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Commentary

Blockade of an innate immune amplifier to fight immune hyperactivation in COVID-19?

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Long before reaching its peak, the SARS-CoV-2 pandemic has already met the 1 million death toll worldwide. Since whether and when an effective vaccine will be available is unknown, there is an urgent need for therapeutic approaches to target this novel viral disease. The repurposing of drugs approved for clinical use of other diseases or of compounds that are in advanced pre-clinical development can help to accelerate drug development, which otherwise takes many years [1]. A respective approach has been pursued for the antiviral compound remdesivir. This broad-spectrum antiviral drug represents an already twice-repurposed compound. It had been unsuccessful as an anti-hepatitis C medication before also failing to meet expectations as an anti-Ebola drug. It has now, however, shown positive actions against COVID-19.

Although detailed knowledge on the complex immune response towards SARS-CoV-2 is constantly evolving, it is widely established that a cytokine storm resulting from a myeloid overactivation in combination with thrombosis and vascular leakage contribute to morbidity and mortality [2]. Therefore, the search for therapeutic strategies has strongly focused on the suppression of the innate immune response. In this context one recently suggested approach focuses on the innate immune protein CD14 [2].

CD14, which exists in a membrane-bound (mCD14) and a soluble form (sCD14), represents a critical factor for the activation of innate immune cells [3]. It can act as an adaptor or co-receptor for either bacterial or viral molecular structures termed pathogen-associated molecular patterns (PAMPs). CD14 also represents an accessory protein to recognize host-derived factors during inflammation and cell lysis, termed damage-associated molecular patterns (DAMPs). SARS-CoV-2 induces cell lysis especially in the early phase of the disease, while the later phase of COVID-19 is governed by severe acute respiratory distress syndrome (ARDS), which is widely independent of viral replication [2]. CD14 levels are increased in lung lavage fluids of patients with ARDS and plasma concentrations of sCD14 correlate with disease severity [2, 3]. Higher activity of the inflammatory transcription factor NF-κB was linked to monocytes expressing high CD14 levels in patients with severe COVID-19 [4]. These findings support CD14 to contribute to a hyperactivated phagocyte phenotype.

Ongoing clinical studies are testing the efficacy of CD14 neutralization in ARDS by antibody treatment (NCT04391309, NCT04346277 on clinicaltrials.gov) with first encouraging results [2, 5]. Based on these promising findings Jimenez-Duran et al. [5] employed a genome-wide gRNA CRISPR screen to identify druggable regulators of CD14 expression. For that, they employed a gRNA CRISPR-library in a model of macrophage differentiation since CD14 is distinctly upregulated in the differentiation process from monocytes to macrophages. This approach identified several hits/genes coding for proteins suggestive to affect CD14 expression. Interestingly, most of them had previously not been known to regulate CD14 or macrophage differentiation. In order to validate the function of the identified regulators, the group employed proprietary compounds from Glaxo Smith Kline (GSK), which had been characterized earlier as potential inhibitors. One of the five tested compounds, GSK3360825A, proved to be a very promising candidate. It represents an inhibitor of MAP2K3 (and was therefore termed iMAP2K3) and was confirmed to reduce the expression of CD14 on the monocytic leukemia cell line THP-1 and also to attenuate sCD14 production by THP-1 cells. Most importantly, iMAP2K3 reduced the differentiation of primary human monocytes into macrophages as assessed by morphology and CD14 and CD16 surface staining and attenuated secretion of the inflammatory cytokines IL-1b, IL6, and TNF-α upon PAMP activation. These data show a novel role for MAP2K3 as a druggable target for inflammatory cell differentiation and activation. Supporting MAP2K3 as a potential drug target, it was very recently suggested to be involved in the regulation of lung inflammatory processes [6]. Its action on CD14 seems important since CD14 is upregulated in innate immune cells of obese people and type 2 diabetes patients. Both populations are representatives of groups with an increased risk for severe COVID-19 [3].

Interestingly, though, several data from the literature might also suggest anti-inflammatory actions of MAP2K3 / CD14: CD14 has been associated with resolution of inflammation and an immunosuppressive M2 macrophage phenotype and has been reported to be induced in immune tolerance [3, 7]. In line with these findings, also MAP2K3 showed increased expression during immune tolerance [8]. Also recent findings put therapeutic approaches to attenuate macrophage differentiation in COVID-19 into question: monocyte to alveolar

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macrophage differentiation seems to be reduced in severe COVID-19 patients [4, 9].

Several kinase inhibitors have been suggested to be useful as anti-viral and immunosuppressive compounds in COVID-19 [10]. It is too early to judge whether the inhibition of the pathway MAP2K3 → CD14 might serve as a life-saving intervention. This requires a more mechanistic understanding of the immune response in COVID-19, e.g. by extending the ongoing comprehensive immunophenotyping approaches to distinguish mild from severe COVID-19 cases. Knowledge of immune responses in COVID-19 is evolving at an enormous speed, which makes the search for drugs an attempt to hit a moving target. The use of available small molecule inhibitors for target validation might, however, allow killing two birds with one stone by focusing on targets, for which inhibitors are already available.

Declaration of interest

Dr. Kiemer has nothing to disclose.

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