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Review Article

Natural Killer Cells in Bipolar Disorder

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ABSTRACT

Among the mechanisms implicated in the pathophysiology of Bipolar Disorder (BD), neuroinflammation and peripheral immune dysregulation are now known to play a major role. In particular, dysregulation of the fine-tuned equilibrium of immune responses that involve both innate and adaptive immunity has repeatedly been implicated. Within the innate immune system, abnormalities of Natural Killer (NK) cells could play an important role, which is why we have reviewed here the role of NK cell abnormalities in the pathophysiology of BD. In this review, we discuss our current knowledge regarding the phenotypes and functional features of peripheral and brain NK cells in BD and in major brain disorders, in the context of well-established environmental factors as well as the cross-talk between NK cells and other immune cells. The permanent activation of NK cells and specific expansion of a cell subset, called adaptive NK cells, which is usually associated with several viral infections, has also been reported in patients with BD. This prompts us to discuss the putative role of non-resolved infectious events in BD, possibly arising from suboptimal, genetically determined, anti- infectious responses, and/or from other BD-related processes. The permanent activation of NK cells observed in patients with BD could contribute to a vicious cycle of impaired functions, heightened inflammation, neuro-immune damage and cognitive dysfunction.

INTRODUCTION

Bipolar Disorder (BD) is a heterogeneous common condition affecting up to 4% of the population. It is characterized by cycling periods of relative wellness with varying degrees of persistent low-grade abnormalities and recurrent manic and depressive episodes [1]. BD is highly heritable with a complex genetic background interacting with environmental risk factors. The efficacy of a mood stabilizer combined with psychotherapy and life style measures has been demonstrated; however, novel mechanism-based treatments are needed to decrease the burden of disease especially the resistance to usual treatments observed in subsets of patients [2].

It is thus important to improve our understanding of the pathophysiology of BD. In this context, the deregulated immune processes that underpin BD and its somatic comorbidities constitute promising candidate pathways worthy of exploration [3]. Indeed, it has been amply reported that immune-related diseases such as autoimmune disorders including hyper-/hypothyroidism, rheumatoid arthritis, and polymyalgia rheumatica are more frequently observed in patients with BD than in the general population [4]. Evidence of inflammation in BD has been demonstrated by numerous

studies showing elevated levels of proinflammatory cytokines, such as Tumor Necrosis Factor (TNF)-alpha, soluble Interleukin-2 (IL-2) receptor, IL-1 beta, IL-2, IL-4, and IL-6, depending of the polarity of the mood episode. During mania, proinflammatory IL-2, IL-4 and IL-6 cytokines are increased, while alone Il-6 is in depressive patients [5-8]. In summary, studies have consistently demonstrated elevated levels of inflammatory molecules during manic and depressive states, however the results are more controversial regarding euthymia. As another stigma of inflammation, the C-Reactive Protein (CRP) is also significantly increased in BD [9,10]. This variation in inflammation could be associated with modulation of monocyte capacity or T cell responses, changes in the expression of cell-surface receptors, or increased susceptibility to apoptosis. Data regarding immune cell subsets in BD remain scarce and controversial. A few studies have evaluated the count of $CD14^+$ monocytes in patients with BD, however, yielding somewhat conflicting results [11]. Patients with BD seem to be characterized by a reduced level of total $CD3^+$ T lymphocytes [12,13] that possibly migrate to the brain. It has also been observed that changes in lymphocyte subpopulation types strongly depend on the phase of bipolar disorder; patients with BD who are depressed or hypomanic are characterized by a low percentage of $CD3^+$ T cells compared with healthy people while those in remission are characterized by low levels of both $CD4^+$ and $CD8^+$ T cells [14]. Furthermore, an increased number of late-differentiated $CD8^+$ T cells that lack CD28 expression has been reported in euthymic patients with BD; a cell subset known to be expanded during aging and that accumulates during persistent infections by Human Immunodeficiency Virus (HIV), Human T-Lymphotropic Virus 1 (HTLV-1) and Cytomegalovirus (CMV) [15]. Some studies have shown that other T cell subsets could also play a role in the development of inflammation in BD, as suggested by variations over time in the circulating levels of T helper 17 (Th17) and $CD4^+$ T regulatory (Treg) cells. In particular, decreased frequency of Treg cells has been correlated with raised expression of inflammatory genes in $CD14^+$ monocytes [16-18], in favor of fluctuating numbers of pro- and anti-inflammatory T cell subsets over the course of the disease. Given the well-known involvement of innate immune Natural Killer (NK) cells in themodulation of inflammation, the purpose of the present work is to describe the role of NK cellsin general and to review their implications in BD.

NATURAL KILLER CELLS

It has generally been assumed that the innate NK cells provide surveillance in the early defense against viruses and tumor cells [19] These cells present an inherent capacity to recognize and kill stressed target cells, and to modulate the transition between innate and adaptive immune responses like the dendritic cell maturation and T cell polarization, via the production of chemokines and cytokines, and more particularly interferon-γ (IFN-γ), TNF-α, and granulocyte macrophage colony-stimulating factor (GM-CSF) [20-22] (Figure 1).

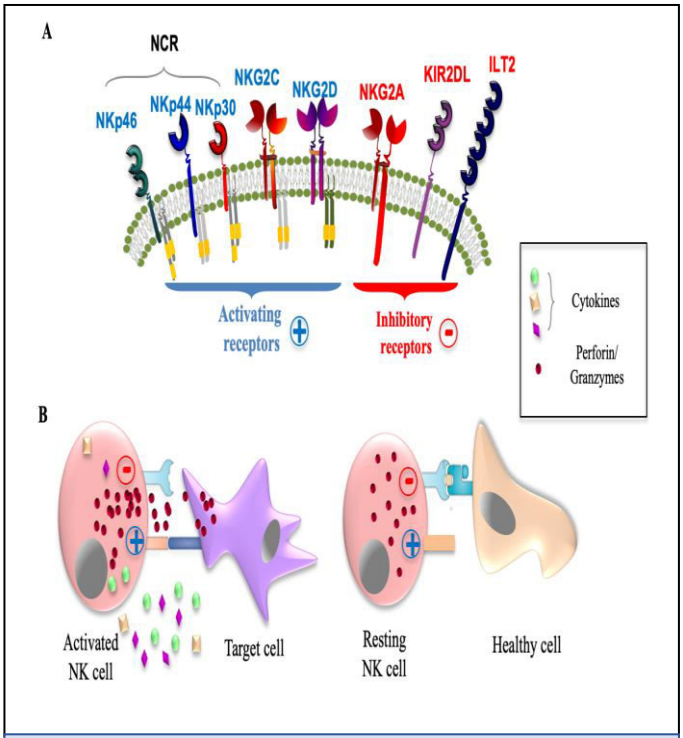

Figure 1: Characteristics of peripheral blood NK cells. (A) NK cells express many cell surface receptors that can be grouped into activating (blue), and inhibitory (red) receptors. The list of cell surface molecules involved in the regulation of NK cell function is not exhaustive. (B) The dynamic regulation of NK cell effector function. NK cells sense the density of activating and inhibitory receptors and their respective ligands. The integration of these distinct signals dictates the quality and the intensity of the NK cell response. NK cells spare healthy cells that express self-MHC class I molecules and low amounts of stress-induced self-molecules, whereas they selectively kill target cells "in distress" that down-regulate MHC class I molecules and/or up-regulate stress-induced molecules.

These functions are finely tuned by a balance between activating and inhibitory receptors; inhibitory receptors, like KIR-Ls, Ig-Like Transcript (ILT)-2 and NKG2A, which recognize MCH class 1 molecules. In contrast, activating receptors that

include CD94-NKG2C heterodimeric receptors, NKG2D, DNAM-1/CD226, and Natural Cytotoxicity Receptors (NCRs), such as NKp30, NKp44, and NKp46, recognize stress ligands [23] (Figure 1).

While NCRs were originally considered to be confined to NK cells, they can be expressed by other subtle cell subsets; in particular, NKp30 has been described on gamma-delta (γδ) T and $CD8^+$ T cells, which acquire "NK-like" antitumor activity [24,25]. Remarkable phenotypical and functional heterogeneities are reported within the NK cell lineage due to a high degree of cell-to-cell variability in terms of the numbers and relative intensities of different types of markers that are expressed. Using mass cytometry (CyTOF), it has been estimated that in any individual there may be at least 30,000 or more distinct NK cell phenotypes [26]. In summary, NK cells can either promote or limit disease by their intrinsic capacity to alter the adaptive immune responses or to preserve immune homeostasis. This Jekyll and Hyde paradigm of NK cells has been observed in several situations, including infections, autoimmunity and pregnancy, but their roles in psychiatric disorders remain unclear. everal studies have also highlighted the potential for NK cells to shape immune memory and differentiate into specialized memory-like cells, now commonly referred as adaptive NK cells [27]. These adaptive NK cell subsets have been mostly characterized in the setting of viral infection, like that induced by CMV [28]. Indeed, adaptive NK cells display an array of functional, phenotypic, epigenetic, and homeostatic differences as compared to the global NK cell compartment that warrants their classification as a distinct subset. These cells express the HLA-E-specific activating receptor CD94/NKG2C and bear a highly differentiated cell surface signature, namely, self-$KIR^+NKG2A^-LILRB1^+CD57^+Siglec7^-$. It is however, still unclear which are the exact signals provided by viral infection, capable of remodeling the NK cell epigenetic landscape. Together with the engagement of activating receptors and co-receptors, exposure to proinflammatory cytokines (e.g. IL-12, IL-18, IL-15), seems crucial to drive the expansion of specialized subsets. Alternatively, adaptive NK cells have been shown to express checkpoint receptors, such as LAG-3 and PD-1, upon chronic stimulation through activating receptor engagement [29]. This phenomenon, reminiscent of characteristic T cell responses, can render adaptive NK cells hypofunctional in certain circumstances. Taken together, these data indicate that, in response to cytokines, and/or to receptor engagement by a stress signal, NK cells can modulate their phenotypic and functional properties, highlighting hence a high degree of functional and developmental plasticity.

NK CELLS IN BRAIN PATHOPHYSIOLOGY

NK cells are known to actively screen non-lymphoid and lymphoid organs in search of infected targets and transformed cells, and the CNS appears as a "new" compartment for future investigation of their trafficking. The CNS is often described as an immuno-privileged site, in which the blood–brain barrier limits the movement of cells and macromolecules between the peripheral blood and CNS tissue. Recent data suggest, however, that the CNS is under close surveillance by the immune system, and pathogens or aberrant cells in the CNS are well controlled. Both resident microglia and immune cells from the general circulation function as primary guardians of the CNS and contribute to maintenance of the optimal functioning of the brain and spinal cord. Conceptually, sentinel macrophages and dendritic cells are competently capable of presenting antigens to, and activating, patrolling T cells, and thus together these immune cells constitute a robust line of defense against stressor events in the CNS [30,31]. The significance of NK cells in CNS homeostasis remains more elusive, although experiments in mice have shown that NK cells gain access to the CNS through the blood–brain barrier. In humans, it is conceivable that NK cells scan the CNS milieu through their surface receptors or by interaction with brain-resident immune cells. These cells are recruited and directed to the CNS in response to CCL19 and CXCL10, which are constitutively expressed in the CNS, and recognized, by CCR7 and CXCR3 receptors, highly expressed on NK cells [32]. NK cells reside mainly in the CNS parenchyma where they exert immune surveillance under the control of local neurotransmitters and immune mediators (Figure 2). Although NK cell biology remains understudied in the brain, there are arguments to think that specific brain factors could modulate

NK cell function and vice versa [33]. For example, the kinetics of NK cells is modulated by the circadian rhythm through the

influence of norepinephrine, which inhibits cytotoxic function after engagement of β–adrenergic receptors [34]. Alternatively, NK cells can impact CNS physiology by killing glial cells or by secreting IFN-γ [33]. However, their mode of entry into the CNS and the molecules leading to their recruitment are poorly understood even if a role of CNS resident cells, like microglia, that secrete chemokines involved in NK cell recruitment and migration, such as CCL2, CXCL10, and CX3CL1, is evoked [35]. Brain NK cells are observed in greater abundance following CNS infection; for example, their recruitment is essential for controlling mouse hepatitis virus within the CNS through an IFN-γ-dependent mechanism [33].

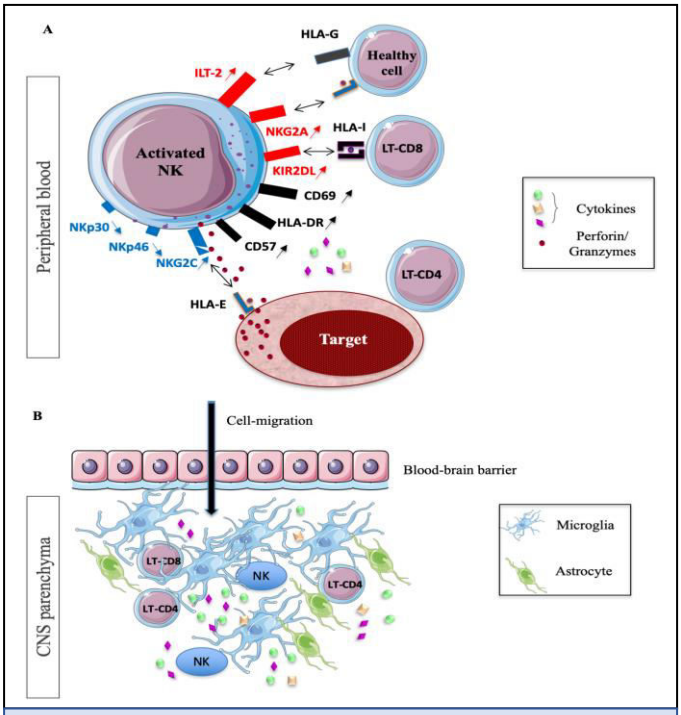

Figure 2: Characteristics of peripheral blood NK cells in BD and their hypothetical role in the CNS (central nervous system) parenchyma. (A) In BD, peripheral blood NK cells overexpressed markers of cell-activation (CD69 and HLA-DR), and inhibitory receptors (red). In contrast, most of activating receptors (blue) are down-modulated, excepted NKG2C that recognized HLA-E. Consequently, NK cells are cytotoxic (perforin/granzyme capacities) but exhibited a lack of efficient IFN-γ production. (B) Although NK cells could be recruited in the CNS in response to several neurological disorders (20), there is no data about the phenotype/function of CNS NK cells in BD. Some first evidences suggest that NK cells could interact with astrocytes and microglia to control inflammation.

In several pathological conditions, when the blood–brain barrier integrity is compromised, NK cells can be recruited in large quantity to the CNS. For example, in:

Multiple sclerosis (MS)

The role of NK cells in neuroinflammation remains controversial. In an experimental autoimmune Encephalomyelitis (EAE) model, it was shown that the CX3CR1-dependent recruitment of NK cells into the CNS contributes to control autoimmune neuroinflammation [36], suggesting that CX3CR1-expression may be related to the migration of NK cells to mediate "protective" function. In patients, different reports have established that NK cells could be implicated in Relapsing–Remitting MS (RRMS) patients and more particularly by their capacity to kill oligodendrocytes in acute inflammatory lesions [36,37]. Furthermore, in patients with suspected MS, an increased number of $CD56^{low}$ $CXCR3^{+}$ NK cells was measured in their cerebrospinal fluid [33], but their role remains to be assessed.

Infections of the CNS

The rare patients completely devoid of NK cells are extremely susceptible to infections by viruses of the herpes family [38]. Children with herpetic encephalitis have been shown to have functional NK cell deficiencies [33]. It seems that a rapid, sustained, and coordinated recruitment of peripheral leukocytes, including NK cells, to the brain results in effective control of viral replication and inflammation, whereas their delayed infiltration is associated with an exacerbated inflammatory response induced by Herpes Simplex Virus (HSV) encephalitis (HSE) [39]. By using a mouse model of HSV1 encephalitis, Adler et al. [40] suggested that NK cells could clear the virus in the brain. Interestingly, TLR3-deficient patients are susceptible to HSE, and they present impaired NK cell IFN-γ secretion following stimulation with polyinosinic-polycytidylic acid [41], suggesting that TLR3 dysfunction could be at the origin of this disease entity mediated by NK cells.

Brain ischemia

The impairment of systemic immune responses that follows brain ischemia is thought to protect the brain from further inflammatory insults, but at the same time it leads to increased susceptibility to infections. In this context, Liu et al. [42] have documented NK cell infiltration and activation in the brain of patients after cerebral infarction. They also demonstrated that distinct neuro-endocrine pathways inhibit NK cell responses in the CNS and the periphery and identified Jak inhibitor SOCS3 (suppressor of cytokine signaling 3) and

RUNX3 (runt-related transcription factor 3) as cellular factors differentially modulated in NK cells in the brain and the spleen, respectively.

Neurodegenerative diseases

One of the consequences driving age-related neurodegenerative diseases is the accumulation of senescent cells. Several immune subsets with essential functions in the adult brain, contribute to neurogenesis and learning. Jin et al. [43] showed that accumulation and activation of NK cells in the brain impairs neurogenesis. Senescent neuroblast cells that accumulate in the dentate gyrus during aging secrete IL-27, which promotes local expansion and activation of NK cells; these cells, in turn, eliminate senescent neuroblasts in a process that results in cognitive and synaptic plasticity decline [43].

- Alzheimer's Disease (AD) represents the most common cause of dementia in the elderly. In patients with AD, NK cell activity is inversely correlated with the cognitive status evaluated by the analysis of MMSE (Mini Mental State Examination) score. Infiltration of peripheral NK cells in the brain has been observed in AD, leading to an aberrant production of TNF-α and IFN-γ by NK cells possibly implicated in the neurodegenerative process [44]. In addition to these reports that imply dysregulation of NK cell function, it has been demonstrated that NK cells' sensitivity to apoptosis is increased in patients with AD and correlated with Bcl- 2 expression [44]. A possible association between AD, human herpesvirus 6 (HHV-6) infection, and a specific KIR/HLA NK cell signature has also been suggested; indeed, the combination of inhibitory KIR2DL2 and HLA-C1 is correlated with a lower MMSE score, representative of a severe AD status and an increased susceptibility to HHV-6 infection [45].

- Parkinson's Disease (PD) is another major neurodegenerative disease, generally associated with an abnormal accumulation of a-synuclein (a-syn), leading to the degeneration of dopaminergic neurons. Evidence has shown that NK cells interact with a-syn in the brain of patients with PD. During PD progression, the infiltration of NK cells in the CNS parenchyma participates in dopaminergic neuronal degeneration [46].

During acute stress

There is a rapid mobilization of NK cells into the blood, certainly coordinated via secretion of catecholamines from the sympathetic nervous system into the blood and associated to b2-adrenergic receptors [47]. In contrast, in the context of depression, the level of NK cell decreased, as well as their functional activities (49). Interestingly, antidepressants that block the reuptake of serotonin are associated with upregulation of NK cell functions in depressed individuals [49]. The mechanism by which mental dysfunction acts on NK cells are still debated. Among the proposed hypotheses, the most promising is a possible deregulation of the hypothalamic/pituitary/adrenal axis leading to elevated levels of glucocorticoids, which further inhibit NK cell functions [50]. Although we are only beginning to better understand the role of NK cells in the CNS, its dysregulation in BD remains poorly documented [31,51]. The evidence that brain NK cells play roles in numerous of CNS-associated pathologies briefly discussed above, encourages us to dissect the phenotypic and functional characteristics of NK cells infiltrating the CNS in patients with BD.

NK CELLS IN BIPOLAR DISORDER

The first evocation of NK cell involvement in depressive illness came up three decades ago, when Kronfol et al. [52] published a preliminary report suggesting that NK cell activity is decreased in patients suffering from a major depressive episode. More recently, decrease in NK cells was observed in patients with mania, while in stable BD patients there was no difference in the number and/or frequency of NK cells, in comparison with healthy controls in several independent studies [13,16,17,53-58]. Snijders et al have also analyzed the impact of the genetic and environmental on NK cells in BD; they observed in discordant twin pairs, higher levels of NK cell frequency in patients with BD, compared to their healthy twin, although the significance was lost after including smoking, as an additional confounding factor [58]. In sum, the modulation in the number or frequency of peripheral NK cells does not seem to be a strong characteristic of BD. In contrast, an increased proportion of activated peripheral NK cells was observed among patients with BD, as previously reported for monocytes and T cells [54,58]. In addition, NK cells from patients with BD mostly

express inhibitory receptors, like NKG2A and ILT-2, while activating NKp30 and NKp46 receptors are greatly decreased, suggesting a functional impairment. Consistently, NK cells of patients with BD exhibit a profound inability to produce IFN-γ (Figure 2) [55], as previously reported in acute mania [59]. Clinically, lithium treatment increases the level of IFN-γ-producing NK cells, what promotes social behavior [60,61]. Consistently the level of IFN-γ produce by NK cells in BD is correlated with clinical scores, like the Montgomery–Åsberg Depression Rating Scale (MADRS) and the Positive and Negative Syndrome Scale (PANSS) (56). Interestingly, Furlan et al. [62] suggests a link between of cytokine-production by NK cell, White Matter (WM) integrity, and connectivity in BD; they reported that NK cells producing IFN-γ, but also GM-CSF and IL-17 are positively associated to fractional anisotropy measures and inversely with radial and mean diffusivity [62]. The most intriguing, but nevertheless interesting, observation concerns the observation of an overexpression status of adaptive NKG2C^{+} NK cells in patients with BD (Figure 2). In this context, we have recently reported that the circulating level of the soluble form of HLA-E (sHLA-E) is significantly higher in patients with BD as compared to that of healthy controls [63]. It is of interest that the non-classical HLA-E molecules constitute ligands for the NKG2C receptors that exist as either a cell surface membrane-bound or soluble isoform, resulting in metalloproteinase-mediated shedding of the membrane-bound molecules during stressful events, such as inflammation. Hence, it is possible that the impairment/inhibition of adaptive NK cells in BD could be modulated upon interaction with sHLA-E. As mentioned above, the development of adaptive NK cells results almost strictly from viral infectious events, in particular that due to CMV [64]. To the best of our knowledge, no study has reported either increased risk for CMV infection in patients with BD or correlated CMV serology with clinical severity. Within this line, the NKG2C overexpression we previously reported is also observed irrespective of the CMV seropositivity status in the studied patients with BD, thereby excluding a CMV-mediated process [57]. It is of note that NKG2C overexpression status is also found in patients with Autism Spectrum Disorder (ASD), again independently of CMV infectious status [65].

Nevertheless, the implication of infectious events in the development of psychiatric diseases has a long-lasting history based on epidemiological data but not always on a functional point of view [66]. It has been hypothesized that BD could be an EBV-driven chronic autoimmune disease [67] on the one hand and on the other that the incidence of BD is higher after HBV/HCV co-infection, when adjusted for sex, age, and comorbidity [68]. However, to date the data remain too fragmented, warranting further validation. Hence, efforts should be made to search for new viral signatures by genomic approaches to determine whether or not expansion of adaptive NK cells in BD is associated with a given viral infectious event. It is also important to emphasize that these immune characteristics are observed only in subsets of patients, suggesting a yet-to-be-defined "adaptive" phenotype. In this case, it has been hypothesized that BD could have several distinct triggering events necessary for its development; which open the way to personalized treatments. Another indirect tag of NK cell involvement in BD recently arose from a huge pan-genomic study. Mullins et al. recently published a genome-wide association study involving more than 40,000 patients with BD that uncovers several statistically significant signals including in the MHC region [69]. Interestingly, the most associated SNP in this region, i.e. *rs*13195402, is related to the butyrophilin subfamily 2 member A1 (BTN2A1) locus which is essential for the modulation of γδ T cells, a subset interacting with the NKG2D receptor that is mainly expressed by NK cells and to a lesser extent by some T cell subsets [70], suggesting that NK cells could potentially act through different pathways in BD. It is of interest that BTN2A molecules have previously been associated with autoimmunity, metabolic syndrome, and dysbiosis [70]. Furthermore, the butyrophilin molecules are major players in microbiota homeostasis and gut barrier integrity by counteracting the cytotoxic activity of the gut-resident γδ T cells also termed Intraepithelial Lymphocytes (IEL) and well known to be pivotal for mucosal immunity.

Accordingly, we can hypothesize that NK cells are likely involved in various immunopathological processes known to underpin BD risk or at least BD severity. Furthermore, within this context of genomic/genetic proxies of NK cell involvement in BD settings, we previously reported, in two

ethnically distant population-groups i.e. French and South-Indians that the genetically determined expression of the immunomodulatory non- classical HLA-G, a molecule recognized by two other NK receptors, ILT-2 and KIR2DL4, is involved in the risk of developing BD [71,72]. In summary, NK cells appear to play a central role in BD, either directly via the adaptive NKG2C$^+$ NK cells or via other pathways which will have to be studied more carefully in order to better understand the role of these cells during the evolution of the pathology.

DISCUSSION

Among the most innovative recent data on NK cells involvement in patients with BD is certainly the expansion of NKG2C$^+$ adaptive NK cells which are regularly associated with infection. There is an abundance of epidemiological evidences implicating infectious agents in the etiology of BD, such as Borna disease virus, influenza virus, HSV1 or 2, CMV, and HHV- 6 as well as the intracellular parasite *T. gondii* [66,73,74]. These pathogens are prevalent in humans worldwide and are capable of crossing the blood–brain barrier to cause a latent infection, and as such may influence CNS functions during periods of (re-)activation. It has also been demonstrated that HERV-W Env transcription is increased in psychiatric disorders, with higher values present in BD than in schizophrenia [75,76]. These data suggest that BD is not specific to a pathogen but rather involves a common mechanism to several pathogens. However, most research in BD has restricted the detection of infectious stigma to IgG antibodies, which are informative of a previous exposure but not able to identify the particular period of that exposure, leaving open the possibility that they might even have occurred after onset. It must be considered that worldwide seroprevalence of pathogens like herpes viruses varies between < 5% and > 95% depending on environmental and socioeconomic conditions [77] that could explain the discordant results that have been obtained. It has, however, been proposed that some of these infections could act in utero or early in life; for example, maternal influenza infection, documented during pregnancy, is associated with a 4-fold increased risk of BD in adult offspring, in association with neurodevelopmental abnormalities observed in postmortem brains of BD cases [78,79]. On the other hand, CMV infection in newborn mice induces a strong inflammatory response that deregulates brain homeostasis, leading to the activation of microglia and an influx of innate immune cells, including NK cells, recruited into the brain in a CXCR3-dependent manner. These cells are not only unable to control virus infection in the brain but also orchestrate pathological pro-inflammatory responses mediated by IFN-γ, which lead to delays in brain development [80]. Interestingly, we observed an inverse correlation between peripheral NK cell IFN-γ production and several clinical scores (Global Assessment of Functioning (GAF), PANSS, and MADRS scores), whereas NKG2C, a marker classically linked to viral infections, is positively correlated with the Young Mania Rating Scale (YMRS) score in patients with BD [56], also described in ASD [67]. Although the mechanisms underlying these observations require further investigation, these new data may indicate that a yet-to-be-identified pathogen drives the expansion of adaptive NKG2C$^+$ NK cells in BD and other psychiatric diseases.

CONCLUSION

Overall, it is obvious that NK cells could be directly or indirectly implicated in the development and course of BD even if extensive studies are still lacking. More specifically, monitoring the adaptive NK cell subset as a surrogate marker of disease activity in larger independent cohorts of BD patients; dissecting their phenotypic and functional characteristics; searching for yet-to-be-identified pathogen- or developmental-related processes involved in the expansion of adaptive NK cells in the periphery and the CNS. These new data ~~is~~ could also participate to better understand how they are recruited to infiltrate the brain, and how they function in the context of BD. Such steps, now possible thanks to innovative and high-throughput innovative technologies such as imaging mass cytometry in brain and, could constitute a steppingstone towards the development of NK cell-based therapies in patients with BD.

CONFLICT OF INTEREST

Neither author has any conflicts of interest or other disclosures to make

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