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NK cells on the *ViP* stage of COVID-19

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Clinical course and outcome of viral infections mostly depends on the adequate orchestration of both innate and adaptive immune response to the viral noxa. The loss of this balance emerged to be critical during SARS-CoV-2 infection, in which an unleashed cytokine response (the so called "cytokine storm") has been implicated as the main cause of morbidity and mortality in COVID-19 cases [1]. Therefore, disrupting the escalation of molecular events that lead to severe COVID-19 is an urgent - and still unmet- medical need.

By interrogating over 45,000 transcriptomic datasets of viral pandemics (SARS-CoV-1, MERS, swine flu, bird flu, influenza A/B, Ebola, Zika, HIV, HCV), in this issue of *EBioMedicine*, Sahoo and colleagues [2] progressively shortlist candidate transcripts involved in aberrant host immune response to viral infections, describing an invariant 166-gene signature highly conserved among respiratory viral pandemics (named *Vi*ral *P*andemic, *ViP* signature). Within the *ViP* signature, the authors further identify a 20-gene subset associated with severe/fatal disease (*severe-ViP* signature), eventually pointing out the IL15-IL15RA axis as the major player in immune response derangement, triggering NK cells exhaustion, senescence and apoptosis.

The *ViP* and *severe ViP*-signatures clearly unveil: (i) a paradigmatic host response to infectious noxa, including viral, bacterial and fungal; (ii) a paradigmatic host response derangement associated to a worse clinical course and outcome, centered on IL15-IL15RA cytokine system and its effects on NK cells, eventually providing a mechanistic model of severe COVID-19 in which the prolonged exposure of NK cells to a IL15-storm (originating in the lung) significantly hampers their function, leading to an exhausted phenotype which facilitates virus spread to other organs.

IL-15 is the most important cytokine for NK cell development, activation and function [3,4]. However, it has been shown that chronic NKG2C receptor stimulation on adaptive NK cells in combination with IL-15 exposure, leads to robust proliferation and functional cell exhaustion, supported by genome-wide changes in DNA methylation that mimics T CD8+ cell molecular program of exhaustion [5].

In line with these findings, Liu and co-workers [6] identified time-dependent cell-type-specific signatures associated with COVID-19 severity, represented by gene expression profiles of increased fatty acid-metabolisms and attenuated inflammation in $CD56^{dim}CD16^{high}$ NK cells, reflecting an exhaustion-like state. Consistently with the study by Sahoo et al. [2], this NK profile is positively correlated with high circulating IL15 levels.

In COVID-19, NK cell function is therefore shaping as key element in the switch from an effective to a harmful immune response, critically balancing the direct anti-viral responses– by killing infected cells – and the systemic inflammatory response [2]. Indeed, a growing body of evidence is supporting the concept that NK cells are clearly at the crossroad of divergent immune responses leading to distinct disease course and outcomes: when prolongedly exposed to high levels of IL-15, NK cell gene expression profile, phenotype and function shift toward an exhausted state, which in turn predicts severe disease with potentially fatal outcome [6].

At this point one question still remains unanswered: if the host gene expression signature (including IL15-driven NK cell exhaustion derangement in severe/fatal cases) is highly-conserved not only across different viral pandemics but also – and more in general – across different infectious agents, how can we explain the unprecedented morbidity and mortality of COVID-19?

A possible hint may derive from moving our focus from the *transcript* to the *gene*. The COVID Human Genetic Effort (https://www.covidhge.com/) seeks to understand the genetic requirements for immune control of SARS-CoV-2, in order to identify host genetic variants causal for the severe COVID-19 phenotype [8]. The first results emerging from this joint effort demonstrated that monogenic inborn errors of Type I IFN immunity are associated with life-threatening COVID-19 pneumonia. These inborn errors disrupt TLR3- and IRF7-dependent immune response, leading to impaired Type I IFN production [9].

Indeed, INF and IFN-induced cytokines program immune cells to mount responses that promote viral control. A type I-INF-rich inflammatory milieu is critical for IL15-driven NK cell activation and function [10]. Therefore, we can envision a model of immunopathogenesis of severe COVID-19 in which a "overzealous" IL15 production arising in a host genetic background of defective type I-INF production, may lead to a NK-mediated derangement of the host immune response, potentially resulting in fatal disease.

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Declaration of Competing Interest

The authors declare no conflict of interest

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