Enhanced T cell cytotoxicity drives endothelial cell dysfunction in severe COVID-19

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COVID-19 is a multisystem disorder with a strong involvement of the endothelial system. In addition to direct, virus-mediated cytopathology, the observed tissue pathology in severe manifestations of COVID 19 is propagated by a dysregulated host immune response. Along this line, T cell infiltration and associated endothelial cell injury, known as lymphocytic endotheliitis are frequently observed in severe COVID-19. Here, we describe a prominent infiltration of CD16 expressing CD4+ and CD8+ T cells in the blood and lungs of patients with severe manifestations of COVID-19. Single cell RNAseq profiling revealed increased cytotoxic potential of CD16 expressing T cells as evidenced by broad transcription of genes encoding for cytotoxic molecules such as Granzyme B. Stimulation with anti-CD16 antibodies or SARS-CoV-2 spike protein & patient serum-coupled beads triggered degranulation and release of cytotoxic cargo. Co-culturing anti-CD16 stimulated, non-naïve CD8+ T cells from severe COVID-19 patients with primary lung microvascular endothelial cells resulted in enhanced production of the neutrophil and macrophage recruiting chemokines CXCL8 and CCL2 by endothelial cells in comparison to control T cells. Furthermore, T cells from severe COVID-19 patients amplified Concanavalin A-induced loss of transendothelial electrical resistance indicating endothelial barrier disruption. Based on these findings, we propose a pathomechanism by which formation and stimulation of CD16 expressing T cells induce endothelial cell activation and dysfunction causing release of chemoattractants, infiltration of myeloid cells and thus further tissue destruction.

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