmonary damages. SREBP-2 is activated by cytokines or pathogen, such as virus or bacteria, but its association with diminished cholesterol levels in COVID-19 patients is unknown. In recent report, we found that SREBP-2 was activated in peripheral blood mononuclear cells of COVID-19 patients and SREBP-2 C-terminal fragment in COVID-19 patients’ blood was observed. We report that SREBP-2 C-terminal fragments could be as an indicator for determining severity. We confirmed that SREBP-2-induced cholesterol biosynthesis was suppressed, while the SREBP-2-induced inflammatory responses was upregulated in COVID-19 ICU patients. These results suggest that SREBP-2 can serve as an indicator for severity diagnosis and therapeutic target for preventing cytokine storm and lung damage in severe COVID-19 patients. Taken above, our study identifies SREBP-mediated lipid biosynthesis with broad relevance to human viral infections and represents SREBP as an undescribed target for the development of broad-spectrum intervention strategies, especially for tackling novel viruses causing emerging infectious diseases.

 Key words: SREBP-2, COVID-19, viral infection, lipid biosynthesis, inflammatory response