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Review

Guardians of Immunity: NK Cell-Mediated Defense in COVID-19 and Post-COVID Scenarios

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Abstract

The COVID-19 pandemic has left a lasting impact on global health, challenging communities, healthcare systems, and researchers worldwide. As we navigate this unprecedented crisis, this paper embarks on a multifaceted exploration of the pivotal role played by natural killer (NK) cells in the context of COVID-19. A significant portion of this paper is devoted to dissecting the nuanced role that NK cells assume in the context of COVID-19. From the initial acute infection to post-recovery immunity, NK cells emerge as critical players. We scrutinize the activation and dysregulation of NK cells during SARS-CoV-2 infection, shedding light on their potential contribution to disease severity. Moreover, we explore the fascinating landscape of post-COVID immunity, where NK cells are known to interact with adaptive immune responses, providing a foundation for long-term protection. In light of their central role, we investigate therapeutic strategies targeting NK cells in COVID-19 management, presenting an overview of current research efforts and their promise in mitigating disease progression. Lastly, we draw attention to research gaps, emphasizing the need for further investigation into NK cell dynamics during COVID-19. These gaps represent opportunities for advancing our understanding of NK cell biology and, by extension, enhancing our strategies for combating this global health crisis. This comprehensive exploration not only highlights the intricate interplay between NK cells and the COVID-19 pandemic but also underscores the importance of these innate immune warriors in shaping both the acute response and long-term immunity, ultimately contributing to the broader discourse surrounding the pandemic's pathophysiology and therapeutic approaches.

Keywords

COVID-19, NK cells, SARS-CoV-2, post-COVID

INTRODUCTION

At the end of 2019, a new pathogen was isolated in Wuhan and introduced to the public, later called Coronavirus 2 of the severe acute respiratory syndrome (SARS-CoV-2), causing acute respiratory distress syndrome (ARDS), commonly known as COVID-19.[1] The strong and persistent influence of the virus on the world population led to the announcement that in 2023 there was going to be an evident pandemic with 770 085 713 confirmed cases of infection, including 6 956 173 deaths for the whole period globally.[2] Apart from the epidemiological factors and comorbidities, a prominent influence on the course of the disease has the impaired immune functionality. The damage on a cellular level caused by SARS-CoV-2 infection leads to immense secretion of proinflammatory cytokines and the gathering of other proinflammatory cells, which can cause a systemic inflammatory response called macrophage

activation syndrome (MAC) or secondary hemophagocytic lymph histiocytosis (sHLH), commonly labeled as "cytokine storm" (CS).[3] A possible explanation can be provided by two hypotheses: I) direct viral infection can be the cause of this excessive cytokine release by the immune cells; II) an impaired functionality or suppressed cytolytic activity of the effector natural killer cells (NK cells), which destroy infected cells, restricting the CS and viral load in the body. The NK cell function in SARS-CoV-2 infection remains unclear. Gathering more data on NK cell status and antiviral role post-infection is crucial. The major role of NK cells as key mediators between cell-mediated immunity and humoral immunity leads to the necessity of conducting longitudinal analyses and obtaining a clearer view of how SARS-CoV-2 inhibits the innate resistance components of our immune system. The aim of our research was to summarize and present more information about the intriguing role of NK cells in the defense against SARS-CoV-2 and post-COVID scenarios.

NK cell biology and function

Natural killer cells are innate lymphocytes that function critically in defense against viral infections and malignancies. They fulfill these roles through multiple mechanisms that collectively exert both direct antiviral and antitumor responses while helping to shape adaptive and innate immune responses. NK cells are classified within the innate lymphoid cell (ILC) family, which includes conventional NK cells and tissue resident ILC cells.[4] ILC1 and NK cells share developmental factors like Id2 and Nfil3, but ILC1s also need PLZF and IL-7, while NK cells require IL-15.[5,6] They release perforin and granzymes from lytic granules upon activating signals, playing a distinct role in innate immunity due to their cytotoxic function and abundant lytic granules.[7,8]

NK cells derive from a common progenitor, with some authors reporting a putative population of NK cell progenitors, in human bone marrow, blood, and secondary lymphoid organs, characterized by the following cell surface markers: Lin^-, $CD34^+$, $CD38^+$, $CD123^-$, $CD45RA^+$, $CD7^+$, $CD10^+$, and $CD127^-$ which can only give rise to NK cells both *in vitro* and *in vivo*.[5] Commonly, natural killer cells are defined as $CD3^-CD56^+$, and they are divided into two major subsets with different functions and maturation statuses: $CD56^{bright}CD16^-$ and $CD56^{dim}CD16^+$. The $CD56^{dim}CD16^+$ NK cells are known as a highly differentiated subset with expression of immunoglobulin-like receptor (KIR) in high concentrations and low expression of CD94 and CD62L, potent cytotoxicity and capacity to induce antibody-dependent cellular cytotoxicity (ADCC). More less mature $CD56^{bright}CD16^-$ NK cells lack KIR expression but are the major cytokine producers and are associated with regulatory functions.[9] KIRs and Ly49 receptors recognize host-derived major histocompatibility complex class I (MHC-I) molecules, contribute to the "licensing" and "learning" processes that occur during NK cell development, and ensure that only NK cells capable of engaging self-MHC molecules with their inhibitory receptors are allowed to become functionally competent but are also prevented from killing healthy cells.[10,11] Activation of NK-cell receptors, including NK group protein 2 family member D (NKG2D), cytotoxic receptors (NKp30, NKp46 and NKp44), DNAX accessory molecule-1 (DNAM-1); and the co-receptors: NTB-A, 2B4, NKp80 and CD59[12] are critically involved in the NK-cell activities.

NK cells have two main mechanisms of cytotoxicity: 1) granule-mediated apoptosis activated by pro-inflammatory cytokines, along with a number of cell surface receptors, and mediated by perforin and granzyme, and 2) antibody-dependent cell-mediated cytotoxicity. Upon NK cell activation, cytotoxic granules are exocytosed, allowing perforin to form pores in the cell membrane of target cells.[13] After disruption of the cell membrane, granzyme-serine proteases are delivered to the cytoplasm of the cell, where they induce apoptosis via diverse range of pathways **(Fig. 1)**.

NK cells express TNF family cytokines, crucial for apoptosis and immune regulation. TRAIL (Apo2 ligand), a TNF superfamily member, binds TRAIL-R1/DR4 and TRAIL-R2/DR5 receptors, inducing apoptosis. TRAIL is upregulated on NK cells upon IL-2, IFNs, or IL-15 stimulation, reflecting its role in IFN-associated innate immunity.[14,15]

NK cells also express Fas-L, contributing to tumor suppression by inducing Fas expression via IFN-secretion and mediating Fas-dependent killing.[16] FLIP inhibitors hinder Fas-L cytotoxicity against tumors.[17]

NK cell effector functions are blocked when inhibitory receptors bind MHC class I. Although human KIRs and CD94/NKG2A receptors dictate NK cells faith, stimulatory receptors are vital for their initial activation.[17]

NK cells in COVID-19

In association with lymphopenia in patients with COVID-19, the number of NK cells in the peripheral blood is consistently and significantly reduced and is inversely proportional to the severity of COVID-19[5,16-25], although some authors report no changes in terms of NK cell numbers[5,17,19,24-29]. NK cell numbers reclaim normal levels after clinical recovery from COVID-19.[18,19] The depletion of peripheral blood NK cells in patients with COVID-19 could potentially, in part, be due to their mobilization and homing to various tissues or their death following activation by SARS-CoV-2. Infection of NK cells with a virus leads to their death. These mechanisms of NK cell depletion in patients with COVID-19 need to be further clarified.

NK cells are generally divided into subsets of cytokine-producing $CD56^{bright}$ NK cells and cytotoxic $CD56^{dim}$ ones.[6] Most studies have shown that in COVID-19 the proportions of the former are reduced[5,14,30-33], with some exceptions.[17,26,34] However, data on $CD56^{dim}$ NK cells in COVID-19 remain conflicting: some authors report reduced proportions[5,17,27,32,33], while others show increased

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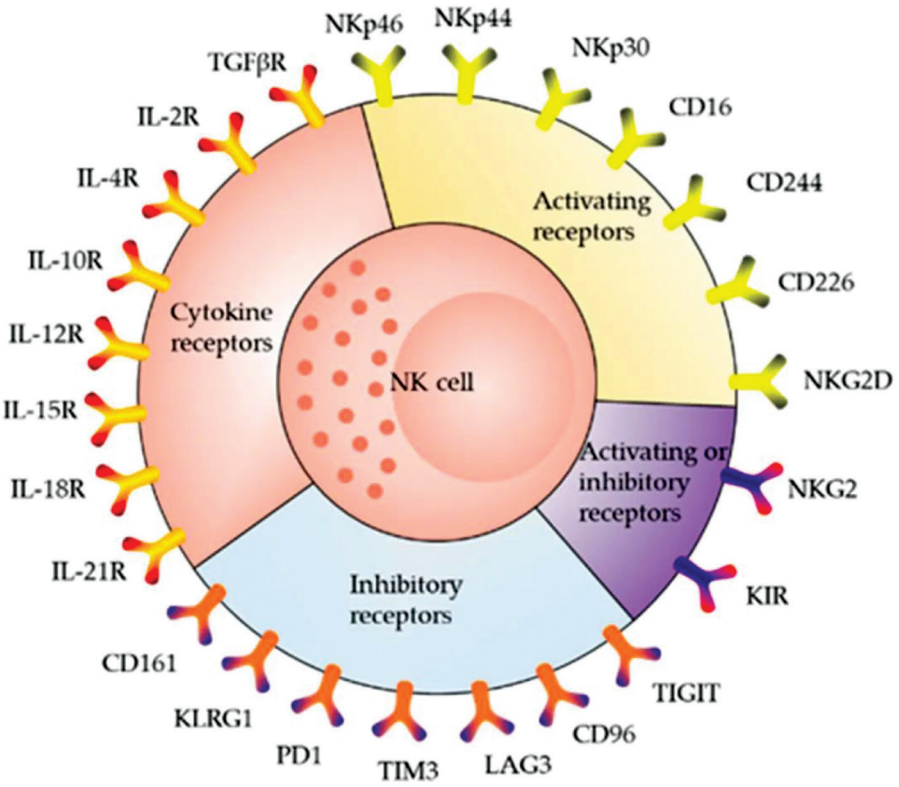

Figure 1. NK cell surface receptors.

proportions[14,28,30] or no change[26,29,31,34]. The reason for these conflicting results in patients with COVID-19 is currently unknown, and the correlation between NK-cell subsets and patient status requires further studies.

Antiviral effects of NK cells may be mediated through the cytokines they produce, in addition to cross-talk with other innate immune cells and the regulation of the adaptive immune response. Therefore, the cytokine-producing capacity of NK-cells is an important parameter for the investigation of their function, in addition to their activity. Impaired IFN-γ and TNF-α production may be due to soluble factors in plasma from patients with COVID-19, as shown by a study on NK-cell activity in response to K562 cell stimulation.[31] These results indicate that cytokine production by peripheral blood NK cells is impaired and exhibits a bias toward redistribution of NK cells to sites in the inflamed lungs.[32]

The primary mechanism by which NK cells eliminate virus-infected or transformed cells involves granule exocytosis, with the direct release of cytolytic granules containing perforin and granzymes that kill target cells by apoptosis.[35] Examination of the expression levels of perforin, granzyme A (GrA) and granzyme B (GrB) in NK cells from patients with COVID-19 shows conflicting data. Some authors reported an increased level of perforin expression[20,29,34,36], while others reported unchanged expression. Regarding granzyme levels in patients with COVID-19, results also vary between studies. Both increased levels of GrA[36] and decreased levels have been found. Discrepancies between studies may be caused by the sampling period during the course of the disease and its severity.

The NK cell activity in patients with COVID-19 is assessed also via flow cytometry-based CD107a expression (degranulation). The percentage of CD107a-expressing NK cells is consistently lower in patients with COVID-19 than in controls.[14,18,28,31] There is a statistically significant decrease in the expression level of CD107a, which is negatively correlated with C-reactive protein levels, indicating that under conditions of exaggerated systemic inflammation, NK cells are dysfunctional in the peripheral blood of patients with COVID-19.[31]

Upon SARS-CoV-2 infection, innate immune cells like NK cells, DCs, and alveolar macrophages swiftly respond in infected tissues, initiating immune reactions to eliminate the virus. Effective NK-cell recognition of infected cells requires high activating receptor levels and low inhibitory receptor levels, enabling enhanced degranulation, cytokine secretion, and cytotoxicity for early virus elimination.[33,37-39] However, COVID-19 patients often exhibit dysfunctional and exhausted NK cells[31,40] linked to disease severity[41]. SARS-CoV-2 can impair the NK-cell function by elevating inhibitory receptor NKG2A via the viral spike protein. Exhausted NK cells may shift cytokine storm induction to non-NK sources like IFN-γ. Type I interferons, strong NK cell activators, potentially link interferon deficiencies to impaired antiviral NK cell function.[42] The correlation between functional NK cell numbers and COVID-19 severity underpins their role in controlling SARS-CoV-2, awaiting definitive validation.[24,25,31,32]

Upon acute SARS-CoV-2 infection, NK cells display activation markers (Ki67, CD69, HLA-DR, CD38) and inhibitory receptors (LAG3, TIGIT, TIM3)[20,23,36], alongside reduced peripheral function.[24,25] In severe cases, single-cell transcriptome analysis reveals an increase in "inflammatory CD56^{dim}" (IFI6, ISG15, etc.) and "proliferating CD56^{dim}" (MKI67, LGALS1, etc.) subsets.[31] Recovering NK and T cell numbers contrast with the NK cell loss in fatal cases.[32] IFN-γ and TNF-α expression decrease, particularly in severe forms.[31] COVID-19 patients exhibit heightened NKG2A and reduced NKG2D receptors[29,33,36], indicative of functional exhaustion, possibly influenced by IL-6-induced NKG2D down-regulation.[34]

Post-COVID immunity and NK cells

Having some information about the consequences of long COVID on NK cell activity[25], suggesting a contribution to organ damage, the role of NK cells in post-COVID syndrome, which is a condition where some patients experience persistent symptoms after recovering from COVID-19, is not well understood. In a recent study, Malengier-Devlies et al.[43] reported that NK cells from COVID-19 patients displayed hyper-activation and increased expression of activation markers, such as CD69 and NKG2D, although the total number of NK cells were decreased. Another discovery was that NK cells from post-COVID patients expressed lower levels of GZMB and PRF, and upregulated HLA-DR, compared to healthy control group. They also found that NK cells formed aggregates with platelets, which may enhance their cytotoxicity and cytokine production. However, they noted that post-COVID-19 patients showed slow recovery of NK cell frequencies and phenotype, suggesting that NK cell function may be compromised in the long term.

Another recent study depicts an increase in NK-effector functions in patients' samples for up to six months post symptoms onset.[44] The research team found that NK cells show an enrichment in antibody-dependent Fc-effector functions in patients presented with milder symptoms. Similar findings, although in severely ill patients, are reported by another team of researchers[45] last year. They found an increase in CD56^{dim} NK cells in recovered patients 3 months after dehospitalization.

These studies, which are similar on the one hand but contradictory on the other, indicate that NK cells are involved in the pathogenesis and recovery of COVID-19, but their role in post-COVID syndrome is still unclear. More research is needed to elucidate the mechanisms and consequences of NK cell impairment or hyper-activation.

Therapeutic strategies targeting NK cells

The global scientific community has been engaged in an intense endeavor to decipher the intricate interplay between the immune system and the SARS-CoV-2 virus, which has led to the ongoing COVID-19 pandemic. As we delve deeper into understanding the multifaceted immune responses elicited by this novel coronavirus, the role of NK cells emerges as a captivating focal point. These innate immune cells, known for their rapid and versatile effector functions, have garnered attention for their potential in combating viral infections, including COVID-19.

In the pursuit of effective therapeutic interventions, a compelling question arises: can harnessing the power of NK cells be a viable strategy to ameliorate the severity of COVID-19 and improve clinical outcomes? As researchers and clinicians strive to unravel the complexities of NK cell biology in the context of COVID-19, several intriguing avenues for therapeutic exploration have emerged.

One approach is NK-cell infusion, which is the administration of exogenous NK cells from healthy donors or cell lines to COVID-19 patients. The aim is to boost the antiviral immunity and reduce the viral load and inflammation. An experimental clinical trial is currently testing the safety and efficacy of an allogeneic NK cell therapy (DVX201) in hospitalized COVID-19 patients.[46]

Another experimental tool for the induction of NK cells is cytokine stimulation. This is the use of cytokines or cytokine inducers to enhance the activation, proliferation, and survival of NK cells in COVID-19 patients. The most commonly used cytokines are IL-2, IL-15, and IL-18. Cytokine stimulation can also improve the expression of NK cell receptors, such as NKG2D and CD16.[47,48]

Another method is the administration of monoclonal antibodies. They bind to specific antigens on the surface of SARS-CoV-2 or infected cells and can recruit NK cells to mediate antibody-dependent cellular cytotoxicity and eliminate the virus-infected cells. Some examples of monoclonal antibodies are bamlanivimab, casirivimab, and imdevimab. [49]

An additional strategy commonly used in cancer therapy is the chimeric antigen receptor (CAR) expressing cells. CAR-NK cells are NK cells that can be genetically modified to express a chimeric antigen receptor that recognizes SARS-CoV-2 spike protein. They can directly target and kill SARS-CoV-2-infected cells without the need for antibodies or other immune cells. CAR-NK cells have shown promising results in vitro and animal models.[50]

Research gaps

Despite significant progress in unraveling the intricate interplay between the immune system and the SARS-CoV-2 virus, numerous gaps remain in our understanding of the role of NK cells in the context of COVID-19 and its aftermath. While existing research has shed light on the dynamic changes in NK cell populations and their functional adaptations during acute infection, many questions persist regarding the precise mechanisms through which NK cells exert their influence on disease outcomes. Moreover, as the global health community turns its attention to the multifaceted phenomenon of post-COVID conditions, investigations into the enduring impact of NK cell dysregulation

and the potential contributions of these cells to long-term immune dysfunction are only in their nascent stages.

CONCLUSIONS

The lack of significant complications in most healthy people who are exposed to SARS-CoV-2 highlights the fact that an effective innate immune response may be able to prevent the pathological symptoms of COVID-19 and clear the body of infection. However, as an escape and resistance strategy, SARS-CoV-2 has shown an unusual ability to counter the innate immune defense by either distorting its basic function or disabling key players involved in the immune response, such as NK cells. A cytokine storm is a clear sign of a deviation of the immune system in the effective response to infection, which occurs when the virus enters the affected cells, including macrophages, forcing them to produce an increasing amount of inflammatory mediators. Such an imbalance in the production of inflammatory cytokines does not only support an effective fight against the virus, but also ultimately leads to widespread inflammatory damage, especially in the lungs, which is one of the main complications of the disease and one of the leading causes of death in patients. In the face of such a situation, the role of NK cells in the elimination of virus-infected macrophages and their state after the encounter with the virus seems very important and deserves to be studied in detail.

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Competing Interests

The authors have declared that no competing interests exist.

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Защитники иммунитета: защита, опосредованная NK-клетками, в сценариях COVID-19 и пост-COVID

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Резюме

Пандемия COVID-19 оказала долгосрочное воздействие на глобальное здравоохранение, сложные сообщества, системы здравоохранения и исследователей во всём мире. Пока мы преодолеваем этот беспрецедентный кризис, данная статья приступает к многогранному исследованию ключевой роли, которую играют естественные клетки-киллеры (NK) в контексте COVID-19. Значительная часть этой статьи посвящена анализу нюансов роли, которую NK-клетки берут на себя в контексте COVID-19. От первоначальной острой инфекции до иммунитета после выздоровления NK-клетки играют решающую роль. Мы внимательно изучаем активацию и нарушение регуляции NK-клеток во время инфекции SARS-CoV-2, проливая свет на их потенциальный вклад в тяжесть заболевания. Более того, мы исследуем захватывающий пейзаж иммунитета после COVID, где NK-клетки, как известно, взаимодействуют с адаптивными иммунными реакциями, обеспечивая основу для долгосрочной защиты. Учитывая их центральную роль, мы исследуем терапевтические стратегии, нацеленные на NK-клетки при лечении COVID-19, представляя обзор текущих исследовательских усилий и их перспектив в смягчении прогрессирования заболевания. Наконец, мы обращаем внимание на пробелы в исследованиях, подчёркивая необходимость дальнейшего изучения динамики NK-клеток во время COVID-19. Эти пробелы представляют собой возможности для улучшения нашего понимания биологии NK-клеток и, как следствие, для улучшения наших стратегий борьбы с этим глобальным кризисом здравоохранения. Это всестороннее исследование не только подчёркивает сложную взаимосвязь между NK-клетками и пандемией COVID-19, но также подчёркивает важность этих воинов врождённого иммунитета в формировании как острого ответа, так и долговременного иммунитета, что в конечном итоге способствует более широкому дискурсу о патофизиологии пандемии. и терапевтические подходы.

Ключевые слова

COVID-19, NK клетки, SARS-CoV-2, пост COVID