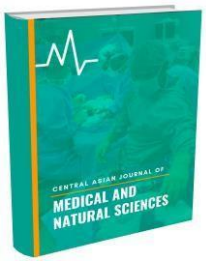

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Article

Natural Killer Cells in Multiple Sclerosis: Dual Roles in Neuroinflammation and Neuroprotection

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Abstract: Multiple Sclerosis (MS) is a chronic, immune-mediated neurological disorder characterized by demyelination and neurodegeneration within the central nervous system (CNS). Among the diverse immune cells involved in the disease's pathophysiology, Natural Killer (NK) cells have garnered increasing interest due to their complex and seemingly contradictory roles. Traditionally recognized for their cytotoxic function against infected and transformed cells, NK cells are now understood to exert both pro-inflammatory and regulatory effects in MS. This review explores the dual roles of NK cells in MS, highlighting their contribution to neuroinflammation and potential in mediating neuroprotection. On one hand, NK cells can exacerbate disease activity by promoting the destruction of oligodendrocytes and releasing inflammatory cytokines such as IFN-γ and TNF-α. On the other hand, subsets of NK cells particularly the CD56^bright population—demonstrate immunoregulatory properties by modulating dendritic cell function and suppressing autoreactive T cells, thereby contributing to CNS immune homeostasis. We also discuss how NK cell frequency, phenotype, and function are altered in MS patients, and how current disease-modifying therapies impact these cells. Understanding the conditions under which NK cells shift from pathogenic to protective roles may unlock new therapeutic avenues aimed at enhancing their regulatory capacity while minimizing their harmful effects. Ultimately, targeting NK cell responses holds promise for more precise immunomodulation in MS, potentially balancing disease control with CNS preservation.

Keywords: Natural Killer Cells, Multiple Sclerosis, Neuroinflammation, Neuroprotection, Immunoregulation, Cytokines

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1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system (CNS), primarily affecting young adults. It is the most common cause of non-traumatic disability in this age group. The first stages of the disease are characterized by transient inflammation of the brain and spinal cord which damages myelin and axons, resulting in episodes of neurological dysfunction. As a result of the relatively young age at onset, the lifelong accumulation of disability, the increasing worldwide prevalence and the lack of a curative treatment, MS continues to pose a major socioeconomic burden. Current disease-modifying therapies (DMTs) in MS and autoimmune disorders primarily target the adaptive immune system, i.e., T and B cells. However, the contribution of innate

immune cells such as natural killer (NK) cells is gaining attention in autoimmune disorders, including MS [1].

MS is a complex multifactorial disease characterized by demyelination, loss of oligodendrocytes, neuroinflammation and neurodegeneration in the CNS. MS is driven by an aberrant immune response to myelin antigens. Autoreactive immune cells belonging to the adaptive immune system (Th1 and Th17 and B lymphocytes) are the main players in the initiation of MS after their activation and subsequent passage through the blood-brain barrier (BBB) [2]. When autoantigens arrive in the CNS, adaptive immune cells gain access to the CNS. To maintain immune tolerance in the CNS, various cells including astrocytes, microglia, and oligodendrocytes detoxify the substances which enter the CNS and remove potential danger signals. Additionally, factors including TGF-β, IL-10, and mucosal addressesin cell adhesion molecule (MadCAM)-1 can attenuate CNS inflammation. However, these attempts are not always successful, leading to inflammation and neurodegeneration [3].

The dendritic cells (DCs) as the main antigen-presenting cells (APCs) of the body play an important role in priming and activation of Th1, Th2, and Th17 cells toward production of IFN-γ, IL-4, and IL-17. Chances of inflammation and neurodegeneration enhance when patients with genetically susceptible haplotype encounter potential environmental triggers. The CNS is well protected from peripheral immune cells through the BBB. A specific set of vascular endothelial cells expressing angiotensin II type 1 receptor (AT1R) and α4 subtype of integrin (VLA-4) in flanking the CNS can be targeted by autoantibodies and other non-cell type specific agents in MS [4]. As a result, T lymphocytes including Th1 and Th17 cells and antibodies produced by B lymphocytes and plasma cells can breach the BBB. These changes could serve, in turn, as the basis for recruiting and activation of additional immune cells via a cascade of events. Several studies have indicated a primary role of both the innate and adaptive immune systems in the pathogenesis and improvement of MS [5].

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system (CNS), primarily affecting young adults. It is characterized by the accumulation of lesions in the brain and spinal cord that consist of inflammatory molecules, demyelinated axons and degenerating axonal elements. The inflammatory processes result mostly from aberrant activation of the adaptive immune system. An elementary aspect of the dysregulated immune system in MS is the profound change in the lymphocytes, which compose the backbone of the adaptive immune system [6]. An increased number of T helper (Th) 1 and Th17 lymphocytes, and B lymphocytes and antibodies, have been implicated extensively in MS pathogenesis. In both the peripheral blood and the CNS, Th1 and Th17 cells are increased in the active form capable of passing BBB. Clusters of B lymphocytes in the form of ectopic germinal centers have been observed in the white matter lesions in a subset of MS patients [7].

With the help of disease modifying therapies (DMTs), MS has appeared to reduce some immune abnormalities. Immunoablation or down-regulation of T/B lymphocytes are the main mechanisms of action of most DMTs currently under clinical practice. However, it has been proposed that activation of innate immunity is an early event in MS, which can promote and perpetuate neurodegeneration independently of adaptive immune effects. Growing evidence has shown the roles of various innate immune cells including natural killer (NK) cells, natural killer T (NKT) cells, macrophages/microglia and dendritic cells in the pathogenesis and the improvement of neuroinflammation in MS. The involvement of NKT and most recently NK cells in MS are relatively new fields of research [8].

NK cells are large granular lymphocytes best known for their capacity to kill virally-infected, malignant and stressed cells. They are generally divided into two main subsets: the cytotoxic CD56dimCD16+ (CD56dim) and the regulatory CD56brightCD16− (CD56bright) NK cells. In peripheral blood (PB), the CD56dim NK cells account for up to

90% of all NK cells. The CD56bright NK cells constitute the majority of NK cells in secondary lymphoid organs and inflammatory sites. The distinct functionalities and distribution of NK cell subsets in health and in autoimmune disease are the result of distinct repertoires of activating and inhibitory NK cell receptors as well as chemokine receptors. MS is a chronic autoimmune disorder of the CNS, primarily affecting young adults. It forms the most common cause of non-traumatic disability [9].

2. Overview of Multiple Sclerosis

Multiple sclerosis (MS) is a chronic immune-mediated disorder of the brain and spinal cord in which there is a loss of myelin, leading to a wide variety of symptoms affecting the visual, motor, sensory, and cognitive systems. In the inflammatory phase of the disease, clinical attacks may arise due to a breakdown of the blood-brain barrier allowing the infiltration of numerous immune cells leading to neuroinflammation. The innate and adaptive immune response to the neuro-antigen myelin basic protein (MBP) can activate microglia and neuroinflammatory monocytes initially responding to clearing necrotic cells in MS [10]. However, activated myeloid cells can become pathogenic and damage oligodendrocytes, disrupt the blood-brain barrier, and drive T-cell activation propagating the demyelination cascade. Loss of myelin leads to neurodegeneration contributing to the irreversibility of symptoms. Ultimately, alterations to the immune components driving this duality are needed to inform current and future avenues of therapeutic development [11].

Classic alpha beta ($\alpha\beta$) T-cells and increasingly other immune subsets have been described in abundance in brain lesions of MS. Recently, they have been implicated not only in MS but also in other neurodegenerative diseases. Only a small population of CD56 bright Natural Killer (NK) cells normally reside in the healthy CNS controlling immune quiescence preventing pathogenic cell activation. These cells can proliferate in pathological situations, and although it is belied that they retain their regulatory function some can become pathogenic. In MS, these cells which also produce the proinflammatory cytokines have been shown to be impaired whereas higher percentages are observed in secondary progressive MS. Pathogenic NK cells are commonly studied in cortical lesions of MS and are believed to promote regulation of $\alpha\beta$ T-cells or neuroprotection and differentiation of oligodendrocyte progenitor cells facilitating remyelination [12].

Restoration of an intact BBB has also been observed in lesions of MS but whether this is protective or pathogenic is currently unclear. Modulation of the function of CNS-resident cells such as astrocytes, microglia, and oligodendrocytes is now being studied in models of MS and other neurodegenerative diseases believing that they too modulate immunity and compromise tissue homeostasis. Further advancements in understanding the duality of immune components in under-explored neuroinflammatory conditions should also invite key discoveries, especially as they include CNS myelin loss and axonal degeneration but with distinct mechanistic origins [13].

2.1. Pathophysiology of Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) caused by the destruction of the myelin sheath of neurons. By inflammatory damage to myelin with concomitant recruitment and activation of immune cells, MO in the brain can respond to neurodegenerative processes. The steady state of the CNS is preserved by several innate and adaptive cellular compartments. In addition, successful development of the pathogenic adaptive response requires complex interaction between various immune cells in periphery. Autoreactive immune cells belonging to the adaptive immune system (Th1 and Th17 and B lymphocytes) are the main players in the initiation of the disease after their activation and subsequent passage through the barriers [14]. To initiate autoimmunity, a cognate interaction occurs between the autoantigens with the antigen presenting cells which is followed by activation, expansion and enrichment of Th1 and

Th17 cells. These cells trafficking into the CNS upregulate MMP-9 and MMP-2 in addition to the production of chemokines to help migration of more leukocytes into the CNS site of inflammation. Subsequent influx of myeloperoxidase+ (MPO+) Neutrophils and IL-1β secreting MO triggers matrix metalloproteinase-9 (MMP-9) and matrix metalloproteinase-2 (MMP-2) production from MO leading to the upregulation of VCAM-1 and ICAM-1 on the endothelium and recruitment of T cells [15]. Neuropil inflammation CD45high inflammatory MO are most dominant in the subcortical white matter of chronic MS plaques which can engulf the post-mortem MS demyelinated axons and possess an upregulated gene signature that is associated with neurodegeneration. Several hurdles for successful management of MS include the underlying pathophysiology of MS sporadic/unpredictable attacks, heterogeneity of disease course clinical heterogeneity in symptoms and response to therapy, lack of specific biomarker for diagnosis and response to treatment and significant side effects of drugs currently used for the treatment of MS [16].

2.2. Clinical Manifestations

Multiple sclerosis (MS) is the most prevalent demyelinating disorder of the central nervous system (CNS) in adults and a major cause of disability among young people. Characterized by auto-reactive T and B lymphocyte proliferation, it results in neuroinflammation and consequent neurodegeneration due to demyelination, axonal transection, and neuronal loss [17]. In the absence of immune cells, there might be neuroprotection pathways by CNS-resident microglia and natural killer (NK) cells. A better understanding of the dual roles of NK cells in both neuroinflammation and neuroprotection is critical for preventing disease onset or slowing disease progression. The clinical manifestations of MS depend on the location of the demyelinating lesions in the CNS. Patients typically experience one or more acute neurological deficits (relapses), followed by periods of stability (remission). Initial attacks are usually followed by a relapsing-remitting course, including stable remission episodes or further relapses or progredience due to neurodegeneration (secondary progressive MS) [18]. However, about 15% of patients progress from the beginning (primary progressive MS). Clinical manifestations might include motor deficit and ataxia due to brainstem or cerebellar lesion; sensory deficit, hemianaesthesia, and facial pain due to the involvement of ascending pathways, thalamus, or cortex; visual disturbance due to the involvement of the optic nerve, optic chiasm, or brainstem; sphincter disturbance or sexual dysfunction due to the involvement of the spinal cord or hypothalamus. More diverse and insidious manifestations might occur later during the course due to the cumulative effect of lesions [19]. The diverse clinical manifestations and variable clinical courses pose a challenge to the differential diagnosis of MS. Patients undergo MRIs to evaluate brain and spinal cord lesions. Lumbar puncture for cerebrospinal fluids could reveal oligoclonal bands and elevated immunoglobulin G index [20]. However, due to varying sensitivity and specificity, incidental findings in asymptomatic individuals, and inaccessibility in developing regions, a minority of cases might be missed. Early diagnosis of MS in the era of modern neuroimaging is still clinical-oriented, with patients submitting their prior medical history and growing concerns [21].

2.3. Current Treatment Strategies

Multiple sclerosis (MS), an autoimmune disease targeting the central nervous system, is regarded one of the most significant health concerns and is consequently extensively studied around the world. It is a progressive, inflammatory disease that primarily affects young people with severe and various symptoms. Focal inflammatory lesions in the brain and other areas of the central nervous system (CNS) lead to myelin sheath destruction. In the early course of MS, commonly termed relapsing-remitting MS (RRMS), symptoms vary based on the location of the lesion [22]. Individuals report acute and transient neurological dysfunction in accordance to their lesion site. After some years of disease progression,

irreversible damage to the CNS is commonly observed, and symptoms often become permanent. This later stage is termed secondary progressive MS (SPMS). Greater understanding of the pathogenesis of MS has led to the introduction of numerous disease-modifying therapies (DMTs). Most DMTs are specific for the adaptive immune system, which includes lymphocyte subsets, such as T and B cells [23]. Accordingly, numerous scientific endeavors have aimed and are still trying to efficaciously modulate immune responses using immunotherapy [24].

Natural killer (NK) cells are lymphocytes with an innate type of immunity distinct from T and B cells. Their primary roles include being cytotoxic against cancer cells and virally infected cells and producing cytokines to modulate the activity of other immune cells, including both innate and adaptive immunity. In addition to cytotoxicity, NK cells can also limit immune disorders, such as dampening chronic inflammation in autoimmune diseases [25]. On the other hand, NK cells also possess the capacity to modulate acquired immune responses, either by enhancing or suppressing disease. NK cells account for approximately 10–20% of peripheral blood lymphocytes circulating in the body, with two well-studied main NK cell subsets, one type being regulatory and the other being cytotoxic. Due to their prominent roles in immunity, NK cells have been characterized in numerous pathologic conditions, including autoimmune diseases such as MS. Interest in NK cells has largely increased in the field of MS research, demonstrating their potential role in the immunopathogenesis of MS [26].

Previous studies revealed significant alterations in the frequency and function of NK and NKT cell populations in patients with MS and how disease-modifying therapies modulate them. Understanding the roles of NK and NKT cells in the immunopathogenesis of MS may identify these cell types as potential new therapeutic targets to treat MS [27].

3. Immune System Overview

The immune system is a sophisticated system with a diverse constellation of cells, tissues and signaling mechanisms. The function of the immune system is to maintain homeostasis or "tolerance" to self-antigens while defending against pathogens, tumors, and other threats to health. Immune mechanisms involve diverse cell types and elaborate interactions between communication molecules, known as cytokines or chemokines, in both innate and adaptive immunity [28]. The distinctive cellular and molecular components of innate and adaptive immunity evolved in response to requirements for the detection and destruction of increasingly complex pathogens [29]. It generally comprised various types of antigen receptors or co-stimulatory cytokines on host cells determining protective functions. Major cellular components of the immune system include specialized myeloid and lymphoid cells and their precursors. Myeloid cells (neutrophils, macrophages, dendritic cells, and mast cells) are typically derived from bone marrow progenitors and reside in barrier tissues with access to outside [30]. Abundant systemic myeloid cells include monocytes, granulocytes, and dendritic cells (DC), recruited in response to danger signals, they become transiently-amplified and specialized immune-protective effectors. Lymphoid progenitors are derived from the fetal liver and thymus, or later (spleen and bone marrow) [31]. B-cells recognized cognate antigens, primarily within the g-globulin like immunoglobulin superfamily, in peripheral lymphoid organs, and developed sequin, amplified, and tailored affinity and isotype. Interleukin-2 (IL-2), a cytokine critically involved in T-cell homeostasis, proliferation, and development, is also required for NK-cell development, activation, and inhibition of tumor growth. Alongside several activating/differentiating or agranulating factors, IL-2 supports proinflammatory-functioning NK cells [32]. During these processes, tissue-derived IL-15, IL-18, and a transforming growth factor – b cytokine strengthen their protective functions and chemotaxis. After a cytokine-induced increase in IFN-g-production, an infection-resolving mechanism becomes active, including IL-10 induction, O-glycosylated GlyCam1 upregulation, and vascular-pn-attenuated chemokine production. Murine and human NK

cells display an innate memory-like phenotype. Some of their pathogen-remnant chemokine receptors are sustained, contribute to localized/prolonged immunity, and accelerate activation [33].

The immune response consists of many components working together in pathways formed by chemokines, cytokines, and soluble receptors. Many distinct types of cells involved in the immune response exist, and understanding the relative contributions of different cell types in each pathology is a monumental challenge. For instance, many cell types produce pro-inflammatory and anti-inflammatory cytokine isoforms which complicate this narrative [34]. Such complexity must be understood on a case-by-case basis, with many specific immune cell functions identified for each pathology. Natural Killer (NK) cells are a type of innate lymphoid cell found in tissues throughout the body, including the central nervous system (CNS). A growing body of literature is investigating how NK cells can shape the course of multiple sclerosis (MS) and have protective or pathological roles. This section will serve as an overview of the immune system, NK cell biology, and the dual role of NK cells in MS [35].

Fighting against viral infection, and identifying and killing malignant cells are unique roles of NK cells in the innate immune system. A diverse range of study areas, anatomy locations, types of receptors, effector and signaling pathways, and experimental methods used to investigate NK cells have complicated the investigation of protein functions in NK cells. NK cells predominantly circulate in blood, although they can be found in many tissues, including lymphoid organs, bone, liver, gut, and brain spaces [36]. Simply looking at pro-inflammatory and anti-inflammatory cytokines does not help, as many immune cells produce both types. Measuring many immunological markers over time is often impractical, expensive, and not insightful, given the complexity of cross-pathway effects [37]. Many NK cell receptors send both activating and inhibitory signals. In MS, understanding the role of NK cells in gliomas is simplified by a more uniform tumor environment than in neurodegeneration. In both MS and neurodegeneration, for a fuller understanding of NK cell roles, measuring, and manipulating NK cell functions in a more compositional and dynamic manner is a priority [38].

3.1. Components of the Immune System

The immune system can be partitioned into several components according to their specificity, function, and cellular types. In the immune system, though not normally located in the cerebral parenchyma, resident immune cells, including astrocytes, microglia, oligodendrocytes, and endothelial cells, play a crucial role in normal homeostasis and effective immune response maintenance [39]. Blood-brain barrier (BBB)-forming endothelial cells were originally thought to be a physiological immunological shield that prevents the infiltration of 99% of blood-borne immune cell types from the periphery. However, increasing evidence supports a direct role for innate immune cells in CNS immunopathology and neurodegenerative diseases such as multiple sclerosis (MS) [1]. Components of the immune system include Microglia, Activated astrocytes, Dendritic cells, Natural killer (NK) cells, and T cells [40].

Microglia from the yolk sac colonize the CNS during embryogenesis and remain in the parenchyma thereafter. Following birth, microglia are crucially important for the refining of neural circuit architecture, maintenance of normal plasticity, and myelination in the maturing CNS. However, activated microglia produce neurotoxic factors, which may contribute to neurodegenerative processes. As the most abundant glial cells in the CNS, astrocytes have a tight control over the local environment [41]. When the CNS is challenged by neurotoxic factors, astrocytes become activated and dysregulate the homeostasis through the production of inflammatory cytokines, knockout of glutamate transporters, and impairment of ion homeostasis. In the context of neuroinflammatory processes, activated astrocytes have been demonstrated to be detrimental to BBB integrity, oligodendrocyte survival, and the regeneration of demyelinated axons [42]. Dendritic cells

(DCs) are the most powerful antigen-presenting cells (APCs) in initiating and conducting health and disease immune responses of high specificity. In MS patients, DCs are considered to have gained a potent pro-pathogenic phenotype owing to the upregulation of surface molecules such as CD54 and the secretion of inflammatory cytokines, particularly IL-6. In autoreactive immune cells entry into the CNS, DCs are crucially involved in activating T cells to promote immune-mediated neuroinflammation and demyelination [43].

NK cells are lymphocytes of the innate immune system that play a major role in the regulation of the immune response against virally infected cells and tumors through the recognition of transformed and infected cells and consequent lysis or localized cytokine production. In recent years, the dual role of NK cells in CNS autoimmunity has emerged [44]. On the one hand, NK cells are involved in the regulation of CNS-resident and infiltrating immune responses and are believed to have a neuroprotective effect in MS pathogenesis by limiting neuroinflammation, on the other hand, NK cells infiltrating the CNS during MS have been shown to mount a neurotoxic response that may ultimately lead to neuronal cell death. T cells and especially CD4+ T helper cells are considered to be the main effector cells of MS pathogenesis. Different subtypes of effector T helper cells, including Th1, Th2, Th17, and T follicular helper (TFH) cells, have been studied in the context of MS and EAE [45].

MS is a chronic autoimmune disease of the CNS with chronic inflammation and neurodegeneration. It is characterized by the presence of demyelinated lesions in the CNS that lead to different neurological problems in patients. CD4+ Th1 and Th17 lymphocytes, and to a lesser extent B cells, are the main drivers of disease development in EAE and MS [46]. However, recent evidence indicates that on the one hand, lymphocyte crosstalk with the innate immune system, mainly with microglial cells, NKT cells and macrophages, is important for disease development. On the other hand, lymphocyte crosstalk with CNS infiltrating innate immune cells is important for sustained low levels of neuroinflammation that cooperate with neuroprotective mechanisms to ultimately support the neurological recovery of MOG844-854 peptide vaccination in EAE [47].

MS is an inflammatory disease of the CNS caused by the destruction of the myelin sheath of neurons. This process is orchestrated by various immune cells, of which autoreactive immune cells belonging to the adaptive immune system (Th1 and Th17 and B lymphocytes) are the main players in the initiation of MS after their activation. Their activation requires antigen presentation by professional antigen-presenting cells (APC) like dendritic cells (DC). Once activated, lymphocytes can now leave the blood and infiltrate the CNS, where they cause inflammation and damage to the myelin sheath of neurones, resulting in astrogliosis and resulting oligodendrocyte death [48]. Currently, several first-line Disease Modifying Therapies (DMTs) including injected systemic drugs such as interferons and glatiramer acetate are available. Since their introduction into the clinics, several high-efficacy monoclonal antibody medications have been developed that are injected either systemically or intrathecally [49].

These treatments employ different mechanisms to ease MS symptoms by either modulating the function of immune cells or depleting them completely from the periphery or CNS. However, an underlying challenge in developing MS treatments is the complex interplay between steady-state/protective mechanisms and loose neuroinflammatory processes [49]. If the neuroinflammatory phase is not corrected correctly timewise or excess neuroinflammation is hampered, it can lead to the loss of crucial components important for both immune surveillance and neuroprotection, resulting in cognitive disabilities [50].

3.2. Role of Innate Immunity

Multiple sclerosis (MS), a chronic demyelinating disease of the central nervous system (CNS), is characterized by inflammation leading to myelin destruction and

neuronal degeneration. Chimeric receptor-modified T cells with an anti-CD19 activity were 1st used in children who had relapsed acute lymphoblastic leukemia, and they provided a powerful tool in the clinical management of malignancies, including MS [51]. Events that lead to MS pathogenesis including aberrant production of antibodies, immune system dysregulation, antigen presentation-related changes, and autoreactive T/B cell activation have been extensively studied. However, understanding how disease-modifying therapies modulate the inherent immune response is also critical. Due to immune infiltrate properties in MS, it seems innate immune response should also be involved in the 1st onset of MS or as a secondary response following immune therapy [52].

After the 1st descriptions of the role of innate immunity cells along with digital pathology AI, the in vivo role of invariant (iNKT) and variant (vNKT) cells with comprehensive function were further performed in murine models of MS. The dual role of both NK and NKT cells, which have been well spelled out, were further investigated regarding respective innate and adaptive function. In addition to ex-vivo plasticity, there are hints for the dual role of innate immunity in DMT. As they have the capacity to adapt and change states, both the profile of effector genes like IFN-γ for NK or transcription factors like E4BP4 for NKT, and cellular states such as memory have been addressed [53]. As opposed to the originally defined property of passive immunological memory, there are examples that documented the antigen-independent ability of NK to retain long-term memory of pseudo-exposure to viruses and give rise to better immune response, which is defined as 'long-term immunological memory.' Re-exposure to a cognate antigen can directly affect either adaptive immunity or innate memory [54].

Natural killer (NK) cells, the main effector cells of the innate immune system, play a crucial role in both viral control mechanisms and antigen recognition. Their presence in tissues supports or modifies the local activity of other immune cells through the release of interferon (IFN)-γ along with inflammatory or anti-inflammatory chemokines. They are a source of nitrogen exposed to astrocytes and oligodendrocytes, or neuroprotective vascular endothelial cells, in response to cerebrospinal fluid (CSF) inflammatory signals. The maturation status of NK cells influences their capacity to secrete cytokines upon IL-2 stimulation, with cellular interactions influenced by the expression of early adhesion molecules. NK cell function appears to be controlled locally in MS lesions, with the effects dependent on its stimulatory or inhibitory modulation [55]. NK cells contribute to neuroinflammation, the initial step. They propagate T cell proliferation and are sources of direct neurotoxic agents, as well as mediators of neuroprotection. These seemingly contradictory functions highlight a potentially bimodal or circumscribed role for NK cells in MS. Member, tissue infiltrating NK cells may orchestrate the development of incipient MS lesions. Macrophages and T cells release IFN-α, that polarizes infiltrating NK cells to the inflammatory phenotype, which then release IFN-γ and TNF-α that are crucial for the K126 biopten from MBP by local APCs [56]. Active lesions bear a compliment of Tbet/+ cells and NK cell activating ligands, alongside the expected expression of cognate receptors by infiltrating brain resident NK cells. Alternatively, brain resident NK cells may prime the local adaptive response in the early stages. Where tissue resident NK cells are rapid aggressors and executioners of MS transgression, prolonged hyper-inflammation may lead to down modulation of the autoimmune response [57].

NK cells have local access to all CNS compartments and are equipped with mechanisms capable of modulating neuroinflammation and fine tuning tissue repair. Secretion of pro-inflammatory and chemotactic cytokines that counteract tissue damage and direct reparative processes by other glial cells. TGF-β, along with neurotropic and angiogenic agents are among the chemokines secreted when NK cells are exposed to pro-inflammatory signals or as part of early lesions. The action of pro-inflammatory mediators on resident glial cells, switches the tissue TLN potential from neurotoxic to neuroprotective [58].

3.3. Adaptive Immunity in MS

Multiple sclerosis (MS) is the most common demyelinating disease of the CNS, and the treatment of MS over the past decade has diversified with the introduction of oral medications, but therapy remains limited for progressive forms of MS where neurodegenerative processes predominate and in advance stages. As with many immune-mediated diseases, the pathology and potential treatment of MS are directly related to the immune system, and thus more in-depth understanding of the immune system is required [59]. The immune system can be broadly separated into innate and adaptive arms. The innate immune system, which includes professional antigen presenting cells such as dendritic cells, microglia and macrophages, and a wide variety of other cells such as NK cells, is composed of cells that do not require prior exposure for activation [60]. The adaptive immune system, which includes T and B cells, is composed of cells which require presentation of a cognate antigen for activation, and thus required to behave in a manner which can be described as acquiring memory. MS pathology is thought to be dependent on both innate and adaptive immune cell activity [61]. Interfering with a specific component of the immune system is an active area of research for many diseases. For MS specifically, numerous immune-modulatory therapies are administered or undergoing trials. The experience from these trials shows not only the plasticity of immune regulation, but also complications in dissecting the effects, and hence the pathology itself. The plasticity of immune cell response complicates dissection of the underlying pathology of MS, yet makes the immune system a powerful target for therapy as it is a driving force of disease [62].

The role of adaptive immunity is generally accepted to be crucial in the development of MS, especially Th17 CD4+ T cells. They are abundant in MS lesions and believed to produce relevant cytokines such as IL-17, IL-21, and IL-22. While both T and B cells are involved in the development of MS, most studies so far have focused on Th17 CD4+ T cells, partly because they are abundant in MS lesions. The Th1 subset of cells can also produce proinflammatory cytokines and have been involved in MS pathogenesis [63]. Xbp1 deletion in T cell progenitors leads to increased Th1 and Th2 populations infiltrating the CNS, increased Th17 T cells at the disease onset, and earlier onset of paralysis in MOG-EAE. Inhibition of Th1 cell differentiation can also ameliorate disease symptoms. By providing insight into the role of T cells in other neuroinflammatory diseases, these studies can provide an important opportunity to study their role in MS, where their dynamic change and plasticity are difficult to tackle directly with human tissues [64].

Using various rodent models of MS-like neuroinflammation, B cells have been implicated in the disease's propagation via an antibody-dependent pathway. For example, the production of IgM and IgG is locally upregulated in capillary blood vessels within the spinal cord during the EAE. In mice that are deficient in B cells, disease development is markedly reduced. Monocytoid B cells in peripheral immune organs can also secrete autoantibodies against CNS antigens such as myelin oligodendrocyte glycoprotein; MS patients and patients with NMO commonly develop B cell accumulation and T-test also suggest a prominent pathogenic role for humoral immunity in NAWM [65]. It is assumed that antigen-nonspecific polyclonal activation of B cells in the compartment of tertiary lymphoid structures may also cause the chair-circuit of MS. B cells that are activated in the PPMS frontal lobe produce oligoclonal IgG and can react with the B cell receptor against oligodendrocyte lineage proteins. In a transgenic model where the B cell receptor is specific for an oligodendrocyte lineage protein, there is accumulation of B cells that are reacting to oligoclonal IgM in the brain parenchyma, but not in the periphery. Taking together the latter observations, development of B cell aggregation in the brain found in MS patients is assumed to be due primarily to the polarisation of naturally occurring autoreactive B cells rather than de novo generation of B cells against target antigens [66].

4. Natural Killer Cells

Natural Killer (NK) cells are innate lymphocytes that are essential in the defense against viral infection and cancer. As large granular lymphocytes, they can swiftly kill virally infected, malignant, and/or stressed cells via exocytosis of cytotoxic granules. Mice with functional NK cells are protected from death from lymphocytic choriomeningitis virus (LCMV) or streptococcus pneumoniae. Cytotoxic lymphocyte antigen-4 (CTLA-4)-deficient mice succumb to cancer, but CD4-positive (CD4+) T cell-depleted or functional NK cell impaired mice established tumors, demonstrating that NKG2D-positive (NKG2D+) NK cells are necessary for tumor immunosurveillance [67]. NK cells can also behave like an adaptive arm of the immune system, as they can show memory-like or memory phenotypes and confer stronger protection throughout the secondary and/or tertiary infections [65]. The global transcription program of human NK cells -normal and proliferation-induced-, resting and activated mouse NK cells, and mouse NK cell + T growth factor-induced NK-like T cells revealed a substantial difference. Finally, strategies employed by human and mouse HIV-1-encoded proteins obfuscate NK cell cytotoxicity to evade innate immune surveillance [68].

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) characterized by myelin and oligodendrocyte loss, and axonal injury. The etiology of the disease is not yet fully understood, but evidence points towards a complex interaction of genetic susceptibility, environmental triggers and dysregulation of the immune system. Initial disease attacks are commonly characterized by infiltration of pro-inflammatory T cells and monocytes into the CNS and subsequent neuroinflammation of the brain and spinal cord [69]. MS results in the visible destruction of myelin and axons, in turn leading to episodes of neurological dysfunction and permanent disability. Ultimately, the disease becomes progressive as the underlying pathology shifts from inflammation to a more gradual degenerative process underlining the need to consider the various contributing roles of the innate immune system in MS, next to the currently implemented treatments targeting primarily T and B cells [70]. Studies have begun to broaden the scope of innate immune cells such as microglia, mast cells, neutrophils and NK cells in the context of MS [71]. In contrast to all the other innate immune cells actively being studied in the context of MS, NK cells have largely been neglected during the past decades. While multiple studies did examine NK cell function during MS and in several animal models, most efforts were uncoordinated and the relevance of the findings incomplete. So far, major advances in the understanding the benign side of NK cells have been made, as well as whatever data available on the putatively detrimental role of NK cells [72].

4.1. Characteristics of Natural Killer Cells

NK cells are large granular lymphocytes best known for their capacity to kill virally-infected, malignant and stressed cells. Beyond their direct killing potential, they secrete a variety of immunomodulatory cytokines activating different immune cells. NK cells are part of the innate immune system, developing from dedicated CD34+ progenitors in the bone marrow. They are mainly present in the liver, peripheral blood (PB), and secondary lymphoid organs, with substantial numbers in the brain [73]. In PB, NK cells constitute 5–20% of all lymphocytes and are divided into two main subsets: the cytotoxic CD56dimCD16+ (CD56dim) and the regulatory CD56brightCD16- (CD56bright) NK cells. CD56dim (or CD56dimCD16+) NK cells account for up to 90% of all NK cells in peripheral blood. They are considered the more mature effector subset with high cytotoxic activity mainly through their production of perforin and granzymes A and B [74]. The CD56bright NK cells constitute the majority of NK cells in secondary lymphoid organs and inflammatory sites. These cells are considered less mature and are generally more immunoregulatory, producing cytokines like interferon (IFN)-γ. NK cell subsets are characterized by their surface expression of CD56 and CD16. The distinct functionalities and distribution of NK cell subsets are the result of distinct repertoires of both activating and inhibitory NK cell receptors as well as chemokine receptors [75]. Activation of NK

cells is mediated by a balance of signals received through their inhibitory and activating receptors. An expanding amount of literature is now describing various NK cell subsets portraying adaptive-like immunological memory and long-lived antigen specificity. Three main types of adaptive NK cells have been described: NK cells found in the murine liver, human NKG2C+ and murine Ly49H+ NK cells, and human and murine cytokine-activated NK cells showing memory-like features [76]. In addition, infiltrating effector memory-like NK cells have been reported in tumors. Up until the last decade, NK cells have largely been ignored in the MS field, and literature on their contribution to MS immunopathogenesis is starting to accumulate. Experimental studies are starting to emerge demonstrating the presence and different roles of NK cells in various models of neuroinflammation, including EAE. These findings may open new avenues for therapeutic anti-TNF-α strategies targeting the recruitment and cytotoxic NK cell functions [77].

4.2. Development and Activation

NK cells develop from a common lymphoid progenitor in the bone marrow and mature in the bone marrow and secondary lymphoid organs, a process regulated by several cytokines. Signals provided by IL-15 and other cytokines are required for NK cell growth, survival and functionality. NK cells express a unique set of receptors provided by the germline, which include activating receptors recognizing stress-induced ligands and a wide range of inhibitory receptors, mainly recognizing MHC Class I molecules [78]. Signals generated by release of PAMPs and DAMPs in response to danger lead to the activation of innate immune cells, including the recruitment of NK cells. Both conventional DC and plasmacytoid DCs produce large amounts of IL-12, subsequently enhancing the ability of NK cells to produce IFNg. Activated NK cells down-regulate their IL-15Rα chain, subsequently engaging in serial killing of target cells [79]. NK cells migrate to different sites within the body in response to different chemokines. Subsets of NK cells in the PB tend to segregate based on their receptors for specific chemokines. Migration of NK cells to sites of inflammation requires the presence of specific cytokines and chemokines, leading to a redistribution of the NK cell pool within the body. Inflammatory influences in the CNS induce increased recruitment of NK cells, where they may influence the clinical features of these diseases through direct targeting of both resident and infiltrating immune cells, but also through influence on glia and neuronal functions [80]. Very modest CNS infiltration by NK cells has been noted in RAG−/− and CD4−/− mice with EAE, pointing to a crucial role for the adaptive immune system in the development of the disease [81]. The early involvement of NK cells in MS has been studied in the postmortem material of patients suffering from other forms of CNS inflammation, wherein chronic and virtually exclusive NK cell custom at the presence of macrophages, microglia and lymphoid cells was reported. Recently, the involvement of NK cells in the development of RAG−/− mice with chronic WML was studied by selective depletion of these cells, revealing a delaying effect on the appearance of WML, pointing to their crucial role in neuroprotection under certain conditions [82]. The role of NK cells in the experimental autoimmune encephalomyelitis (EAE) model of mouse CNS autoimmunity is also described, focus being upon their recruitment and activation within the CNS. Although pro-inflammatory roles of NK cells have been revealed within this model, also their major regulatory, neuroprotective and anti-inflammatory functions have recently been uncovered. Neuroprotection was associated with cytotoxicity directed at CD4+ infiltrating T and B cell [83].

4.3. Cytotoxic Mechanisms

NK cells exert their cytotoxic actions through different interacting pathways. They can directly kill cells through hard-wired mechanisms such as perforin and granzymes, or indirectly suppress these cells by secreting cytokines or by engaging death receptors. In either case, MHC class I recognition through the NKG2A/CD94 complex inhibits NK cell activity. Conversely, the recognition of missing MHC class I through activating receptors (NKG2D, CD16, NKp30, NKp46, or 2B4) induces target cell death [84]. Abundant evidence

indicates that some type I MS lesions are infiltrated with activated cytotoxic NK cells while other type II lesions are infiltrated primarily with regulatory-type NK cells. Various reports are providing direct evidence of the anti-viral effects exerted by NK cells [85]. Dicinfection of the central nervous system with MV induces an encephalitis characterized by widespread replication of the virus in astrocytes and other brain parenchymal cells. These cells, acting as antigen presenting cells, can activate the adaptive immune response leading to further tissue injury mediated by MHC class II restricted T cells. Mice lacking NK cells develop a more severe MV infection with higher mortality rates [86]. NK cells eradicate the virus by killing infected cells during the critically early phases of the disease. This antiviral activity, along with secretion of interferon-γ, may also help to repair the damaged CNS tissue. Before activation, naïve NK cells reside in a resting state in the peripheral blood. Upon Cytomegalovirus infection NK cells dramatically expand in frequency and effector functions [87]. Unlike T and B cells, this expansion is not driven by viral proteins or peptides but seems to be attributed to development of heterologous memory especially inducing type I Interferon production. NK cells are early responders to viral infections and represent the first line of defense against this pathogen form. Besides directly killing infected cells, NK cells can influence adaptive immunity by limiting the expansion of virus specific T and B cells. In diverse pathological conditions, NK cells can exert paradoxical pro- and anti-inflammatory functions [88],

5. Role of Natural Killer Cells in Neuroinflammation

Injury or infection leads to an inflammatory reaction in the CNS that has both beneficial and detrimental effects. Once the inciting stimulus is removed, the inflammatory response must be eliminated, and homeostasis returned to the CNS. Both local and peripheral immuno-regulatory mechanisms are activated to cease the inflammatory response and restore homeostasis in the CNS [89]. An initial layer of immuno-regulatory mechanisms involves the activation of suppressor T cells, particularly T regulatory cells (Tregs), along with numerous anti-inflammatory regulatory cytokines, including IL-10 and TGF-beta. NK cells are also components of the CNS immune system with the ability to influence neuro-inflammation. They are cytotoxic lymphocytes that develop in the hematopoietic compartment of the bone marrow via a unique set of transcription factors [90]. Mature NK cells migrate to the blood and then enter the tissues to search for infected or malignantly transformed cells not expressing MHC-I or altered versions of MHC-I. Recognition of target cells occurs through a unique combination of inhibitory MHC-I-restricted receptors and activating non-MHC-I-restricted receptors [91].

TIA-1 and perforin-mediated apoptosis occurs following the engagement of this receptor combination. Early studies established that NK cells pro-actively survey the body for signs of disease, a function still favorably viewed by many investigators. In this regard, it is also interesting to consider whether, given their potential to kill, they could end the slow propagation of disease in late-stage HIV-1 infection. Recently, a protective role for NK cells in the CNS has been discovered in both models of MS and autopsy specimens of human MS [92]. Development of disease following EAE induction in nude or severe combined immuno-deficient mice lacking $\alpha\beta$ T cells has been attributed to excess production of pro-inflammatory cytokines by activated macrophages [93]. NK cells from the periphery of MS patients were shown to attenuate proliferation of myelin-reactive T cells in vitro and decrease peripheral-efferent CD4 T cell recruitment into the CNS after adoptive transfer. It was subsequently demonstrated that NK cells can enter the CNS in response to haptens applied to the skin, where they kill myelin-reactive CD4 T cells and suppress localized encephalitis [94].

Increased numbers of activated NK cells (CD56dimCD16+CD69+/CD107a+) have been detected in the blood of relapsing-remitting MS patients, suggesting that peripheral NK cells can enter the CNS following breakdown of the blood-brain barrier and contribute to local immuno-regulatory mechanisms of MS [95]. On the other hand, an ability to lyse

a wide variety of effector cells co-expressing MHC-I and ligands for NKG2D, as well as oligodendrocytes and astrocytes that are stressed and express MHC-I and ligands for NKG2A and NKG2D, raises the possibility of an unwanted toxicity to surrounding healthy cells that are not the subjects of the initial inflammatory insult. In the last two decades, several independent studies have arrived at conflicting conclusions with respect to the influence of NK cells on MS pathogenesis. Several studies have concluded that NK cells do not participate in the initiation of MS or appear to remain in a resting non-cytotoxic state if a CNS immune response is present [96].

5.1. NK Cell Activation in MS

Multiple sclerosis (MS) is an inflammatory disorder of the central nervous system (CNS) that results in demyelination and destruction of neurons by an autoimmune response. T- and B-cells are considered to be the most important cells involved in this process, whereas the role of NK cells is controversial. In this regard, several studies have shown that NK cells ameliorate experimental autoimmune encephalomyelitis (EAE), which is a well-established model of MS, because of their ability to lyse cells that aggravate the MS disease [97]. Accordingly, depleting NK cells before immunization of mice with myelin oligodendrocyte glycoprotein peptide leads to a severe relapsing EAE model, resulting from increased T-cell proliferation and production of Th1 cytokines. Similarly, defective recruitment of NK cells into CX3CR1-deficient mice, which fail to generate migratory T-cell lymphatic patterns, leads to a severe form of disease, as NK cells inhibit the accumulation and activation of inflammatory Th17 cells [98].

Studies in relapsing-remitting MS patients have shown that higher NK cell activity correlates with a higher risk of developing active FLAIR lesions. Astrocytes in MS brain white matter lesions produce IL-12, which promotes NK cell development that secretes IFN- and TNF-, enhancing T-cell activation by increasing the surface expression of MHC class I and II molecules. In another study, the blockade of NK cells by treating animals with anti-CD49b or anti-asialo GM1 mAb, resulted in diminished EAE clinical disease [99]. Following a well-described EAE experimental system, NK cells were found there to play a dual role, in which they initially migrated to the inflamed CNS and produced several factors that attenuated EAE severity but started to migrate preferentially toward the periphery and contributed to maintaining signals that caused continuous recruitment of pathogenic T cells into the CNS, which aggravated the disease. Understanding the role of these cells in this complex environment in MS may improve MS treatment and ensure successful progress towards curative therapies [100].

5.2. Cytokine Production and Inflammatory Response

Multiple sclerosis (MS) is one of the most common neurodegenerative diseases, characterized as a chronic autoimmune disease of the central nervous system (CNS), in which myelin is damaged by an inflammatory and ultimately autoimmune process. MS patients have focal regions of demyelination usually associated with a perivenous infiltration of immune cells and use CD4+ T cells as a major effector population in the pathogenesis of the disease [101]. Despite such pathogenic roles, numerous lines of evidence indicate that regulatory T cells (Tregs) play a pivotal negative regulatory role and contribute to the resolution of MS lesions. With efficient antitumor immunity, well-activated natural killer (NK) cells are prevalent in the peripheral blood and mucosal organs and are enriched in the pleural and peritoneal cavities. However, equivocal ideas suggest that NK cells either protect against or mediate neurodegeneration. As a prototype of CNS-intrinsic protective immune surveillance, NK cells respond to pathogens, clear tumor cells, decline in response to stress, and deteriorate under abnormal priming. Granulated NK cells have potent cytotoxicity against visceral smooth muscle [102]. Extremely activated NK cells secrete a variety of pro-inflammatory cytokines that potentiate neuroinflammation. Histological studies in experimental autoimmune encephalomyelitis show that increased NK cell cytotoxicity is correlated with oligodendrocyte apoptosis.

Localizing the transient loss of the brain-sparing blood-brain barrier, recruitment of NK cells is followed by robust neuroinflammation, severe ionization of microglia, and exacerbated CCS clear amyloid-beta deposition [103].

Compared to other innate lymphoid cells (ILCs), NK cells are currently the best characterized ILC family member with an extensive understanding of their development, maturation, and activation, along with functional versatility in anti-tumor and anti-viral immunity, regulatory immune response, and in the cross talk with other immune cells. Compelling evidence persists in support of their vital roles in multiple immune-mediated diseases, including infections, cancers, autoimmune disorders, and transplant rejection [104]. In MS, a common neurodegenerative autoimmune disease of the CNS and increasing health problem among the middle-aged, the role of NK cells is still poorly understood and remains controversial. Initial studies clump to the anti-inflammatory role of NK cells in MS, including a recent report showing that NK cells can directly inhibit the process of neuroinflammation by effectively killing polio virus-infected astrocytes. However, there are also increasing lines of evidence suggest that NK cells may contribute to the process of neuroinflammation and neurodegeneration in human MS and in animal model of demyelinating diseases [105].

5.3. NK Cells and T Cell Interactions

Multiple sclerosis (MS) is characterized by a complex heterogeneity, with some patients developing an acute, aggressive course and others a gradual accumulation of disability. The nature and extent of the pathogenic immune response that underlie such different natural courses are still poorly understood [106]. Conventionally, a dominant role has been attributed to T lymphocytes in the immunopathology of MS. However, there is growing evidence of the importance of activated B cells in the CNS in MS lesions. In addition, one cannot rule out the possibility that natural killer (NK) cells are involved in the pathogenesis of MS, as they can be regarded as mediators of substantial inflammatory processes occurring in the CNS under a wide range of pathophysiological conditions [107].

Knowledge on possible (patho)physiological roles of NK cells in MS was gained from patient-based studies analyzing peripheral blood, cerebrospinal fluid (CSF), or CNS biopsy samples, studies of the expression of MS susceptibility genes in NK cells with stress-induced lysis of MS-relevant cells, and experimental autoimmune encephalomyelitis (EAE) studies examining the impact of NK cells on the course and severity of the disease. The data suggest that NK cells have both the capability to contribute to the pathogenesis of MS as well as to be protective against MS. This duality of NK cells in MS is similar to the one observed for T-helper 1 (Th1) and Th17 autoreactive T cells in MS [108].

In MS, a scenario is envisioned wherein the accumulation of pro-inflammatory cytokines and chemokines in the CNS elicited by the attack of T and B lymphocytes against myelin antigens stimulates activated NK cells that cross the blood–brain barrier. The NK cells migrate in response to the chemokines, where they exert their cytotoxicity on activated T cells, B cells, and other cell types in the CNS. Activated NK cells secrete various cytokines and may be neuroprotective after CNS injury [109]. In this regard, CNS-traversing NK cells in MS lesions have a broad cytotoxic profile that targets not only activated T cells but also B cells, astrocytes, microglia, and oligodendrocytes. However, the potential for NK cells to target these autoimmune cells may hasten the evolution of MS. Although B cells and antibodies against the oligodendrocyte glycoproteins are more characteristic of secondary progressive MS, CD138-positive plasma cells are found in the plaques of white matter early on in the disease [110].

6. Neuroprotective Functions of Natural Killer Cells

While NK cells were initially thought to be primarily involved in innate defense against grossly transformed or virally infected cells, more recent evidence suggests that NK cells can actively shape the adaptive immune system through various kinds of cross-talk with other cell types. They can produce a variety of immunomodulatory cytokines to elicit anti-viral, pro-inflammatory, or regulatory functions depending on their exposure to specific combinations of cytokines and signals. This ability to switch between pro-inflammatory and tolerogenic function has also been suggested for NK cells. NK cells may shape the immune response to MS by exerting opposite effects depending on the amount of cognate antigens in their microenvironment [111]. The view of immune system components as merely 'good' or 'bad' on a functional axis is an attractive oversimplification that has perhaps hindered MS research on other players than the major actors T and B cells. In addition, this conservative view should be interrogated experimentally, as the opposing functions of NK cells in MS both 'pro' and 'con' should leave distinct traces in the cellular make-up and secretion profiles of MS periphery blood and tissues [112]. The emergence of highly sensitive technologies allowing for the detection of simultaneous expression of large panels of proteins from limited samples should help to determine the plethora of interactions of NK cells in the MS context. Following this, it may be possible to design specifically engineered NK cells for therapeutic purposes. This fine characterization of NK cells at different developmental stages, classes, and activation states may also allow distinguishing patients with rapidly progressing forms of MS from others with a benign course or slow progression [113].

In addition to their roles as potentially pathogenic cells the effects of NKs in disease amelioration have also been studied. Although conflicting results have been found on the role of NKs in MS, there is some evidence to suggest that these cells might contribute to repair and resolution mechanisms. Two of the main immune mechanisms of NKs have been found to aid in neuroprotection after immunological insults to the CNS. One mechanism is that activated NKs directly enhance neuronal apoptosis by exocytosis of cytoplasmic vesicles containing perforins and granzymes. The other mechanism is indirect, by suppressing pathogenic autoreactive T-cells that initiate and propagate CNS inflammation. NKs might improve the overall prognosis of MS by acting on one or both of these targets early in the disease. In human tissue MS plaques with areas of demyelination were not found to contain NK cells, while further away in unaffected tissue large numbers of NKs are present [114].

A quantitative test of the global effect of activated NKs on survival of T-cells, neurons, and glia would help elucidate this issue. After immune regulation by NKs acute but reversible changes in T-cell activation have been reported, as well as a decrease in the number of pathogenic T-cells and microglia in the brain. The NK-mediated decrease in pathogenic T-cells is seen after EAE symptoms are present. Although it is not clear whether recovery from EAE occurs as a cumulative effect of transient regulatory events or whether a delta-like repair event occurs a clearer understanding of the NK-mediated regulation of immune responses will contribute to efforts to find a therapeutic regimen for MS patients [115].

NK cells may play an essential role in CNS pathology resulting from prolonged and overt immune responses to presumed self-constituents. On the other hand, the fact that many patients carrying MS-related alterations in inflammation do not develop overt immune disease and accompanying CNS pathology demonstrates that overt pathology must arise from an additional factor, such as additional infiltrating T-cells directed against 'foreign' targets. In this context, understanding the potential dual roles of NKs in anti-viral defense and autoimmunity will be an arduous but important challenge. In summary understanding NK-mediated immunopathology in MS is an essential endeavor and studies on the impact of NKs in MS are a prospective area of research which is only just beginning to unfold [116].

6.1. Regulation of Neurotrophic Factors

The balance between pro-survival and pro-apoptotic factors affects the survival and activity of immune cells. The importance of neurotrophic factors in regulating the survival of NK cells and their relation to MS remains unknown. BDNF induces the proliferation of NK cells and sustains the activity of CD3^−NKp46^+NK cells (intraCNS NK cells) by suppressing the apoptosis-promoting activity of TRAIL. BDNF-R tyrosine kinase receptor TrkB is expressed in both peripheral blood NK cells and intraCNS NK cells [117]. Activation of NK cell TrkB enhances MAPK/ERK, MAPK/p38, and PKB/Akt pathways which lead to the activation of nuclear factor κB (NFκB) and inhibitory factor κB (IκB) kinase (IKK) signaling pathways. The interactions of BDNF with the corresponding receptors attune different death factors and their receptors; thus, the members of the Bcl2 family proteins regulate the sphingomyelinase-ceramide pathway and promote the activation of mitochondrial apoptotic pathway members in TRAIL-induced apoptosis of NK cells [118].

GA treatment significantly lowers the percentage of BDNF-producing cells and, as a result, the concentration of BDNF released in the medium, indicating that BDNF is targeted mainly by GA treatment. The percentage of cells producing BDNF in the remission and treatment groups was significantly lower in the GA group compared to the other groups. GA treatment may ameliorate the course of MS by reducing the concentration of BDNF produced by astrocytes and enhancing the apoptosis of genetic-resilient T helper 1 (Th1) cells. Of interest in regard to BDNF may be its effects on NK cells, the focus of this review [119].

Neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and multiple sclerosis (MS), are a heterogeneous group of disorders that share common features of progressive degeneration of neurons. One of the mechanisms responsible for cellular demise is neuroinflammation, characterized by the activation of glial cells and by the release of pro-inflammatory cytokines in the central nervous system (CNS). Accumulating evidence indicates that natural killer (NK) cells play a pivotal role in the regulation of neuroinflammation in the CNS [120]. As the first line of defense, they limit infections and tumors by exerting cytotoxic effects through the release of perforin/granzymes and other pro-inflammatory effector cytokines. Moreover, they are also capable of cross-talk with other types of immune cells, including other innate immune cells like mast cells, macrophages, and dendritic cells, as well as adaptive immune responses, particularly CD4+ and CD8+ T cells and B cells [121]. Ultimately, this crosstalk leads to the maturation of other immune cells within the infected CNS: on one hand, the seizure of viral clearance and lymphocyte infiltration; on the other hand, the generation of immune tolerance, axonal protection and elevated neurotrophic factors (NTF) expression. The amounts of various NTFs secreted by different CNS populations comprise a very complex interplay. Some of these factors exert neuroprotective effects while others enhance neuroapoptosis. These differential effects of NTFs are well established on neurons. However, evaluating the effects of neuroinflammatory treatment on the modulation of NTF secretion by NK cells or under various pathological conditions is only emerging. It is now quite apparent that NK cells express and secrete NTFs [122].

6.2. Modulation of Apoptosis

Present throughout the body, NK cells provide a powerful first-line defense against transformed infected or stressed cells. When triggered by pro-inflammatory signals, NK cells release pre-formed lytic granules containing cytotoxic proteins, granzymes (GZMB, GZMA, and GZMH), and perforin. In neurodegenerative diseases, there is emerging evidence for a role of NK cell-mediated apoptosis in the CNS. NK cells, which are rich in TH1 polarizing cytokines, can also kill DCs and thus, maintain the immune balance in the CNS. Here, we investigated the effects of GA on subsets of NK cells and their apoptosis-related molecules in relapsing remitting and progressive forms of MS [123].

NK cells are stimulated with cytokines such as IL-12, IL-18, and IL-15; these cytokines enhance the expression of perforin (PRF1) mRNA in human NK cells. GA augmented the induction of PRF1 and GZMA and GZMB by C18 alone and thus, enhanced the NK cell-mediated killing of immature DCs induced by fatty acids and lipids. In MS patients, GA impaired the expression of osteopontin and enhanced the production of IL-10, a potent anti-inflammatory and neuroprotective cytokine[124]. Treatment with GA modified NK cell number and function in MS patients, leading to a reduction in pro-inflammatory cytokines (IL-17A, IL-23, IL-20, IL-1β, and TNF-α) and an increase in anti-inflammatory ones (IL-10, MCP-1, and VEGF). The ability of the pro-inflammatory cytokines to enhance cytolytic activity against target cell lines was impaired. Studies in immune-competent mouse lymphoid tissues confirmed a direct action of GA on NK cells. GA-treated NK cells expressed lower levels of IFN-γ and CD107a and released less degranulation lysosomal proteins MIP1β and MCP-1, in response to Th1 polarizing cytokines, in a dose-dependent manner [125].

Natural killer (NK) cells are important lymphocytes in the innate immune system and provide protection against a variety of cancers and viral infections. Data collected over the past several years demonstrate that NK and NKT cells are involved in the pathogenesis of MS and EAE. These alternative roles include: 1) involvement in neuroinflammation and destruction of neural tissue, and 2) neuroprotection, which halts inflammatory cascades, prevents damage from excessive immune responses, and stimulates the active repair and regeneration of neural tissue. The participation of lymphocytes in either the pro-inflammatory or anti-inflammatory responses is driven by the immunological context, in which stimulating or inhibitory factors created by other cells determine which immune response dominates [126].

Apoptosis is defined as a programmed cell death that is considered a normal physiological phenomenon. This phenomenon serves a number of purposes, such as eliminating unwanted cells during development and maintaining tissue homeostasis. In normal physiological conditions, apoptosis involves: 1) a decrease in cell volume and a retraction of cell processes (pyknosis), 2) condensation of chromatin, resulting in the formation of distinct aggregates within the nucleus (karyorrhexis), 3) loss of plasma membrane asymmetry and the exposure of phosphatidylserine on the external membrane leaflet, 4) dissipation of the mitochondrial membrane potential and electron transport chain dysfunction, leading to reactive oxygen species production (ROS) and other byproducts, and eventually mitochondrial swelling, and 5) early or late activation of endonucleases or proteases, resulting in the fragmentation of chromatin or proteins, respectively [127].

Although often viewed as solely eliminating the target cells, various forms of apoptotic processes can modulate the subsequent adaptive immune responses. During apoptosis, various molecules, including ATP, heat shock proteins in different families, and lipid mediators, may be released from either the apoptotic cells or the effector cells. This bidirectional communication, which can promote, prevent, and redirect the following immune responses, necessitates the decision of which cells should be damaged, forming the basis for the dual roles of apoptosis in immunity against cancer [128].

6.3. Impact on Neurogenesis

In addition to protecting neurons and modulating the effects of Th1 and Th17 cells, NK cells may have a protective impact in the context of MS-based neurodegeneration. It has been hypothesized that neurodegenerative processes may counterbalance the damaging effects of neuroinflammation in MS. Neurogenesis is responsible for the constant replacement of newborn neurons in the human brain and is a key process of regenerative neuroplasticity. Neurogenesis dampens neuroinflammation by counteracting the damaging effects of inflammatory cytokines [129]. Dysregulation of neurogenesis is likely to facilitate disease progression in MS, whereas strategies to boost neurogenesis may

promote self-repair mechanisms and limit tissue damage. Recent findings indicate that neurogenesis is dysregulated in the white matter lesions of patients with post-mortem MS tissues, and in the brains of experimental autoimmune encephalomyelitis (EAE)-induced mice [130].

Classical innate and adaptive immune cells in inflammation contribute to the regulation of neurogenesis, ranging from beneficial to detrimental roles depending on contextual factors. As a large, heterogeneous population of innate lymphocytes, NK cells are emerging as novel modulators of neurogenesis [131]. The observation that NK cells accumulate in the brains of inflamed mouse models of neurodegenerative disorders, together with the finding that the blocking of IFN-γ signalling partially rescues neurogenesis, suggest that stimulated CACs may secrete an NK cell attractant, and that infiltrating NK cells, which largely express higher levels of IFN-γ than do splenic NK cells, may dampen neurogenesis in chronic models of neuroinflammation. NK cells may represent a new therapeutic target to limit permanent cognitive deficits associated with neurodegeneration [132].

Specific microglia-neuron signalling and inflammatory mediators may also play protective roles within the CNS, but the mechanisms by which this is accomplished remain largely unknown. In addition to proposed actions on the vascular compartment, NK cells have been reported to impact on neurogenesis in the adult brain of healthy animals. It is hypothesized that NK cells may promote activation of the neurogenic niche in inflammatory contexts, and that this action may depend on various factors, such as the intensity of neuroinflammation [133].

Neurogenesis, the formation of new neurons from either neural stem cells (NSCs) or neural precursor cells (NPCs), occurs not only during development but also in the adult brain at a lower rate. Neurogenesis is a highly regulated process influenced by a plethora of intrinsic and extrinsic factors, consisting of, respectively, genetic and epigenetic factors as well as environmental factors. The neurogenic capacity of the brain declines with age and is impaired under neurodegenerative diseases. Nevertheless, increasing evidence demonstrates the existence of neurogenesis-promoting factors [134]. These factors can be categorized into the following four groups: (1) neuroprotective factors, (2) transcription factors, (3) factors limiting the formation of glial cells from NSCs and favoring the generation of neuronal lineage/glutamatergic progenitors and (4) pro-inflammatory but neurogenic factors [1]. An innate immune component, natural killer (NK) cells are large granular lymphocytes that can kill stressed cells such as virally infected cells or cancer cells. However, naïve NK cells also have more immunomodulatory functions such as cytokine production and the presentation of activating ligands [135].

Recent evidence indicates that most neurodegenerative diseases, including Alzheimer's disease and Huntington's disease, involve NK cells. In Alzheimer's disease, both activated and resting NK cells are found in the brain, with activated NK cells adopting a pro-inflammatory profile characterized by elevated levels of cytokine release. These activated NK cells also exert neurotoxic effects via the increased expression of the cytotoxic granule protein granzymes. On the contrary, pNK cells secrete neuroprotective factors and exert other anti-inflammatory effects. Hence, pNK cells play a neuroprotective role in neurodegenerative diseases [136]. NK cells are bone marrow-derived lymphocytes that belong to innate lymphoid cells. They are pores-forming lymphocytes currently being actively studied as potential therapeutic tools in multiple sclerosis (MS) given their capacity to regulate immune responses and immune homeostasis in the CNS. That being said, the contribution of NK cells to the pathophysiology of MS is multifaceted and still incompletely understood [137].

7. Dual Roles of Natural Killer Cells

Ever since the emergence of multiple sclerosis (MS) as an autoimmune disorder of the central nervous system (CNS), and especially since the introduction of highly effective drugs targeting the adaptive immune system, the focus has been on T and B cells as key players in the disease process. However, as with any battle, the outcome is determined by many more factors as well as the precise balance between the various fighting parties. Over the last decades, attention for innate immune cells has gained momentum in their involvement in MS. One of the more elusive cell types in this aspect, but not less intriguing, are the innate lymphoid NK cells [139]. Originally a branch of the innate immunity, it is now well established that they can also adapt to the environment in which they mature, proliferating and acquiring long-lived antigen-specific receptors, reminiscent of T and B cells. Remarkably, the majority of the evidence for such adaptive NK entities comes from viral infections, which are not main players in MS. Over the last decade, different lines of research have started to unravel the enigmatic functions of NK cells in both acute and chronic inflammation [140]. Based on their widely diverged functions, it is not astonishing that NK cells have dual functions in MS. Starting from early impacts in the periphery throughout the CNS, various mechanisms of action have been reported. It remains to be elucidated how microglia affect NK cells in either direction, and what the mechanisms are by which A1 astrocytic activation is induced. On the other hand, when inspecting the two most investigated targets of NK cells in MS, OC and myelin debris, perhaps it would be best if NK cells focused on the former, providing ignorance of the latter. To increase research scrutiny, considering limitations for an exact understanding of the role of NK cells in MS, retrospective studies utilizing patient cohorts with a variety of subtypes of MS could provide insight into not only their relevance in which subtype but also their potential role as emerging biomarkers [141].

7.1. Balancing Inflammation and Protection

Natural Killer (NK) cells, early responders of the innate immune system, play a crucial role in the neuro-immune system. It has become clear that they perform dual roles in neuroprotection and neuroinflammation, and besides their cytolytic capacity, NK cells contribute to immune memory by producing cytokines that further amplify the inflammation. A potential therapeutic approach may include modulation of NK cell activity or inhibiting their recruitment to brain lesion sites [142].

NK cells are categorized as large granular malanoid (LGL) lymphocytes that are cytotoxic against tumors and virus-infected cells, and are critical players in tumor surveillance and virally infected cells. NK cell activity first requires the integration of signals from stimulatory and inhibitory receptors. Common activating receptors, which are involved in the lysis of tumor cells or virally infected cells, include the natural cytotoxic receptors, and the activation receptor NKG2D. Stimulatory co-receptors (CD16, CD2) are usually involved in facilitating cytotoxicity. However, the expression level of those activating receptors, especially in their glycosylation state, plays a critical role in determining functions of NK cells [143].

A potentially intensifying approach to induce NK cell activity in vivo is based on treatments with antibodies directed against first immunoglobulin (Ig)-like receptors that inhibit NK cell functions. Cytokines such as IL-15, IL-12, IL-18, and IL-2 can enhance killer-cell cytotoxicity; however, the prolonged use of these cytokines might have a detrimental impact on normal tissue and may induce potential toxicity. On the other hand, inhibitors may control the proliferation and cytotoxicity of NK cells in inflammatory diseases and eliminate their impact on normal tissue [144].

7.2. Implications for Disease Progression

NK cell dysfunction in patients with MS increases the severity of the disease, similar to MS animal models in which NK cells are deleted or inhibited. Data from MS patient studies show that NK cells play a significant role in curtailing the severity of the disease.

Also, among the drugs used to treat MS, those that enhance NK cell cytotoxicity have been shown to be disease modifying. Current treatment for MS is associated with increased NK cytotoxicity in the majority of therapeutic situations, whereas when MS infection is exacerbated, NK cytotoxicity is lower. These findings are compatible with a previously published two-compartment model of MS disease mechanism wherein TNF-alpha/IL-1-independent activation of MMPs by lymphocyte-astrocyte interactions predominates, ultimately leading to CNS damage with NK cells playing a pivotal role in controlling the disease [145]. Lack of cytotoxic NK cells or lack of control over MMP levels in the brain may facilitate unwanted propagation of the disease. Agents including drugs that inhibit MMPs, antibodies to the TNF family of ligands, and various antiviral compounds may be worth evaluating for their ability to alleviate MS illness through enhanced control over NK cell activity. A more severe form of MS that is characterized by loss of NK cells and increased severity of the disease may be worth investigating as a possible model of disease exacerbation. This form of the disease may be characterized more by a systemic loss of NK cell function than by NK cell loss in vitro or in blood [146].

8. Research Methodologies

Animal Models: It is commonly accepted that multiple sclerosis (MS) is an autoimmune disorder of the CNS, leading to inflammation and subsequent neurodegeneration, resulting in clinical neurological symptoms and progressive disability. This hypothesis is widely supported by the although misguided nearly 40-year-old 'hygiene hypothesis' in which the immune system become unbalanced under sterile conditions and starts to attack self. In particular, CD4+ T helper cells provide neuroinflammation following antigen-presentation and proinflammatory cytokine release by autoreactive antigen-presenting cells, probably located in the cerebrospinal fluid, in the menyinges or in the CNS itself [148]. Although current disease-modifying therapies (DMTs) only target this adaptive immune response of the Th1 and Th17 pathway, other components of the immune system are also of importance in MS pathology, like B-cells and the innate immune system. The latter, although they are known since the last century, only recently are gaining more attention, especially regarding the involvement of natural killer (NK) and NKT cells [149].

Up until the last decade, nothing was know about NK and NKT cells in MS. However, with the rapidly evolving new methodologies and technologies, the last few years have seen an explosive growth in publications describing these innate lymphocytes and their potential involvement in MS pathology. Despite this growth, publications are still rare in which all the available results are bundled together, and the findings are interpreted as a whole picture regarding what it means for MS pathology, in particular regarding the role of NK and NKT cells, how it relates to the adaptive immune system, and how it may influence future therapies in MS. Additionally, especially for NK cells, research and publications frequently describe targets present on many different cell types. However, some of these targets are absent or infrequently present in specific models, making it impossible for researchers to replicate the results, which hampers progress in the field and limits the relevance of many available data [150].

Research in animal models, genetic studies of polymorphisms, especially genome-wide association studies (GWAS) in MS, ex vivo studies of primary human material from MS patients, and finally in vitro studies of NK and NKT cells as well as from other components of the immune system in an MS environment, are reviewed. After a discussion on the translational relevance of these findings, the current gaps in knowledge are outlined that need to be addressed before NK and NKT cells can be translated and included in the clinical practice in the treatment of MS patients [151].

8.1. In Vitro Studies

A variety of in vitro studies have explored the interactions between NK cells and glia in a controlled environment, outside the complex in vivo system. These studies have

addressed both sides of the interaction: the influence of CNS cells on NK cell behavior, and the influence of NK cells on the activation state and effector functions of CNS cells.

NK Cells Respond to CNS-Derived Factors

Numerous in vitro studies have examined how several factors, secreted or presented by glial cells, promote NK cell cytotoxicity, migration, or cytokine production. Some factors can originate from dying glial cells, and therefore might be considered an indirect effect. These studies have yielded conflicting results, demonstrating the delicate balance of factors that influence NK cell behavior, and revealing glial cell type- and activation state-specific effects on NK cells.

Direct Interactions Between CNS Cells and NK Cells

A relatively more limited number of studies have explored how CNS-derived factors influence NK cell behavior by means of direct interactions. These studies have examined the interactions of NK cell receptors and their specific ligands present on glia, and evaluated how they influence NK cell behavior. A more thorough understanding of these interactions may reveal new insights into both the mechanisms by which the CNS influences NK cells and the ways by which NK cells exert effector functions [152].

8.2. Animal Models

A commonly studied animal model is experimental autoimmune encephalomyelitis (EAE), in which susceptible rodents develop CNS autoimmunity upon immunization with myelin-derived self-antigens. The disease resembles several cardinal features of MS including the presence of CNS infiltrating leukocytes, demyelination, gliosis, axonal degeneration and neurological deficits. The majority of EAE studies have reported a regulatory role for NK cells. This regulatory role has been indirect and reported as an inhibition of disease progression, which can be causally linked to the presence of this subset of lymphocytes [153]. The mechanisms attributed to such regulatory action of NK cells in EAE include general T cell suppression, killing of autologous autoreactive T cells, inhibition of the differentiation of myelin-reactive T helper type 1 (Th1) or 17 (Th17) cells in the CNS and secretion of neurotrophic factors. In contrast to these studies, some work has been more suggestive of a detrimental role for NK cells and the presence of NK cells, and more specifically NK cell-derived IFN-γ, is postulated to be a prerequisite for development of EAE pathology. However, this concept is in strong contrast with the numerous findings that mice in which IFN-γ is depleted exhibit an exacerbated form of EAE or develop the disease in strains that are normally not susceptible to develop EAE. In the absence of NK cells, either by NKR-P1A or Anthrax toxin receptor-1 (AtxR) depletion, mice similarly exhibit a more severe clinical form of disease with more pronounced demyelination and increased CD4+ and CD8+ T cell activation in the CNS and cerebral spinal fluid (CSF) [154]. Moreover, while it is clear that in humans and mice subpopulations of NK cells exist that can be classified based on the expression of various surface receptors, stage of maturation and cytokine producing profiles, this aspect has long been underappreciated in EAE studies where only cardiovascular disease and a few characteristics of this subset have typically been explored. This is likely due to lack of widespread availability and applicability of the relevant tools to phenotype human and mouse NK cell subpopulations. Nonetheless, there is now increasing evidence of the existence of NK cell subpopulations with pro-disease, as well as anti-disease roles in EAE [155]. Some of this work has clearly demonstrated the existence of tissue-resident NK cells with more pronounced preventative functions in the gut and the heart and of a more mature human NK cell subset in the acute phase of MS (i.e. the conditions which also prevail in the acute phase of EAE) recently shown to exhibit an indisputable pro-inflammatory function. The contradictory reports on the role of NK cells in EAE may be attributed to the use of different animal backgrounds, divergent immunization procedures or NK cell depletion performed at different time points during development of the disease.

The involvement of NK cells in EAE is mediated through a complex array of mechanisms in large part underscored by cellular heterogeneity [156].

8.3. Clinical Trials

A growing body of preclinical and clinical data points to an aberration in the activity of natural killer (NK) cells in genetically susceptible individuals, predisposing them to the development of MS as a consequence of breaks in peripheral tolerance. Also reviewed are proinflammatory, pathogenic effects of NK cells driving neuroinflammation and its consequences in classical MS, as well as protective, regulatory roles of NK cells and their modulation by interacting immune cells and therapeutic agents that restrain MS. A model in which aberrant NK cell reactivity against neuroantigen-subsequent breaks in peripheral tolerance facilitate the development of MS is foreseen, as well as NC cell and agent-specific implications for the pathogenesis and treatment of this disease [157].

Despite mounting evidence supporting a role for NK cells in MS, their activity remains poorly defined. Reports of absolute numbers of and/or changes in the activity of NK and NKT cells in MS are generically equivocal. Clinical trials systematically testing the safety and efficacy of NK cell–based immunotherapies for MS have yet to be conducted. Growing appreciation of the remarkable substrate diversity and heterogeneity of NK cells warrants extensive, comprehensive studies of NK cell composition and activity in MS [158]. Consideration of the immune status to aid in the management of MS is anticipated to encourage these efforts. Possible geographical and/or population group differences in NK cell composition or frequency associated with disparate risks for developing MS are intriguing and require further investigation. Advances in our understanding of NK cell biology and technology facilitate the manipulation of these cells outside the body, such as expansion and transfection with additional receptors or models of confusion with dendritic cells that provide costimulation. In light of a growing appreciation of the involvement of NK cells in a broad range of other diseases including neurodegenerative conditions such as Parkinson's disease, a future role for NK cell replacement therapies for MS might be envisioned [159].

9. Future Directions in Research

Preliminary efforts have already explored the role of NK cells in MS with an emphasis on single-cell sequencing approaches. This initial research delves into population frequencies and relative abundances of NK cell subsets in peripheral blood and cerebrospinal fluid in patients with MS, which present interesting and age-dependent changes that could be related to the MS pathogenesis. To advance knowledge in this domain, further experiments must address some of the shortcomings found in the existing studies. The potential influence of the peripheral immune activation on the NK cell population must be further investigated to determine whether changes are indeed confined to the CNS compartment [160]. Up to now, NK cell studies in MS have been centering on relatively low-dimensional end-stages of cellular responses and states, whereas MS is likely a multi-faceted disease that develops over time. In addition to the revealed population shifts, more attempts on monitoring individual NK cell phenotypic changes over time especially within newly diagnosed patients without treatment and in CYP/CCMP would surely provide more insights. Genomic approaches could deepen understanding of the epigenetic, transcriptomics, and proteomics of NK cells in MS pathogenesis as well [161]. Consideration of the extensive cellular heterogeneity of NK cells, determination of the disease developmental trajectories of both qualitatively and quantitively distinct NK cell populations, along with the endogenous adaptive immune responses induced by choosing the proper platform to explore the interactions of NK cells and CNS microglia may enhance current understanding of NK cells in MS pathogenesis and contribute to the treatment arena. The ease of accessibility may provide an alternative advent of first-in-its-kind platform for in-depth studies of NK cells in MS [162].

9.1. Targeting NK Cells in Therapy

Multiple Sclerosis (MS) is a chronic neuroinflammatory disease characterized by aberrant T-cell and B-cell responses targeting myelin, the axonal protective sheath. However, it is now established that NK cells, members of the innate immune system, contribute to MS pathogenesis and exert a dual role, either promoting or reducing disease dependent on circumstances. Most studies focus on aberrations in their cytotoxic functions. However, contradictory results exist, and changes in cytotoxicity might not be the only mechanisms by which NK cells influence MS pathogenesis. Hence, it is necessary to broaden the understanding of their multifaceted functions during disease and unravel their dual role in contributing to adaptive responses against pathogens and the unprovoked, aberrant, self-destructive inflammatory responses [163]. After being almost ignored in MS research for a long time, it is now increasingly recognized that innate immune cells, such as NK cells, contribute to MS pathology. After the first onslaught of damage to the myelin sheath of nerve fibers and the parenchyma, NK cells invade the CNS and might contribute to the subsequent neuroprotective responses. Understanding the dual role of NK cells in promoting and inhibiting neuroinflammation and neuroprotection seems valuable for developing immunotherapeutic avenues. Obvious first candidates for therapy seem to use antibodies to block inflammatory NK cells' actions. Such approaches are currently evaluated or have led to established treatments for other autoimmune diseases. However, targeting NK cells for therapy remains delicate and complex. Any therapeutic approach should cautiously regard NK cell heterogeneity, dual roles, and tissue-specificity [164]. A possible therapeutic monoclonal antibody against NK cell CD16 is expected to reduce NK cell-mediated antibody-dependent cellular cytotoxicity and MTX efficacy in RA. Several other strategies that enhance the cytotoxic activity of tumor-targeting NK will likely also be suitable for further enhancement of the anti-tumor response in MS. However, more work clarifying the NK cell components and mechanisms involved in spreading and controlling the neuroprotective response in the CNS is needed. After this understanding, treatment could focus on recruiting and activating relevant NK cell subsets rather than blocking them [165].

9.2. Biomarkers for NK Cell Activity

There is currently no validated biomarker to identify patients who will respond to treatment against central nervous system (CNS) inflammatory activity before the occurrence of clinical and/or radiological signs. The circulating levels of CD56bright NK cells represent a potential biomarker of treatment efficacy, as these cells strongly and consistently increase upon treatment with various therapies. Moreover, in RRMS patients treated with 1 year of fingolimod therapy, the reverse of circulating CD56bright NK cell count and the number of newly formed lesions detected by monthly MRI scans was statistically significant. In a subset of patients with the greatest treatment effect, the circulating CD56bright NK cell count was threefold higher than baseline values at week 12 [166]. Following treatment, there is also evidence of an increase of not only absolute numbers but also the regulatory function of CD56bright NK cells in RRMS patients. The most commonly used drugs, which were able to increase the number of circulating CD56bright NK cells, will be evaluated in terms of their known effects on these cells. In newly diagnosed MS patients and in healthy donors all treated with therapy, the number of circulating CD56bright NK cells was significantly increased after 6 months of treatment, and this increase was significantly greater in MS patients who did not require a dose escalation after 12 months than in those who did [167]. Moreover, at 12 months of treatment, the circulating CD56bright NK cell count was significantly increased compared with baseline values only in the treatment responders, but not in non-responders. Thus, the number of circulating CD56bright NK cells in peripheral blood may be used as a biomarker to identify patients who will benefit from treatment with first-line DMTs, because good responders characteristically showed greater increases of these cells than unmatched or low responders. Furthermore, this is the only study of any immune cell

subset to use a longitudinal design with multiple time points to prevent false positive results [168].

9.3. Longitudinal Studies and Patient Outcomes

Currently available clinical and imaging measures in MS are reviewed with an eye toward identifying which measurements inform the predilections and outcomes of DMTs. Measurements with current use in DMT are presented, considering equally assessments of the mechanisms through which treatment is administered (safety) and the efficacy of the treatment strategies themselves. DMT efficacy metrics broken down by mechanism of action into analyses of levels of lymphocyte populations, assessments of neuroinflammation, injury and protection, and impact on complex systems, such as assessors relying on multiple imaging modalities, are expounded. Biomarkers used in DMT research that are not routinely used clinically are also highlighted in an eye toward how they might enter the clinical toolbox [169].

The cornerstone of current MS therapeutics is a class of agents known as disease modifying therapies (DMTs) that have been approved across a decade-spanning timeline. A major DMT objective is not only mitigatory, seeking to protect the brain from further loss, but also presumptively regenerative, aiming to promote hijacked cellular mechanisms toward global regrowth of what is missed. Critical to DMT success is using pharmacologically appropriate agents for the job at hand as well as administering agents early in disease when responses are greatest and when the ability of MS pathogenic mechanisms to laterfully adopt measures to bypass mediation via known targets is lowest [170]. Clinical DMTs are mostly burdened by the responsibility to explain biologically plausible neuroprotective effects via a single measurable mechanism of action, to show that the target is hit, and to do so in carefully designed studies that pass FDA and EMA standards for statistical significance in relevant phase IIIB/IV clinical trials to provide traditional regulatory pathways for drug approval [171]. Keep in consideration MRI and CSF analyses for MS, which stand-in for proximal measures of DMT mechanisms, clinical measures answer a crucial, separate question: what outcome will be seen by routine clinical measures across neT and longer time horizons post-initiation? The ability of clinical measures to assess DMT efficacy, particularly those that call for introduction to general use outside of research settings, is considered [172].

10. Conclusion

MS is a chronic disease of the CNS with heterogeneous pathologies, which are partly attributed to a combinatory repertoire of neuroinflammation and neurodegeneration. To date, several treatments approved by the FDA are available to control either the inflammatory or neurodegenerative aspects of the disease. However, with limited efficacy in halting the course of the disease, there is a critical need for developing advanced treatments. Accumulating evidence supports that NK cells as immune gatekeepers are involved in immunopathogenesis of MS. While it is widely demonstrated that the neuroinflammatory role of NK cells in MS exacerbation is by enforcing the adaptive immune attack, recent studies disclosed that NK cells exert potent neuroprotective action and regulate immune homeostasis in the CNS periphery, thus preventing the incursion of autoreactive T cells into the CNS. These dual and diverse actions, dependent on NK cell responses or the environmental contexts, warrant the characterization of NK cell subpopulations with different origins and neuroimmune functions in MS. To create NK cell-based immunotherapy, the challenge is to balance the antagonistic roles of NK cells to support the desired protective functions, while inhibiting the undesired nefarious functions.

Recent studies employing single cell RNA sequencing revealed novel roles of NK cells in MS by identifying an NK17 subset that produces IL-17. The production of IL-17 from CNS-resident NK cells is induced by the infiltration of Th17 cells and is independent of IL18 or IL23. The detrimental role of IL-17 in promoting MS-like symptom has been

confirmed. Two concepts were put forward regarding the role of NK cells in MS disease: the autoimmune response in MS could be mediated by various mechanisms such as antigen presentation, cytokine secretion, cytotoxic effects against myelin components or their producing cells, and a more global mechanism involving the role of NK cells in the activation of and proliferation increase of other immunity cells in the rubber process. The other concept is that, during therapy of the MS disease, increased numbers of NK cells or activity is observed that were able to reverse or control the autoimmune processes while other cells switch to tolerance. A plausible explanation for these contradictory effects is the presence of different subsets of NK cells. Overall, these observations should provide new insights into neurodegenerative diseases and the knowledge can be utilized for formulating new strategies to treat these diseases.

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