Archives of Advances
in Biosciences

Review Article:
Natural Killer Cells: New Suspects in the Cytokine Storm of COVID-19 Infection

Hamid Chegni[1*], Nasim Rahmani-Kukia[2], Ardeshir Abbasi[3], Nafiseh Pakravan[4], Manoochehr Pourshaban[5], Zuhair Mohammad Hassan[3]

1. Department of Medical Laboratory Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2. Department of Biochemistry, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.
3. Department of Immunology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran.
4. Department of Immunology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran.
5. Department of Environment and Primary Prevention, Istituto Superiore di Sanità, Rome, Italy.

Use your device to scan and read the article online

Cite this article as: Chegni H, Rahmani-Kukia N, Abbasi A, Pakravan N, Pourshaban M, Mohammad Hassan Z. Natural Killer Cells: New Suspects in the Cytokine Storm of COVID-19 Infection. Archives of Advances in Biosciences. 2021; 12(4):58-62. https://doi.org/10.22037/aab.v12i4.36514

https://doi.org/10.22037/aab.v12i4.36514

Article info:

Received: 23 Oct 2021

Accepted: 12 Nov 2021

Published: 20 Nov 2021

***Corresponding author:**

Hamid Chegni, PhD.

Address: Department of Immunology, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

E-mail: h.chegini2010@yahoo.com

Abstract

Context: Various studies show that contracting the Covid 19 disease can affect the normal functioning of the immune system. In some patients, lack of stimulation of the specific immune system causes excessive innate immune activity and secretion of inflammatory cytokines.

Evidence Acquisition: It seems that the occurrence of cytokine storm depends on various factors. One of the immune system cells that can play an important role in cytokine storm is Natural Killer (NK) cell. Thus, more attention should be paid to the role of NK cell in patients with Covid-19.

Results: In this article, we seek to examine the role of NK cell in cytokine storms.

Conclusion: Perhaps the difference between the characteristics of NK cell in children and adults is due to the difference in the severity of symptoms after infection with Covid-19.

Keywords: Natural killer cell, Cytokine storm, Covid-19

Context

Natural Killer (NK) cell, as the most important cell of innate immunity, functions at the first line of defense against viral infections. This cell directly destroys the virus or leads to the apoptosis of viral-infected cells. NK cell responds even more quickly than T cell to virus, cancer, and infectious agents [1]. In addition, NK cell activates the adaptive immunity against viral infections by releasing cytokines [2]. $CD3^-$, $CD56^+$, and $CD16^+$ markers generally identify NK cells. According to CD56 marker, NK cells are divided into two sub-sets: dim and bright. In a way that $CD56^{dim}$ NK cells have cytotoxic power, while $CD56^{bright}$ are more likely to produce pro-inflammatory cytokine [3]. Studies have shown that $CD56^{dim}$ NK cells commonly comprise more than 90% of NK cells of the peripheral blood in healthy people. However, in older adults as well as in acute/chronic viral infection states, phenotype change occurs in NK cells and they become more likely to have the dominant $CD56^{bright}$ phenotype to release inflammatory cytokines (IFN-c, TNF-α, GM-CSF) [4-8]. The function

of NK cells is controlled by the surface receptors such as Killer cell Immunoglobulin-like Receptors (KIRs), Natural Cytotoxicity Receptors (NCRs), and C-type lectins. Interestingly, KIRs express only at the surface of $CD56^{bright}$ cells, which are more common in the elderly [9]. In children, however, the most important receptors of NK-activated cells (NKp30 and NKp46 receptors) are reduced. This means that NK cells are less active and potentially supportive in children [10]. It has been shown that as one ages, NKG2A receptor of NK cells decreases and, instead, the active KIR receptor family increases.Therefore, in the case of NK cells some thought-provoking items are very exciting and should be considered. These items include changing in number, subtype, receptor and function of NK cells that differ by gender, race, age, genetic polymorphisms, geographical location, pathological conditions and infectious diseases. These matters are very important, and some of which will be discussed here.

Evidence Acquisition

The number of NK cells is affected by gender, which is more in men than women. A study has found that the Iranian men who had more NK cells than women are more likely to produce inflammatory cytokines (IL-6 and TNFα) [11]. Other studies have revealed similar results as well [11-13]. It seems that estrogen reduces the expression of CD69, NKp46, and NKG2DL at the surface of NK cells, resulting in the suppression of NK cells activity in women [14]. Moreover, the number of NK in different races differs by geographical locations; this has been confirmed by the results of a study where the rate of NK cells in the Iranian population is higher than the Caucasian population [15]. In this regard, another study has found that the NK rate of the Chinese population to Caucasus is similar to that of Iranians' [16]. Besides, the number of NK cells was higher in Iranian men than Saudi men [17]. It seems that these differences affect public susceptibility to infections.

The rate of NK cells also changes by age in a way that a study in Iran has shown the highest rate of NK cells for 50- 60 ages and the lowest one for below 30 [11]. In children, NK cell has frequent suppressive phenotype, regardless of age, the inhibitory receptor NKG2A decreases and instead the family of active KIR receptors increases. Since, phenotype of NK cells changes with age, it can be predicted that their different functions depend on the physiological conditions in which they are located. KIR is one of the activating or suppressing receptor which expresses the surface of NK cells. The KIR gene is polymorphism and has a genetic diversity. Therefore, KIR is expressed by specific phenotypes and different function. A study on Italian population has revealed that framework genes (KIR3DL3, KIR3DP1, KIR2DL4 and KIR3DL2) are found in all cases and a haplotype had the most prevalence (28.5%) between them and these KIR genes expressions significantly increased in old ages. Another study has found that Chinese people were positive for 3DL3, 3DP1, 2DL4, and 3DL2 like Italians and A haplotype showed the highest prevalence (58.7%) [18]. In contrast, the level of heterogeneity and polymorphism of A haplotype in KIR gene of Japanese population was much lower than the Italian and Chinese populations [19]. A study has presented that the activating genes KIR2DS1 and KIR2DS3 are associated with increased mortality by Ebola virus infection. These findings suggest that mortality and morbidity from the Ebola virus may be partly related to the kind of the KIR gene in host; this indicates the key role of KIR in increasing susceptibility to infection [20]. On the other hand, it has been found that the combination of HLA-KIR genotype is associated with susceptibility to autoimmune diseases such as arthritis and type 1 diabetes. Additionally, it has also been reported that HLA Bw4 and Bw6 epitopes are identified by NK cells. The polymorphic receptors KIR3DL1/S1 and HLA Bw4 increase the potential of NK cells activation against infection [21].

The Covid-19 infection pandemic has recently emerged and is rapidly spreading in more than 200 countries around the world. According to the World Health Organization, 1,536,094 global cases of Covid-19 were confirmed on April 9th with a mortality rate of 3.4%. Unfortunately, the worldwide rate of morbidity and mortality of COVID-19 is increasing on a daily basis. One reason for these severe effects is septic shock which is due to the production of cytokine storms by the immune system against COVID-19 infection in people under intensive care. Septic shock finally leads to organ dysfunction, secondary infection and Ventilator-Associated Pneumonia (VAP), and eventually death [22]. It has been observed that in the alveoli of lungs of people who could not survive, lymphocytopenia makes decreased Treg while triggers innate immune cells proliferation. Cytokines storm appears to be the result of over activity of innate immune cells in the region of existing NK cells. Therefore, our concern is that septic shock may be due to NK cells activity. It is interesting that the number of NK cells in peripheral blood of covid-19 patients is decreased as is seen in septic shock of other infections. Several hypotheses could be made in the study of NK cells reduction in peripheral blood and cytokine storm of NK cells in the local lung zone of infected Covid-19 patients.

Results

Reduction in the quantitative NK cells following Covid-19 infection

The first scenario is that the decline in the number of NK cells in the peripheral blood may be due to a reduc-

tion in the number of $CD56^{dim}$ NK cells with the cytotoxicity strength as mentioned above. Although NK cells are 90% in the peripheral blood on the normal conditions, but during septic shock recruit to the lung and make cytokine storm by secreting inflammatory cytokines. However, the number of NKs in this area has not been investigated yet. This hypothesis could be supported by previous reports showing that the level of $CD56^{dim}$ NK cells decrease during septic shock. Furthermore, in septic shock the level of $CD107^{+}$ in the peripheral blood decreases compared to healthy individuals as is seen in Covid-19 patients [23].

On the other hand, viral-infected cells or residing immune cells, promote proliferation and activation of immune cells by releasing cytokines. Thus, NK cell is one of the fastest cells of innate immune in response to viruses, quickly arrive the affected areaand after proliferate become overactive. This hypothesis could be supported by a study which reported that one of the causes of septic shock is the secretion of IL-15 by some residual cells and activated NK and CD8 cells, resulting to death of patients by septic shock [24]. Thus, septic shock initiates in Covid-19 patients by proliferation of NK cells as a result of increased IL-15 in the lung.

Alteration in NK cells functions and phenotype following COVID-19 infection

In the second scenario, it could be supposed that due to the existence of different subtypes of NK, a special subtype of NK cells can be activated in the conflict zone. Similarly, in a study of patients who had died by septic shock, the number of NK cells with $CD3^{-}$, $CD56^{+}$ were significantly reduced, while the number of NK in $CD69^{+}$ and $CD57^{+}$ were increased compared to the survival group [25]. The study found that NK with $CD69^{+}$ and $CD57^{+}$ were so many in most patients with septic shock death on the third day and it may be similar to septic shock from Covid-19. On the other hand, the reduction in the mortality rate of COVID-19 infection in women may be related to a decrease in $NKCD69^{+}$. In approval of NK cells effect on Covid-19 patients, it is reported that the Chinese have used the drug hydroxychloroquine to combat Covid-19 and could almost reach acceptable results. Previous studies have shown that hydroxychloroquine could regulate NK cells responses by reducing changes in TNF-α secretion and decrease NK cell function [26].

Another study found that hydroxychloroquine reduces the cytotoxic activity of NK cells [27], the function and the proliferation of these cells as well [28-30]. To the best of our knowledge, however, no studies have explained the mechanism by which NK cell function is reduced and which subtypes of NK cell are affected.

Conclusion

It can be proposed that the increased rate of Italian and Chinese mortality with COVID-19 compared to the lower ones in Japanese may be related to the number and subtypes of NK cells, age and sex of individuals, and geographical location. Besides, it might be associated to the incidence and polymorphisms of KIR-related genes that affect NK subtypes. According to the mentioned hypothesis, any changes in the balance of NK cells' expressed receptor, subtypes and its relation to pathogenesis and susceptibility to infection and inflammatory diseases are remarkable. Moreover, by observing the mortality and morbidity statistics of COVID-19, age, gender, and geographical locations of affected public, the outcomes can corroborate our aforementioned points about NK cells. Consequently, we suggest that by investigating the phenotypes and functions of NK cells in the affected parts of body, we can better recognize the physiopathology of COVID-19 in order to use therapies in the early stages. It seems that drugs such as azathioprine, prednisolone, pyrimethamine and mefenamic acid which could specifically regulate NK cells activity, could be a good suggestion for the treatment of Covid-19 and the prevention from septic shock.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research was Funded by Shahid Beheshti University Of Medical Sciences

Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

We would like to extend our appreciation and thanks to all participants, staff, and managers who made this study possible.

References

[1] Vivier E, Raulet DH, Moretta A, Caligiuri MA, Zitvogel L, Lanier LL, et al. Innate or adaptive immunity? The example of natural killer cells. Science. 2011; 331(6013):44-9. [DOI:10.1126/science.1198687] [PMID] [PMCID]

[2] Golden-Mason L, Rosen HR. Natural killer cells: Multifaceted players with key roles in hepatitis C immunity. Immunol Rev. 2013; 255(1):68-81. [DOI:10.1111/imr.12090] [PMID] [PMCID]

[3] Carvelli J, Piperoglou Ch, Bourenne J, Farnarier C, Banzet N, Demerlé C, et al. Imbalance of circulating innate lymphoid cell subpopulations in patients with septic shock. Front Immunol. 2019; 10:2179. [DOI:10.3389/fimmu.2019.02179] [PMID] [PMCID]

[4] Dessouki O, Kamiya Y, Nagahama H, Tanaka M, Suzu Sh, Sasaki Y, et al. Chronic hepatitis C viral infection reduces NK cell frequency and suppresses cytokine secretion: Reversion by anti-viral treatment. Biochem Biophys Res Commun. 2010; 393(2):331-7. [DOI:10.1016/j.bbrc.2010.02.008] [PMID]

[5] Golden-Mason L, Madrigal-Estebas L, McGrath E, Conroy MJ, Ryan EJ, Hegarty JE, et al. Altered natural killer cell subset distributions in resolved and persistent hepatitis C virus infection following single source exposure. Gut. 2008; 57(8):1121-8. [DOI:10.1136/gut.2007.130963] [PMID]

[6] Lee S, Watson MW, Flexman JP, Cheng W, Hammond T, Price P. Increased proportion of the CD56bright NK cell subset in patients chronically infected with hepatitis C virus (HCV) receiving interferon-α and ribavirin therapy. J Med Virol. 2010; 82(4):568-74. [DOI:10.1002/jmv.21742] [PMID]

[7] Lin AW, Gonzalez SA, Cunningham-Rundles S, Dorante G, Marshall S, Tignor A, Ha C, et al. CD56+dim and CD56+bright cell activation and apoptosis in hepatitis C virus infection. Clin Exp Immunol. 2004; 137(2):408-16. [DOI:10.1111/j.1365-2249.2004.02523.x] [PMID] [PMCID]

[8] Oliviero B, Mele D, Degasperi E, Aghemo A, Cremonesi E, Rumi MG, et al. Natural killer cell dynamic profile is associated with treatment outcome in patients with chronic HCV infection. J Hepatol. 2013; 59(1):38-44. [DOI:10.1016/j.jhep.2013.03.003] [PMID]

[9] Lutz CT, Moore MB, Bradley S, Shelton BJ, Lutgendorf SK. Reciprocal age related change in natural killer cell receptors for MHC class I. Mech Ageing Dev. 2005; 126(6-7):722-31. [DOI:10.1016/j.mad.2005.01.004] [PMID] [PMCID]

[10] Sundström Y, Nilsson C, Lilja G, Kärre K, Troye-Blomberg M, Berg L. The expression of human natural killer cell receptors in early life. Scand J Immunol. 2007; 66(2-3):335-44. [DOI:10.1111/j.1365-3083.2007.01980.x] [PMID]

[11] Entezami K, Khazrae M. [Study & determination of natural killer cells in the peripheral blood of healthy population of Iran University of Medical Sciences within different age group (18-60 years) (Persian)]. Razi J Med Sci. 2004; 10(37):687-92. http://rjms.iums.ac.ir/article-1-216-en.html

[12] Augusto DG, Lobo-Alves SC, Melo MF, Pereira NF, Petzl-Erler ML. Activating KIR and HLA Bw4 ligands are associated to decreased susceptibility to pemphigus foliaceus, an autoimmune blistering skin disease. PloS One. 2012; 7(7):e39991. [DOI:10.1371/journal.pone.0039991] [PMID] [PMCID]

[13] Howard RR, Fasano CS, Frey L, Miller CH. Reference intervals of CD3, CD4, CD8, CD4/CD8, and absolute CD4 values in Asian and non-Asian populations. Cytometry. 1996; 26(3):231-2. [DOI:10.1002/(SICI)1097-0320(19960915)26:3<231::AID-CYTO9>3.0.CO;2-H]

[14] Qin HD, Shi YQ, Liu ZH, Li ZG, Wang HS, Wang H, et al. Effect of chlorogenic acid on mast cell-dependent anaphylactic reaction. Int Immunopharmacol. 2010; 10(9):1135-41. [DOI:10.1016/j.intimp.2010.06.018] [PMID]

[15] Reichert T, DeBruyère M, Deneys V, Tötterman T, Lydyard P, Yuksel F, et al. Lymphocyte subset reference ranges in adult Caucasians. Clin Immunol Immunopathol. 1991; 60(2):190-208. [DOI:10.1016/0090-1229(91)90063-G]

[16] Dhaliwal JS, Balasubramaniam T, Quek CK, Gill HK, Nasuruddin BA. Reference ranges for lymphocyte subsets in a defined Malaysian population. Singapore Med J. 1995; 36(3):288-91. [PMID]

[17] Shahabuddin S. Quantitative differences in CD8+ lymphocytes, CD4/CD8 ratio, NK cells, and HLA-DR+-activated T cells of racially different male populations. Clin Immunol Immunopathol. 1995; 75(2):168-70. [DOI:10.1006/clin.1995.1067] [PMID]

[18] Jiang K, Zhu FM, Lv QF, Yan LX. Distribution of killer cell immunoglobulin-like receptor genes in the Chinese Han population. Tissue Antigens. 2005; 65(6):556-63. [DOI:10.1111/j.1399-0039.2005.00412.x] [PMID]

[19] Yawata M, Yawata N, McQueen KL, Cheng NW, Guethlein LA, Rajalingam R, et al. Predominance of group AKIR haplotypes in Japanese associated with diverse NK cell repertoires of KIR expression. Immunogenetics. 2002; 54(8):543-50. [DOI:10.1007/s00251-002-0497-x] [PMID]

[20] Wauquier N, Padilla C, Becquart P, Leroy E, Vieillard V. Association of KIR2DS1 and KIR2DS3 with fatal outcome in Ebola virus infection. Immunogenetics. 2010; 62(11-12):767-71. [DOI:10.1007/s00251-010-0480-x] [PMID] [PMCID]

[21] Thananchai H, Gillespie G, Martin MP, Bashirova A, Yawata N, Yawata M, et al. Cutting edge: Allele-specific and peptide-dependent interactions between KIR3DL1 and HLA-A and HLA-B. J Immunol. 2007; 178(1):33-7. [DOI:10.4049/jimmunol.178.1.33] [PMID]

[22] Pelekanou A, Tsangaris I, Kotsaki A, Karagianni V, Giamarellou H, Armaganidis A, et al. Decrease of CD4-lymphocytes and apoptosis of CD14-monocytes are characteristic alterations in sepsis caused by ventilator-associated pneumonia: Results from an observational study. Crit Care. 2009; 13(6):R172. [DOI:10.1186/cc8148] [PMID] [PMCID]

[23] Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cell Mol Immunol. 2020; 17(5):533-5. [DOI:10.1038/s41423-020-0402-2] [PMID] [PMCID]

[24] Guo Y, Luan L, Patil NK, Wang J, Bohannon JK, Rabacal W, et al. IL-15 enables septic shock by maintaining NK cell integrity and function. J Immunol. 2017; 198(3):1320-33. [DOI:10.4049/jimmunol.1601486] [PMID] [PMCID]

[25] de Pablo R, Monserrat J, Torrijos C, Martín M, Prieto A, Alvarez-Mon M. The predictive role of early activation of natural killer cells in septic shock. Crit Care. 2012; 16(2):413. [DOI:10.1186/cc11204] [PMID] [PMCID]

Archives of Advances
in Biosciences

[26] Roder JC, Argov S, Klein M, Petersson C, Kiessling R, Andersson K, et al. Target-effector cell interaction in the natural killer cell system. V. Energy requirements, membrane integrity, and the possible involvement of lysosomal enzymes. Immunology. 1980; 40(1):107-16. [PMID] [PMCID]

[27] Kiykim A, Ogulur I, Baris S, Salzer E, Karakoc-Aydiner E, Ozen AO, et al. Potentially beneficial effect of hydroxychloroquine in a patient with a novel mutation in protein kinase Cδ deficiency. J Clin Immunol. 2015; 35(6):523-6. [DOI:10.1007/s10875-015-0178-9] [PMID]

[28] Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. Semin Arthritis Rheum. 1993; 23(2 Suppl 1):82-91. [DOI:10.1016/S0049-0172(10)80012-5]

[29] Green MRJ, Kennell ASM, Larche MJ, Seifert MH, Isenberg DA, Salaman MR. Natural killer cell activity in families of patients with systemic lupus erythematosus: Demonstration of a killing defect in patients. Clin Exp Immunol. 2005; 141(1):165-73. [DOI:10.1111/j.1365-2249.2005.02822.x] [PMID] [PMCID]

[30] Sacre K, Criswell LA, McCune JM. Hydroxychloroquine is associated with impaired interferon-alpha and tumor necrosis factor-alpha production by plasmacytoid dendritic cells in systemic lupus erythematosus. Arthritis Res Ther. 2012; 14(3):R155. [DOI:10.1186/ar3895] [PMID] [PMCID]