Chapter 9
Immunosenescence and Alzheimer's Disease

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Abstract Alzheimer's disease (AD) is the most frequent cause of dementia due to neurodegeneration. It is stated that the most important risk factor for the late onset AD development is age. AD develops during decades and appears most of the time after 65 years of age. Even though its incidence is increasing with age but not all the centenarians are suffering from AD. The most important underlying age-related factor is immunosenescence/inflammaging. Indeed, aging is associated with immune changes which are thought to be the most prevalent cause of the age-related chronic inflammatory diseases. However, it is now postulated that the changes occurring with aging in the immune system may not be only detrimental but also adaptive. Therefore,

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in this review we will describe whether and how immunosenescence/inflammaging may contribute to the development of AD. We will also examine whether this can lead to novel treatment approaches different form the current.

Keywords Alzheimer's disease (AD) · Mild cognitive impairment (MCI) · Immunosenescence · Inflammaging neuroinflammation · Monocytes · Macrophages · Phagocytosis · Free radicals · Cytokines · Signaling

9.1 Introduction

Aging is considered by many scientists as the most important risk factor for the development of the so-called chronic age-related diseases (ARD) (Fülöp et al. 2016; Franceschi et al. 2018; Barbé-Tuana et al. 2020). What are these diseases and why it is so? This concept gained popularity mainly because most of these diseases such as diabetes, neurocognitive disorders (dementia), cancers and cardiovascular diseases have a common denominator which is chronic inflammation (Hansen 2018; Kurakim and Bredsen 2020). Therefore, as aging is associated with immunosenescence including its corollary the inflammaging, the slipping extension of this fact became a true overarching paradigm (Barbé-Tuana et al. 2020). Thus, as aging is characterised by immunosenescence/inflammaging and most of the ARD have inflammation as a common root, therefore age is the most important risk factor for these chronic inflammatory diseases, especially AD (Tam and Pasternak 2012; Kern and Behl 2009). However altogether only around 10% of older subjects over 65 of age are affected by AD (Solana et al. 2018). So, could age be the greatest risk factor for AD? Considering these data, the obvious conclusion is no, however it should be recognised that the age-related immune changes may contribute.

Among these diseases one of the most frequent and devastating is dementia and most specifically the Alzheimer's disease (AD) (Prince et al. 2013). This disease was named after Alois Alzheimer who more than 100 years ago described the main pathological hallmarks of the disease from the pathological and clinical point of view (Hardy et al. 2002). This led to the extraordinary development of the research on AD but unfortunately this was not translated neither in the real understanding of the etiology of AD nor in even a minimal capacity of treatment (Mehta et al. 2017; Long et al. 2019). So, until now we struggle with a devastating disease that we do not know the cause and have no cure nor prevention. In this chapter we will briefly describe what is AD, what are the putative causes of its onset and how it may be considered as a consequence of the age-related immune changes and what could be the resulting interventions to mitigate the effects of this eventual role of immunosenescence (Fig. 9.1).

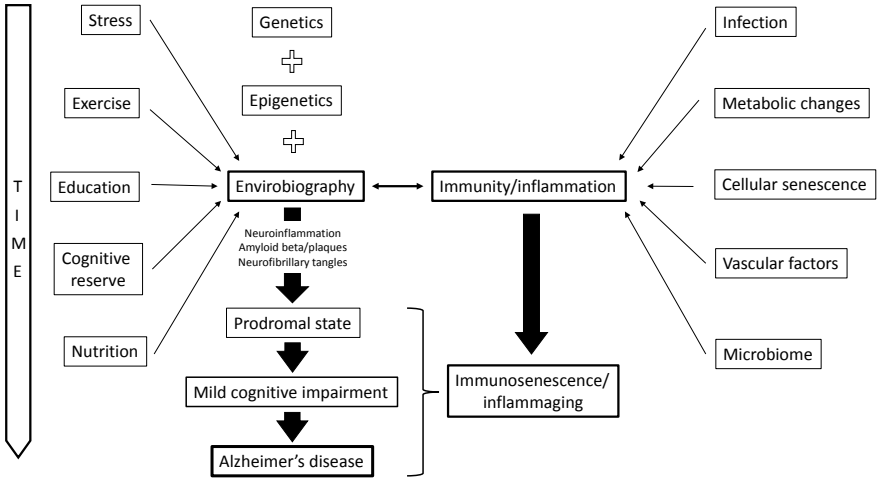

Fig. 9.1 Schematic conceptualization of the role of various factors in the development and clinical development of Alzheimer's disease

9.2 What is AD?

As a systemic inflammatory and clinical syndrome, AD is the most frequent type of dementia mainly affecting the brain (Solana et al. 2018; Paouri and Georgopoulos 2019; Walker et al. 2019). This starts in most of the cases with the loss of memory and speech capacity to continue until the complete disorganization of the whole cognitive sphere and even personality. However, the clinical presentation may be more nuanced and sometimes starting by other symptoms like frontal manifestations. From a pathological aspect, the AD is characterized by the deposition of the extracellular amyloid plaques composed by amyloid beta (Aβ) and by intracellular neurofibrillary tangles composed by hyperphosphorylated tau protein (pTau) (McGeer and McGeer 2013; Hardy and Allsop 1991). This was originally described by Alois Alzheimer, however he already noted that this was not the whole story, but some other alterations might be as important as these changes in the brain. This is even more important as the patient who served to describe the later named AD was most probably a familiar AD, and so her disease was genetically driven (causing around 5% of all cases of the disease).

It is now recognized that AD is a lifelong process which is revealed clinically as we age but the whole pathological process occurs well before old ages when we are only able to diagnose it (Shen et al. 2020). When the cognitive alterations become clinically noticeable the pathological process has been present for decades. Therefore, the pathological process whatever is its cause would not exist as a disease if some changes related to the physiological aging process would not reveal it. It could

be strongly suggested that the immune changes manifesting as so called immunosenescence/inflammaging are the driver of this clinical manifestation of the lifelong process, but not of the disease as currently conceptualized (Constantini et al. 2018; Zhao et al. 2020).

9.3 What Could Be the Cause(s) of AD?

There are many theories to explain the causes of AD. The most prevalent theory is the amyloid cascade hypothesis. This hypothesis states that the depot of Aβ, forming amyloid plaques and initiating the Tau hyperphosphorylation, causes the AD by destroying first the synapses and later leading to a neurodegeneration. Moreover, according to this hypothesis, the deposition of amyloid-beta (Aβ) in senile plaques, leads to inflammation and ultimately to the death of neurons (McGeer and McGeer 2013; Hardy and Allsop 1991; Beyreuther and Masters 1991). However, attempts to decrease the Aβ load or to prevent its formation had no effect on AD (Sacks et al. 2017; Cummings et al. 2018), even if we consider the recent very controversial approval of Aducanumab by the FDA. No cure whatsoever exists or seems to be on the horizon (Mehta et al. 2017; Long et al. 2019). These facts seriously question the validity of this mainstream hypothesis (Itzhaki et al. 2016; Herrup et al. 2015; Ricciarelli and Fedele 2017).

Therefore, new research needs to be pursued to unravel new pathomechanisms which may include the Aβ cascade hypothesis. It is certain that AD is initiated decades before its clinical diagnosis, suggesting that the driving pathological processes occur well before the appearance of symptoms. It has been also observed that AD, as an irreversible condition, displays signs of a systemic inflammation (Paouri and Georgopoulos 2019; Walker et al. 2019; McManus and Heneka 2017; Bolós et al. 2017), suggesting that systemic inflammation could precede the well-established AD hallmarks i.e. deposit of Aβ plaques, neurofibrillary tangles and neuroinflammation (Akiyama et al. 2000; Giunta et al. 2008). This implies that AD results from the chronic progression of these noxious inflammatory events in the brain, notably via Aβ production and accumulation (Webers et al. 2020). This local neuroinflammation continues at a low level throughout life with little negative effect, but repeated stimulations by infections, dysbiosis, vascular (ischemia), metabolic (glucose, lipids) or other insults (free radicals) result each time in an acute inflammatory response which culminate and is particularly severe in the elderly (Maloney and Lahiri 2016; Whalley et al. 2006; Fülöp et al. 2013; Fülöp et al. 2016; Li et al. 2010). These insults gradually cause damage to the blood–brain-barrier (BBB) (Nation et al. 2019; Noe et al. 2020) allowing brain inflammatory mediators to reach the periphery and trigger peripheral innate and adaptive inflammatory responses (Le Page et al. 2018; Ellwardt et al. 2016; Šimić et al. 2019; Dionisio-Santos et al. 2019; Shad et al. 2013).

Recent studies also suggested that neuroinflammation and systemic inflammation could progress over decades following triggering events of infectious origin. Latent virus infections e.g. cytomegalovirus (CMV) have been described as major chronic

innate immunity activators that contribute to inflammaging and therefore to AD development Bauer and Fuente 2016; Biagi et al. 2012; Thevaranjan et al. 2017). It could sound provocative to propose that AD may result from infection, but some major scientific discoveries were made from offensive hypotheses. Nobody would have bet few years ago that peptic ulcer diseases and cervical cancer were both caused by infections (respectively by Helicobacter pylori and human papillomavirus) (Kelly 1998; Caselli et al. 1997; Kessler 2017).

Infection by specific microorganisms as a plausible AD pathomechanism had been voiced several years ago but did not receive significant attention (Block 2019; Dominy et al. 2019; Osorio et al. 2019; Singhrao and Olsen 2019). The demonstration of the presence of HSV-1 viral DNA or spirochetes in AD brains was too instrumental to consider infections as contributors of AD pathogenesis (Wozniak et al. 2007, 2009; Miklossy 2016). Based on the most recent evidence, the infectious hypothesis provides a plausible stimulus for neuroinflammation. Local brain neuroinflammation may exist at a low level throughout life with little negative effect. However, when exacerbated by reactivation of infections or by the persistence of microbial metabolites, the ongoing inflammatory response combined with immunosenescence/inflammaging becomes difficult to control in order to repair the injury (Kritsilis et al. 2018; Blach-Olszewska et al. 2015; Busse et al. 2017). When it becomes chronic and a threshold of neuron death is surpassed, the disease manifests itself clinically in the brain with irreversible damages (Leszek et al. 2016; Di Benedetto et al. 2017; Goldeck et al. 2016).

It is of interest to mention that this infection hypothesis was strongly supported by the recent discovery that Aβ is an antimicrobial peptide able to protect the brain tissue from viral and bacterial infections (Bourgade et al. 2015, 2016; Soscia et al. 2010). The epidemiological data as well as the susceptibility genes (e.g. Apolipoprotein E4) also support the infection hypothesis (Lopatko et al. 2019). The fact that Aβ is an antimicrobial peptide explain also why these amyloid plaques may be found in normal brains as the so-called cemetery for microbes inside the biofilms (Miklossy 2016; Perl 2010; Fülöp et al. 2018a, b, c).

Besides this infection hypothesis since many years other hypotheses gain importance for the development of AD, the vascular hypothesis being one of the oldest. Even if there are plaques, AD is only clinically manifested when the vascular burden becomes overwhelming as it was shown in the Nunn study. Ischemia was also shown to be one of the triggers of Aβ production (Li et al. 2007; Han and Fukunaga 2009). Ischemia is a powerful trigger of the neuroinflammatory process by the production of the free radicals, pro-inflammatory cytokines and chemokines. All these processes initiated by ischemia contribute to AD development by inducing the preceding linflammation (Marchesi 2011). Recently, the cellular senescence was also favoured as the main source of the neuroinflammation (Walton et al. 2020).

Whatever is the exact cause of AD the main factors are age, genetics, epigenetics and environmental factors in its development (Kurakin and Bredesen 2020; Komleva et al. 2021; López-Otín et al. 2013). Besides central or peripheral infections, other peripheral stressors including gastrointestinal inflammation, dysbiosis, toxic products as well as metabolic disorders (diabetes, obesity and atherosclerosis)

via innate immunity activation leads to neuroinflammation resulting in AD (Komleva et al. 2021; Kowalski and Mulak 2019; Cai et al. 2013). These environmental factors contribute for at least 40% to AD development, beside the well-established genetic markers (Kremen et al. 2019). This means that age could be a risk factor but in reality, lifelong environmental factors have much more influence in the development of the disease. All the envirobiographic changes, including nutrition, physical activity, cognitive stimulation/education, hand-in-hand with the lifelong immunobiography and genetic susceptibility, contribute to the development of AD (Ngandu et al. 2015). This envirobiography is the key to explain the heterogeneity of the pathological process, the clinical manifestations and the difficulty to find a single treatment. Therefore, it seems to be much more important that age but also an elusive health parameter to measure yet.

9.4 What is Immunosenescence/Inflammaging?

Aging is accompanied by many physiological changes which lead to the decrease of the body reserves ending up with a homeostenosis condition (i.e. a reduction in the ability to maintain homeostasis/homeodynamics). The immune system is not an exception from this dynamic change leading also, due to the lifelong immunobiography/envirobiography, to a homeostenosis state composed from adaptative and maladaptative parts depending on the hormesis capacity of the entire organism (Fülöp et al. 2020a, b). The preponderance of one or the other will determine the protective role or disease-favouring-role of the older immune system.

The constant internal and external challenges are shaping the immune system through the entire life. Immune cells are able to react to various challenges via the damage associated molecular patterns (DAMPs) generated by injured cells and pathogen associated molecular patterns (PAMPs) (Kumar et al. 2011; Magrone et al. 2020). This is occurring through patterns recognition receptors (PRR) including the Toll-like receptors (TLRs), NOD-like receptors (NLR) and retinoic acid-inducible gene-I-like receptors (RLRs). As the immune system is in a such central position via its fundamental role for life by fighting all noxious stresses that its changes during aging will likely influence the clinical manifestation of most of the age-related diseases (Fülöp et al. 2018). Therefore, it is conceivable that these changes in the immune system may also drive the clinical apparition of AD (Fülöp et al. 2018a).

We will briefly describe the most important changes which may affect the development of AD. The innate immune system is an ancestral immune response assuring the first line of defence against internal and external challenges such as pathogenic microorganisms and damaged cells. In its prime, the innate immune system is able to return to a quiescent state after neutralizing the aggressions, but with the time-dependent accumulation of stressors, the innate immune cells become more permanently activated even at its "resting" state constituting the "trained innate memory" (Fülöp et al. 2016; Kleinnijenhuis et al. 2012; van der Heijden et al. 2017; Arts et al. 2016; Domínguez-Andrés et al. 2020). This is an excessively adaptable and useful

process based on epigenetic and metabolic changes in innate immune cells. This contributes at any moment of the organism life to protect earlier and stronger to each successive challenge (Ciarlo et al. 2019; Fransceschi et al. 2017).

However, constant challenges lead to an exhaustion and the system become tolerogenic and could result in detrimental effects (Salani et al. 2019). The pro-inflammatory and anti-inflammatory balance will determine the outcome of the aggression as being resolved with an innate memory or becoming chronic and harming the organism. Therefore, this permanent antigenic stimulation contributes to low but significant secretion of pro-inflammatory mediators creating an activation/inhibition disequilibrium and participating to inflammaging (Fransceschi et al. 2000, 2007, 2018a, b).

Non-infectious agents have been implicated in the spreading of inflammatory processes fueling inflammaging over time. The senescence-associated secretory phenotype (SASP) is considered as the main non-infectious trigger of inflammaging (Walton et al. 2020; Magrone et al. 2020; Coppé et al. 2018; Tchkonia et al. 2013; Birch et al. 2017). Senescent cells secrete pro-inflammatory molecules but also exosomes that can modulate immune system functions by transporting regulatory micro-RNAs and proteins through bodily fluids (Campisi 2016; Giuliani 2017; Terlecki-Zaniewicz et al. 2018). The appearance of senescent cells is primarily a protective mechanism against cancer development and reinforcing immunosurveillance, but their continuous formation is becoming detrimental along aging. Therefore, cellular senescence represents a dual process depending on its time of manifestation and the type of secretome induction (Walton et al. 2020).

The innate immune system as the main primary defense of the organism contributes to the immune changes and to inflammaging (Franceschi et al. 2000). All cells composing the innate immune response are impacted by aging but to different degrees (Müller et al. 2019; Goldberg et al. 2020; Bandaranayake and Shaw 2016). Their phenotypic and functional changes may all contribute to the development and progression of AD (Le Page et al. 2018). The monocytes are particularly changing in their phenotypes shifting towards the more inflammatory and senescent type of the so called intermediary and non-classical phenotype (Costantini et al. 2018; Zhao et al. 2020; Magrone et al. 2020). The monocytes at the periphery are also more activated than in physiological conditions. Paradoxically, essential defense functions such as chemotaxis and killing are decreased. These monocytes are able to infiltrate the brain because of the increased permeability of the BBB (Di Benedetto et al. 2017; Huang et al. 2020). Their differentiation in macrophages is skewed with mainly M2 subset with immunosuppressive functions (Nyugen et al. 2010). There is also alteration in Natural Killer (NK) cell phenotype and function with aging (Solana et al. 2018; Solana et al. 2012). Similarly, dendritic cell (DC) antigen presentation to T cells is altered with aging (Gupta 2014). Noteworthy, most of the changes are controversial as they were obtained in laboratory animal models. In humans as it was shown that controlled inflammation was a better predictor of longevity than any other previously thought biomarkers such as telomere shortening (Arai et al. 2015).

The adaptive immunity is taking over when the innate immunity may not cope efficiently with the aggression. Therefore, the adaptive immune system functioning

is basically dependent on the efficiency of the innate immune system and its antigen presenting capacity (e.g. with DCs) and the controlled cytokine production (e.g. IL-12). The antigen presenting capacity but also the number of the naïve CD4+ and CD8+ T cells are decreased with aging (Wong et al. 2013). These data led to the common concept that the adaptive immune system is profoundly altered with aging being responsible for the well-known ARD (Castelo-Branco and Soveral 2014; Pawelec 2018). However, there are still many unsettled questions to really declare that the adaptive immunity is globally decreased. We do not know to what extent the antigen presentation is altered, to what extent the naïve T cells are decreased with aging and most importantly, how these changes may be part of an adaptative process occurring with aging (Fülöp et al. 2020a, b; Pawelec 2020; Pawelec et al. 2020). Therefore, it will be important to optimize the immune resources to assure a better survival and functionality inside the already known challenges. There should be also a balance between the proinflammatory Th17 T cells and regulatory T cells (Tregs) (Magrone et al. 2020). With aging this equilibrium is perturbed; while Th17 become more inflammatory the anti-inflammatory control of Tregs is decreasing as even if their number is increasing the secretion of IL-10 by Tregs is decreased (Schmitt et al. 2013; Salminen 2020; Churov et al. 2020).

Inflammaging was introduced by Franceschi et al. (2000) as a basic characteristic of the biology of aging. Since its original description, the concept of inflammaging evolved considerably. From the concept of disbalance between the innate and adaptive immunity, in favour of the innate part other factors have been discovered and the molecular bases were also described. Thus, the roles of cellular senescence (SASP), the microbiome, the mitochondrial metabolic changes have been associated (Fülöp et al. 2019). The central role of the NF-kB is now well recognized as it is activated via various receptors and transduction pathways, but also by ROS, cellular senescence and DNA damage, in the increased production of IL-6, TNFα as hallmark of inflammaging (Smale 2011; Salvioli et al. 2013). In the meantime, another way to produce pro-inflammatory cytokines (e.g. IL-1) is via the NLR mediated the inflammasome activation (Humphries and Fitzgerald 2019). Inflammasome activation has numerous similar mediators than the NF-kB activation and among them, particularly the ROS and Aβ (Hu et al. 2019). It is also to mention that the nature has foreseen many possible control mechanisms to avoid the overactivation of inflammasome such as the stimulation of AMPK, Sirtuins, the type I interferon and autophagy (Bae et al. 2016; Price et al. 2012; de Kreutzenberg et al. 2015).

Together, inflammaging is characterized by an inflammatory status that is chronic, systemic and low grade. The level of cytokines often remains within the normal range (Sanada et al. 2018; Frasca et al. 2017; Rubino et al. 2019), justifying why inflammaging is also referred as low-grade inflammation. Considering all these factors, aging, associated with inflammaging, may be the most important risk factor for the clinical manifestation of late onset AD (Tam et al. 2012; Kern and Behl 2009; Castellani et al. 2010). Thus, this progressive pro-inflammatory situation, exacerbated with age, creates local and systemic inflammatory responses that activate cytotoxic microglia, unbalanced cytokine production, Aβ accumulation and irreversible

brain damage. Therefore, the innate immune system activation by some still unspecified triggers will result over time in a baseline inflammatory state. At younger age this is compensated by the anti-inflammatory environment however with the passage of time in susceptible individuals the ravages of the environmental damages would lead to AD as it is not anymore counterbalanced. It is of note that in many older subjects this scenario is either delayed or efficiently combatted. This once again means that aging is not the most important risk factors, but the conglomerates of pathological processes driven by lifelong bad habits/envirobiographie. Thus, the question is naturally occurring how immunosenescence/inflammaging may contribute to AD?

9.5 What is the Role of Inflammation in AD Development and Progression?

It took many years to the AD community to accept that inflammation is part of the pathogenesis of AD however it is still mainly considered as the direct result of the Aβ deposition (McGeer and McGeer 2013). In this concept the neuroinflammation is the consequence of AD and not the cause as Aβ produced under various situations would trigger the activation of microglia in the brain via TLR2 and TLR4 receptors resulting in pro-inflammatory cytokine and chemokine production (Selkoe and Hardy 2016; Kumar 2019). Assuming the antimicrobial role of Aβ as described above (Bourgade et al. 2015, 2016; Soscia et al. 2010), still this protective process becomes detrimental when the Aβ can not be anymore ingested and cleared by the cumulative exhausted/senescent microglia and become deposited in diffuse amyloid plaques which in turn continue to activate/stimulate/exhaust microglia (Costantini et al. 2018; Cunningham et al. 2013; Regen et al. 2017; Floden et al. 2011; Wyatt-Johnson and Brutkiewicz 2020). In the meantime, the peripheral immune system is also activated (as the Aβ is both an antigen and enhancer of the T cell reactivity) (Jóźwik et al. 2012) making AD a systemic disease and could be an earlier biomarker of brain inflammation. Therefore, changes in peripheral innate immune biomarkers may also precede by decades the clinical appearance of AD (Busse et al. 2017; Morgan et al. 2019).

Considering the recent progress, the picture is much more complicated than that. It is now well-recognised that the inflammation is preceding by decades the clinical manifestation of dementia. This inflammation may originate from the brain where it would be a reaction to local noxious agents of any sort which would initiate an inflammatory reaction and results in the activation of the local innate system by the stimulation of PAMP and DAMP (Paouri and Georgopoulos 2019; Walker et al. 2019; McGeer and McGeer 2013). One of the most important cytokines implicated is IL-1β which has also a dual role. IL-1β is beneficial at the beginning by activating the microglia to protect the brain, but at long-term becomes deleterious and causes microgliosis in AD (Licastro et al. 2000; Dansokho et al. 2016). The local innate system is composed mainly from microglia and astrocytes. These cells under

continuous stimulation will secrete pro-inflammatory mediators via the activation of NF-kB and inflammasome which will reinforce the secretion of antimicrobial Aβ by neurons (Kurakin and Bredesen 2020; Costantini et al. 2018). This Aβ will initially fight the infections and may neutralize other toxic substances (Kumar et al. 2016a, b). Thus, the activated microglia will try to eliminate the aggressors and create dense core plaques which will be a sort of Aβ dense cemetery for the aggressors fueled and organized by the Aβ (Fyfe 2021). These new data shed light on the complex role of microglia which at the beginning of the process, by their inflammatory action, have a strongly protective activity (Wyatt-Johnson SK and Brutkiewicz 2020). Indeed, this is a very efficient way for decades to control both the aggressions/pathogens and the Aβ deposition by creating the dense-core plaques. Therefore, amyloid plaques may be seen in almost every aging brain (Rodrigue et al. 2009). However, as we will describe later the specific changes occurring concomitantly with aging may alter this equilibrium and AD may eventually develop. Indeed, meanwhile this neuroinflammation will have progressive systemic effects and induce a peripheral inflammation. The inflammatory mediators released from the brain will stimulate the peripheral innate immune response. Among these cells at a very early stages are monocytes and NK cells (Solana et al. 2018). This will result to the maintenance of the activation of the innate immune system which will in turn activate the adaptive immune response. We should mention that this phenomenon may also occur in another way, specifically a systemic inflammation by the mediation of the inflammatory molecules and the migration of peripheral innate cells to the brain (Kurakin and Bredesen 2020). This may increase the BBB permeability which is letting to penetrate the inflammatory mediators and cells to penetrate into the brain and leading to neuroinflammation. Thus, a vicious circle will develop either whether the inflammation originate from the brain and spread to the periphery or vice versa (Paouri and Georgopoulos 2018; Tejera et al. 2019; Yang et al. 2020).

The reactive permeability of the blood brain barrier (BBB) is an important aspect of neuroinflammatory process (Nzou et al. 2020; Kowalski and Mulak 2019; Festoff 2016). In normal situation this is a semi-impermeable entity between the periphery and the central nervous system. Either aging or any inflammatory processes will impair this impermeable status of BBB (Chen 2011). This results in the passage of pro-inflammatory mediators and cells from the periphery to the brain and vice versa. Not only the BBB becomes permeable, but also the transporters are also altered. Comorbidities occurring with aging such as obesity and diabetes (diabesity) favor the increased BBB permeability and are also risk factors for AD (Chiu et al. 2015). Another probable contribution of the periphery to control the brain inflammation and physiology is the gut-brain axis (Kowalski and Mulak 2019; Cattaneo et al. 2017). This was known for a while but recently it became a major way for the interaction and mutual control between the brain and the gut. The study of this crosstalk axis is of utmost importance to understand the role of immunity and inflammation in central nervous degenerative diseases.

Collectively, this data suggest that inflammation is the basic process fighting and later maintaining the development and progression of AD.

9.6 Immunosenescence/Inflammaging and AD

From what we have described it can be easily concluded that the are-associated immune changes may contribute to the development of AD and consequently, it is very tempting to blame immunosenescence/inflammaging for the development of AD. However, it would be very reductionist to think that age-related immune changes may play a fundamental role in the development of AD. Nevertheless, considering what are the main characteristics of immunosenescence/inflammaging it is more than plausible that they play a role in the clinical manifestation/appearance of AD.

Immunosenescence/inflammaging will result in a clinically imperceptible, chronic low-grade inflammatory state which will maintain the innate immune system stimulation, the production of more than normal pro-inflammatory cytokines and finally the stimulation of the adaptive immune system (Franceschi et al. 2000; Fülöp et al. 2019). This will manifest by the decrease in naïve cells and the increase in memory cells, further contributing to the inflammation (Müller et al. 2019). This is clearly occurring as a reaction to the lifelong (immunobiography) constant external and internal challenges (Fülöp et al. 2020; Franceschi et al. 2017). Therefore, this is primarily a defense mechanism that may lead to AD in the long run. In this way the age-related immune changes may contribute by several ways.

The constant inflammation may have detrimental role and induce the neuronal death. Furthermore, the constant stimulation will result in the sustained production of pro-inflammatory mediators preventing the action of anti-inflammatory processes. We should also mention that these pro-inflammatory challenges will result in exhaustion of the immune cells mainly that of the adaptive immune system by the increase of memory CD8+ T cells. In the brain this stimulation will result in the apparition of the senescent microglia which will contribute to the inflammation and neurodegeneration instead of fighting this.

However, if we consider that AD develops through decades before its clinical apparition, immunosenescence/inflammaging will have a very little role in the development of AD as the neuroinflammation is independent of the aging process. Nevertheless, when the process proceeds the immunosenescence/inflammaging through the exhaustion of the innate and adaptive immune response, it may contribute to the clinical appearance of AD (Solana et al. 2018; Costantini et al. 2018; Magrone et al. 2020).

As mentioned, under the constant stimulation, microglia will become exhausted and instead of being protector it becomes harmful. This has been shown through the progression of AD. It was a major progress to establish the dual role of microglia (Subhramanyam et al. 2019; Colonna and Butovsky 2017). The same process may also affect the astrocytes (Garwood et al. 2017).

Another way that the aging immune system may contribute is the deregulation of the immune suppressive system. The changes in Tregs and myeloid-derived suppressor cells (MDSC) cells will favor the appearance of higher specific immune reactions suppression but concomitantly the fueling of the chronic inflammatory process (Le Page et al. 2017).

Therefore, we should be very cautious before we attribute the major risk factor title to aging with its immunological attribute because this can have far reaching conceptual and treatment consequences. However instead if we integrate these changes in a complex systems biology view of the AD development we could perhaps improve the possibilities of prevention and slowing down the disease progression (Ardura-Fabregat et al. 2017).

9.7 Cues for Intervention Targeting the Inflammation and the Immune Changes Contributing to AD

So far, most of the anti-inflammatory drug trials were failures besides many epidemiological data demonstrating the use of non-steroidal anti-inflammatory drugs (especially in arthritis patients) reduced the risk of AD (Rivers-Auty et al. 2020). This may be explained by considering that these trials did not consider the complex role of inflammation in the pathogenesis of AD. At the beginning inflammation should be sustained to fight the aggression and later it should be downsized to avoid the aggravation and the ongoing nature of the neuroinflammation reinforced by the dysregulated immunosenescence/inflammaging.

Presently many trials are ongoing targeting different molecules, pathways and cells of the immune system to modulate the inflammation (Fülöp et al. 2020, 2021). None of them directly is addressing the altered immune system with aging, with the exception perhaps the tentative reduction of Tregs (Ballard et al. 2020). All of them targets the original neuroinflammation. This should lead either to the prevention or the decreasing/delaying of the progression of AD (Munafò et al. 2020).

Presently the only way to prevent and influence the immune changes with aging is the intervention in multimodal way on the envirobiography (Ngandu et al. 2015). This intervention would consist of a very early implementation of good nutritional habits, regular exercise, decrease of bad stress (hormetically negative), cognitive reserve increase implemented since the middle age (Komleva et al. 2021; Atri 2019; Eiser and Fülöp 2020; de Oliveira Silva et al. 2019). In this way the use of a ketogenic diet may increase some cognitive functions in MCI subjects by potentially acting as a better fuel for the brain and an inhibitor of the inflammasome (Fortier et al. 2021; Myette-Côté et al. 2021; Wissler et al. 2020).

Another popular anti-aging intervention is the use of senolytics which would eliminate one source of aging, namely the senescent cells and as such would alleviate inflammaging, hoping that the organism will be capable to better fight against the aggressions (Zhao et al. 2020; Schubert et al. 2018; Mannick et al. 2014; Kang 2019). We really at this stage do not know neither the short nor the long-term effects of such interventions.

9.8 Conclusion and Translational Perspectives

AD is clearly a neuroinflammation mediated neurodegenerative disease. Aging is considered as one of the most important risk factors mainly by its attribute influencing the immune system changes. The development of inflammation is preceding decades before the clinical apparition of AD. In this way immunosenescence/inflammaging may play some role. The clear conceptualization and better understanding of AD will tone down the role of aging and will bring viable treatment opportunities. However, considering the envirobiography and the genetic origins of AD it is hardly conceivable that a monotherapy may be available, even if the aducanumab (Aduhelm) was very recently approved by the FDA. We should aim to treat AD by a multimodal approach in a system biology perspective which could lead to a real personalized approach (Gauthier et al. 2018; Fülöp et al. 2021).

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Compliance with Ethical Standards

Conflict of Interest Author declare no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by the author.

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