



# Natural Killer Cells and Alzheimer's Disease

# 101

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### Abstract

Alzheimer's disease (AD) is an irreversible neurodegenerative disease that affects an increasing number of individuals worldwide. The underlying cause (s) of the late-onset form (LOAD) of the disease is still a matter of intensive investigations. The possibility that infectious organisms are involved in the etiology of AD has been gaining momentum. Furthermore, a wealth of data has suggested the involvement of the immune system in AD. In this context, properties of cells of the innate immune system such as natural killer (NK) cells specialized in destroying virus-infected cells have recently been investigated in amnesic mild cognitive impairment (aMCI) subjects and patients with a mild form (mAD) of the disease and data compared to healthy elderly individuals. These studies revealed an absence of differences in immune senescence between the three experimental groups. However, there were differential phenotypic changes in aMCI and mAD patients. This was the case of TLR2 and TLR9 (both decreased in AD) and NKG2A (decreased in aMCI). However, functional assays revealed an absence of modification of killing and degranulation activity in the cohort despite increased CD95 receptor, granzyme B expression, and upregulation of TNF $\alpha$  and IFN $\gamma$  production. Furthermore, decreased chemotactic activity to CCL19 but not to CCL21 was observed in aMCI and mAD patients. Increased CD16 expression was observed in mAD patients. The bulk of these data suggested that NK cells of aMCI subjects were in a state of activation state in response of an as-yet-unidentified challenge.

### Keywords

Natural killer cells · Alzheimer's disease

### List of Abbreviations

AD	Alzheimer's disease
ADCC	Antibody-dependent cell-mediated cytotoxicity
BBB	Blood-brain barrier
CD	Cluster of differentiation
CNS	Central nervous system
EOAD	Early onset of Alzheimer's disease
IFN	Interferon
KIR	Killer-cell immunoglobulin-like receptor
LOAD	Late onset of Alzheimer's disease
MHC	Major histocompatibility complex
NK	Natural killer
TLR	Toll-like receptor
TNF	Tumor necrosis factor

## Introduction

### NK Cells

NK cells are lymphocytes that belong to the innate immune system. NK lymphocytes along with innate lymphoid cells 1 (ILC1) constitute the innate lymphoid group 1 (Lanier 2013; Walker et al. 2013). As innate lymphoid cells, NK cells are effectors and regulators of innate immunity and tissue modeling and repair. As a member of group 1 of ILC, they are characterized by their capacity to produce  $\gamma$ -interferon (IFN $\gamma$ ) (Spits et al. 2016). NK cells take part in the major processes of the immune system which are maintenance of homeostasis, surveillance against malignancy, immunosenescence (Iannello and Raulet 2013; Sagiv and Krizhanovsky 2013), and pathogen protection, specifically destruction of virus-infected cells (Lam and Lanier 2017). Systemic NK cell subsets can be distinguished according to expression of characteristic cell surface markers. For instance, CD56<sup>dim</sup>CD16<sup>+</sup> NK cells possess distinct phenotype and function and account for approximately 90% of total NK cells, whereas CD56<sup>bright</sup>CD16<sup>-</sup> NK cells amount to approximately 10%. These subsets possess different homing property, the majority of CD56<sup>bright</sup>CD16<sup>-</sup> cells being located in the secondary lymphoid organs, whereas CD56<sup>dim</sup>CD16<sup>+</sup> NK cells are largely found in the blood (Carrega and Ferlazzo 2012). NK cells can also be found in the brain in the case of experimental autoimmune encephalomyelitis (EAE), although the mechanism of recruitment of NK cells to the CNS under normal physiological conditions remains unclear (Poli et al. 2013). These two NK cell subpopulations also possess characteristic functions. For example, CD56<sup>dim</sup>CD16<sup>+</sup> NK cells are more cytotoxic and express more CD16 (Fc $\gamma$ RIII) and immunoglobulin-like receptors, whereas CD56<sup>bright</sup>CD16<sup>-</sup> NK cells mainly produce type I pro-inflammatory cytokines such as tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) and IFN $\gamma$  (Cooper et al. 2001). Activation of NK cells and production of IFN $\gamma$  can be triggered by IL-12, IL-15, or IL-18 stimulation (Long et al. 2013). NK cells can also produce other immune factors such as immunosuppressive cytokine IL-10, growth factors such as granulocyte macrophage colony-stimulating factor (GM-CSF) and granulocytes colony-stimulating factor (G-CSF), and a series of chemokines such as CCL2, CCL3, CCL4, CCL5, and CXCL8 (Narni-Mancinelli et al. 2013). NK cells also act as regulatory cells to influence various other cell types of the innate and adaptive system such as monocytes/macrophages, DCs, T cells, B cells, and endothelial cells. NK cells also exert a negative feedback on macrophage activation following microbial infection (Vivier et al. 2008).

### Alzheimer's Disease (AD)

Alzheimer's disease (AD) is characterized by memory loss and cognitive decline, often associated with behavioral disorders (Scheltens et al. 2016). As neurodegenerative progresses, dead neurons are primarily found in hippocampal structures until it involves the whole brain (Selkoe 2011; Serrano-Pozo et al. 2011). The pathological characteristics of AD present extracellular accumulation of amyloid- $\beta$  peptides (A $\beta$ ) that aggregate

into plaques and intraneuronal hyperphosphorylation of the Tau protein which generates neurofibrillar tangles (DNF) (Querfurth and LaFerla 2010). According to recent surveys, 900 million of people worldwide are older than 60 years, and it is projected that 5% to 8% of these individuals will be afflicted with dementia during their lifetime (Prince et al. 2015). Up to 60% to 80% of the cases of dementia are of the Alzheimer type (Prince et al. 2009). Current estimates are that 47.5 million of people are AD sufferers in the world (Prince et al. 2015). According to the World Health Organization, this number could increase to 135.5 million individuals by the year 2050 (Prince et al. 2015). There are two forms of AD. A genetic early onset form (EOAD) characterized by identified genetic mutations that lead to an overproduction of A $\beta$  in the patient's AD brain. The second form of AD has a sporadic onset, and progression occurs over a period of several years to culminate in neurodegeneration in the elderly. This form of AD is referred to as late-onset AD (LOAD). In the case of LOAD, the main risk factor is age. Women are more affected than men (Carter et al. 2012). It is now well accepted that the first pathological changes are initiated as early as 20 years before the appearance of the clinical symptoms. One obligatory but not exclusive, stage of the progression to full-blown AD is the clinical stage of amnesic mild cognitive impairment (aMCI). aMCI patients display alterations in their cognitive ability which can be clearly identified by neuropsychological tests (Petersen 2009). Approximately 50% of aMCI individuals progress to AD within 3–4 years following their diagnostic (Ganguli et al. 2004). Thus, aMCI subjects represent a particular interest in the study of the progression to AD. Whereas neuroinflammation is well described in the AD brain, its detection in the periphery is less clear. The main factor identified to date is high baseline levels of TNF $\alpha$  in sera that is associated with a fourfold increase in the rate of cognitive decline (Holmes et al. 2009; Lyman et al. 2014; Calsolaro and Edison 2016). Changes in peripheral innate and adaptive immune systems have been associated with AD. In addition, the possibility that microbial infection may have an implication in AD pathogenesis has been suggested by several investigators (Holmes and Cotterell 2009; Miklosy 2011; Monastero et al. 2014; Itzhaki et al. 2016). The microbial culprits may be of bacterial, viral, fungal, and protozoan origins (Harris and Harris 2015; McNamara and Murray 2016).

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## NK Cells and Aging

### NK Cell Alterations with Aging

Cellular senescence is one of the nine hallmarks of aging (López-Otín et al. 2013). Senescence was originally described by Hayflick's group following quantification of the number of passages that cultured human fibroblasts could undergo before dying (Hayflick and Moorhead 1961). Cellular senescence is defined as a stable arrest of the cell cycle associated with specific phenotype features (Collado et al. 2007; Kuilman et al. 2010). It has been widely assumed that senescence contributes to aging due to the fact that the amount of senescent cells increases with aging. Senescence can be viewed as a beneficial compensatory response to prevent propagation of damaged or

potentially oncogenic cells (López-Otín et al. 2013). In this context, senescence should be detected and regulated by the immune system (Sagiv and Krizhanovsky 2013). However, decreased efficiency of the immune system with aging (immunosenescence) ought also to be taken into account. Immunosenescence consists in a progressive alteration of immune functions through aging which affects all of the components of the system whether it involves the innate, adaptive, humoral, or cellular compartments. Consequently, NK lymphocytes are stricken by senescence as well.

In healthy elderly individuals, an increase in NK cell frequency and number has been reported (Solana et al. 1999; Gayoso et al. 2011). NK cells compartment also remodels with aging (Solana et al. 2012, 2014; Hazeldine and Lord 2013). There is an increased proportion of CD56<sup>dim</sup>CD16<sup>+</sup> NK cells (Campos et al. 2014a; Solana et al. 2014) and a decreased in CD56<sup>bright</sup> NK subset (Chidrawar et al. 2006). These observations suggest that the increase in NK cell frequency with aging originates from accumulation of CD56<sup>dim</sup>CD16<sup>+</sup> NK cells. This subset is prone to be more mature (Krishnaraj and Svanborg 1992; Hazeldine and Lord 2013). Furthermore, a minor population of NK cells characterized by a CD56<sup>-</sup>CD16<sup>+</sup> phenotype has been reported to be increased in healthy elderly patients (Björkström et al. 2010a; Campos et al. 2014b; Solana et al. 2014). This subset expresses low levels of NCR or NKG2A and high levels of inhibitory receptors, compared to classical NK cells (Mavilio et al. 2005; Gonzalez et al. 2009). The function of this NK subset remains to be defined, but it has been suggested to be less effective in NK function assays (Milush et al. 2013; Solana et al. 2014). It is possible that redistribution of this NK cell subset contributes to the deregulation of the adaptive and innate immune responses. CD56<sup>bright</sup>CD16<sup>-</sup> NK cells produce cytokines and are critical for activation of dendritic cells and promotion of monocyte-dependent inflammation (Strowig et al. 2008; Michel et al. 2012). Chronic low levels of inflammation associated with aging (a condition defined as *inflamm-aging*) could be linked to NK cell subset remodeling since the proportion of CD56<sup>bright</sup> NK cells has been inversely correlated to C-reactive protein (CRP) levels (Campos et al. 2014b; Solana et al. 2014).

NK cell functions are altered with aging (Camous et al. 2012; Solana et al. 2012; Manser and Uhrberg 2015; Pera et al. 2015). Phenotype changes include a decrease in CD69 (Borrego et al. 1999; Camous et al. 2012) and CD62L (Juelke et al. 2009) expression, which are, respectively, a C-type lectin and a L-selectin whose expression increases following activation. An additional marker of phenotype changes is KLRG1 which is a lectin-like receptor that shows a decrease in expression on NK cells. KLRG1 is a bona fide marker of senescence, whose functional significance on NK cells is still unclear (Hayhoe et al. 2010). The diversity of activating and inhibitory receptors expressed on NK cells surface allows the precise control of activation and inhibition of NK cells, but some of these receptor expression is altered with aging (Biassoni 2008). Cytotoxicity-activating receptors NKp30 and NKp46 expression is decreased with aging (Garff-Tavernier et al. 2010; Gayoso et al. 2011; Almeida-Oliveira et al. 2011), whereas expression of the NKG2C receptor is increased (Gayoso et al. 2011). Conflicting data concerning steady-state levels or decreased expression of NKG2A and his co-receptor CD94 have been reported (Lutz et al. 2005; Garff-Tavernier et al. 2010), whereas NKG2D expression was unchanged (Gayoso et al. 2011; Solana et al.

2012). Inhibitory KIR expression was maintained or increased (Gayoso et al. 2011; Almeida-Oliveira et al. 2011; Lutz et al. 2011; Solana et al. 2012; Manser and Uhrberg 2015). The expression of HLA-DR, MHC class-I (Borrego et al. 1999), and the senescence marker CD57 are increased on NK cells of elderly patients (Lutz et al. 2005, 2011; Almeida-Oliveira et al. 2011; Hazeldine et al. 2012). In addition, the expression of the DNAX accessory molecule-1 (DNAM-1), an activating co-stimulatory receptor belonging to the immunoglobulin superfamily, is decreased on NK cells of elderly patients (Garff-Tavernier et al. 2010; Almeida-Oliveira et al. 2011; Sanchez-Correa et al. 2012; Solana et al. 2012).

Changes in the function of NK cells with aging alter their ability to proliferate, particularly in response to IL-2 stimulation (Borrego et al. 1999). This alteration has been suggested to be related to telomere shortening (Mariani et al. 2003). By and large, the cytotoxic capacity of NK cells is unchanged with aging. However, since CD56<sup>dim</sup> and CD56<sup>bright</sup> NK cells remodel with age, single-cell cytotoxic capacity is prone to decrease (Hazeldine et al. 2012) (Solana and Mariani 2000; Garff-Tavernier et al. 2010; Solana et al. 2012). Decreased expression or defective function of activating receptors has been suggested (Solana et al. 2012), but defect in target binding (Pera et al. 2015) or in CD107 (Hazeldine et al. 2012) and perforin (Mariani et al. 1996) expression was not altered.

CD16 expression (Solana and Mariani 2000; Lutz et al. 2005; Garff-Tavernier et al. 2010; Hazeldine and Lord 2013; Solana et al. 2014; Manser and Uhrberg 2015) and ADCC function (Solana and Mariani 2000; Solana et al. 2012; Manser and Uhrberg 2015) are unchanged in NK cells with aging. Production of cytokines, chemokines, and IFN $\gamma$  as well as response to cytokines and chemokines remains unchanged in NK cells with aging (Garff-Tavernier et al. 2010). However, production of IFN $\alpha$  and IFN $\gamma$  decreases, whereas production of IL-1, IL-4, IL-6, IL-10, and TNF $\alpha$  increases (Rink et al. 1998; Camous et al. 2012) in response to IL-2 stimulation, but response to cytokines tends to decrease (DelaRosa et al. 2006). Chemokine production by CD56<sup>bright</sup> NK cells decreases in NK cells exposed to IL-2 or IL-12 (Solana et al. 2012). NK cells function alterations in elderly patients have been associated with an increased incidence of infections in aged individuals (Ogata et al. 2001). Accordingly, increased mortality has been linked to lower numbers of NK cells in these patients compared to patients with a normal number of NK cells. Evidence for this interpretation is the fact that healthy, nonagerians, and centenarians possess normal numbers of NK cells (Gayoso et al. 2011).

## Senescence of NK Cells and AD

The involvement of senescence of NK cells with AD has been investigated within the framework of (1) aging as being the main risk factor of AD (Farrer et al. 1997; Ballard et al. 2011), (2) the emergence of the microbial hypothesis, and (3) the microglial senescence hypothesis (Streit and Xue 2014). Expression of the cell surface marker CD57 (also called HNK-1, LEU-7, or L2) (Abo and Balch 1981) has been studied to identify terminally differentiated senescent NK cells (Kared et al. 2016). CD57 is a

100–115 kDa protein with terminally sulfated carbohydrate epitopes that is expressed on senescent T and NK lymphocytes (Kared et al. 2016). A gradual shift from CD56<sup>bright</sup> via CD56<sup>dim</sup>CD57<sup>-</sup> to CD56<sup>dim</sup>CD57<sup>+</sup> NK cells occurs with aging (Gayoso et al. 2011). This cell subpopulation can amount to 60% of the NK cell pool (Garff-Tavernier et al. 2010). This NK subset has been suggested to be associated with reduced proliferative capacity (Lopez-Vergès et al. 2010; Kared et al. 2016), decreased response to cytokines (Björkström et al. 2010a; Campos et al. 2014b; Solana et al. 2014), high cytotoxicity potential (Kared et al. 2016), and increased sensitivity to stimulation via CD16 (Lopez-Vergès et al. 2010). However, a recent study has reported an absence of changes in CD57 expression on NK cells of aMCI and mAD patients compared to healthy elderly controls (Le Page et al. 2015).

The two main NK cell subsets in circulation are composed of two distinct states with different degrees of maturation. CD56<sup>dim</sup>CD16<sup>+</sup>-positive cells correspond to the more mature cells, whereas CD56<sup>bright</sup>CD16<sup>-</sup>-negative cells are less mature. An analysis of NK cell subset distribution in healthy elderly individuals, aMCI and mAD patients revealed the absence of significant differences between these three groups (Le Page et al. 2015). Two subpopulations have been identified among CD56<sup>dim</sup> NK cells. One subpopulation was CD56<sup>dim</sup>CD94<sup>high</sup> positive, whereas the other subpopulation was CD56<sup>dim</sup>CD94<sup>low</sup> positive and corresponded to a more mature phenotype associated with the loss of CD94 expression (Yu et al. 2010). CD94 is a transmembrane adapter glycoprotein related to the C-type lectin superfamily (Chang et al. 1995). CD94 forms heterodimeric disulfide bonds with five different members of the NKG2 family (NKG2A, B, C, E, and H) but not with NKG2D, resulting in the assembly of activating and inhibitory complexes, respectively (Borrego et al. 2006; Long et al. 2013). The natural ligand for these heterodimers in humans is the non-classic MHC class-I molecule HLA-E (Borrego et al. 2006). CD94 and NKG2A expression has been shown to decrease with age (Lutz et al. 2005; Hayhoe et al. 2010). However, a study of a cohort of healthy individuals, aMCI and mAD patients revealed that the percentage of CD56<sup>dim</sup>CD94<sup>high</sup>- and CD56<sup>dim</sup>CD94<sup>low</sup>-positive cells was similar in the three groups of subjects and that there were no differences in expression of CD94 and NKG2A (Le Page et al. 2015).

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## NK Cells and AD

### Subpopulation Distribution

The percentages of NK cells defined by the CD56<sup>+</sup>CD3<sup>-</sup> phenotype in the total population of lymphocytes are similar in the case of healthy individuals and aMCI and mAD patients (Le Page et al. 2015). Similar results have been reported in the case of the number of CD56<sup>+</sup>CD16<sup>+</sup>-positive NK cells in AD patients (Richartz-Salzbürger et al. 2007). An absence of differences has been noted with respect to the CD56<sup>dim</sup>CD16<sup>+</sup> and CD56<sup>bright</sup>CD16<sup>-</sup> subsets in the case of healthy individuals and aMCI and mAD patients (Le Page et al. 2015). Furthermore, the distribution between NK<sup>bright</sup> and NK<sup>dim</sup> populations was not affected in mAD patients.

## Expression of TLR

In humans, NK cells express different levels of the ten known TLRs (Chalifour et al. 2004; Hart et al. 2005; Lauzon et al. 2006). TLR2 and TLR4 recognize bacterial peptidoglycans and lipopolysaccharide, respectively (Della Chiesa et al. 2014). Of particular interest within the context of AD is the fact that TLR2 and TLR4 recognize A $\beta$  (Udan et al. 2008; Liu et al. 2012). MFI analysis of the expression of TLR2 and TLR4 on NK cells has been investigated in healthy individuals and aMCI and mAD patients. Data showed that TLR2 expression was significantly lower in mAD patients with respect to healthy controls but expression in aMCI subjects was similar to controls. However, expression of TLR4 was similar in the three groups. One assumption based on these observations was that TLR2 recognition of A $\beta$  could be compromised in mAD patients, further contributing to alteration in A $\beta$  clearing. In this context, the maintenance of TLR4 expression may compensate for lower TLR2 levels. In accordance with the infection hypothesis of AD (Monastero et al. 2014; Itzhaki et al. 2016), a number of groups have studied endosomal TLRs whose function is to recognize intracellular viruses. In this connection, TLR3 recognizes double-stranded viral RNA, whereas TLR9 ligates unmethylated CpG islands on DNA (Ishii and Akira 2006; Amarante and Watanabe 2010). TLR3 expression in NK cells of healthy individuals and aMCI and mAD patients was similar, whereas TLR9 expression was significantly decreased in mAD subjects compared to healthy controls and aMCI patients (Le Page et al. 2015). This observation suggested a correlation with AD progression as well as an altered capacity to defend against pathogens that was already present at the aMCI stage. Low TLR9 levels on NK cells may be an important step in the pathogenesis of AD, and modulation of TLR9 signaling may represent a novel approach in the management of AD.

## Activating and Inhibitory Receptors

Inflammation associated with AD could affect NK cell functions. As a mean to protect the innate immune system, NK cell activation is repressed under physiological conditions. Activation of NK cells depends on a balance between multiple activating and inhibitory receptors (Pegram et al. 2011). For instance, the activating receptor NKG2D can trigger signaling by itself, whereas NKG2A needs to recruit the transplasma membrane adaptor glycoprotein CD94 (Long et al. 2013). It has been reported that NKG2D expression remains unchanged on NK cells of aMCI and mAD patients as compared to healthy individuals. In contrast, expression of the NKG2A inhibitory receptor has been shown to be severely lower on NK cells of aMCI patients than healthy subjects and mAD patients. However, expression of CD94 was unchanged and similar in the three experimental groups. In view of the fact that the balance between activator and inhibitory receptors determines NK cell function status, it can be suggested that a decrease in expression of an inhibitory receptor is a determining factor which is consistent with a state of activation of NK



cells present in aMCI patients. However, this state of activation is lost in mAD patients and, presumably, in full-blown AD.

## Cytotoxic Activity

The cytotoxic activity of NK cells toward infected cells is crucial to stop pathogen spreading and to allow resolution of the infection. Cytotoxic effector function of NK cells is achieved by two distinct pathways. The granule-dependent pathway generates the release of perforin and granzyme B that form lytic pores in the membrane of infected targeted cells (Pardo et al. 2009). This process of degranulation can be followed by analysis of CD107a (also called LAMP1) upregulation of expression, a lysosomal-associated marker protein 1 (Alter et al. 2004). NK cell capacity to kill target cells in vitro does not appear to be altered in mAD subjects as reported in a comparative study of healthy individuals and aMCI and mAD patients (Le Page et al. 2015). Furthermore, expression of CD107a was similarly conserved among these three experimental groups and was not upregulated in IL-12-stimulated NK cells. The other cytotoxic pathway involves death receptors of the TNF family such as recognition between CD95 (Fas) and CD95L (FasL) (Chávez-Galán et al. 2009). High levels of granzyme B and CD95 have been reported in aMCI subjects compared to healthy individuals and mAD patients, suggesting that this pathway was upregulated in these individuals. Increases in CD95 expression have also been reported in the case of T lymphocytes of AD patients, and it has been suggested to be associated with increased apoptosis and caspase-3 expression (Frey et al. 2006). The bulk of these observations suggest that there is a commitment of NK cells at the aMCI state to be poised to defend against immune challenges although this commitment is lost at the mAD stage.

## Cytokine Receptors and Cytokine Production

Within the context of *inflamm-aging* that affects elderly individuals, AD is associated with a chronic inflammation status (Sardi et al. 2011). NK cells, T cells and monocytes express the cytokine receptors IL-18  $\beta$ -chain and the IL-12  $\beta$ 1- and  $\beta$ 2-chains (Parihar et al. 2002). Furthermore, an increase in expression of the IL-18 receptor has been shown in PBMCs of aMCI and AD patients (Salani et al. 2013). However, an analysis of IL-12 $\beta$ 1, IL-12 $\beta$ 2, and IL-18 $\beta$  receptors on NK cells of aMCI and mAD patients has not revealed changes compared to healthy elderly controls (Le Page et al. 2015). This observation suggested that NK cells did not respond to the elevated levels of IL-12 and IL-18 by receptor downregulation.

NK cells of AD patients have been reported to upregulate cytokine production in in vitro response to IL-2 (Solerte et al. 2000). A recent detailed analysis of TNF $\alpha$  and IFN $\gamma$  production by NK cells of aMCI and mAD patients stimulated by a combination of IL-12 and MHC1-negative K562 cells revealed that production of these cytokines was low in cells of healthy individuals and mAD patients, whereas

it was increased more than tenfold in aMCI subjects (Le Page et al. 2015). These results suggested that NK cells may contribute to the inflammatory status in aMCI patients by increasing production of TNF $\alpha$  and IFN $\gamma$ . The involvement of NK cells in inflammation and in neuroinflammation has also been suggested (Camous et al. 2012). One possibility is that NK cells could play a protective role against AD development by decreasing TH17 differentiation (Jiang et al. 2013), as reported in the case of rheumatoid arthritis and HIV infection (Aggarwal et al. 2013; Jiang et al. 2013).

## Chemokine Receptors and Chemotaxis

NK subsets express distinct chemokine receptors in relationship with their protective functions (Maghazachi 2010). For instance, CX3CR1 is expressed by the CD56<sup>dim</sup>CD16<sup>+</sup> NK subset and is associated with ligation of the CX3CL1 chemokine (fractalkine). The study of CX3CR1 within the context of neurological diseases is of particular interest because it has been implicated in the recruitment of NK cells through the BBB in patients with multiple sclerosis (Infante-Duarte et al. 2005; Huang et al. 2006; Hamann et al. 2011). It is tempting to suggest that CX3CR1 may play an influential role in AD pathology. CCR5 is the receptor for CCL5 (Rantes), CCL3 (macrophage inflammatory protein, MIP1 $\alpha$ ), and CCL4 (MIP1 $\beta$ ) (Maghazachi 2010). CCL5 has been reported to be upregulated in the AD brain (Tripathy et al. 2010). Furthermore, CCR5 expression has been shown to be increased on Th1 cells and DCs in AD patients (Goldeck et al. 2013). However, recent data have shown that CCR5 expression on NK cells was similar in a cohort of healthy individuals and aMCI and AD patients (Le Page et al., 2015). Enhanced expression of chemokines receptors have been found on AD leucocytes. In particular, an increase of CCR6 expression on leucocytes and an increase in CCR4 expression on Th2 cells have been identified on AD patients' immune cells (Goldeck et al. 2013). CCR6 is expressed on CD56<sup>bright</sup>CD16<sup>-</sup> NK cells, whereas CCR4 is found on the CD56<sup>dim</sup>CD16<sup>+</sup> subset (Berahovich et al. 2006; Maghazachi 2010). CCR2 participate in migration of monocytes/macrophages across the BBB in the AD brain (Saresella et al. 2014) and is also expressed on NK cells (Grégoire et al. 2007). CD56<sup>bright</sup>CD16<sup>-</sup> NK cells express CCR7 which is an important chemokine receptor for the function of this NK cell subset (Maghazachi 2010). CCR7 facilitates the homing of the CD56<sup>bright</sup>CD16<sup>-</sup> NK cell subset to lymph nodes where it interacts with monocytes and dendritic cells. In this respect, CCR7 is an important participant in initiation of the adaptive immune response (Griffith et al. 2014). CCR7 expression has been shown to be upregulated in NK cells of aMCI subjects, whereas its expression in mAD patients was similar to healthy controls (Le Page et al. 2015). CCL19 and CCL21 are chemokines abundantly secreted by stromal cells of secondary lymphoid organs. Their sole ligand is CCR7 that is one of the key ligands of the homing mechanism of immune cell migration to secondary lymphoid organs and subsequent defined compartments (Förster et al. 2008). The influence of this process in AD has been addressed in a series of in vitro investigations of NK cell chemotaxis

and migration in response to CCL19 and CCL21 (Le Page et al. 2015). These experiments revealed that migration of NK cells of aMCI and mAD patients was impaired in response to CCL19 but not in response to CCL21. These observations suggested a clear defect in the pathway following CCR7/CCL19 recognition.

## Expression of CD16

CD16 (Fc $\gamma$ III) is a low-affinity receptor for the Fc fragment of immunoglobulins G (Rosales 2017). Whereas no changes in CD16 expression have been reported with aging, it has been shown that CD16 expression was increased in mAD patients but not in aMCI subjects (Le Page et al. 2015). Furthermore, the ratio of CD16 expression was tilted in favor of the CD16<sup>high</sup> subset with respect to the CD16<sup>low</sup> subset in mAD patients compared to healthy controls. Taken together, these observations suggested that changes in ADCC occurred in AD patients. One likely implication is the lower effective IgG-mediated opsonization of infected cells, in support of the implication of viral pathogens in AD.

## Perspectives

Studies of the role of NK cell subsets in AD are still relatively limited and much efforts are needed to understand the involvement of these cells in AD pathology. In particular, investigation of activator and inhibitor receptors expression and analysis of CCR6, CCR4, and CCR2 chemokine receptors and their respective ligand ought to be done to unravel the mechanisms of NK cell activation, migration, and functions within the context of AD development and progression. Studies in aMCI and mAD patients have paved the way to unravel the complex implication of NK cells in AD (Table 1). Of interest is the report that inhibition of HMG-CoA reductase activity by treatment with Atorvastatin<sup>®</sup> attenuates the increase in NK cells number in the brain of rats challenged with A $\beta$  by limiting the production of IFN $\gamma$ , MCP-1,

**Table 1** Immune signature of NK cells associated to AD

NK cells properties	Healthy	aMCI	mAD
Blood distribution	Conserved	Conserved	Conserved
Cytotoxic and degranulation activity (against K562)	Conserved	Conserved	Conserved
Activation	No activation	Yes ( $\downarrow$ NKG2A + $\uparrow$ Fas and granzyme B + $\uparrow$ TNF $\alpha$ production)	No activation
Chemotaxis	Conserved	$\downarrow$ toward CCL19 (despite $\uparrow$ CCR7 on CD56 <sup>bright</sup> )	$\downarrow$ toward CCL19
ADCC	Conserved	Conserved	$\uparrow$ CD16
TLR expression	Conserved	Conserved	$\downarrow$ TLR2 and TLR9

and IP-10 (Lyons et al. 2011). In this context, modulation of IFN $\gamma$  production by NK cells could limit microglia activation and interfere with AD progression. This observation may provide an important clue in the clinical treatment of AD.

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## Conclusions

An obvious challenge with respect to NK cell involvement in AD is to relate brain viral infection to NK cell activation. Promising therapeutics strategies may come from this approach.

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