Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Fatal COVID-19 infections: Is NK cell dysfunction a link with autoimmune HLH?

Dear Editor.

Shoenfeld [1] postulates that in COVID-19 infected patients a clinical constellation of cytokine storm, respiratory failure and eventually death is reminiscent of a “hyperferritinemic syndrome” a condition that resembles a hemophagocytic lymphohistiocytosis (HLH)-like syndrome. One of the most prominent immunological features of patients with primary or infection associated HLH (also referred to as macrophage activation syndrome) is the loss of natural killer (NK) cell effector functions in most types of HLH [2–4].

NK cells, unlike T lymphocytes, are governed by the balance of activating and inhibitory receptors, and as initially described by Kärre [5], the loss of inhibitory signals potentiate NK cell effector functions such as cytotoxic capacity (which require perforin (PERF) and granzyme B) and the release of interferon gamma (IFNγ) [6]. A functional NK cell population is not only important in the direct response to the virus through the elimination of virally infected cells, but it is also critical in limiting the systemic inflammatory response by killing activated inflammatory dendritic cells, monocytes, and T cells [7,8] – which are the primary drivers of this “hyperferritinemic syndrome” when other immunomodulatory mechanisms such as those mediated by tolerogenic dendritic cells are dysfunctional [9]. The importance of NK cell cytotoxic functions is highlighted in both infection-related HLH and HLH-related to inflammatory diseases. For instance, patients with influenza and systemic juvenile idiopathic arthritis that developed severe HLH more frequently were heterozygote carriers for mutations in genes implicated in NK cell cytotoxicity (e.g. PERF and LYST (lysosomal trafficking regulator) [10,11]. Similarly, NK cells may develop decreased cytotoxicity in the presence of circulating pathogenic autoantibodies targeting surface inhibitory receptors [12].

The inflammatory microenvironment may shift the balance to reduce NK cell effector functions in both COVID-19 and inflammatory forms of secondary HLH. For instance, during an acute viral infection affecting the lungs, the microenvironment becomes relatively hypoxic. Hypoxia may result in diminished cytolysis, although it does not impact antibody dependent cellular cytotoxicity (ADCC) by NK cells [13]. Also, elevated IL-6 and IL-10 levels, as observed in SARS-CoV2-infected patients [14], have the capacity to directly reduce NK cell cytotoxicity and the expression of PERF and granzyme B [15,16]. IL-6 may also reduce the expression of NKG2D, which is important in killing virally infected ones [17]. Alternatively, as it has been shown that SARS-CoV-2 binds to ACE2 [18], COVID-19 may infect NK cells to suppress their functions, as NK cells express angiotensin converting enzyme 2 (ACE2) [19]. Although not published in COVID-19, other RNA viruses that cause acute pulmonary infections such as influenza A, promote NK cell apoptosis and reduce their cytotoxicity following their infection [20,21]. With all of these mechanisms that tip the balance to favour suppression of NK cell functions (*as summarized in* Fig. 1), and thereby potentiate HLH, are there available therapies which target mechanisms that can help restore this balance in patients with SARS-Cov-2 infections?

As suggested by Shoenfeld [1], intravenous immunoglobulin (IVIG), a relatively safe non-immunosuppressive intervention, may help restore NK cell functions – although there have been no studies to date that have assessed the effects of IVIG on NK cell functions in the setting of an acute viral infection. IVIG (2 g/kg ideal body weight) may help improve outcomes in patients with COVID-19 [22]. In a pre-clinical model for graft-vs-host disease, IVIG promotes the expansion of functional NK cells [23]. In patients with Kawasaki's disease, who also develop a cytokine storm, treatment with IVIG increases NKG2D expression which may promote their cytolytic functions [17]. It may also reduce the re-

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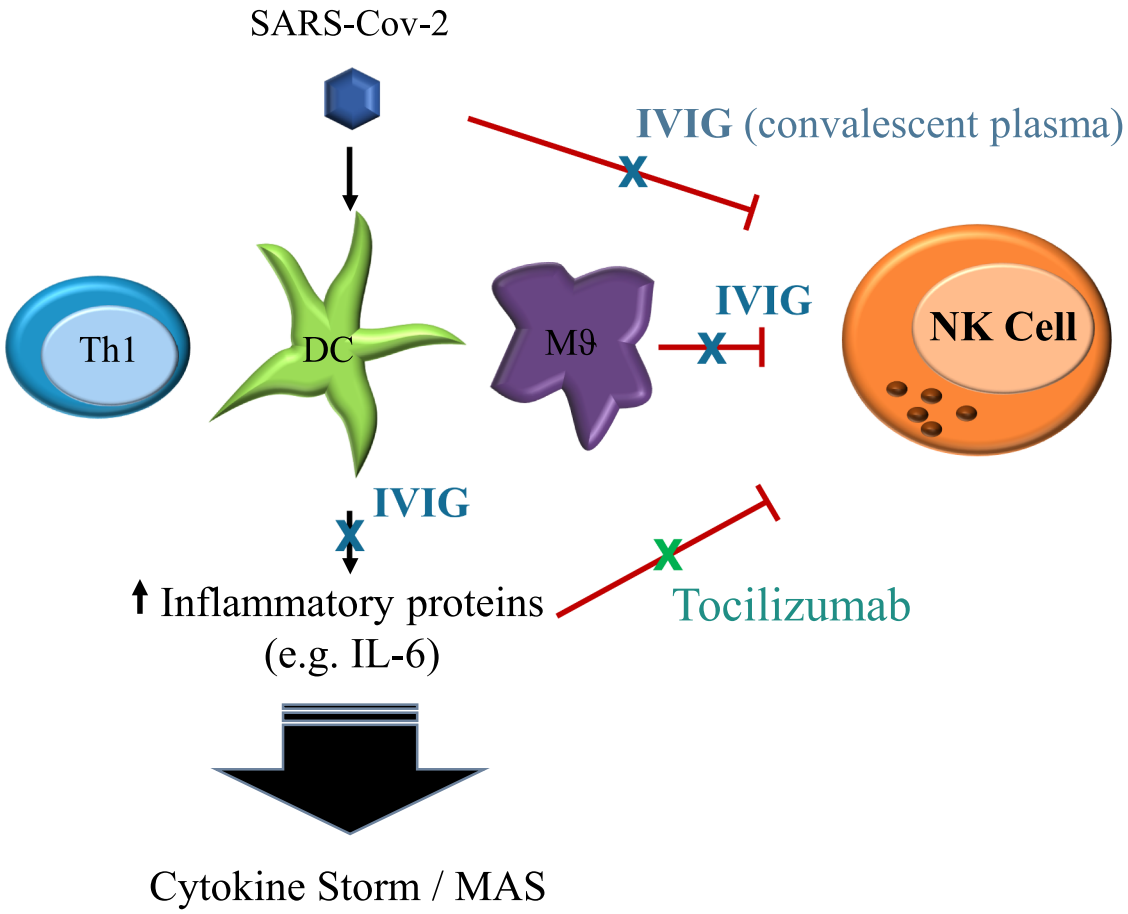

Fig. 1. SARS-CoV-2 and the subsequent immune cell inflammatory responses suppress NK cell cytotoxicity which promotes a severe cytokine release syndrome, and inadequate termination of immune responses. Intravenous immunoglobulin (IVIG) promotes NK cell cytotoxicity by promoting ADCC and subsequent dendritic cell apoptosis, reducing circulating viral particles (convalescent plasma), and by reducing inflammatory cytokine levels. Tocilizumab reduces IL-6-dependent suppression of NK cells.

lease of IL-6 by activated inflammatory cells [24]. Moreover, IVIG may directly promote NK cell-mediated termination of inflammatory responses by promoting NK-cell mediated ADCC of activated dendritic cells [25]. A different form of IVIG which may be most beneficial when given prophylactically, particularly to patients most at risk for complications is convalescent serum, which may reduce circulating viral particles and possibly promote NK cell ADCC towards virally infected cells (26–28). Other therapies that are currently used in patients with HLH due to COVID-19 include anti-IL6 receptor monoclonal antibodies (29) Anti-IL6R may increase NK proliferation and cytotoxicity [26]. Future studies defining the effects of IVIG and possibly anti-IL6R on NK cells in patients that are infected with COVID-19 may provide further insight if and how they may limit the cytokine storm that is observed in severe cases.

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