Experimental Gerontology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Review

Role of the peripheral innate immune system in the development of Alzheimer's disease

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ARTICLE INFO

Keywords:
Peripheral innate immune system
Alzheimer disease
Microglia
Infections
Amyloid beta
Blood brain barrier
Neutrophils
NK cells

ABSTRACT

Alzheimer's disease is one of the most devastating neurodegenerative diseases. The exact cause of the disease is still not known although many scientists believe in the beta amyloid hypothesis which states that the accumulation of the amyloid peptide beta (Aβ) in brain is the initial cause which consequently leads to pathological neuroinflammation. However, it was recently shown that Aβ may have an important role in defending the brain against infections. Thus, the balance between positive and negative impact of Aβ may determine disease progression. Microglia in the brain are innate immune cells, and brain-initiated inflammatory responses reflected in the periphery suggests that Alzheimer's disease is to some extent also a systemic inflammatory disease. Greater permeability of the blood brain barrier facilitates the transport of peripheral immune cells to the brain and vice versa so that a vicious circle originating on the periphery may contribute to the development of overt clinical AD. Persistent inflammatory challenges by pathogens in the periphery, increasing with age, may also contribute to the central propagation of the pathological changes seen clinically. Therefore, the activation status of peripheral innate immune cells may represent an early biomarker of the upcoming impact on the brain. The modulation of these cells may thus become a useful mechanism for modifying disease progression.

1. Introduction

Alzheimer's disease (AD) is the most frequent form of major neurocognitive disorder (dementia) (Ridge et al., 2013; Tam and Pasternak, 2012). The pathological hallmarks of AD as originally described by Aloïs Alzheimer in 1907 (Alzheimer, 1907), are senile plaques composed of deposits of amyloid beta peptides (Aβ) and neurofibrillary tangles composed of hyperphosphorylated tau protein (pTau) (Ballard and Corbett, 2013; Sun et al., 2015; Hanger et al., 2014). These pathological findings have led to the amyloid cascade hypothesis (Beyreuther and Masters, 1991; Hardy and Allsop, 1991; Karran and De Strooper, 2016; Jack Jr et al., 2013) which states that Aβ derived from amyloidogenic cleavage of the trans-membrane amyloid protein precursor protein (AβPP) accumulates as deposits in the brain and acts as a trigger of microglial activation that results in a neuroinflammatory process (Rogers et al., 1992; McGeer and McGeer, 2013; Bolós et al., 2017). Microglial-dependent clearance of Aβ can therefore be viewed as a protective mechanism to prevent accumulation of Aβ (Zuroff et al., 2017; Bourgade et al., 2016a, 2016b). However, in the aging brain microglia functionality is altered which attenuates their phagocytic activity, which leads to Aβ accumulation, sustained microglia activation, and eventual neuronal death (Regen et al., 2017; Udeochu et al., 2016).

The amyloid cascade hypothesis has dominated the field of Alzheimer research for decades, but recent data have challenged it (Ricciarelli and Fedele, 2017; Herrup, 2015). A number of recently published reports have suggested alternative causes of AD because all clinical studies that have attempted to modulate the concentration of Aβ in the brain have failed to show any significant clinical benefit (Mehta et al., 2017; Sacks et al., 2017). Moreover, it has been clearly

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https://doi.org/10.1016/j.exger.2017.12.019
Received 14 July 2017; Received in revised form 27 November 2017; Accepted 20 December 2017

documented that in many demented patients, deposits of Aβ are absent (Hyman et al., 1993; Chételat, 2013; Hatashita and Wakebe, 2017; Tse and Herrup, 2017). Reciprocally, Aβ deposits can be observed in the post-mortem brains of elderly patients not showing any clinical evidence of AD. Of significance, recent studies have provided convincing evidence that Aβ peptides have an initial beneficial role in the brain as anti-microbial (Soscia et al., 2010) and anti-viral factors (Bourgade et al., 2015, 2016a, 2016b), however later their accumulation will have neuron-damaging consequences. Consequently, decreasing Aβ in the brain by means of clinical interventions may lead to catastrophic consequences, such as encephalitis (Ferrer et al., 2004).

AD is also now recognized as a chronic inflammatory disease of the brain, where neuroinflammation in the central nervous system (CNS) is the driving factor (Bagyinszky et al., 2017). As with Aβ production, there are no confirmed data on the initiating factors for such neuroinflammation, but consistent with the amyloid beta hypothesis, Aβ deposition is thought to be the initiating factor (Rogers et al., 1992; McGeer and McGeer, 2013). It is now beginning to be recognized that this inflammation is not restricted to the AD brain, but some form of inflammation also exists at the periphery, making AD at least partially systemic (Le Page et al., 2015, 2017; Larbi et al., 2009; Guerriero et al., 2016; Schwartz and Deczkowska, 2016). Thus, if AD is a systemic disease, the innate immune system may not be activated only in the brain but should also be activated in the periphery. This review summarizes our present knowledge of the possible implications of the peripheral innate immune system in AD development and progression with an emphasis on its role in the early stages of the disease (mild cognitive impairment).

2. Neuroinflammation and Alzheimer's disease

As mentioned above, the prevailing hypothesis to explain AD is the amyloid beta hypothesis which states that Aβ deposition extracellularly in the form of senile plaques is the cause of AD concomitantly or subsequently generating the other hallmark of the disease, the neurofibrillary tangles with the intracellular accumulation of pTAU and neurofibrillary tangles (NFT) formation (Ballard and Corbett, 2013; Sun et al., 2015; Hanger et al., 2014). During the last few years this hypothesis has been modified to accommodate the observed neuroinflammatory processes (Rogers et al., 1992; McGeer and McGeer, 2013; Bolós et al., 2017) up to a point that it is now well accepted that neuroinflammation plays a role in the development and progression of AD (McManus and Heneka, 2017; Busse et al., 2017). However, there is still a debate as to whether this inflammation is the cause or the consequence of the disease (Rogers et al., 1992; McGeer and McGeer, 2013; Bolós et al., 2017; VanItallie, 2017). According to the amyloid cascade hypothesis model, inflammation is viewed as the consequence of overproduction of Aβ (Rogers et al., 1992; McGeer and McGeer, 2013; Bolós et al., 2017). So, the question is what is causing Aβ overproduction in the first place?

Aβ is the product of the amyloidogenic cleavage of amyloid precursor protein (APP) either directly in the plasma membrane by beta amyloid secretase (BACE) and gamma-secretase or by intracellular proteolytic conversion of peptide fragments (Rivest, 2009; Siegel et al., 2017). Physiologically, APP is metabolized by the non-amyloidogenic pathway and the peptides produced are soluble (Chow et al., 2010). When there are changes in the neuronal membrane, such as increased cholesterol content (Burns et al., 2006) or other stress events such as infections or innate immune cell derived pro-inflammatory cytokines (Bourgade et al., 2016a, 2016b), metabolism is shifted toward the amyloidogenic pathway initiated by the activation of BACE. This is followed by activation of γ-secretase resulting in the production of amyloidogenic peptides Aβ (O'Brien and Wong, 2011; Siegel et al., 2017). Of these, the two most important are composed of 40 or 42 amino acids and have propensity to form fibrils and plaques. It is of note that Aβ42, even if not the most abundant, is the most toxic (Galante et al., 2012). Moreover, Aβ binds a variety of microglial plasma membrane receptors (Su et al., 2016; Eugenín et al., 2016) and also binds to other cells of the innate immune system (Hui et al., 2016). The receptors are mainly scavenger receptors that include TLRs, RAGE and CD36. They are pattern recognition receptors that transduce intracellular signals leading to activation of NFkB and production of pro-inflammatory cytokines (Singh et al., 2017; Guerriero et al., 2016). Furthermore, ligation of these receptors triggers free radical production, as well as other toxic products resulting from upregulation of the process of inflammation. A sustained, unregulated production of Aβ that may have initially been beneficial to resolve an immune insult, then generates a state of chronic inflammation, increased production of inflammatory cytokines, free radical production, mitochondrial dysfunction, migroglia exhaustion, destruction of neurons and necrosis of neighboring tissue (Leuner et al., 2012; Schwartz and Deczkowska, 2016).

TLRs have been reported to play a major role in Aβ recognition (Su et al., 2016; Venegas and Heneka, 2017). Ligation of Aβ results in cell activation or Aβ clearance. The TLR family members TLR2 and TLR4 and their CD14 co-receptor have been shown to be the major mechanism for Aβ phagocytosis and, consequently, free radical production in a murine model of AD (Fassbender et al., 2004; Liu et al., 2012). In this setting, the stimulation of TLR2 and TLR4 by bacterial products such as LPS results in massive neuronal loss via production of free radicals and other toxic mediators by microglia. Consistent with this, humans with a functional TLR4 gene polymorphism (Asp299Gly) that blunts inflammatory reactions may have less susceptibility to developing AD (Minoretti et al., 2006; Balistreri et al., 2009). These studies imply a role for TLRs and microglia in neuroinflammation and AD. Furthermore, the data suggest a dual involvement of TLR in AD, being beneficial for the physiological clearance of Aβ but pathological under conditions of Aβ overload. In the latter case, they serve to maintain a state of chronic inflammation and progressive neuronal death.

Variants of Triggering receptors expressed on myeloid cells (TREM) receptors are considered as a major risk factor for the development of AD (Cheng et al., 2016; Yeh et al., 2017). TREM signaling is intimately linked to TLR signaling (Ito and Hamerman, 2012). TREM1 is an amplifier of the inflammatory signaling mediated by TLR and NLR, while TREM2 attenuates the TLR initiated inflammatory signaling and as such may activate the phagocytic activity in microglia (Raha et al., 2017). Their role is also dual depending on the stage of the disease because they may maintain a balance between inflammation and the clearing processes of the microglia (Song et al., 2016).

Astrocytes and oligodendrocytes also contribute to the inflammatory process. Via their scavenger receptors, these cells also sense Aβ and react by increasing the inflammatory process again contributing to neuronal destruction. Thus, it can be suggested that these inflammatory processes progress over decades following some triggering event(s) of currently unknown nature trying to limit and repair the initial injury, however when it becomes chronic and a threshold of neuron destruction is surpassed, the disease manifests itself clinically.

3. The reason why neuroinflammation may not be the consequence of AD but may rather be its cause

The hypothesis that neuroinflammation in the AD brain is the direct consequence of Aβ overproduction suggests, that in principle, reduction or elimination of Aβ production would eliminate or at least block progression to AD. However, none of the clinical trials exploring this approach have met with success (Mehta et al., 2017; Sacks et al., 2017) and, worse, have resulted in untoward side effects (Ferrer et al., 2004). These observations beg for critical reassessment of the amyloid cascade paradigm as the central cause of AD (Herrup, 2015). Furthermore, as noted above, recent data have shed light on a protective role of Aβ in situations of response to microbial and viral aggression (Bourgade et al., 2016a, 2016b). It is important that the described neuroinflammatory