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Opinion: The Interplay of NKT Cells in Severe SARS-COV-2 Human Infections

Ibrahim MS Shnawa*

College Of Biotechnology, University of Qasim and Hilla University College Babylon, Iraq

Corresponding author: Ibrahim Shnawa MS, College Of Biotechnology, University of Qasim and Hilla University College Babylon, Iraq

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Abstract

Natural Killer T lymphocytes [NKT cells] share the characteristics of innate and adaptive immune cells. Though their immune cell identity is still a matter of debate among lymphocyte immunologists. Currently, NKT cells are of three subsets as; NKT type I, NKT type II and NKT like cells. NKT type I is quite filling this cell definition. Three immune phenomena are evident concerning NKT interplay with viral infected human host as; immune evasion, immuno-pathogenesis, and immune protection. Immuno-pathogenesis and immune protection appeared to be operable in COVID-19 disease. The present opinion paper was aimed at briefing the role interplayed by NKT cells in severe SARS-COV-2 human infections. Host response showed reduced circulating total NKT cells, but some NKT immune subtypes may express an increment shifts in this severe infection form. The biology of NKT cells in severe SARS-COV-2 infections own an array of immune features as; immune-metabolic dysfunction, mitochondrial dysfunction, marked expression of apoptotic and inhibitory receptor genes and ramified in to six immune subtypes.

Keywords: *Evasion, Immune, Inhibitory, Metabolism, Pathogenesis, Protection, Receptors and SARS-COV-2*

Introduction

Human lymphocytes are of several immune-types as; B, T, NK and NKT. The efforts of scientists concerning the immunology of NKT cells appeared to be little as compared to other lymphocyte immune-types. NKT as an immune-type and definition is a matter of debates among lymphocyte immunologists. Recently, evident published efforts concerning NKT cells. They share characteristics of both innate and adaptive immune functions. NKT can be immune-pathogenic and/or immune-protective depending on the intensity of the tissue micro-environmental stimuli during human microbial infections. Some human pathogenic viruses displayed an immune mediated evasion mechanism against NKT cells both in function and in count limiting. The present opinion was aimed at briefing the interplay of NKT in human severe SARS-COV-2 infection [1-5].

NKT Cell Biology

Ontogeny

Lymphoid cell progenitor migrates from bone marrow to thymus. Arrival of these progenitors to the thymic micro-environment insults these cells to undergo positive and negative selection procedures. These selection procedures mediated by variety of cytokines cell surface molecule, signal transducers, transcription factors and other regulatory factors. A key step in NKT maturation is their acquisition of innate effector function mediated by pro-myelocytic leukemia zinc finger PLZF. Another key step is the acquisition of cytokine secretion ability in which an adoption of constitutional expression of cytokine gene transcripts. Such cytokine gene transcripts need intra-thymic signaling through GM-CSF in order to become competent cytokine secretors. VDJ recombination via stochastic events leads to generation of invariant TCR. Acquisition of NKT phenotype appear to be driven by invariant TCR CD1d. Positive selection of NKT needs interaction of invariant TCR on immature NKT expressing both CD4 and CD8 with CD1d expressed on cortical thymocyte themselves. Both alpha galactosyl Cer NKT agnosts and DCs overexpressing CD1d played critical role in NKT thymic negative selection [4].

Identity

NKT cells are defined as lymphocyte expressing CD3+CD56+ surface receptors [6,7]. Lipid antigen reactive CD1d restricted T cells most of which do not express CD56 [8]. Koay et al. [9] were formulating important NKT defining criteria as; (i) CD56+ T cells do not equate NKT cells, (ii) CD56+ T cells are heterogeneous T cells but not NKT cells and (iii) The use of CD56 T cells in predicating COVID-19 outcomes needs more validation. Khan and Khan [3] mentioned three subsets of NKT of which only NKTtype I with Koay et al. [9] defining criteria as in Table 1 as well as six subtypes, Table 2.

NKT Cell Molecular Biology

NKT cells recognize lipid stimulating antigens through CDR3 alpha and CDR3 loops. These complementary determining regions are the hyper-variable regions of TCR that complement an antigen shape. Crystallographic and biophysical analysis of alpha galactosylceramide (alpha GalCer) recognition by human CD-1d resistant TCR that utilize a V alpha 3-1-J alpha 18 re-arranged and displays more restored specificity of alpha linked glycolipid than iNKT TCRs. TCR alpha and CDR2 alpha loops have frequent divergence. This TCR employs convergence recognition strategy to engage CD-

Table 1: NKT CELL subsets*

Subsets	Cell molecular Characteristics
NKT type I	Alfa Galcer reactivity ,TCR V alfa 24 J alfa18 TCRVB2 VB7 & VB11
NKT type II	CD14-dependent secret TH1 anTH2 cytokines, sulfated and lyo-sulfated reactivity
NKT like Cells	CD 1 d independent,produce Th1 cytokines No Galcer reactivity,Diverse TCR alfa chain and diverse TCR B chains

*Based on Khan and Khan [3].

Table 2: NKT subtypes*

NKT subtypes	Cell molecular Characteristics
1	NKT CD4 Tim3 CD62L
2	NKT CD8
3	NKT CD8 CD40LG
4	NKT CD8Tim3
5	NKTDN ITGAX
6	NKT CD147 CD26 Tim3

*Based onto Yang et al.[10].

1d (Alpha Galcer) with binding affinity approximate 2um almost identical to that of an iNKT [10,11]. The hydrophilic groups of the lipoidal antigen contribute relatively little to CD-1d groove and the top of the alpha helcies are involved in lipid antigen presentation which suggest a conventional mode of presentation and recognition. NKT differentiation has unique management for their differentiation which is highly lympha-toxin dependent [12].

NKT Cellular Evasion

Pathogenic human viruses adopt number of strategies for evasion of both innate and adaptive arms of immune responses in human host. HIV weakens the immune system functions by depleting the numbers of CD4 T cells [13]. HIV-1 reduces the expression ofCD-1d molecules by increasing internalization and retains them in the trans-Golgi network. The down regulation in cell surface CD-1d is caused by interaction with in the continuum of intra-cytoplasmic tyrosine with HIV-1 NEF protein, leading to an early NKT depletion in HIV-1 infected individuals. West-Nile virus interferes with the interaction of DCs with NKT cells with net result of pro-inflammatory cytokine secretion [3].

NKT Cellular Immunobiology

T lymphocytes are of many subsets among which the NKT cells that have common surface markers and functional characteristics with both conventional T lymphocyte and natural killer cells. Major NKT cells express semi-invariant T cell receptor TCR that reacts with glycolipid antigens presented by major histocompatibility complex class I related protein CD-1d on the surface of antigen presenting cells APC. Both infectious and inflammatory conditions do activate NKT to be rapidly producing immune-modulatory cytokines. NKT may influence the function and the activation state of other immune cells [4]. The NKT semi-invariant alpha Beta TCRs recognize mammalian glycol-sphigo-lipid and microbial alpha glycuranylceramides found on the cell wall LPS of gram negative bacteria. This dipartite recognition of the auto and microbial ligands underlies innate-like antimicrobial functions mediated by CD40L induction, massive helper TH1, TH2 cytokines and release of chemokines. NKT and DCs performed a sort of reciprocal activation NKT can regulate a range of immunopathologic condition through unknown mechanisms. NKT legends holds a position between innate and adaptive immunity serving as a model system for structural biology of glycolipid trafficking and recognition [14]. NKT lymphocyte tissue distribution is unusual, they are found in large numbers in liver and lymph nodes but to a lesser extent La Jolla Institute of Immunology [15]. NKT served as an important regulator of the immune responses [16].

NKT Immune Functions

NKT cells are able to substantial cross-talk with other innate and adaptive immune cells. NKT when activated with alpha-GalCer, the activation will lead to rapid cytokine production of both Th1 and TH2 cytokines and chemokines though other NKT subsets when activated produce IL17 cytokine. The mode of cytokine activation of NKT cell starts rapid early in activation events, then late in the activation process the production ceased. NKT can mediate immune protection against a wide range of pathogens including bacteria viruses, fungi and parasites. In an experimental laboratory animal settings NKT mediate immune protection against low dose pathogenic challenge. Though in high dose challenge can induce hyper-cytokinemia terminated by sepsis [4].

NKT in Virus Disease

NKT Cells have anti-viral potentials against hepatitis B virus [17], herpes simplex virus-1, lymphocytic chorio-meningitis virus and influenza A virus [18]. They constitute an important arm of the innate immune responses against pathogenic viruses and can regulate adaptive immune responses through modulation of the antigen presenting cells. NKT exerts direct cytolytic effects and retards viral replication [3].

NKT in SARS-COV-2 Infections

A show case analysis of four series of severe SARS-COV-2 infection in different parts of the world is performed by four different research teams. The analysis covered number of patients, age/sex, clinical samples, and nature of the cellular investigations. At most single cell RNA sequencing, transcriptomic analysis and flow cytometery. The tracked immune cell types were NKT, NK, and T cells. As the SARS-COV-2 infection progressed NKT cells reduced with an apparent immune-metabolic dys-regulation, cellular dysfunction as well as mitochondrial dys-regulation (Table 3) [7,10,19,20]. Among these four studies Yang et al. [10] presented a novel detailed investigation on the role of NKT in SARS-COV-2 severe infection and be briefed in the following paragraph.

Table 3: NKT interplay in severe and mild sars-cov-2 human infections

Features	Zingaropoil et al 2020[7]	Zingaropoil et al.2020[7]	Gurshaney etal 2021[20]	Yang et al 2022[10]	Odak et al 2020[19]	Odak et al 2020[19]
Demography	15 patients, severe form, age 56-69 males	15 patients ,mild form Age 56-69 males	20 patients Both sexs	205 patients in various disease forms	15 severe form,19-61 age range	15 mild form,19-61 age ranges
Samples	Peripheral blood	Peripheral blood	Peripheral blood	Peripheral blood	Peripheral blood	Peripheral blood
Investigation	Flow cytometery	Flow cytometery	Single cell sequencing,BALF transcriptomic analysis	Single cell transcriptional profiling	Flow cytometery	Flow cytometery
NKT	Low count levels	Normal count levels	Mitochondrial and cellular dysfunction of NKT count reduced with severity	Total NKT reduced as the disease progressed	Low NKT count levels	Normal count levels
NK	Low count levels	Normal count levels			Low count levels	Normal count levels
T cell	Low effector T cell ,high naive CD8+	Normal T cell profiles	CD8 T cell dysfunction, and impaired CD8 differentiation		Gamma delta T cell reduced counts	Normal cell count levels
Conclusions	Low NKT cell count in severe form	Normal NKT ,high T reg. count	Total circulating NKT reduced with severity, NKT cellular and mitochondrial dys-regultion	Total NKT count decreased as the disease progressed	All lymphocyte subsets reduced on disease progression	Lymphocyte activation in mild form but not in severe form

In a clinical setting in to which COVID-19 series of patients and controls were subjected to single cell RNA sequencing in order to determine lymphocyte and mononuclear cell profiles. The number of patients and subjects were; mild 24, moderate, severe 36, critical, died 13, mild recovered 79, severe recovered 50. Fifty patients were tested by single cell RNA sequencing. There was evident that decrease in percentages of lymphocyte in patients is associated with severity. The lymphocyte profiles in PBMC were found that CD8+ T, MAITs, gamma delta T cell, Mono DCs and pDCs decrease significantly as disease progress. While the percentages of plasma B CD94+, monocytes and platelets increased significantly. The NKT cell percentages in severe COVID-19 decreased significantly as the disease progressed and in convalescent. TM3 expression in NKT cells of 202 COVID patients and controls were grouped into six cell subtypes. Increased Tm3 expression in NKT associated with NKT depletion in severe SARS-COV-2 infections [10]. In the followings a deduction of features of NKT in COVID-19 from Yang et al. [10] study;

i. Decrease in circulating NKT counts as the disease progressed.

ii. High expression of Tim3 promotes NKT depletion and dysfunction.

iii. High levels of expression of CD147CD26

iv. High expression of apoptotic and mitochondrial genes.

v. Tim3NKT has capacity to secret IFNgamma, IL4 and IL10.

vi. Expression of co-stimulatory inhibitory receptors PD-L, CTL4 and LAG3.

Conclusions

Lymphocyte profile studies of SARS-COV-2 infection forms have shown variable picture of increase in one immune-type and decrease in others. Generally speaking, lymphogenesis increased as the disease progressed. T, NK, and NKT were affected to a variable degree. Total NKT count in circulation decreased as the disease progressed. Though there are some subtypes of NKT cells increased as the disease progressed.

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