RESEARCH HIGHLIGHT

Hematopoietic memory of severe COVID-19 infection

Anaisa V. Ferreira [1] and Mihai G. Netea [1,2]✉

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A new study describes that individuals who recovered from severe coronavirus disease-19 (COVID-19) exhibit long-term epigenetic changes in their hematopoietic stem and progenitor cells, which are subsequently conveyed to circulating progeny myeloid cells. This epigenetic memory of hematopoietic cells is partly mediated by IL-6 induction in the acute phase of the infection and may account for the long-term altered myeloid cell function after COVID-19.

Coronavirus disease-19 (COVID-19) emerged in December 2019 and has become a major global health crisis with considerable morbidity and mortality, particularly affecting individuals with co-morbidities and the elderly.[1] In the past 3 years, the intense study of the pathophysiology of COVID-19 highlighted the role of dysregulated immune responses, which led to the successful identification of immunomodulatory drugs, such as steroids and blockers of IL-1 or IL-6 bioactivity.[2] These novel therapies, and most importantly, the subsequent development of effective vaccines have mitigated the effects of the COVID-19 pandemic.

Unfortunately, in addition to its acute morbidity and mortality in populations at risk, COVID-19 is also followed by long-term complications in a significant minority of patients. These post-COVID-19 complications are associated with dysregulation of the immune responses, but the mechanisms underlying these defects are poorly understood. Now, in a new study in *Cell*, Cheong et al. describe the epigenetic alterations of hematopoietic stem and progenitor cells (HSPCs) in individuals recovering from severe COVID-19.[3] This epigenetic hematopoietic memory may account at least in part for the post-COVID-19 related symptoms.[3]

Certain infections and vaccines induce long-term epigenetic and metabolic rewiring in innate immune cells and their progenitors,[4] resulting in increased responsiveness to heterologous stimuli, a process termed innate immune memory or trained immunity.[5] While innate immune memory is beneficial to improve host defense against infections, inappropriate induction of trained immunity has also been associated with inflammatory diseases and complications.[6] The elegant study of Cheong and colleagues now provides evidence that similar epigenetic changes in HSPCs underpin innate immune memory in individuals recovering from COVID-19.[3]

The authors applied cutting-edge single-cell technology to HSPCs and monocytes isolated from severe COVID-19 patients that have recovered for up to 1 year. First, the authors reported that severe COVID-19 triggered persistent changes in the epigenetic landscape of circulating monocytes. These epigenetic alterations may contribute to enhanced responsiveness, as illustrated by the increased stimulated production of IL-6 by post-COVID-19 monocytes. This is supported by earlier studies showing that individuals who have recovered from moderate or severe COVID-19 exhibited long-term transcriptional and epigenetic activation of circulating monocytes associated with higher production of the pro-inflammatory cytokine IL1-β.[7] In contrast, mild and moderate convalescent COVID-19 patients displayed only minor transcriptional changes of immune cells and no alteration of their cytokine secretion capacity,[8] arguing that disease severity impacts its long-term effects.

Second, in order to determine the substrate of the long-term effects of COVID-19 on immune function, the authors hypothesized that progenitor cells would also be altered by COVID-19 and these changes would be carried over to their mature progeny. Because bone marrow HSPCs are difficult to obtain in humans, the authors developed a novel method to isolate and study HSPCs from blood as a proxy for bone marrow progenitors. They also showed that the circulating HSPCs mirror the epigenetic and transcriptional landscapes of bone marrow HSPCs. Using this new methodology, the authors described significant transcriptome and epigenome changes in HSPCs from recovered severe COVID-19 patients, who show a bias towards myelopoiesis. Previous studies also provided indications of dysregulated hematopoiesis bias towards myelopoiesis in patients with acute COVID-19.[9] Here, the authors go one step further and show that the altered transcription factor programs following recovery from severe COVID-19 are still found in not only HSPCs but also monocytes. Together, these findings highlight that the functional, transcriptional, and epigenetic rewiring post-COVID-19 observed in circulating monocytes may be inherited via the skewed differentiation of epigenetically altered HSPCs.

Third, the authors argue that IL-6R signaling during the acute phase of the disease contributes to the epigenetic reprogramming of HSPCs. Patients treated with IL-6R blocker during acute infection exhibited dampened HSPC skewing towards myelopoiesis after recovery when compared to untreated recovered patients. The mitigation of HSPC phenotypes by IL-6R blockade was recapitulated in a mouse model of COVID-19 convalescence. The authors also suggest that during recovery, the enhanced myelopoiesis and epigenetic poising of inflammatory genes in HSPCs may affect the resolution of inflammation and tissue repair. Indeed, the authors observed that recovered mice exhibited persistent monocyte recruitment to the lungs, which was partially mitigated by blocking IL-6R signaling during acute infection.[3]

The study by Cheong et al. has both biological and clinical relevance. On the one hand, it describes for the first time persistent epigenetic and transcriptional reprogramming of HSPCs

[1]Department of Internal Medicine and Radboud Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, The Netherlands. [2]Department of Immunology and Metabolism, Life and Medical Sciences Center, University of Bonn, Bonn, Germany. ✉email: Mihai.Netea@radboudumc.nl

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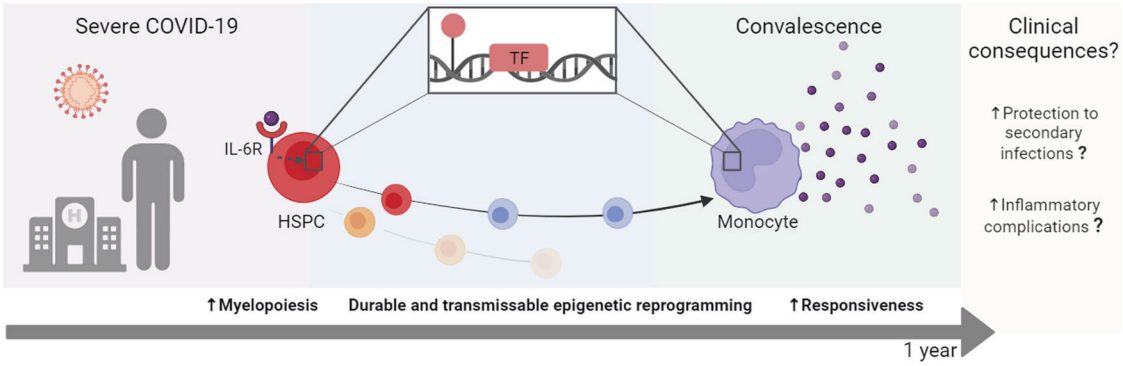

Fig. 1 Schematic diagram of COVID-19-induced hematopoietic innate immune memory. Up to one year after severe COVID-19, HSPCs exhibit epigenetic changes, which are transmitted to their myeloid progeny. IL-6 signalling contributes to the long-term increase in myeloid function, which may play a role in the pathophysiology of long-COVID or provide some protection to secondary infections. IL-6R interleukin-6 receptor, TF transcription factor. Created with BioRender.com.

after a human infection, which has the potential to open a new field of research in the long-term complications of infections. On the other hand, by describing the epigenetic and immunological mechanisms underlying altered immune responses after COVID-19, this study opens the door for potential novel therapies, e.g., blockade of the IL-6/IL-6R pathway. Finally, the novel methodology developed by the authors to study HSPCs in circulation can facilitate the study of other diseases as well.

While the study of Cheong et al. is an important step to understanding the mechanisms of altered immunity after COVID-19, many questions remain. Additional immunological and molecular pathways that may contribute to hematopoietic memory, e.g., the known hyperactivation of the IL-1 pathway in acute COVID-19, need to be investigated in future studies. Similarly, the clinical consequences of this hematopoietic memory are unclear: are these changes responsible for (some of) the post-COVID-19 pathologies, and what are the differences between different long-COVID phenotypes (e.g., post-acute sequelae of SARS-CoV-2 infection, multisystem inflammatory syndrome in adults and children[10])? Also, may these changes protect the host against heterologous (viral) infections, as is the case with trained immunity induced by vaccines (Fig. 1)? Finally, future studies should test in clinical trials the therapeutic potential of targeting these pathways that induce long-term dysregulation of the immune system after COVID-19, as only this will drive forward the clinical potential of the important discoveries made by Cheong and colleagues.

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ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Mihai G. Netea.