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lymphopenia that correlates with clinical severity and involves all lymphocyte subpopulations (1–3). In addition lymphocyte subset alterations have been observed and indeed, CD8 T- and B-cell quantities as well as CD4/CD8 ratio seem to act as independent predictors of COVID-19 survival (8). A major question, however, remains how myeloid hyperactivation and T-/B-cell dysfunction contribute to SARS-CoV-2 immunopathology. Also, can SARS-CoV-2 exert direct and indirect cytopathic e□ects on immune cells? For this to happen, an alternative SARS-CoV-2 “entry mechanism,” other than the one for respiratory epithelial cells involving viral spike-glycoproteins and angiotensin-converting enzyme 2 (ACE2) receptor interaction, must exist for immune cells that do not strongly express ACE2 receptors (2, 3, 9). In this regard, on the one hand SARS-CoV-2 may gain cellular entry via the CD147 receptor that is widely expressed on immune cells, accounting for direct immunocytopathic e□ects (10, 11). On the other hand, in analogy with e.g., dengue and influenza viruses (12), an indirect immunocytopathy may exist through antibody-dependent enhancement (ADE) mechanisms, in which

In the end, a combination of both intrinsic host-related immune features and an excessive persistent viral attack on the immune system can be mediating the pathological features of COVID-19.

Confirming this model on a mechanistic level would require a high degree of harmony between methodological initiatives and clinical study-design, starting with the collection of dedicated and hard-to-get (invasive) patient samples. These should include samples of di□erent tissues (lung, heart, spleen, liver, bone marrow and lymph nodes upon autopsy, and bronchoalveolar lavage), and longitudinal blood samples. For instance, there is a huge scarcity of high quality autopsy analyses in COVID-19 deceased patients, thereby severely compromising our understanding of this complex disease in the terminal time-frame (24). In addition to basic immunoprofiling technologies (flow cytometry/cytokine profiling), single cell-transcriptomics should be included in the workflow. This will allow in-depth dissection of the fundamental immune cell-states: i.e., immune cell di□erentiation and functional trajectories as well as discrimination of virus infected or uninfected immune cells. Such integrated knowledge will play a major role in understanding COVID-19 pathophysiology and will ser

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