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Review

Natural killer cells in sepsis: Underprivileged innate immune cells

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ABSTRACT

Sepsis is a devastating health condition originating due to the dysregulated immune response in response to the severe systemic infection. The innate immune system serves as the first line of defense against invading pathogens, and the failure to clear the infection leads to the development of sepsis via generation of a proinflammatory immune response. Natural Killer (NK) cells are highly recognized potent innate immune cells that play a very important role in the generation of an antiviral and antitumor immune response. These are also unique innate immune cells due to the existence of NK cell-mediated memory due to the process of education and learning as shown by the cells of adaptive immunity. However, developing data has shown the importance of NK cells in mounting a potent immune response against invading bacterial pathogens that if not contained accordingly may lead to the development of sepsis. Thus, the present review article is designed to highlight the previously unrecognized function of NK cells during sepsis as indicated by both clinical and experimental animal-based findings. However, a brief introduction regarding their development, subtypes, and function is also mentioned before describing their role in sepsis. Thereafter, the subsequent section is included describing the NK cell immunometabolic reprogramming during homeostasis, infection, and sepsis. NK cell immune memory and their therapeutic targeting to manage the sepsis as a future therapeutic approach emphasized before closing the manuscript.

1. Introduction

Sepsis is a disease of a medical emergency with a very complex immunopathogenesis. The complex pathogenesis of sepsis is due to the involvement of both extreme upregulations of the innate immune response and immunosuppression. That is why it is considered a disease of severe immune dysregulation. The role of various components of the immune system including cellular components (i.e. macrophages, neutrophils, dendritic cells (DCs), endothelial cells (ECs) and T cells etc.) as well as humoral components including complement system (CS) and various cytokines are studied well and described elsewhere (Boisrame-Helms et al., 2013; Kumar, 2018a,c; Kumar and Sharma, 2008). As per sepsis 3 or third consensus of sepsis, it is defined as a condition of systemic infection causing one or more organ damage due to dysregulated immune response (Gül et al., 2017; Singer et al., 2016). While severe sepsis is a condition where sepsis is accompanied by hypotension and hypoperfusion causing lactic acidosis, oliguria, acute respiratory distress syndrome (ARDS) and disturbed mental status of the patient (Munford, 2006). Thus, sepsis 3 guidelines have only focused on the use of the term sepsis. The term severe sepsis is considered useless now and has been omitted from current sepsis definitions (Sartelli et al., 2018). Septic shock is the most severe stage of sepsis where hypotension persists even during volume resuscitation and requires the administration of vasopressors including adrenaline, noradrenaline, dobutamine, and isoproterenol etc. to maintain the mean arterial pressure (MAP) ≥65 mm Hg and having serum lactate level > 2 mmol/L (18 mg/dL) (Plevin and Callcut, 2017; Singer et al., 2016). Severe circulatory (i.e. disseminate intravascular coagulation (DISC)), cellular, and metabolic abnormalities are observed during septic shock and show higher mortality as compared to sepsis alone (Singer et al., 2016). Thus sepsis can lead to the development of its most lethal phenotype called septic shock causing a higher incidence of mortality among patients. However, immunopathogenesis of the sepsis is a complex process that requires a very detailed attention to different immune cells during its pathogenesis.

Natural killer (NK) cells are another type of innate immune cells with their very important role in immunity against viral infections and generation of an effective immune response against different types of

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cancers or tumors (Barrow et al., 2018; Jost and Altfeld, 2013; Lam and Lanier, 2017; Morvan and Lanier, 2016). However, despite their important role in antiviral immune response, tumor immunology, and tumor immunotherapy they have been shown to play an important role during bacterial infections including *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Mycobacterium bovis,* bacillus Calmette-Guérin (BCG), *and Nocardia farcinica* etc. directly via the recognition of different PAMPs due to the expression of TLR2, TLR4, TLR5, Nod2 (ligand for muramyl dipeptide (MDP)) and NKp44 that directly binds to mycobacteria and other bacteria (Athié-Morales et al., 2008; Chalifour et al., 2004; Esin et al., 2008; McSharry and Gardiner, 2010; Souza-Fonseca-Guimaraes et al., 2012c). While, an indirect activation of NK cells during various bacterial infections including Listeria monocytogenes, Staphylococcus aureus, Lactobacillus johnsonii, Mycobacterium tuberculosis, and M. bovis BCG has also been reported due to the activation of accessory cells that produce IL-12 and IL-18 and activating NK cells (Clark et al., 2016; McSharry and Gardiner, 2010; Newman and Riley, 2007). The depletion of NK1.1 cells in mice causes an increase in bacterial load and mortality in mice with pulmonary nontuberculous mycobacteria (NTM) infection due to exacerbated NTM (Nontuberculous mycobacteria)-induced pathogenesis caused by reduced macrophage-mediated phagocytosis, dendritic cell (DC) development, cytokine synthesis, and granuloma formation in lungs (Lai et al., 2018). A similar pathology is observed in IFN-$\gamma^{-/-}$ mice subjected to pulmonary NTM infection and an adoptive transfer of NK1.1 cells in these mice prevent the severity of NTM infection (Lai et al., 2018). The protective action of NK cells during NTM infection is seen due to the production of IFN-γ mainly by these cells as early as one-day post infection along with the production of IL-12 and stimulatory action of macrophage-mediated phagocytosis (Lai et al., 2018). Thus the activation of NK cells during bacterial infections in a direct or indirect manner causes the profound production of various cytokines including IFN-γ, TNF-α, GM-CSF (Granulocyte-macrophage colony-stimulating factor) and expression of various membrane proteins including CD69 (required for lymphocyte migration and proliferation) and CD25 (IL-2RA, IL-2 receptor alpha chain) and affects the function of other immune cells including DCs (Clark et al., 2016; Ferlazzo et al., 2003; Souza-Fonseca-Guimaraes et al., 2012a, c). The activation of NK cells during *Citrobacter rodentium* infection is shown to exhibit a protective action against the development of sepsis (Hall et al., 2013). Thus, NK cells are critical innate immune cells with a potential role in the immunopathogenesis of sepsis and its therapeutic targeting due to their role in microbial recognition, immune response and crosstalk with other immune cells including DCs (Ferlazzo and Munz, 2009; Horowitz et al., 2011; Malhotra and Shanker, 2011). Hence the primary aim of the current manuscript is to highlight the role of NK cells in the immunopathogenesis of sepsis, immunometabolic changes among NK cells during sepsis and their therapeutic targeting.

2. NK cell development, subtypes and immunological function

The phrase “natural killer” was first coined in 1975 by Swedish researchers known as Rolf Keissling and colleagues for the cells with a great natural tendency to kill various tumor cells without any prior immunization and antibody treatment (Greenberg, 1994). However, they were first identified by the research group led by Prof. Ivan Roitt in 1973 and were called "Null" killer cells due to their characteristics from previously categorized T and B cells (Greenberg, 1994). The NK cells are serving as an important component of cellular innate immunity long before the arrival of adaptive immunity (T and B cells immunity) almost more than 500 million years ago (Cooper and Alder, 2006). How we missed these important components of immune cells needs to be clarified either the earlier scientific community was more focused towards adaptive immunity or ignored the branch of the immune system called innate immunity that comes in action after the discovery of macrophages by Ilya Ilyich Mechnikov or Elie Metchnikoff in 1882 (Gordon, 2016; Underhill et al., 2016).

NK cells arise from common lymphoid progenitor (CLP) cells shared by T and B cells but do not show the process of gene recombination influenced by RAG (Recombination activating gene) recombinase instead it is expressed in a subset of developing NK cells where its endonuclease activity is required for their function and fitness of matured peripheral NK cells (Held et al., 2018; Karo et al., 2014; Kondo et al., 1997). The development of NK cells primarily occurs in bone marrow but fetal thymus and liver also contain bipotent T/NK cell with a great potential to develop into NK cells (Douagi et al., 2002; Sun, 2016). The development of NK cells also requires the presence of the common gamma chain of the IL-2R complex (Sun, 2016). An absence of common gamma chain of IL-2R and IL-15 causes a complete loss of NK cells even under homeostasis (Di Santo, 2006; Ma et al., 2006). Even after their development in bone marrow, they continue to develop and mature in their target organ via undergoing the process called "tuning" that acquires them a functional competence and tolerance under different physiologic conditions (Orr and Lanier, 2010; Sun, 2010). The development of NK cells is controlled by various transcription factors (TFs) including Id2, E proteins, STAT5 (Signal transducer and activator of transcription 5), IRF-2 (Interferon regulatory factor-2), Tox (Thymocyte selection-associated high mobility group box factor), Ets1 (ETS proto-oncogene 1), and Nfil3 (Nuclear factor interleukin-3) or E4BP4 (E4-binding protein 4, a critical factor for NK cell lineage commitment affecting mature NK cells) that are required for early development of NK cells (Geiger and Sun, 2016; Sun, 2016, 2016). While, T-bet (T-box transcription factor), Eomes (Eomesdermin), and Blimp-1 or PRDM1 (PR domain zinc finger protein 1) TFs are required for specific stages of NK cell development and their maturation (Sun, 2016) and the effector functions of NK cells is regulated by various other TFs called STAT1, STAT4, BTB-ZF (broad-complex, tramtrack and bric-à-brac–zinc finger) transcription factor Zbtb32 (also known as ROG, FAZF, TZFP and PLZP), and AhR (Aryl hydrocarbon receptor) under various inflammatory and infectious conditions (Beaulieu et al., 2014; Nguyen et al., 2002; Shin et al., 2013; Sun, 2016). However, the description of each of these TFs in NK cell development and function is beyond the scope of the article and is not the main theme, therefore, readers are requested to see the references (Brillantes and Beaulieu, 2018; Beaulieu, 2018; Geiger and Sun, 2016; Sun, 2016; Montaldo et al., 2014; Sun, 2016; Vosshenrich and Di Santo, 2013)

Traditionally human NK cells are defined by the expression of CD56 (a 140-kDa isoform of neural cell adhesion molecule (NCAM)), CD16, NKH1, NK cell activating and inhibitory receptors, and CD2 antigens and the absence of CD3 (a marker used for T cell population) (Lanier et al., 1989; Moretta et al., 1990; Ritz et al., 1988). On the basis of the expression of CD56 and CD16 human NK cells are categorized as $CD3^{-}CD56^{high}CD16^{low}$ or $CD3^{-}CD56^{low}CD16^{high}$ NK cells. While, murine NK cells are characterized by the presence of NKp46 (encoded by *Ncr1*), a member of the highly conserved natural cytotoxicity receptor (NCR) family of NK-activating receptors as CD56 is not expressed by murine NK cells (Sivori et al., 1997; Walzer et al., 2007b). Although NKp46 is also expressed by human NK cells and recognizes hemagglutinin (HA) of influenza virus and the hemagglutinin-neuraminidase of parainfluenza virus and thus is involved in the induction of NK cell-mediated lysis of virus-infected cells expressing these glycoproteins (Mandelboim et al., 2001). The binding of NKp46 component to these viral glycoproteins requires the sialylation of NKp46 oligosaccharides, a process consistent with the known sialic acid binding capacity of viral glycoproteins (Mandelboim et al., 2001). The NKp46 component that binds and recognizes various viral hemagglutinins has been identified as alpha 2, 6-linked sialic acid, while its highly conserved carrying residue, Thr 225 is responsible for recognizing tumor cells (Arnon et al., 2004). It is interesting to note that at any one time there are likely more than 2 billion circulating NK cells in an adult human being (Blum and Pabst, 2007). In addition to peripheral circulation, NK cells are also found in spleen, lymph nodes, and other tissues

and organs including liver (called as liver-resident NK cells or Trail$^+$ NK cells), thymus (Thymic NK cells, express IL-7Rα or CD127 and require GATA-3 (GATA-binding protein 3) for their development), and female reproductive tract (Seillet et al., 2016; Vosshenrich et al., 2006). However, Bone marrow-derived conventional NK (cNK) cells do not require GATA-3 for their development but it is required for their maturation and the process of production of IFN-γ (Seillet et al., 2016). These NK cells are now studied under innate lymphoid cell (ILC) category under the group 1 ILCs that express T-box transcription factor T-bet (T-box expressed on T cells) and/or Eomes and secrete IFN-γ (Kumar, 2014).

The CD56^{high} NK cells express chemokine receptor 7 (CCR7) but do not express CXCR1, CXCR2, and CXCR3 (Campbell et al., 2001). CCR7 is required to enhance the entry of CD56^{high} NK cells into the secondary lymphoid organs, whereas, CXCR1, CXCR2, and CXCR3 are required for the migration of immune cells towards the site of inflammation and infection (Cichocki et al., 2016; Gregoire et al., 2007). However, high levels of EOMES and T-bet TFs are expressed on both CD56^{high} and CD56^{low} NK cells due to their potent role in the expression of components of cytolytic granules (Cichocki et al., 2013). The CD56^{high}CD62L$^+$ NK cells present in circulation express very low levels of perforin and cytolytic granules or granzymes and exhibit the less cytotoxic phenotype of NK cells (Chiang et al., 2013; Cichocki et al., 2016). However, CD56^{bright}CD62L$^+$ NK cells express low PLZF (Promyelocytic leukemia zinc finger) levels but exhibit a uniform expression of co-activating receptors and their activation through cells lacking MHC class I expression can initiate the cytolytic action of these circulating NK cells due to altered cytokine responsiveness compared to canonical CD56^{low} NK cells during viral infections (Chiang et al., 2013; Schlums et al., 2015). These circulating CD56^{high}CD62L$^+$ NK cells produce the very little amount of TNF-α and IFN-γ upon target cell recognition (Cichocki et al., 2016). However, they produce a higher amount of IFN-γ in the presence of cytokines IL-18 and IL-12 or IL-15 and in the presence of IL-12 and IL-15 these cells produce IL-10 (an anti-inflammatory cytokine) (Fauriat et al., 2010; Fehniger et al., 1999). Thus, these circulating NK cells via producing several cytokines (i.e. IL-5, IL-10, IL-13, the growth factor GM-CSF, and the chemokines MIP-1α, MIP-1β, IL-8, and RANTES) act as immunoregulatory innate immune cells in response to different combinations of cytokines secreted during diverse inflammatory conditions (Bluman et al., 1996; Cuturi et al., 1989; Fehniger et al., 1999; Roda et al., 2006; Warren et al., 1995). While canonical CD56^{low} NK expresses very high levels of perforin and granzymes with a higher cytotoxic action against infected cells (Schlums et al., 2015). However, these cells produce low levels of IFN-γ in the presence of combinations of IL-12 and IL-15 or IL-12 and IL-18 due to the absence of CD62 L (L-selectin that acts as a homing receptor to lymphocytes to enter secondary lymphoid organs) and presence of CD57 (alternatively, HNK-1, LEU-7, or L2, a marker of terminal differentiation on human CD8$^+$ T cells) (Bjorkstrom et al., 2010; Fauriat et al., 2010; Fehniger et al., 1999; Juelke et al., 2010; Kared et al., 2016; Lopez-Verges et al., 2010). These CD57$^+$ CD56^{low} NK cells show both memory-like characteristics and potent effector functions including increased cytotoxicity (Kared et al., 2016; Nielsen et al., 2013). However, these NK cells do not produce TNF-α under the combinations of IL-12 and IL-15 or IL-12 and IL-18 (Fauriat et al., 2010). Thus, these CD56^{low} NK cells are cytolytic in action and are responsible for immunosurveillance.

The CD56^{low}PLZF$^-$ NK cells are also called adaptive NK cells and also express NKG2C or KIR (Schlums et al., 2015). These cells also express a higher level of perforin and granzyme but do not exhibit immunoregulatory cytotoxic action due to a variegated silencing of FcεRγ and EAT-2 (EWS/FLI1 activated transcript 2) expression that shows the central role for NKp30, NKp46, and SLAM (Signaling lymphocytic activation molecule) family receptors for NK cell-mediated killing of activated T cells (Cichocki et al., 2016; Schlums et al., 2015). These cells do not respond to IL-12 and IL-18 due to the methylation-dependent silencing of IL12RB2 and IL18RAP that encode key components of the IL-12 and IL-18 receptors (Schlums et al., 2015). Thus, adaptive CD56^{low} NK cells are deficient in exhibiting cytokine-mediated immunoregulatory action but retain responsiveness to IL-15 and uniqueness to each host due to target cell specificity (Cichocki et al., 2016). Due to the frequent expression of rapidly evolving NKG2C and activating KIR these adaptive CD56^{low} NK cells play an important role in immunosurveillance of persistent viral infections but do not participate in the killing of infected or activated immune cells, thus are devoid of immunoregulator role (Cichocki et al., 2016). However, these NK cells significantly produce IFN-γ and TNF-α upon recognition of infected or susceptible tumor cells (Cichocki et al., 2016). The detailed discussion of heterogeneity and function among NK cells is beyond this manuscript and described elsewhere.

3. NK cells during sepsis

3.1. Role of NK cells in human cases of sepsis

Clinical studies have shown that the patient suffering from sepsis with their circulating NK cells number below 20% of the total lymphocyte population showed unfavorable outcome including death but an early increase in circulating NK cell population increased the survival benefit due to an increase in serum level of soluble triggering receptor expressed on myeloid cells^{-1} (sTREM-1) (Fig. 1) (Giamarellos-Bourboulis et al., 2006). sTREM-1 inhibits the proinflammatory action of neutrophils including their migration regulated by membrane-bound TREM-1 and the release of proinflammatory cytokines (Fig. 1) (Baruah et al., 2015). Thus sTREM-1 inhibits the proinflammatory action of membrane-bound TREM-1 including TLR signaling in macrophages (Ornatowska et al., 2007; Roe et al., 2014). Another human study (n = 42), where blood samples were collected less than 48 h after admission to intensive care unit (ICU) indicated that the absolute number of peripheral blood CD3–CD56$^+$ NK cells were reduced significantly during all stages of sepsis including severe sepsis and septic shock (Forel et al., 2012). However, the NK cells isolated from healthy controls and septic patients did not show any significant difference in terms of their degranulation (expression of CD107 or LAMP-1 (Lysosomal-associated membrane protein-1)) and cytotoxicity (Alter et al., 2004; Forel et al., 2012). NK cells isolated from sepsis and septic shock patients release the significantly lesser amount of IFN-γ as compared to healthy controls under antibody-dependent cell cytotoxicity (ADCC) conditions (Forel et al., 2012). It is well established that IFN-γ exerts potent antimicrobial and immunoregulatory action (Johnson, 2014). However, another clinical study indicated that the NK cells isolated from sepsis patients (within 24 h of the first admission into ICU) upon treatment with LPS produce a higher amount of IFN-γ as compared to the NK cells isolated from healthy controls (Giannikopoulos et al., 2013). And the NK cells isolated from septic shock patients exhibit higher production of IFN-γ as compared to both sepsis and healthy controls under similar conditions (Giannikopoulos et al., 2013). Thus NK cells remain active early after the development of clinical sepsis and remain active throughout the sepsis pathogenesis to produce the IFN-γ. Hence it is the host environment, the immunologic status of the host, and the causal organism of the sepsis that determines the production of IFN-γ from NK cells during sepsis.

NK cells have a higher number of both extra and intracellular TLR4 (Toll-like receptor 4) that can activate TLR4 signaling during bacterial sepsis to produce IFN-γ but NK cell-mediated production of IFN-γ is independent of TLR4 signaling (Kanevskiy et al., 2013). However, IL-23 produced from monocytes/macrophages are capable of stimulating the production of IFN-γ from CD56^{high} NK cells via the activation of MEK1/MEK2 (Mitogen-activated protein kinase kinase), JNK (c-Jun N-terminal kinase), PI3K (Phosphatidylinositol-4,5-bisphosphate 3-kinase), mammalian target of rapamycin (mTOR), and NF-κB signaling pathways without the involvement of STAT-1, STAT-3, and p38MAPK

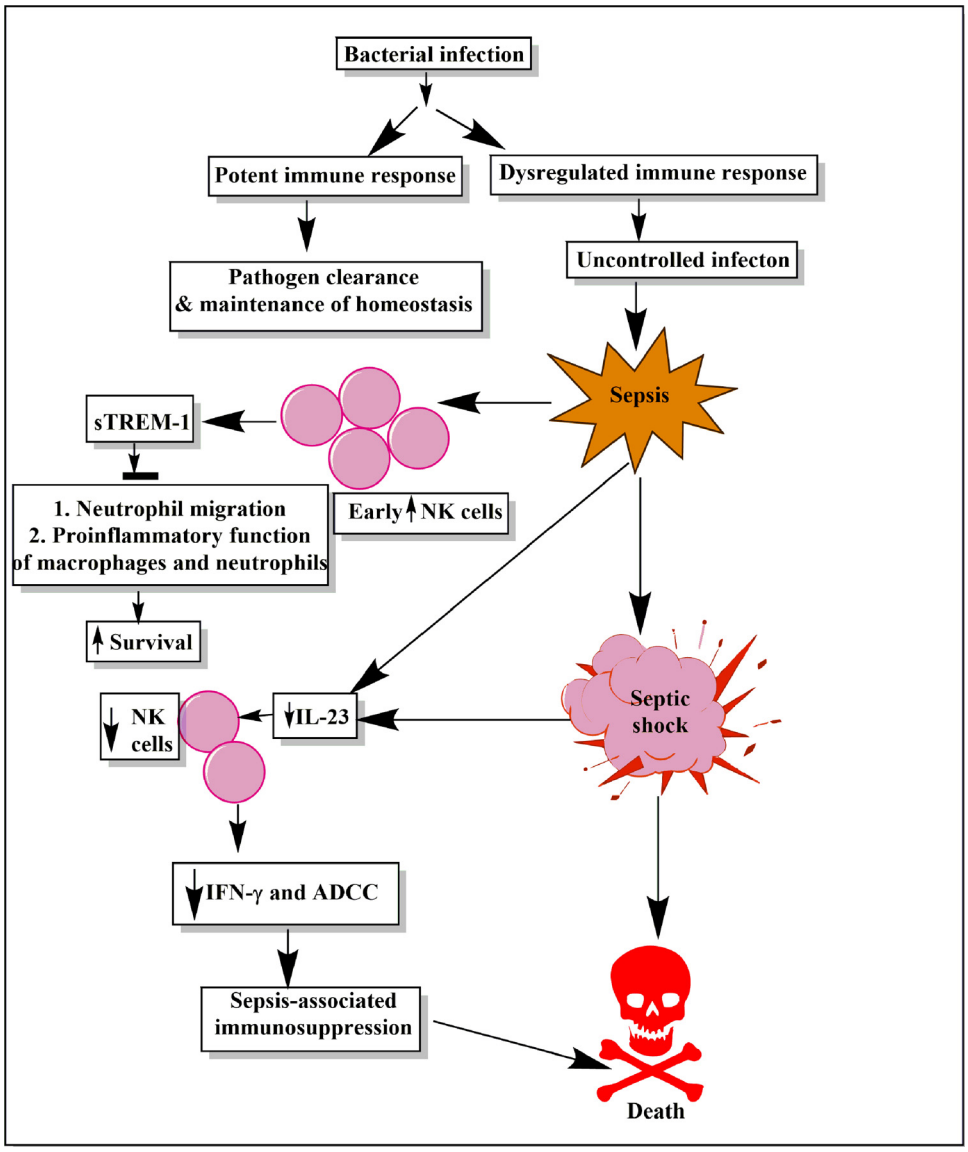

Fig. 1. NK cells during sepsis. Bacterial invasion into the host is recognized by innate immune cells or system, the first line of the defence system. If the infection is not severe and the initial innate immune response is potent enough then the infection/pathogen is cleared and the normal stage of the homeostasis is maintained. However, depending on the severity of the infection, the immune response may dysregulate causing a bystander tissue or organ damage and developing sepsis. The sepsis may further develop into septic shock depending on the severity and pathophysiological symptoms. However, the early activation of NK cells during sepsis proves beneficial to the host and increase the survival. This effect is seemed to be due to the release of sTREM-1 from activated NK cells. sTREM-1 exerts its immunomodulatory action on other innate immune cells including the inhibition of neutrophil migration regulated by membrane-bound TREM-1 through neutralization of TREM-1-mediated inflammatory process and via acting as a decoy receptor in circulating blood. While a decreased activity of NK cells during sepsis, severe sepsis, and septic shock due to the decreased levels of IL-23 into the circulation causes a decreased production of IFN-γ and ADCC. This decrease in NK cell number, IFN-γ, and ADCC also contributes to the sepsis-associated immunosuppression and increased mortality among these patients.

pathway (Ziblat et al., 2017). This effect of IL-23 on the production of IFN-γ is synergized by IL-18 in both $CD56^{high}$ and $CD56^{low}$ NK cells due to the priming effect of IL-23 for IL-18 responsiveness (Ziblat et al., 2017). A human study has shown the significantly lower levels of circulating IL-23 in patients with sepsis admitted to ICU during early stages, however, at later stages, both IL-23 and TNF-α mRNA levels are directly related (O'Dwyer et al., 2008). Thus lower serum IL-23 levels during sepsis can be associated with lower levels of IFN-γ produced via NK cells (Fig. 1).

A later study has indicated an early (within 24 h of sepsis detection) increase in circulating NK cells (> 83 cells/mm3) is correlated with the early death of the patient (Andaluz-Ojeda et al., 2011). However, the number of NK cells from day 1 to day 10 kept increasing in sepsis survivors (Andaluz-Ojeda et al., 2011). Another clinical study by Colombia-based researchers showed an increase in the population of NK cells ($CD56^{high}/CD16^{-}$, $CD56^{high}/CD16^{low}$, and $CD56^{high}CD16^{-}$) during sepsis with an increased level of IFN-γ (Toro et al., 2013). Thus, an early increase in circulating NK cells may demonstrate their prognostic importance in sepsis and associated mortality during its early hours. However, clinical studies are required to further strengthen these findings as different causes of sepsis may impact NK cells differently. This can be proven by the findings of a study with a large patient population (n = 505), where the number of NK cells are identified and counted in blood within 24 h of the first advent of sepsis (Gogos et al., 2010). This study clearly shows a significantly different rate of apoptosis among NK cells in patients with sepsis and septic shock due to ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP). The patients with sepsis show the significantly lesser number of circulating NK cells as compared to patients with community-acquired pneumonia (CAP) (Gogos et al., 2010). Both granzyme A (gzmA) and granzyme B (gzmB) are increased in NK cells of patients suffering from sepsis and septic shock. These patients show severe multi-organ dysfunction and increased mortality (Zeerleder et al., 2005).

The increase in gzmA and gzmB in NK cells is well correlated with their increased apoptosis responsible for the immunosuppression as the decreased level of pro-inflammatory cytokines including TNF-α, IFN-γ, IL-12p70, and IL-6 is also observed in the patients showing increased mortality during sepsis and septic shock. The level of plasma granzymes including gzmA and gzmB increase transiently and remain higher during the 72-hour study period in humans suffering from severe bacterial infection and sepsis (Fig. 2) (Lauw et al., 2000). However, a decreased plasma level of gzmA is seen in burn patients developing a severe form of the sepsis and succumb to it (Accardo-Palumbo et al., 2010). Another granzyme called granzyme K (gzmK) also increases in plasma of patients admitted to ICUs due to sepsis (Rucevic et al., 2007).

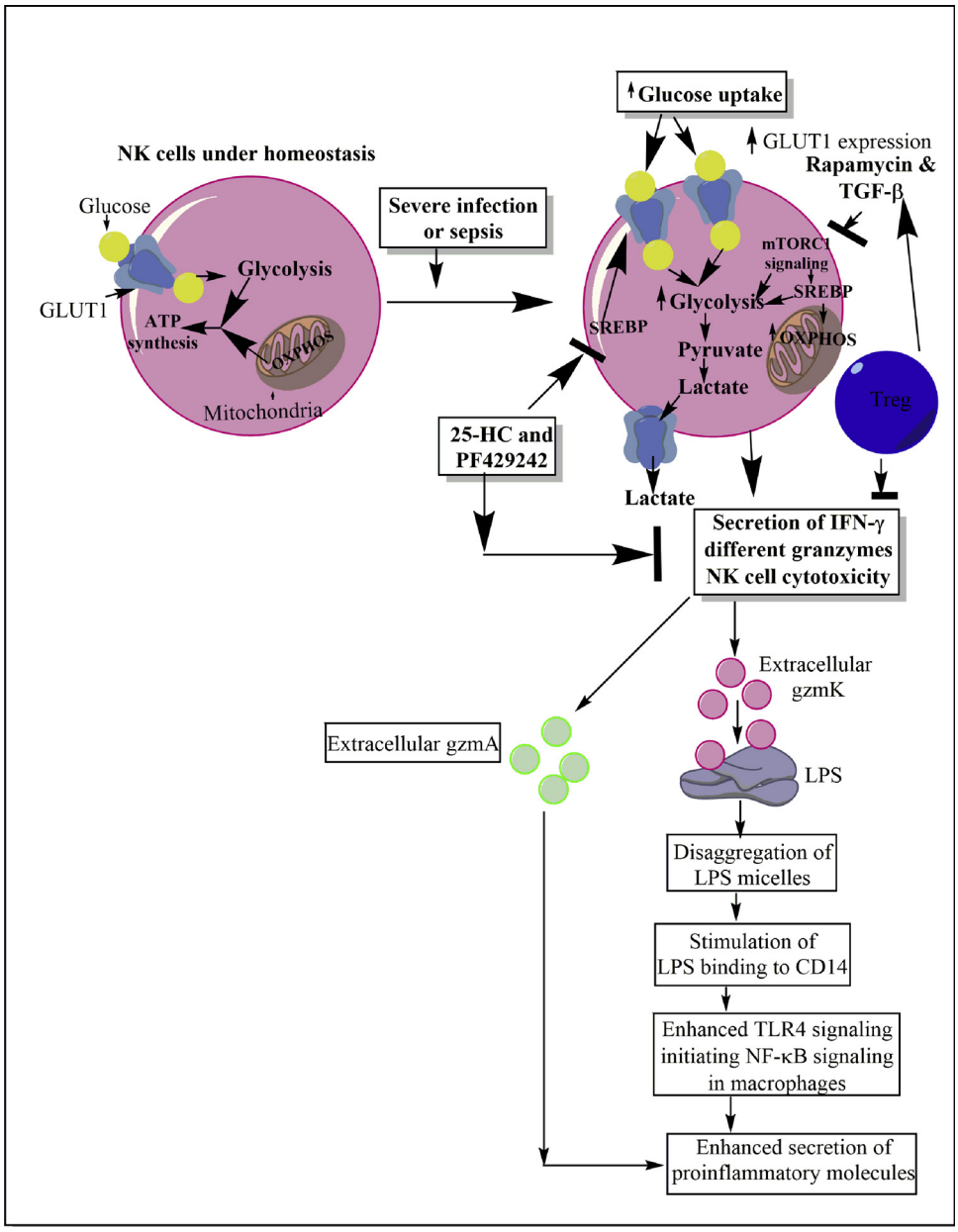

Fig. 2. NK cell immunometabolic reprogramming during homeostasis and sepsis. Under normal homeostatic conditions, the energy requirement of NK cells for their health maintenance is dependent on glycolysis and OXPHOS. However, during severe infection or sepsis, the rate of glycolysis is further increased due to increased uptake of glucose via an increase in GLUT1 expression. The pyruvate synthesized during glycolysis is further converted into lactate and is exported outside of the NK cells to maintain their increased energy demand. The increase in glycolysis and OXPHOS is further maintained by mTORC1 signaling. mTORC1 signaling along with increasing other factors regulating glycolysis and OXPHOS also upregulate SREBP protein molecule that upregulates the glycolysis and OXPHOS via increasing the GLUT1 expression. Furthermore the inhibition of SREBP with 25−HC and PF429242 inhibits the NK cell function including the release of IFN-γ, granzymes (i.e. A, B, and K etc.), and NK cell-mediated cytotoxicity. Both the gzmA and gzmK enhance the proinflammatory TLR-signaling in macrophages by enhancing the binding of LPS to CD14. The release of TGF-β from regulatory T cells (Tregs) during sepsis also inhibits the mTORC1 signaling in NK cells and thus their immunostimulatory action leading to the development of sepsis-associated immunosuppression and the increased susceptibility to hospital-acquired or other secondary infections. See text for the detail.

Hence plasma granzymes can be used as potential biomarkers in determining the severity of sepsis. Thus, NK cells play an important role in sepsis immunopathogenesis and its outcome. Hence it becomes important to find the direct and mechanistic function of NK cells during sepsis and septic shock by using viable and established animal models of sepsis for future NK cells-based therapeutic approach to managing sepsis.

3.2. NK cells in animal models of sepsis

The experimental model of pneumonia induced by *P. aeruginosa* causing an increase in splenic NK cell population that secreted a higher amount of IFN-γ but no immunosuppressive IL-10, provided protection to the animals (Broquet et al., 2014). While a deficiency of NK cells increases the severity of pneumonia by increasing the number of bacteria in the lungs and their susceptibility to sepsis despite an increased infiltration of neutrophils. The induction of sepsis in C57BL/6 mice via cecal-ligation and puncture (CLP) followed by an injection of lipopolysaccharide (LPS) increases the numbers of liver NK cells with low levels of IL-18R expression (Hiraki et al., 2012). The number of liver NK cells are well correlated with serum IL-10 levels. The inhibition or neutralization of IL-10 increases the expression of IL-18R on liver and spleen NK cells and restores the IFN-γ response in septic mice (Hiraki et al., 2012). Thus, IL-10 neutralization affects the NK cell function during sepsis to improve the survival of septic animals. In contrast to this animal finding, Goldman et al observed that NK cell-depleted C3H/HeN mice subjected to *Streptococcus pyogenes*–induced septic shock show an increased survival and slower development of sepsis as compared to normal C3H/HeN mice due to the lower levels of pro-inflammatory cytokines including IFN-γ, IL-12, and IL-16 during the early phase of sepsis (Goldmann et al., 2005). Another study in IL-15$^{-/-}$ mice (Phenotype lacks NK cells) subjected to septic shock through CLP-induced sepsis or LPS-induced endotoxic shock show an improved survival, hypothermia, and lower levels of proinflammatory cytokines including IFN-γ as compared to wild-type (WT) animals (Guo et al., 2016).

IL-15 superagonists called, IL-15SA, IL-15/IL-15Ra complex treatment to IL-15$^{-/-}$ mice induces the regeneration of NK cells causing an

increased mortality during septic or endotoxic shock (Guo et al., 2016). This observation is further supported by the findings that the neutralization of IL-15 function by IL-15-neutralizing IgG M96 antibody in WT mice as these mice show protection against septic shock. However, for this effect, the M96 antibody should be given to animals at least 4 days before the actual sepsis challenge as the immediate treatment of animals with M96 does not deplete NK cells and not protects the animals against septic shock. Thus, IL-15 increases the severity of sepsis leading to the development of septic shock and increases the mortality in animals subjected to CLP due to their positive impact on NK cell growth and proliferation and their proinflammatory action. However, Inoue et al have observed the opposite findings and have shown that the administration of IL-15SA after CLP-induced sepsis attenuates the apoptosis of various immune cell types (i.e. NK cells, dendritic cells (DCs), $CD8^+$ T cells, and gut epithelial cells) causing the reversal of immune dysfunction and increases the survival of animal subjected to sepsis via CLP and *P. aeruginosa*-induced infection (Inoue et al., 2010; Rimmele et al., 2016). This decreased apoptosis is observed due to an increase in anti-apoptotic Bcl-2 protein and decrease in pro-apoptotic proteins called Bim and PUMA (p53 upregulated modulator of apoptosis) (Inoue et al., 2010). Also, IL-15SA treatment expands the NK cell population in spleen and liver during burn injury but fails to prevent burn wound infections and thus the development of sepsis and associated loss of NK cells along with other immune cells (i.e. $CD4^+$. $CD8^+$ T cells, B cells, and NKT cells) (Patil et al., 2016). However, it will be interesting to observe similar findings in other models of sepsis including pneumonia-induced sepsis. This difference in sepsis outcome can be inference on the basis of the difference in mouse strain used for the experiment, mode of induction of sepsis (i.e. CLP-induced sepsis, pneumonia-mediated sepsis or direct inoculation of the pathogen into the bloodstream via tail vein etc.), use of different pathogens, and the timing of the study.

Sepsis induces migration and infiltration of $CD11b^+CD27^+$ NK cells into the brain in a mouse model that promotes the neuroinflammation via inducing the neutrophil migration into the brain (He et al., 2016). The neutrophil infiltration into the brain via NK cells is mediated by the higher expression of CXCL2. However, prior depletion of NK cells before sepsis challenge severely impairs the neutrophil infiltration into the brain and the induction of neuroinflammation and associated neurobehavioral changes (He et al., 2016). The rapid NK cell infiltration at the site of bacterial infection and sepsis is also observed that adds in proinflammatory immune response responsible for the generation of septic shock during CLP-induced sepsis via mediating the activation of peritoneal macrophages and myeloid cells (Etogo et al., 2008; Guo et al., 2018). For example, the rapid (within 4–6 hours of infection) NK cell infiltration into the peritoneal cavity during intraabdominal sepsis is also observed due to the expression of CXCR3 on NK cells that serves as a ligand for chemokines called CXCL9 (Monokine induced by interferon γ, MIG) and CXCL10 (interferon γ-induced protein 10, IP-10) (Herzig et al., 2012a, 2014). This increase in NK cell number into the peritoneum is accompanied by a decrease in $CXCR3^+$ NK cells in the spleen. Furthermore, an inhibition of CXCR3 activity by anti-CXCR3 antibody significantly inhibits the sepsis-induced hypothermia and decreases the systemic cytokine production of IL-6 and macrophages inflammatory protein-2 (MIP-2) with an improved survival (Delano and Moldawer, 2012; Herzig et al., 2012a,b). Furthermore similar to anti-CXCR3 antibody treatment, the $CXCL10^{-/-}$ mice or treatment with anti-CXCL10 antibody exerts an improvement in sepsis-induced hypothermia, decreases levels of IL-6 and MIP-2 in plasma, and decreases the activation of NK cells (Herzig et al., 2014). These $CXCR3^+$ NK cells show a high expression of CD69 and secrete a high amount of IFN-γ and TNF-α that are inhibited by anti CXCR3 antibody treatment (Etogo et al., 2008; Herzig et al., 2012b).

Studies have also shown an induction of tolerance to TLR2, TLR4, and TLR9 agonists among NK cells isolated from mice subjected to polymicrobial sepsis upon stimulation with PAMPs targeting these TLRs (Souza-Fonseca-Guimaraes et al., 2012b). These tolerant NK cells produce a very low amount of IFN-γ and GM-CSF as compared to the NK cells isolated from sham animals after challenging with LPS (a TLR4 agonist), Pam3CysSK4 (a TLR2 agonist), and CpG (a TLR9 agonist) (Souza-Fonseca-Guimaraes et al., 2012b). The polymicrobial sepsis also causes a reduction of $CD27^+CD11b^-$ splenic NK cells. The reduction in splenic NK cells and induction of tolerance among NK cells during polymicrobial sepsis is mediated by regulatory T cells (Tregs) via the production of IL-10 and TGF-β. However, depletion of the splenic NK cells before sepsis onset completely prevents the induction of tolerance among NK cells (Souza-Fonseca-Guimaraes et al., 2012b). NK cell granzymes (serine proteases found in cytotoxic cells) mainly gzmM and gzmA play important role in the Pathogenesis of TLR4-mediated endotoxic shock and generation of inflammatory response by regulating the generation of IL-1α, IL-1β, TNF-α, and IFN-γ as both $gzmA^{-/-}$ and $gzmM^{-/-}$ mice show resistant to develop endotoxic shock (Anthony et al., 2010; Ewen et al., 2012; Joeckel and Bird, 2014; Metkar et al., 2008). A recent study has indicated that gzmA and gzmK differentially exaggerate the LPS or endotoxin-mediated release of cytokines during endotoxic shock (Wensink et al., 2016). The extracellular gzmK mediates the release of proinflammatory cytokines from monocytes and macrophages during endotoxic shock by directly interacting with LPS and disaggregating the LPS micelles to stimulate the binding of LPS with CD14 and thus potentiating the TLR4-LPS signaling required to initiate the induction NF-κB signaling and mediated release of proinflammatory cytokines and reactive oxygen species (ROS) (Fig. 2) (Wensink et al., 2014). gzmA also increases the release of proinflammatory cytokines and molecules from both murine and human macrophages treated in vitro with LPS or gram-negative bacteria or during endotoxemia without binding to the LPS and augmenting the CD14-LPS complex formation and TLR signaling (Fig. 2) (Wensink et al., 2016).

In addition, gzmA also plays an important role in the mouse pathogen *Brucella microti* (a gram-negative bacteria)-induced of sepsis in mice (Arias et al., 2014). The $gzmA^{-/-}$ mice show an increased survival when subjected to lethal sepsis due to the decreased production of pro-inflammatory cytokines including IL-1α, IL-1β, TNF-α, IL6, and MIP-1α and disseminated intravascular coagulation (DIC) without affecting the clearance of the bacterial pathogen (Fig. 2) (Arias et al., 2014). The authors further showed that the mice deficient in NK cells survived the *B. microti* infection. However, the susceptibility to develop sepsis increases with the transfer of WT NK cells to $gzmA^{-/-}$ mice (Arias et al., 2014). Thus NK cell-derived gzmA regulates the pathogenesis of gram-negative bacterial sepsis and exerts detrimental effect during experimental sepsis. Furthermore during abdominal sepsis caused by *E. coli* the percentage of NK cells expressing gzmA and gzmB decreases in the peritoneal lavage fluid (PLF) along with an increase in the percentage of gzm^+ cells (Garcia-Laorden et al., 2017). In addition, the deficiency of both gzmA and gzmB increased the bacterial load at the site of infection during the late stage of sepsis without affecting the neutrophil infiltration into the peritoneal cavity (Garcia-Laorden et al., 2017). gzmA and gzmM also determine the effectiveness of the pulmonary immune response during *Klebsiella pneumoniae-induced* pneumonia (Garcia-Laorden et al., 2016). Thus it becomes very important to study the role of NK cells during sepsis and its different stages in detail.

However, previous mouse models of sepsis used to elucidate the mechanistic role of NK cells in the pathogenesis of sepsis have their own limitations. For example, some researchers used $IL\text{-}15^{-/-}$ mice to study the role of NK cells in sepsis but this cytokines also affects other immune cells and their function (Perera et al., 2012). Thus, sepsis studies executed in $IL\text{-}15^{-/-}$ mice to predict the role of NK cells during sepsis and septic shock do not provide the exact scientific information needed in the case. For example, a study has clearly shown that IL-15 is not required for the induction of a protective immune response mediated by NK cells or $CD8^+$ T cells during *Toxoplasma gondii* infection (Lieberman et al., 2004). Whereas other studies have depleted NK cells via using

different NK cell depleting antibodies including anti-asialoGM1, anti-NK1.1 or antiNKp46 that do not completely deplete NK cells (for example, the anti-asialoGM1 antibody does not deplete kidney NK cells playing important role in renal damage) and instead affect other arms of immunity also including basophils (Nishikado et al., 2011). Thus, animal models specifically depleted of NK cells in both circulation and various target organs will provide great evidence of the direct role of these cells in sepsis pathogenesis and an induction of septic shock. For example, recently diphtheria toxin (DT) or cre-flox-based approaches are used to completely deplete NK cells via targeting NKp46 or Ncr1 (Eckelhart et al., 2011; Walzer et al., 2007a). However, these NKp46-DTR mice and Stat5 Ncr1-Cre mice are not easily available for sepsis study. Thus their easy availability has a potential to explore the unknown but NK cell-specific function in sepsis pathogenesis. However, recently Ncr1/NKp46 overexpressing transgenic mice are developed that show increased NK cell immunity (Glasner et al., 2017). Thus, these mice can be used to elucidate the exact role of NK cells during bacterial sepsis as Ncr1 (Natural cytotoxicity receptor 1)/NKp46 along with recognizing viral ligands also recognize several bacterial ligands or pathogen-associated molecular patterns (PAMPs) (Gur et al., 2013).

4. NK cell immunometabolism during homeostasis and sepsis

NK cells under homeostatic conditions have limited energy or biosynthetic demand as similar to other lymphocytes and utilize glucose efficiently for their energy demand or adenosine triphosphate (ATP) synthesis via the process of glycolysis and oxidative phosphorylation (OXPHOS) (Fig. 2) (Gardiner and Finlay, 2017; Poznanski et al., 2018). Upon activation during severe infection causing sepsis or during tumor the glucose utilization by these cells increases that is mediated by the increase in the expression of glucose transporter 1 (GLUT 1) and an increase in the process of aerobic glycolysis where pyruvic acid (PA) or pyruvate produced during the process is converted into lactic acid or lactate that is secreted outside the cells otherwise the over-accumulation of PA can inhibit the process of aerobic glycolysis (Fig. 2) (Donnelly et al., 2014; Keating et al., 2016). This glycolytic reprogramming of NK cells is maintained by mTORC1 signaling and regulates the effector function of NK cells including the production of IFN-γ and an increased expression of gzmB (Donnelly et al., 2014; Keating et al., 2016). This process of metabolic reprogramming during inflammatory condition by NK cells is more efficiently shown by $CD56^{high}$ NK cells as compared to $CD56^{low}$ NK cells due to higher expression of GLUT1 and a high uptake of glucose (Keating et al., 2016). The high uptake of glucose and its metabolism (glycolysis and OXPHOS) by NK cells is regulated by a transcription factor called sterol regulatory element-binding protein (SREBP) independent of its regulatory role in lipid metabolism (Assmann et al., 2017). This promotion of glycolysis and OXPHOS in NK cells by SREBP involves metabolism of glucose to cytosolic citrate via the citrate-malate shuttle and the prevention of the activation of SREBP by 25-hydroxycholesterol (25HC) and PF429242 or direct inhibition of the citrate-malate shuttle diminished the production of interferon-γ and NK cell cytotoxicity (Fig. 2) (Assmann et al., 2017). The inhibitors of mTORC1 including rapamycin also inhibit the expression of SREBP target genes in cytokine-stimulated NK cells (Assmann et al., 2017). mTORC1 regulates the several steps in SREBP activation in various other cells (Bakan and Laplante, 2012).

A high rate of OXPHOS supports both the process of increased cytotoxicity and IFN-γ production by both $CD56^{high}$ and $CD56^{low}$ NK cells (Keating et al., 2016). However, the inhibition of OXPHOS in human NK cells decreases the production of IFN-γ in response to IL-12/15 but does not inhibit the little IFN-γ production upon treatment with IL-2 alone (Keating et al., 2016; Keppel et al., 2015). While the inhibition of mTORC1 signaling via rapamycin inhibits the NK cell cytotoxicity in both mice and human NK cells (Marcais et al., 2014). Another study has identified a TF called Rfx7 or RFX domain containing 2 (RFXDC2) as an internal regulator of mTORC1 signaling in NK cells as the deficiency of this TF causes a heightened energy stage as indicated by the increased oxygen consumption and extracellular acidification rate in these cells (Castro et al., 2018). The Rfx7-mediated inhibition of mTORC1 signaling occurs due to the increased activity of Ddit4 (DNA-damage-inducible transcript 4, also called REDD1 (Regulated in development and DNA damage response 1) or RTP801 or Dig2) that positively regulates TSC1 (Tumor suppressor complex 1 or Hamartin)/TSC2 (Tumor suppressor complex 2 or Tuberin) complex by reversing Akt-mediated inhibition of the TSC1/TSC2 complex during hypoxia or at higher levels of hypoxia-inducible factor 1-α (HIF1-α) (Brugarolas et al., 2004; Huang and Manning, 2008). Recently it is shown that along with HIF-1α, the cMyc expression also plays an important role in NK cell metabolism and function (Loftus et al., 2018). The expression of cMyc is regulated by the process of glutaminolysis or uptake of glutamine amino acid via SLC7A5 that is not involved in OXPHOS involved in NK cell metabolism (Loftus et al., 2018). Thus, the regulation of cMyc expression by glutamine in NK cells acts as an important metabolic rheostat that controls NK cell function and growth. For example, activated NK cells exhibit an eight-fold increase in cMyc as compared to HIF-1α (Loftus et al., 2018). $Myc^{-/-}$ NK cells exhibit a significant decrease in glycolytic rate and reduced glycolytic capacity upon activation along with a reduced OXPHOS and reduced maximal respiration rate in comparison to WT NK cells (Loftus et al., 2018). The expression of cMyc in NK cells upon activation is regulated by mTORC1 signaling pathway (Loftus et al., 2018). However, glutaminolysis and TCA cycle do not sustain OXPHOS in activated NK cells instead the glutamine-dependent cMyc expression sustains NK cell function and response (Loftus et al., 2018).

TGF-β is another immunosuppressive cytokine that also inhibits the mTORC1 signaling in NK cells (both human and mice) and thus the immunometabolic reprogramming required for efficient functioning of NK cells during severe infections including sepsis (Fig. 2) (Viel et al., 2016). A recent study has shown that TGF-β inhibits OXPHOS, glycolytic capacity, respiratory capacity and cytokine-induced expression of the transferrin nutrient receptor CD71 in NK cells (Zaiatz-Bittencourt et al., 2018). However, these inhibitory effects of TGF-β on NK cell metabolism are independent of mTORC1 inhibition (Zaiatz-Bittencourt et al., 2018). Thus the secretion of TGF-β by Tregs during sepsis may suppress the NK cell function by altering the immunometabolic stage of these cells required for effective immune function and pathogen clearance (Fig. 2) (Souza-Fonseca-Guimaraes et al., 2012b). It is interesting to note that the synthesis of IFN-γ at protein level after short-term (4–6 h) stimulation of primary NK cells with either NK cell activating cytokines (IL-12 plus IL-18) or natural killer cell receptor (NKR) stimulation does not mediates a significant change in glucose flux via glycolysis as measured by extracellular acidification rate (ECAR) or OXPHOS as measured by oxygen consumption rate (OCR) within 6 h of their activation (Keppel and Cooper, 2016; Keppel et al., 2015). But an elevation in mTORC1 activity and promotion of glycolysis and OXPHOS in murine NK cells upon stimulation with IL-15 is observed by other researchers (Keppel et al., 2015; Marcais et al., 2014). However, a greater incubation (72–120 hours) of murine NK cells with a higher concentration of IL-15 showed their greater reliance on glycolysis as indicated by a decreased OCR : ECAR ratio (Keppel et al., 2015; Marcais et al., 2014). Thus the short-term activation of murine NK cells does not require metabolic reprogramming (Mah and Cooper, 2016). However, they are mainly dependent on the glycolysis for the increased energy demand during their prolonged period of activation (more than 3 days). This can be further altered depending on the duration of their activation. Hence the change in immunometabolism of NK cells or their immunometabolic reprogramming should be studied cautiously depending on the stages of sepsis that include sepsis and septic shock or sepsis-associated immunosuppression.

The increased circulating level of IL-12 during septic shock is observed in children admitted to ICUs (Martin et al., 2012). However, an increase in circulating level of IL-12 is observed in adult sepsis survivors

(Wu et al., 2011) that can point to the inference that IL-12-mediated upregulation of NK cell function via altering their immunometabolic reprogramming responsible for the absence of immunosuppression and their susceptibility to secondary infections and increased survival. Furthermore, a genetic polymorphism study has indicated that IL-12Bpro-1 allele (3′-untranslated region and complex polymorphism within the promoter region of IL-12B gene) is associated with sepsis susceptibility, and genotype IL-12Bpro-11 could have a protective effect on the development of sepsis due to its contribution to a higher level of IL-12p40 (Stanilova et al., 2010). Similar to IL-12 a higher plasma level of IL-15 is also observed in adult patients of sepsis exhibiting lymphopenia (T and B cells deficiency) due to the downregulation of anti-apoptotic protein called Bcl-2 (Chung et al., 2015). However, this study lacks the data regarding circulating NK cells. Persistent lymphopenia diagnosed during sepsis can be used to predict early and late mortality (Drewry et al., 2014). Thus, both IL-12 and IL-15 are found to be up-regulated during sepsis and can affect NK cell metabolic reprogramming are needed to study in the context of different NK cells in the context of sepsis exclusively. The lack proinflammatory action of NK cells during sepsis-associated immunosuppression despite the presence of IL-12 and IL-15 can be explained as an induction of dysfunctional NK cells due to the aberrant upregulation of fructose-1,6-bisphosphatase (FBP1) (a rate-limiting enzyme involved in gluconeogenesis, facilitating gluconeogenesis and inhibiting glycolysis) expression causing the inhibition of glycolysis and impairment in their viability (Cong et al., 2018). Thus, NK cell immunometabolism during sepsis and septic shock can serve as a novel therapeutic approach.

Obesity is an altered metabolic stage and is considered as a potential contributing factor for several chronic inflammatory diseases including cancer due to its impact on immunological status or response of the host. However, obesity is also associated with an altered immune response during sepsis in humans (Kolyva et al., 2014). For example, it increases the concentration of TNF-α in visceral adipose tissue (VAT) along with an increase in oxidative stress biomarkers in plasma. Further studies have mentioned an increase in mortality among obese patients admitted to ICU due to sepsis (Papadimitriou-Olivgeris et al., 2016). However, the exact impact of obesity on the pathogenesis of sepsis and its outcome still needs to be clarified and serves as a paradox in sepsis (Ng and Eikermann, 2017; Trivedi et al., 2015). A recent study has indicated that obesity alters the immunometabolic stage of NK cells by inducing the potent peroxisome proliferator-activated receptor (PPAR)-induced lipid accumulation (Michelet et al., 2018). The lipid accumulation in NK cells causes the complete paralysis of their cellular metabolism, trafficking and decreases the expression of *Prf1* (Perforin 1) genes and genes regulating the expression of granzymes along with an increase in the expression of *Ldlr*, *Cd36*, genes encoding fatty acid–-binding proteins (FABPs), and *Cpt1b* (Michelet et al., 2018). Furthermore, the administration of the fatty acids (FAs) and PPARα and PPAR*δ* (PPARα/*δ*) agonists, mimic the obesity phenotype in mice and inhibit the mTOR-mediated glycolysis (Michelet et al., 2018) in NK cells and their trafficking at the site of infection or inflammation including tumor. However, the inhibition of PPARα and PPAR*δ* activity among NK cells and blocking the transport of FAs into the mitochondria of NK cells reverses their immunometabolic or cellular paralysis and restores their cytotoxic action (Michelet et al., 2018). Thus NK cells present in obese people have an impaired immunometabolism causing an impaired NK cell-mediated cytotoxic action (i.e. a decreased release of IFN-γ and lower levels of perforin and granzymes) during cancer and should be studied in sepsis patients also as one of the mechanisms involved in the impaired NK cell function and its role in sepsis pathogenesis.

5. NK cell memory during infection and sepsis

Immunological memory is considered as a part of adaptive (T and B cells) immune response. However, NK cells also exert the phenomenon of immunological memory and their responsiveness to various infections and immunogens is tuned via the process of immunological education or licensing similar to the process of T cell development in the thymus (Geary and Sun, 2017; Kim et al., 2005; O'Sullivan et al., 2015b; Orr and Lanier, 2010). The generation of NK cell-based innate immune memory response is observed during various viral infections including, mouse cytomegalovirus (MCMV), human cytomegalovirus (HCMV), herpes simplex virus (HSV), human papillomavirus (HPV), varicella zoster virus (VZV), and vaccinia virus (Abdul-Careem et al., 2012; Beaulieu, 2018; Gillard et al., 2011; Muccio et al., 2016; Sun et al., 2009; Ugolini and Vivier, 2009). These NK cells with immune memory proliferate with the same rate to naïve NK cells but exert a very potent immune response to clear the infection during lethal pathogen challenge due to their unique transcriptional profile (O'Sullivan et al., 2015a; Sun et al., 2009, 2011; Ugolini and Vivier, 2009). However, in addition to these viral infections, NK cell memory is also observed in bacterial infections including *Mycobacterium tuberculosis* (*Mtb*) and may exert a protective action against the infection during the second challenge (Fu et al., 2011, 2016). In addition to BCG re-vaccination in patients latently infected with *Mtb* also induce the NK cell-based immune memory that persists for more than a year (Suliman et al., 2016). IL-21-based expansion of protective memory NK ($NKp46^+CD27^+KLRG1^+$) cells that provide protection against *Mtb* in healthy individuals with latent infection (Venkatasubramanian et al., 2017). In addition to *Mtb* infection and induction of NK cell memory is also observed during Ehrlichiae infection that causes fatal human monocytic ehrlichiosis (Habib et al., 2016). Additionally, the induction of NK cell memory is also shown to be an inflammasome activation in other innate immune cells (i.e. macrophages)-dependent process (van den Boorn et al., 2016). The depletion of macrophages and the absence of the NLRP3 or NALP3 (NACHT, LRR and PYD domains-containing protein 3) inflammasome, the adaptor protein ASC or Pycard (Apoptosis-associated speck-like protein containing a caspase recruitment domain) or IL-18 abolished monobenzone (a prohapten)-induced contact hypersensitivity (CHS) and an induction of NK cell memory (van den Boorn et al., 2016). And inflammasome activation is shown to play a very important role in sepsis pathogenesis (Kumar, 2018b). Even an alteration in immunometabolic stage among licensed NK cell generated via the process of NK cell education is reported (Schafer et al., 2018). These licensed NK cells generated due to NK cell education increase in number in peripheral circulation and exhibit an increased proliferation in vitro as compared to naïve or unlicensed NK cells (Schafer et al., 2018). These unstimulated licensed NK cells show an increased expression of the glycolytic enzyme called pyruvate kinase M2 (PKM2) and upon stimulation, these licensed NK cells show the phenomenon of immunometabolic reprogramming towards increased glycolysis and mitochondria-dependent glutaminolysis causing an accumulation of glycolytic metabolites and depletion of glutamic acid or glutamate (Schafer et al., 2018). It will be interesting to observe the induction of these licensed NK cell generation in sepsis and their impact on immune response associated with sepsis pathology. Furthermore, the generation of licensed NK cells in vitro and their usage as an immunotherapeutic approach for sepsis should also be explored. Thus NK cell-based immune memory is also observed during certain bacterial infections and it will be interesting to observe this phenomenon in other bacterial infections responsible for frequent cases of sepsis including pneumonia caused by *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Klebsiella pneumoniae*. As this NK cell-based memory will help us to design the NK-cell based vaccines for specific pathogens and thus to decrease the incidence of sepsis in near future via vaccination.

6. Targeting NK cells during sepsis

NK cells are important innate immune cells with their exceptional property to exhibit the immune memory phenotype and have been

targeted as a novel immunotherapeutic target for various cancers (Guillerey et al., 2016; Hofer and Koehl, 2017; Konjević et al., 2016; Messaoudene et al., 2017). These NK cells play a crucial role in the pathogenesis of sepsis and septic shock as indicated in both animal models and human cases. Thus targeting these immune cells via immunomodulatory or immunotherapeutic approach may provide a novel approach towards the management of sepsis. For example, glycogen synthase kinase (GSK) 3 is an active serine-threonine kinase with its two isoforms including GSK3α and GSK3β expressing constitutively and in nucleus this GSK3 targets various TFs along with inducing the phosphorylation of various histone proteins (i.e. histone acetyltransferase and histone deacetylase) (Beurel et al., 2015; Cichocki et al., 2017). The inhibition of GSK3 with CHIR99021 enhances the NK cell maturation causing a marked increase in TNF-α and IFN-γ production along with higher natural cytotoxicity and antibody-dependent cellular cytotoxicity (ADCC) (Cichocki et al., 2017). Thus this strategy can be applied for a patient exhibiting sepsis-associated immunosuppression and susceptible to develop secondary or hospital-acquired infections. Furthermore, decreased IL-23 levels are found in the circulation in patients suffering from sepsis and IL-23 is found to enhance to IFN-γ from $CD56^{high}$ NK cells that can prove beneficial in reverting the sepsis-associated immunosuppression via both activating NK cell and DC function that can further stimulate protective T cell immune response that also gets suppressed (O'Dwyer et al., 2008; Ziblat et al., 2017). Additionally, IL-27 another IL-12 family cytokine is shown to exert a stimulatory action on NK cells in terms of their secretion of IFN-γ, NKp46-dependent NK cell-mediated cytotoxicity, and ADCC (Zwirner and Ziblat, 2017). Thus, IL-27 can also be used to decrease the sepsis-associated immunosuppression, mortality, and susceptibility to secondary community-acquired and hospital-acquired infections. Furthermore, a higher level of circulating IL-12 is shown in sepsis survivors (Wu et al., 2011). This finding further supports the treatment with IL-12 family cytokines (IL-27 and IL-23) to suppress the sepsis-associated immunosuppression.

Immunometabolic reprogramming like other immune cells (macrophages, neutrophils, T cells, and B cells) also plays an important role in the immunostimulatory or immunoregulatory function of NK cells. Thus studying and targeting NK cell immunometabolism during sepsis may also open another avenue for NK cell-based or targeted therapeutic approach for sepsis. For example, increased glycolysis, mTORC1 signaling, and OXPHOS play an important role in the generation of IFN-γ. And IFN-γ treatment during sepsis-associated mortality and immunosuppression improves both the survival and recovery from immunoparalysis (Takeyama et al., 2004). Thus strategies targeting immunometabolism of NK cell depending on the stage of sepsis including septic shock and/or sepsis-associated immunosuppression may prove beneficial. For example at stages like sepsis leading to the development of severe form of sepsis where the exaggerated pro-inflammatory immune response is responsible for sepsis-associated organ damage and mortality, the inhibition of glycolysis via 2-Deoxyglucose (2-DG) or galactose may impair the IFN-γ and other pro-inflammatory cytokine production (Donnelly et al., 2014; Keppel et al., 2015). While the stimulation of mTORC1 signaling and glycolysis among NK cells during sepsis-associated immunosuppression may prove beneficial in overcoming immunosuppression and susceptibility of secondary infections as the inhibition of mTORC1 signaling prevents IFN-γ secretion from NK cells (Donnelly et al., 2014; Marcais et al., 2014). Additionally, a high expression of PD-1 (Programmed death receptor-1) or CD279 and PD-L1 (Programmed death receptor ligand 1) or CD274 on lymphocytes including NK cells is observed in sepsis patients causing their decreased immune function (IFN-γ production, granzyme B, and CD107a expression), sepsis-associated immunosuppression, and increased mortality (Patera et al., 2016; Shao et al., 2016; Wilson et al., 2018). The targeting of PDL-1 with anti-PDL-1 peptide called compound 8 improves the survival during experimental CLP-induced sepsis in mice (Shindo et al., 2017). Furthermore, under in vitro conditions targeting PD-1/PD-L1 interaction with anti-PD-1 or anti-PD-L1 antibody in lymphocytes isolated from septic patients increased their survival and production of IFN-γ and IL-2 via improving the function of NK cell along with other lymphocytes in septic patients (Chang et al., 2014; Patera et al., 2016). Immunotherapy-based on inhibiting PD-1/PD-L1 interaction has already been approved by the USA Food and Drug Administration (USFDA) for certain human cancers (Chen and Han, 2015). A recent study has identified the activation of NK cells during PD-1/PD-L1 blockade-based immunotherapy that can be used during sepsis-associated immunosuppression developing due to the loss of protective function of lymphocytes including NK cells (Hsu et al., 2018; Patil et al., 2017). Thus, NK cell-based immunotherapy and immunomodulatory molecules specifically targeting NK cells and their immunometabolism may open a future avenue to target sepsis.

7. Conclusion

NK cells are essential innate immune cells well recognized for their role in antiviral immune response and tumor immunology. However, their emerging role in controlling various bacterial infections has established them as important immune cells required to mount an effective immune response to clear the bacterial pathogen (Schmidt et al., 2016). For example, NK cell inactivation is reported in *Yersinia enterocolitica* infection, while a profound release of IFN-γ from NK cell due to their activation is reported in scrub typhus (a disease caused by *Orientia tsutsugamushi*) patients (Kang et al., 2017; Koch et al., 2013). The activation of inflammasomes coordinates the pyroptosis and NK cell cytotoxicity response required to clear certain bacterial infections (Maltez et al., 2015). Additionally, the NLRC4 inflammasome-mediated release of IL-18 is also required to generate NK cell-mediated IFN-γ in response to *Salmonella typhimurium* without the involvement of TLR signaling (Kupz et al., 2014). Thus any disruption of the crosstalk between inflammasomes and NK cells may impair their direct protective immune function during sepsis or bacterial infection along with generation of NK cell immune memory phenotype as described earlier.

The regulation of targeting of mTORC1 by a low-dose of a catalytic (BEZ235) plus an allosteric (RAD001) mTOR inhibitor that selectively inhibits target of rapamycin complex 1 (TORC1) downstream of mTOR is shown to decrease the rate of respiratory infections along with several other infections in elderly patients (an age group more prone to develop sepsis due to more susceptibility towards infections). In addition, this treatment also upregulates the antiviral gene expression and improves the immune response against influenza vaccination (Mannick et al., 2018). Thus, it becomes very interesting to observe the impact of this treatment on the number of NK cells in these patients and any alteration in their immunometabolic stage making them resistant to acquire infections and thus towards the development of sepsis. This is because a decrease in circulating NK cells in an elderly population is reported with the increased incidence of viral and bacterial infections (Hazeldine and Lord, 2013). The endogenous glucocorticoids produced during infection acts via glucocorticoid receptors (GRs) expressed on NK cells and cause the expression of the checkpoint receptor PD-1 on these cells (Quatrini et al., 2018). This expression of PD-1 on NK cells due to the interaction between glucocorticoids and GRs on NK cells causes an inhibition of production of IFN-γ by splenic NK cells during viral infection without comprising the clearance of the pathogen (Quatrini et al., 2018). Thus, according to the study, the fine-tuning of the tissue NK cell function due to the activation of the hypothalamic–pituitary–adrenal (HPA) axis preserves the cellular and tissue integrity without any loss in pathogen clearance by NK cells and other innate immune cells. This shows a novel aspect of NK cell function regulation during infection as a phenomenon of neuroimmune regulation. And an interaction between the nervous system and the immune system plays a significant role in the sepsis pathogenesis and neuroimmunomodulation plays a vital role in targeting sepsis (Kumar and Sharma, 2010). Thus it will be a novel approach to identify the

regulation of NK cell function during sepsis via HPA-axis to target NK cell function via neuroimmunomodulation. NK cells are a novel population of immune cells that are present in peripheral circulation as well as in various target organs (i.e. lungs, liver, spleen, and kidneys etc.) affected during sepsis. Therefore, it becomes essential to investigate the exact immunoregulatory role of various NK cells during sepsis and their targeting to design adjunct immunomodulatory or immunotherapeutic approach that can be administered safely along with antibiotics used to overcome severe infection. In near future, these underprivileged innate immune cells will comprise an essential immunomodulatory approach to target sepsis.

Conflict of interest

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