Atherosclerosis licenses for an exceeding immune response in COVID-19 disease

J. Leberzammer[1], W.T. Abplanalp[2], S.F. Glaser[2], B. Schumacher[2], M. Merten[2], M.T. Katschke[2], D. John[2], M. Vehreschild[3], A. Zeiher[2], S. Dimmeler[2], S. Cremer[3]

[1]Goethe University Hospital, Department of Medicine, Cardiology, Frankfurt, Germany; [2]Institute of Cardiovascular Regeneration, Frankfurt, Germany; [3]University Hospital Frankfurt, Department of Medicine, Infectious Diseases, Frankfurt, Germany

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Background: COVID-19 is characterized by emergency hematopoiesis with a dysregulated myeloid compartment, comprising proinflammatory and immunosuppressive immune cells. Preexisting cardiovascular disease (CVD) is a major risk factor for severe and fatal COVID-19 outcomes. Individuals with atherosclerosis are known to have a proinflammatory immune cell phenotype. However, the mechanisms of how CVD causes worse outcomes during SARS-Cov2 infection remain unknown.

Purpose: To investigate the mechanisms of how immune cells link atherosclerosis to worse COVID-19 outcomes

Methods: Single-cell RNA sequencing (scRNA-seq) of peripheral blood mononuclear cells (PBMCs) derived from hospitalized SARS-Cov2 infected patients in an uncomplicated phase of the disease not requiring intensive-care treatment with (n=5) and without (n=6) preexisting atherosclerosis was performed.

Results: Baseline characteristics between the two groups were similar (atherosclerosis vs. no atherosclerosis: mean age 75 vs. 70 years, oxygen requirement 2.2 vs. 3.2 l/min, CRP 10.7 vs. 6.6 mg/dl, IL-6 61.6 vs. 60.6 pg/ml, all $p>0.05$). In accordance with previous COVID-19 scRNA-seq studies, we found low-density neutrophils, immature neutrophils, neutrophil like plasmablasts and mostly classical monocytes in the myeloid compartment. Low-density neutrophils from patients with atherosclerosis demonstrated an increased expression of proinflammatory (IL18R1 fold change (fc) = 3.3, IL18RAP fc=1.9, HMGB2 fc=1.8, S100A12 fc=1.7, TLR2 fc=1.5, S100A9 fc=1.4 C3AR1 fc=1.8, TLR4 fc= 1.4, all adjusted p-values $<1.3x10^{-98}$) and immunosuppressive genes (IL1R2 fc=2.6, ARG1 fc=1.7, ANXA1 fc= 1.6, all adjusted p-values $<4.1x10^{-67}$). Interestingly, we found an enrichment of proinflammatory COVID-19 specific neutrophil like plasmablasts in patients with atherosclerosis (p=0.049) with an increased expression of inflammatory genes (S100A12 fc=2.5, S100A9 fc=2.5, S100A8 fc=1.8, HMGB2 fc=2.8, IL18R1 fc=3.9 S100A10 fc=2, all adjusted p-values $<1.1x10^{-54}$). In accordance, monocytes from patients with atherosclerosis showed an enrichment of inflammatory (S100A9 fc=1.6, NEAT1 fc=1.8, C3AR1 fc= 1.5, TLR2 fc= 1.5, IL13RA1 q=1.3, CCR2 fc=1.2, all p-values $<1.3x10^{-60}$) and immunomodulatory genes (IL1R2 fc=3.5, CD163 fc=2.2, all adjusted p-values $<2.7x10^{-87}$).

Conclusions: Our data show for the first time that patients with atherosclerosis have a dysregulated myeloid immune response already in the uncomplicated phase of SARS-CoV-2 infection. Upregulated genes and cell populations found in this study have previously been associated with severe COVID-19. Therefore, the enhanced inflammatory response may contribute to the worse outcome of patients with CVD and might be addressed by antiinflammatory drugs. Further efforts are needed to understand how atherosclerosis may control chromatin accessibility to predispose for an enhanced inflammatory response.

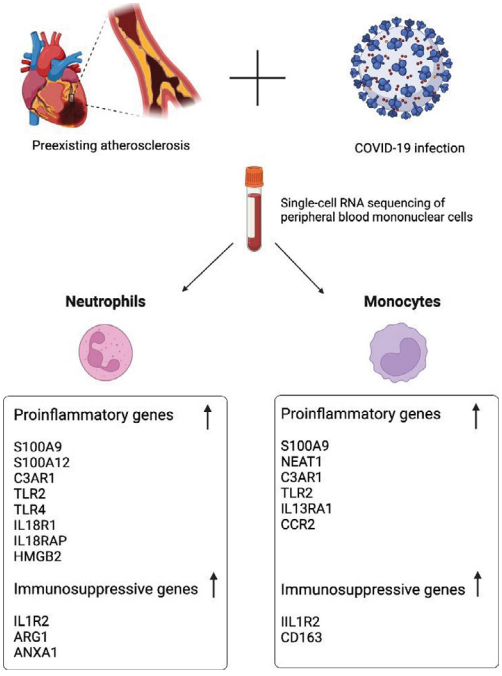

Figure 1