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Current Alzheimer Research, 2017, *14*, 870-882

REVIEW ARTICLE

Impact of Cytokines and Chemokines on Alzheimer's Disease Neuropathological Hallmarks

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ARTICLE HISTORY

Received: December 03, 2016
Revised: February 08, 2017
Accepted: March 13, 2017

DOI:
10.2174/1567205014666170317113606

Abstract: ***Background:*** Alzheimer's disease (AD) is the most common neurodegenerative disorder, neuropathologically characterized by aggregates of β-amyloid peptides, which deposit as senile plaques, and of TAU protein, which forms neurofibrillary tangles. It is now widely accepted that neuroinflammation is implicated in AD pathogenesis.

Method: Indeed, inflammatory mediators, such as cytokines and chemokines (chemotactic cytokines) can impact on the Alzheimer´s amyloid precursor protein by affecting its expression levels and amyloidogenic processing and/or β-amyloid aggregation. Additionally, cytokines and chemokines can influence kinases' activities, leading to abnormal TAU phosphorylation. To date there is no cure for AD, but several therapeutic strategies have been directed to prevent neuroinflammation. Anti-inflammatory, but also anti-amyloidogenic compounds, such as flavonoids were shown to favourably modulate some pathological events associated with neurodegeneration.

Conclusion: This review focuses on the role of cytokines and chemokines in AD-associated pathologies, and summarizes the potential anti-inflammatory therapeutic approaches aimed at preventing or slowing down disease progression.

Keywords: Neuroinflammation, cytokines, chemokines, amyloid precursor protein, β-amyloid, TAU.

1. BACKGROUND

Alzheimer's disease (AD) is the most common chronic neurodegenerative disease and the leading cause of dementia, corresponding to around 60% of all cases [1]. AD prevalence increases with age and the majority of individuals with AD are aged 65 or older. The probability of developing the disease doubles every five years after the age of 65 and above 85, the risk reaches nearly 50% [2].

AD is clinically characterized by progressive cognitive decline leading to impaired memory function (including ability to form recent memories), later evolving to affect other intellectual functions. With the disease´s progression, and due to the widespread cortical dysfunction, patients become demented, aphasic, disorientated, immobile, and can, at later stages, become completely dependent on others.

A large number of factors have been associated with the increased risk of developing AD, namely genetic and non-genetic factors, where age is the single greatest etiological risk factor [3].

Two forms of AD exist: early-onset familial AD (EOFAD) associated with Mendelian inheritance that affects individuals less than 65 years old and represents around 5% of AD cases; and late-onset AD (LOAD), also known as sporadic AD, with no consistent mode of transmission that affects people more than 65 years old and represents the greater number of cases among older people (90-95% of AD cases). Early-onset FAD is mainly caused by rare, fully penetrant mutations in three different genes; the Alzheimer´s amyloid precursor protein (*APP*) and the presenilins (*PSEN1* and *PSEN2*). Genetic polymorphisms of apolipoprotein E (*APOE*), and in particular *APOE* ε4 allele variant, are the major risk factors for sporadic cases, that, combined with life exposure factors, can strongly influence LOAD [4].

At the neuropathological level, AD is characterized by the presence of intracellular neurofibrillary tangles (NFTs) and extracellular amyloid neuritic or senile plaques (SPs), followed by alterations in synaptic signalling, synaptic loss and neuronal degeneration [5-7].

NFTs accumulate early in neuronal cytoplasm and arise due to abnormal TAU phosphorylation. Relevant kinases for TAU phosphorylation include cyclin-dependent kinase 5 (CDK5), glycogen synthase kinase-3β (GSK-3β) and p38 mitogen-activated protein kinases (p38-MAPK). In axons, the TAU protein, is one of the predominant microtubule-associated proteins, that normally binds to microtubules facilitating microtubular and cytoskeletal stability, and also promotes neurite outgrowth [8]. However, in its hyperphosphorylated form, TAU detaches from microtubules and aggregates, leading to microtubule instability and disrupting axonal transport [9-11]. Abnormal phosphorylation of TAU protein is neurotoxic and can cause neuronal death. NFTs are

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present in particular areas of AD brains, exhibiting a higher density in pyramidal neurons of the medial temporal lobe and moderate density in specific layers of the frontal, temporal and parietal lobes of the association cortex [12].

Senile plaques are associated with increased extracellular β-amyloid (Aβ) deposition distributed throughout the brain, but notably in the cerebral cortex and hippocampus of AD patients [13]. Aβ peptide overproduction tends to self-aggregate and form large insoluble β-sheet structures that lead to SPs formation and neurodegeneration. $A\beta_{1-42}$ aggregates are the predominant form found deposited in AD SPs, due to the higher rate of fibrillization and insolubility comparatively to the $A\beta_{1-40}$ peptide [6]. Aβ itself can contribute to TAU hyperphosphorylation by impacting either kinases or phosphatases activities [14-16].

This article reviews the role of the cytokines and chemokines on Alzheimer's neuropathological hallmarks, focusing on their impact on APP processing, Aβ production and TAU phosphorylation.

2. APP PROCESSING AND Aβ PRODUCTION

The APP protein is a transmembrane protein, with a large extracellular portion, a hydrophobic transmembrane domain and a short C-terminus, designated the APP intracellular domain (AICD), which can suffer alternative splicing giving rise to at least eight APP isoforms [17]. It can be proteolytic processed by two distinct pathways: the non-amyloidogenic pathway and the amyloidogenic pathway, involving α-/β-secretases, respectively, and a γ-secretase complex that comprises PSEN, nicastrin, anterior pharynx defective-1 (APH-1) and presenilin enhancer-2 (Pen-2) [18]. The biochemical identities of the secretases have been unravelled. In particular three members of the desintegrin and metalloprotease (ADAM) family; the metalloproteinases ADAM9, ADAM10 and ADAM17/tumor necrosis factor-α converting enzyme (TACE) [19, 20], have been proposed to exert α-secretase activity, while the β-secretase activity has been mainly attributed to the β-site APP cleaving enzyme (BACE1) [21-24]. In the non-amyloidogenic pathway, subsequent cleavage by α-secretase and the γ-secretase complex precludes Aβ formation. The α-secretase cleavage originates the soluble APPα fragment (sAPPα) and a membrane-associated C-terminal fragment consisting of 83 amino acids (C83), which is then cleaved by γ-secretase complex, giving rise to P3 peptide and AICD [25]. In the amyloidogenic pathway, APP is processed by the β-secretase generating a soluble sAPPβ fragment and a membrane associated C-terminal fragment consisting of 99 amino acids (C99). The latter fragment is likewise a substrate for the γ-secretase complex, and cleavage leads to the release of AICD and Aβ peptide generation that can span from 1-38 to 1-43 residues. Under non-pathological conditions, $A\beta_{1-40}$ is the peptide predominantly produced while $A\beta_{1-42}$ is a minor species [26, 27]. APP processing and trafficking can be affected by several factors, including stress conditions [28, 29] and Aβ itself [30-32]. Excessive Aβ generation leads to several pathological events, including neurotoxicity, apoptosis, oxidative stress and neuroinflammation [33-35], as well as to TAU hyperphosphorylation [36] and NFTs formation. These anomalies culminate in synaptic damage and neuronal loss in the specific brain regions of AD affected patients, contributing to disease progression [37].

3. INFLAMMATION IN ALZHEIMER'S DISEASE

Brain inflammation is a neuropathological event implicated in AD. The cells involved in the neuroinflammatory reaction are microglia, astrocytes and neurons, that when stimulated can produce high levels of inflammatory mediators such as pro-inflammatory cytokines and chemokines (chemotactic cytokines) [33, 34]. Prostaglandins, leukotrienes, thromboxanes, coagulation factors, free radicals such as reactive oxygen species and nitric oxide, complement factors, proteases, protease inhibitors, and C-reactive protein can also be produced by these cells [33, 38, 39] and incite the inflammatory process.

During neuroinflammation acute short-lived insults (ranging from a few minutes to a few days) had no long-term effects in neuronal survival. In fact, moderate activation of microglia is thought to have beneficial effects in removing neurotoxins, cellular debris or dying cells, and also in promoting neuronal survival. However, problems may arise when the initial injury lasts for a long period that can even reach several years. This is known as chronic neuroinflammation, as is the case in AD that includes a persistent activation of microglia and release of inflammatory mediators. Hence, an inflammatory cycle is perpetuated since microglia and astrocytes are constantly activated, leading to further increases in the levels of cytokines and chemokines [40-43]. Disturbances in inflammatory and immune pathways in AD have been strongly associated with altered levels of some acute phase proteins and pro-inflammatory cytokines in blood, cerebrospinal fluid (CSF) and in AD brains [38, 44-46]. Signs of chronic inflammation occur in pathologically susceptible regions of AD brains as a response to Aβ peptide deposition and NFTs formation [33]. A raised hypothesis is that both SPs and tangles stimulate a chronic inflammatory reaction. In turn, inflammatory mediators can alter APP levels and amyloidogenic processing potentially increasing $A\beta_{1-42}$ production (further discussed below). These circumstances can also inhibit the generation of sAPPα, a non-amyloidogenic fragment reported to have neuroprotective effects [47, 48]. Furthermore, Aβ itself can induce the expression of several pro-inflammatory cytokines, such as interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) by glial cells, leading to a vicious cycle [33, 43, 49-51]. Several chemokines such as CCL2 (also known as MCP-1, for monocyte chemoattractant protein-1), CXCL8 (IL-8), CXCL10 (IP-10) and CCL5 (also known as RANTES, for regulated on activation, normal T-cell expressed and secreted) are also produced in response to Aβ peptide deposition being responsible for the recruitment of peripheral immune cells [52]. Moreover, during the inflammatory state, non-resident central nervous system cells, as peripheral immune cells with chemokine receptors can cross the blood brain barrier and contribute to the inflammatory response in AD brains [53, 54]. The inflammatory events installed lead to both synaptic and neuronal damage thus contributing to neurodegeneration. Hence, the neuroinflammatory process, initially triggered by Aβ and perpetuated as a vicious cycle, can play an active role in AD progression.

4. CYTOKINES AND CHEMOKINES IN APP PROCESSING

As mentioned above, microglia and astrocytes are able to produce cytokines and chemokines that mediate inflammation and regulate the intensity and duration of the immune response [55]. Cytokines are a large and heterogeneous family of proteins that include the interleukins, TNF-α, IFN-γ and transforming growth factor-β (TGF-β). Since cytokines' levels rapidly change in response to inflammation, some have been classified as pro-inflammatory, such as IL-1β/α, IL-6, IL-18, TNF-α, IFN-γ; while others, like IL-4, IL-10 and TGF-β1, present anti-inflammatory properties and counteract neuroinflammation. The effects of cytokines have been widely addressed in different cellular and animal models [56], and in this review, focus is given to their impact on AD-related pathologies.

Chemokines, an additional group of chemotactic cytokines, are likewise suspected to be major inflammatory mediators in AD. This family with over 50 different molecules, confers chemotaxis, tissue extravasation and functional modulation of leukocyte function during inflammation [57, 58]. Chemokines are classified into four families: CXC, CC, CX3C and C, based on the number and spacing of cysteine residues in the N-terminal, also known as α, β, γ and δ chemokines, respectively [59]. In the adult brain, microglia, astrocytes and neurons are believed to be the main source of chemokine and their receptors' production [45, 60]. The central nervous system produces chemokines, like CCL2, CXCL8, CXCL10, CCL5 and CCL3 (also known as MIP-1α, for macrophage inflammatory protein 1-alpha) in response to several inflammatory and disease conditions. Chemokines may potently regulate microglial migration and recruitment of astrocytes to the area of neuroinflammation, favouring the extent of local inflammation.

In AD, the levels of several cytokines and chemokines have been found changed in vulnerable areas of patients' brains and body fluids [38, 44-46] and cytokine polymorphisms associated in some cases with disease risk [56]. Dysregulated cytokines may prompt the inflammatory processes by enhancing Aβ production thus contributing to AD development. Consequences of these inflammatory proteins on APP processing and Aβ, as well as on TAU phosphorylation will be detailed (summarized in Table **1**).

The pro-inflammatory cytokine IL-1 was described to regulate APP processing and Aβ production. IL-1 was previously reported to affect the synthesis and processing of APP, increasing the release of sAPP and potentially augmenting Aβ production, which may contribute to plaque formation and progression, dystrophic neurite proliferation and to neuronal loss [61-64]. More recently, Kitazawa *et al.* [65] described that blocking IL-1 signalling in 3xtg AD mice with an IL-1R blocking antibody was beneficial, since it leads to a decrease in certain Aβ fibrillar forms and plaques. Among the IL-1 family members are, IL1-β and IL-1α, both increased in AD brain tissue [46, 66]. Controversial data have been reported for IL-1β. While some authors showed that this pro-inflammatory cytokine can render in increased APP mRNA or APP levels [64, 67-69] others mentioned a decrease [70, 71]; it is feasible that the different effects may depend on the cell line an incubation period used. Furthermore, many studies reported an increase in sAPPα secretion in response to IL-1β [64, 70, 72], an effect proposed to be dependent on MEK1/2 and JNK-activated α-secretase cleavage [70] or ADAM17/TACE up-regulation [72]. Moreover, it was likewise described that IL-1β can reduce sAPPβ, $A\beta_{1-40}$ and $A\beta_{1-42}$ levels as a result of decreased β-secretase cleavage [72], suggesting in this case that IL-1β can act as an anti-amyloidogenic factor. In agreement, Shaftel *et al.* [73] showed that IL-1β overexpression in APP/PS1 tg mice promotes microglia activation, reduction of amyloid pathology associated with increased plaque phagocytosis and decreased insoluble $A\beta_{1-40}$ and $A\beta_{1-42}$ concentrations. It was also suggested that increased Aβ clearance by microglia in models of sustained IL-1β neuroinflammation could involve Th2 cytokines, such as IL-4 [74]. A feedback signalling loop between Aβ and IL-1β was proposed in which Aβ can induce the production of IL-1β [39]. In turn, the presence of IL-1β greatly increases the secretion of the cytokine IL-6 as well as of the chemokine CXCL8 by human astrocytoma cells (U-373 MG) [75], which can also have an impact on APP processing.

IL-1α was shown to activate the non-amyloidogenic pathway in astrocytes, *via* stimulation of the α-secretase pathway (ADAM10 and even more so ADAM17/TACE) and consequent sAPPα secretion. Different time periods lead to dual effects on APP. While a short treatment with IL-1α stimulated cell-associated APP, a longer treatment lead to a decrease in both APP and $A\beta_{1-40}$ and $A\beta_{1-42}$ levels [76].

As mentioned, other inflammatory cytokines, such as IL-6, IL-18, IL-10, TNF-α and TGF-β1 can also affect APP metabolism, for example by augmenting APP expression and impacting on Aβ production/deposition (see summary Table **1** and Fig. **1**).

The pro-inflammatory cytokine, IL-6 has been described as having pleiotropic effects and increased levels in AD brains [38, 66]. Previous studies demonstrated differential effects for IL-6 on APP expression, depending on the cellular model. In particular, IL-6 lead to induction of APP expression, in primary rat cortical neurons while no differences were observed in glial cells [77]. Brugg *et al.* [78] showed that increases in both IL-6 and IL-1β mRNA correlate with changes in the expression pattern of APP isoforms (decreases in APP695 and increases in APP KPI levels) in specific brain regions. More recently, Chakrabarty *et al.* [79] showed that IL-6 overexpression induces extensive gliosis and suppresses Aβ deposition *in vivo* in an APP tg mice model, with no significant alterations on APP processing. IL-18 was mentioned to be elevated in brain specimens from AD patients, and to be able to increase the levels of proteins involved in APP processing, namely BACE1 and members of the γ-secretase complex (PSEN1 and Pen-2), as well as the APP levels and phosphorylation in differentiated SH-SY5Y cells [80]. These events were also accompanied by enhanced $A\beta_{1-40}$ production and sAPPβ secretion.

TNF-α is another mediator, actively produced by microglia during inflammation, although its levels are low in healthy brains making it difficult to determine its physiological function. It has been demonstrated to play a key role in neuroinflammation-mediated cell death in different neuropathologies, including AD, and hence its inhibition may consti-

Table 1. Effects of inflammatory mediators on APP, Aβ peptide and TAU in different cellular and animal models.

			APP	APP Processing	Aβ	TAU	Cellular/Animal Models	Refs.
CYTOKINES	Pro-Inflammatory	**IL-1β**	↑ APP mRNA ↑ or ↓ APP levels	↑ sAPPα; ↓ sAPPβ ↑ γ-secretase & AICD ↑ α-secretase (ADAM17/TACE) ↓ β-secretase	↑ or ↓ $Aβ_{1-40}$ ↓ $Aβ_{1-42}$ ↓ Aβ deposition ↑ *Aβ* ↓ $Aβ_{1-40}$ ↓ $Aβ_{1-42}$ ↓ *Aβ deposition*	↑ TAU mRNA ↑ p-TAU ↓ *p-TAU*	Cortical neurons; microglia; neuron-microglial co-cultures Endothelial, neuronal and glial cells IL-1β injected Sprague-Dawley rats IL-1β injected Long-Evans rats Neuroglioma U251 cells Retinal glial cells Neuroblastoma SK-N-SH cells; cortical neurons IL-1β overexpression in APP/PS1 tg mice IL-1β expression in APP/PS1 tg mice APP-based T20 cell line *Rat anti-IL-1R blocking mAb injected 3xtg AD mice* Cortical neurons; microglia; neuron-microglial co-cultures 3xtg AD/IL-$1β^{XAT}$ mice IL-1β pellet implanted Sprague-Dawley rats	**[64]** [67] [68] [69] [70] [71] [72] [73] [74] [88] **[65]** **[132]** **[135]** **[136]**
		IL-1α	↑ or ↓ APP levels	↑ α-secretase (ADAM10; ADAM17/TACE) ↑ sAPPα	↓ $Aβ_{1-40}$ ↓ $Aβ_{1-42}$	---	U373 MG astrocytoma cells	[76]
		IL-6	↑ or = APP mRNA	---	↓ Aβ deposition	↑ p-TAU	Cortical neurons; glial cells C57BL mice; Staggerer mutant mice Murine IL-6 overexpression in APP tg mice Hippocampal neurons	[77] [78] [79] **[133]**
		IL-18	↑ APP levels ↑ p-APP	↑ sAPPβ ↑ β-secretase (BACE1) ↑ γ-secretase (PSEN1 & Pen-2)	↑ $Aβ_{1-40}$	↑ p-TAU	Differentiated SH-SY5Y neuroblastoma cells	[80] **[134]**
		TNF-α	↑ APP mRNA = APP levels ↓ *APP levels*	↑ sAPPβ ↑ β-secretase (BACE1) ↑ γ-secretase & AICD	↑ $Aβ_{1-40}$ ↑ $Aβ_{1-42}$ ↑ or ↓ Aβ deposition ↓ *$Aβ_{1-40}$* ↓ *$Aβ_{1-42}$* ↓ *or = Aβ deposition*	↑ p-TAU ↓ *p-TAU*	APP expressing astrocytes; cortical neurons 3T3-L1 adipocytes Murine TNF-α expression in APP tg mice APP-based T20 cell line *3xtg AD mice/ TNF-α lowering agent (IDT)* *3xtg AD mice/TNF-α lowering agent (3,6′-dithiothalidomide)* *APP/PS1 tg mice/ TNF-α decreasing agent (Infliximab)*	[51] [82] [85] [88] [83] [84] **[139]**
		IFN-γ	= APP levels	↑ β-secretase (BACE1) ↑ γ-secretase & AICD	↑ $Aβ_{1-40}$ ↑ $Aβ_{1-42}$ ↑ or ↓ Aβ deposition	↓ p-TAU = or ↑ p-TAU	APP expressing astrocytes; cortical neurons APP tg mice expressing IFN-γ IFN-γ injected B6/SJL mouse / U373 MG astrocytoma cells APP-based T20 cell line INF-γ expression in 3xtg AD mice Neuroglial cultures / JNPL3 mice; rTg4510 mice expressing INF-γ	[51] [86] [87] [88] **[137]** [138]
	Anti-Inflammatory	**IL-4**	= APP levels	= CTFs	↓ Aβ oligomerization ↑ or ↓ Aβ deposition ↑ $Aβ_{1-40}$ ↑ $Aβ_{1-42}$	↑ p-TAU	IL-4 expression in APP+PS1 tg mice IL-4 expression in APP/PS1 tg mice Murine IL-4 expression in APP tg mice	[92] [93] **[94]**

(Table 1) contd….

			APP	APP Processing	Aβ	TAU	Cellular/Animal Models	Refs.
CYTOKINES		**IL-10**	---	---	↑ Aβ deposition ↓ *Aβ deposition* ↓ $A\beta_{1-40}$ ↓ $A\beta_{1-42}$	---	IL-10 expression in APP tg mice *APP/PS1/IL10$^{-/-}$ tg mice*	[95] [96]
		TGF-β1	↑ APP mRNA	---	↑ Aβ deposition	---	Astrocytes Microglial cell line BV-2 hAPP/TGF-β1 tg mice hAPP/TGF-β1 tg mice	[98] [99] [100] [101]
	Chemotactic	**CCL2 (MCP-1)/ CCR2***	= APP levels	---	↑ $A\beta_{1-40}$ ↑ $A\beta_{1-42}$ ↑ Aβ deposition ↑ Aβ oligomerization ↑ $A\beta_{1-42}$ ↑ *or = Aβ deposition*	---	APP/CCL2 tg mice APP/CCL2 tg mice *APP/PS1/CCL2$^{-/-}$ tg mice* *APP/PS1/CCR2$^{-/-}$ tg mice* *APP/CCR2$^{-/-}$ tg mice*	[105] [106] [107] [108] [109]
		CXCL8 (IL-8)/ CXCR2*	---	↑ *γ-secretase substrates (C99; C83)*	↓ $A\beta_{1-40}$ ↓ $A\beta_{1-42}$	---	*CHO cell line expressing models; HEKsw cells/CXCR2 siRNA* *APP/PS1/CXCR2$^{-/-}$ tg mice*	[113] [114]
		CXCL10 (IP-10)/ CXCR3*	*= APP levels*	---	↓ $A\beta_{1-40}$ ↓ $A\beta_{1-42}$ ↓ *Aβ deposition*	---	*APP/PS1/CXCR3$^{-/-}$ tg mice*	[117]
		CCL5 (RANTES)/ CCR5*	---	↑ *β-secretase (BACE1)* ↑ *γ-secretase substrates (C99)*	↑ $A\beta_{1-42}$ ↑ *Aβ deposition*	---	*CCR5$^{-/-}$ mice*	[119]
		CCL3 (MIP-1α)/ CCR5*	---	↑ *β-secretase (BACE1)* ↑ *γ-secretase substrates (C99)*	↑ $A\beta_{1-42}$ ↑ *Aβ deposition*	---	*CCR5$^{-/-}$ mice*	[119]
		CX3CL1 (fractalkine)/ CX3CR1*	---	---	↓ $A\beta_{1-40}$ ↓ $A\beta_{1-42}$ ↓ *Aβ deposition*	↑ *p-TAU*	*APP/PS1/CX3CL1$^{-/-}$ tg mice* *hTAU-CX3CR1$^{-/-}$ tg mice* *APP/PS1/CX3CR1$^{-/-}$ tg mice / R1.40/CX3CR1-/- tg mice* *CRND8/CX3CR1$^{-/-}$ tg mice*	**[140]** **[141]** [142] [143]

tg: transgenic; CHO: chinese hamster ovary; KO: knockout. References regarding TAU effects are in **bold**.
Data on cytokines modulators or KO/deficiency, as well as data not directly on chemokine but rather on receptor KO/deficiency (*) is in italics.

tute a therapeutic strategy for different neurodegenerative disorders [81]. Yamamoto and colleagues [51], showed that TNF-α stimulates BACE1 expression and enhances amyloidogenic processing from APP expressing astrocytes and cortical neurons. Further, TNF-α was described to induce APP mRNA expression in a dose-dependent manner *via* nuclear factor k B activation [82]. Consistently, TNF-α modulation decreased fibrillar amyloid accumulation [83] and chronic administration of TNF-α lowering agents decreased APP levels, soluble $A\beta_{1-42}$ and Aβ deposition in old 3xtg AD mice [84]. However, expression of murine TNF-α in APP tg mice at early stage rendered in attenuated $A\beta_{1-42}$ and $A\beta_{1-40}$ plaque burden and deposition, without difference in APP levels [85].

IFN-γ is another cytokine up-regulated in AD brains with pleiotropic effects, exhibiting both deleterious and protective functions [66]. In a 3xtg AD mice model (APP tgCRND8) that expressed murine IFN-γ, microglia and astrocytes activation was exacerbated and correlated with a decrease in Aβ deposition, possibly due to synergistic effects of activated glia and innate immune system components that trigger Aβ phagocytosis [86]. No differences were observed in APP C-terminal fragments (CTFs) production or on APP levels. Nonetheless, as reported for TNF-α, IFN-γ could enhance Aβ production and deposition in APP expressing astrocytes and cortical neurons, possible *via* BACE1 expression and suppression of Aβ clearance [51, 87]. Additionally, using a cell based reporter gene assay IFN-γ, TNF-α and IL-1β were

all able to stimulate γ-secretase activity leading to both increased AICD and Aβ production [88]. Moreover IFN-γ was also shown to induce the expression of IL-18 [89], which in turn is capable of promoting the production of toxic inflammatory molecules, such as IL-1β [90] and IFN-γ itself [91], pointing to cytokines interplay.

A cytokine with controversial effects on AD is IL-4. IL-4 overexpression rendered in attenuated Aβ pathology [92, 93], while short-term expression had no effect on APP but exacerbated amyloid deposition [94], which may relate with the glial clearance activity in the different models.

Chakrabarty *et al.* [95] recently showed that the anti-inflammatory cytokine IL-10, increased Aβ deposition and impaired cognition in APP transgenic mouse models expressing this interleukin. Interestingly, increased *APOE* expression (which, depending on the allele, may enhance Aβ deposition) and decreased Aβ phagocytosis by microglia was also reported. In agreement, Guillot-Sestier *et al.* [96] reported that IL-10 deficient APP/PS1 tg mice exhibited reduced Aβ abundance in brains and enhanced microglial phagocytosis of the peptide. Further, IL-10 deficiency preserves synaptic integrity and attenuates cognitive disturbance driven by APP/PS1 tg mice, supporting the notion that IL-10 can at some point contribute to AD pathology.

TGF-β1 plays a central role in the brain response to injury, and elevated TGF-β1 levels have been found in CSF and serum of AD patients [38, 46, 97]. However different data were obtained regarding its impact on APP and Aβ. TGF-β1 was previously shown to increase APP isoform differential expression in cultured astrocytes [98] and microglia cells [99]. Later on, this cytokine was shown to induce Aβ deposition in an APP/TGF-β1 transgenic mice [100] and Aβ accumulation, preferentially in cerebral blood vessels and not in parenchymal plaques [101]. This latter event was associated with robust microglia activation and enhanced inflammatory mediators, which resulted in Aβ clearance and reduction of plaque burden.

Several chemokines and their receptors can likewise be found altered in AD brains or in AD models [45], suggesting a disease pathogenic role for these inflammatory mediators. Exposure of microglial cells to Aβ itself causes their activation and leads to the production not only of cytokines but also of chemokines [102]. As mentioned, astrocytes, the most common cells in the brain, can be activated by Aβ peptides to synthetize various pro-inflammatory molecules, similar to those produced by microglia. In particular, CCL2 is produced by microglial cells and astrocytes [103] and its levels are likewise increased in AD patients' brains [104]. Yamamoto *et al*. [105] showed that overexpression of APP and CCL2 did not render in alterations in APP processing (APP levels and CTFs formation) but it enhanced Aβ levels, aggregation and deposition in APP/CCL2 mice. Further, CCL2 expression renders in increased APOE levels, which may relate to enhanced Aβ deposition due to reduced Aβ clearance. Consistently, CCL2 enhanced Aβ oligomerization, microgliosis and accelerated cognitive dysfunction [106]. Not only CCL2 overexpression affected AD-related processes, but also CCL2 [107] and CC-chemokine receptor 2 (CCR2) deficiencies [108,109] contributed to amyloid pathology and disease progression. CCR2 deficiencies can either result in no significant differences at the amyloid deposition level [108] or lead to Aβ accumulation particular around blood vessels. Taken together data suggest a relevant role for CCL2-CCR2 signalling in AD pathogenesis.

CXCL8, a chemokine produced by macrophage and other cell types, important for the recruitment of activated microglia into sites of damaged brain, was found significantly increased in serum, CSF and AD brains when compared to control individuals [110, 111]. In fact, not only are chemokines altered but also their receptors are increased in AD brains. CXCR2, an CXCL8 receptor is such an example, which is highly up-regulated in dystrophic neurites of SPs [112]. Bakshi and collaborators showed that knockdown or depletion of CXCR2, and treatment with a CXCR2 antagonist, resulted in decreased $A\beta_{1-42}$ and $A\beta_{1-40}$ production and accumulation of γ-secretase substrates C99 and C83, while treatment with agonists enhanced $A\beta_{1-40}$ production. The inhibitory effect of the antagonist is mediated *via* γ-secretase, in particular *via* reduction of presenilin expression (on component of γ-secretase complex) [113, 114]. This data suggested that CXCR2 up-regulation can render in increased γ-secretase activity and enhanced Aβ production.

In AD brains and AD animal models, the chemokine CXCL10, also known as interferon γ-inducible protein 10 (IP-10), was also found in higher levels [115, 116], and Aβ positive plaques were co-localized with high IP-10 expression in APP transgenic mice [116]. A pathogenic role for this chemokine and its receptor CXCR3 in AD may thus be proposed. In agreement, CXCR3 deficiency in APP/PS1 tg mice leads to a reduction in plaque burden and Aβ levels, accompanied by an increase in microglial Aβ uptake [117]. In this model no differences for APP or CTFs were observed, suggesting that CXCR3 might not exert a role on APP processing but rather impact at Aβ clearance level by modulation of microglia. By contrast, the CCL5 and CCL3 chemokine receptor CCR5, similarly found elevated in post-mortem AD brains [104, 118], appear to have a suppressive effect on the development and progression of AD pathology. CCR5 knockout (KO) ($CCR5^{-/-}$ mice model) resulted in higher levels of $A\beta_{1-42}$, Aβ deposition, and expression of BACE1 and C99 when compared with $CCR5^{+/+}$ mice, as shown by Lee *et al.* [119].

In summary, cytokines and chemokines appear to be critical players in AD, either as promoters or suppressors of disease related pathogenic events. These inflammatory mediators can act at different levels, including at the APP proteolytic processing by affecting the secretases' activities, Aβ production and deposition into SPs (see summary Fig. **1**).

Additional inflammatory players, with consequences for APP processing and metabolism, may be considered during the neuroinflammatory process observed in AD [38,120]. Besides cytokines' and chemokines' release, complement proteins, acute phase proteins and oxidative mediators can also be expressed. Complement proteins are essential for the elimination of cell debris and potentially toxic protein aggregates. For instance complement factor C3 is a fundamental component of the complement system and a crucial inflammatory protein activated in AD. It has been suggested that this complement factor could have a beneficial impact in neurons and plaque clearance by reducing Aβ deposition,

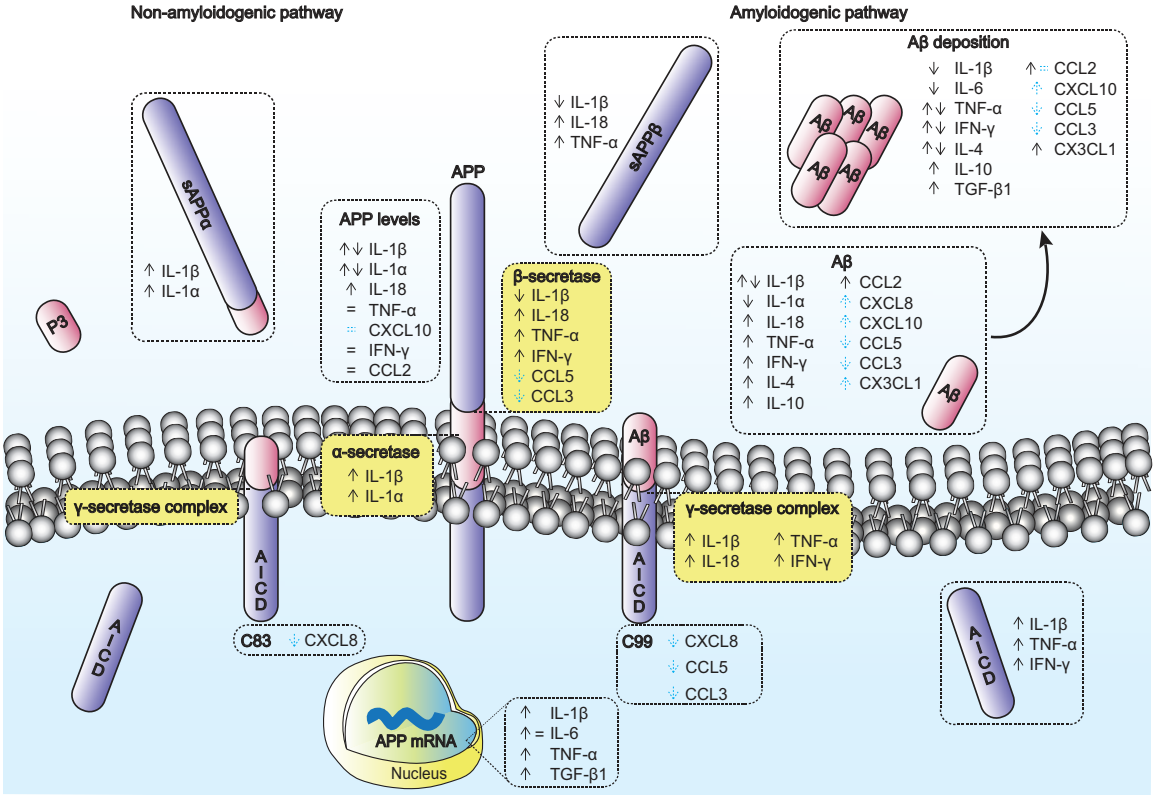

Fig. (1). Impact of cytokines and chemokines on APP and Aβ peptide. APP is proteolytically processed by two main pathways: the non-amyloidogenic and the amyloidogenic pathways, which leads to Aβ production. Aβ can aggregate and deposit as SPs. The *arrows* and *equality symbol* represent the effects prompted by cytokines and chemokines on APP, APP resulting fragments (sAPPα, sAPPβ and AICD), APP secretases (α-, β- and γ-secretases) and on Aβ and its deposition. *Dashed arrows and equality symbol* in blue represent the putative effects based on chemokines receptor KO/deficiency data.

since its deficiency leads to accelerated Aβ deposition and neurodegeneration. Furthermore, it can modulate microglia phenotype, as demonstrated when using complement C3-deficient APP transgenic AD mouse models [121]. Both α1-antichymotrypsin and α2-macroglobulin are examples of acute phase proteins, increased during inflammation, found in association with SPs in AD. α1-antichymotrypsin, is over-expressed in the AD patients' brains, serum and CSF [122], it promotes Aβ polymerization and deposition both *in vitro* and *in vivo* [123, 124]. In contrast, α2-macroglobulin is capable of maintaining Aβ in a soluble state, preventing its aggregation and fibril formation [125, 126]. The cyclooxygenase-2 and cytosolic phospholipase A_2 are inflammatory mediators associated with oxidative stress and reactive oxygen species generation [127]. In particular, cytosolic phospholipase $A_2\alpha$ has been involved in neurodegenerative processes, by increasing APP expression [128]. Further, according to Sagy-Bross *et al.* [129] Aβ is capable of inducing APP expression *via* cytosolic phospholipase $A_2\alpha$, prostaglandin E_2 release and activation of the cyclic adenosine monophosphate response element binding protein.

Other types of inflammatory mediators can be involved in AD pathogenesis. Peroxisome proliferator activated receptor γ (PPARγ), is such an example, since it is a nuclear receptor capable of inhibiting the inflammatory response, and whose levels are altered in AD brains. It has been reported that PPARγ supresses BACE1 gene promoter activity, and hence BACE1 mRNA; consequently PPARγ depletion will result in increased BACE1 expression and Aβ generation [130, 131]. These data support the hypothesis that PPARγ activation may act as a protective mechanism in AD pathophysiology.

5. CYTOKINES AND TAU PHOSPHORYLATION

Inflammation can also contribute to abnormal TAU phosphorylation, although literature is scarce, several cytokines can promote TAU phosphorylation, potentially impacting its function and accelerating NFTs formation. The cytokines IL-1, IL-1β, IL-6, IL-18, TNF-α and IFN-γ, are examples of inflammatory proteins that can modify TAU phosphorylation (see Table **1**) and have implications for AD pathogenesis. Most of these cytokines act on several TAU kinases in the brain, including CDK5, GSK-3β, and p38-MAPK, by increasing their activity and leading to TAU hyperphosphorylation in several residues, including Ser199, Ser202 and Thr205 [64, 65, 132-135]. It has been suggested that besides its increases in Tau phosphorylation, IL-1β may increase the levels of TAU mRNA [136] and that blocking IL-1 signalling lead to decreased Tau phosphorylation [65]. Further, IFN-γ can be either associated with reduced phosphorylated TAU (p-TAU) levels [137] or increased soluble TAU phosphorylation [138]. Different TNF-α modulators

were also shown to decrease TAU phosphorylation in APP/PS1 tg mice [139], APP 3xtg AD mice [84], and to reduce paired helical filaments TAU in the same APP 3xtg model [83], supporting a role for this cytokine in TAU pathology. Additionally, unpublished data by our group suggests that both CCL2 and CXCL8 chemokines can also impact on p-TAU, in a neuroblastoma cell model.

Of note, it is important to refer that some cytokines and chemokines can have opposite effects on both TAU and Aβ pathologies. As an example, Ghosh *et al*. [135] showed that sustained IL-1β overexpression leads to robust increases in TAU phosphorylation (most probably *via* p38-MAPK and GSK-3β) despite a clear reduction (about 70-80%) in the amyloid load. A similar opposite effect on TAU and amyloid pathologies was observed for IFN-γ [137]. Further, deficiency of membrane-anchored chemokine CX3CL1 (fractalkine) in APP/PS1 tg mice also lead to enhanced TAU phosphorylation, *via* the p38-MAPK pathway, and reduced Aβ deposition [140]. Consistently, CX3CR1 receptor deficiency was previously shown to increase TAU phosphorylation [141] and to ameliorate Aβ levels and deposition [142, 143].

Inflammatory mediators, such as cytosolic phospholipase A_2 and PPARs have been likewise associated with alterations in TAU phosphorylation levels at Ser214 and Ser199 and in TAU kinases, namely CDK5 and phosphorylated extracellular signal-regulated kinases 1/2 [144, 145]. α1-antichymotrypsin is capable of inducing TAU phosphorylation at specific residues (Ser202, Thr231, Ser262) and hence tangle formation, through the activation of c-Jun N-terminal kinases, extracellular signal-regulated kinases and GSK-3α/β [122, 146].

In essence, neuroinflammation is a key process that can contribute to the formation of both SPs and NFTs, the major AD neuropathological hallmarks, and thus to disease pathogenesis. Identification of the inflammatory mediators most relevant to disease pathogenesis may aid in the design of novel therapeutic strategies or in the selection of an inflammatory biomarker panel that may potentially aid in AD diagnosis.

6. ANTI-INFLAMMATORY DRUGS AND AD HALLMARKS

Anti-inflammatory drugs like non-steroidal anti-inflammatory drugs (NSAIDs) have been tested in the last decades as an attempt to prevent the onset or to slow down AD progression [38, 147, 35]. As the mode of action NSAIDs can act by targeting AD neuroinflammation and neuropathological hallmarks. In particular, NSAIDS have been proposed to inhibit cyclooxygenase (enzyme responsible for the formation of several eicosanoids involved in inflammation) or to target nuclear factor-κB, Rho-GTPases, PPARγ and APP secretases, impacting on APP processing during the inflammatory state [148]. For example, NSAID ibuprofen treatment reduced the expression of cyclooxygenase-2 and $A\beta_{1-42}$ levels [130], and long *in vivo* treatment of APP transgenic mice, with this drug substantially decreased Aβ deposition [149]. Additionally, NSAIDs can bind to PPARγ activating its transcriptional regulatory activities and inhibiting β-secretase [130, 150], thus rendering in decreased Aβ production. Weggen *et al.* [151] described that a subset of NSAIDs can subtly alter the γ-secretase complex, leading to decreased $A\beta_{1-42}$ levels, independently of cyclooxygenase activity. In addition, NSAIDs were shown to decrease TAU phosphorylation. As reported by Tortosa and colleagues [152], phosphorylated TAU levels at Ser422 decreased, after cell treatment with the acetylsalicylic acid NSAID. Later, a study carried out by McKee *et al.* [153] showed that ibuprofen treatment decreased TAU phosphorylation in 3xtg AD mice. Despite the promising effects on APP and TAU, the actual therapeutic potential of these drugs in AD is still controversial. The failure of NSAIDs in clinical trials have been attributed to various factors including: short duration and inappropriate timing of the trials related to late drug delivery to patients (patients too old or too ill); class of drugs used; NSAID's dose and concentration that can effectively reach the brain; and finally the genetic variability of the patients [154, 155].

In an anti-inflammatory perspective, is an emerging group of natural compounds known as polyphenols, and more specifically flavonoids that appear to reduce AD severity. Flavonoids are natural compounds present in fruits, vegetables, plants and beverages. Besides their anti-inflammatory potential, flavonoids were also described to have anti-oxidant and anti-amyloidogenic properties [156, 157]. In AD these compounds are capable of modulating the production of pro-inflammatory cytokines, for instance by decreasing Aβ aggregation and toxicity, TNF-α and IL-1β generation in microglia [158] or by reducing Aβ-induced cytokine production, possibly *via* PPARs activation [159]. The beneficial effects of these natural compounds have been likewise attributed to their capacity to inhibit neuronal apoptosis and certain TAU kinases like CDK5 [160] and GSK-3β [161], that disrupt Aβ aggregates and modulate APP processing by acting on α- and β-secretases leading to decreased Aβ production [162]. The mechanisms underlying flavonoid based neuroprotection are currently the focus of research, and evidence supports that supplementation of these natural compounds may constitute a new therapeutic approach for AD. Future studies should address the potential of these anti-inflammatory strategies in preventing or slowing down disease progression.

CONCLUSION

Neuroinflammation is a key event linked to AD pathogenesis in which inflammatory molecules such as cytokines and chemokines are released in response to Aβ peptide. These mediators can act at multiple levels and trigger many neurodegenerative events associated with pathology development, including altered APP processing that may in turn render in increased Aβ production, aggregation, and abnormal TAU phosphorylation, thus perpetuating a vicious cycle. Hence, supporting the notion that AD-related inflammatory mediators could represent suitable targets or useful biomarker candidates in AD therapeutics or diagnosis. Based on this and on the fact that anti-inflammatory drugs could revert at least in part the effects prompted by these inflammatory mediators, many studies were directed at NSAIDs, although thus so far, clinical trials have not been completely satisfactory. Flavonoids show great potential as a novel strategy for AD therapy. Nonetheless, collective characterization of the

patients, including individual heterogeneity and disease stages; drug effective dosage; standardization of methods and protocols; correlation of cytokines levels with imagiology information and with gold standard biomarkers, as the case of CSF Aβ and TAU, are some of the aspects that should be considered in future cytokines and therapeutic evaluation studies in AD.

LIST OF ABBREVIATIONS

AD = Alzheimer's disease

ADAM = A desintegrin and metalloprotease

APH-1 = Anterior pharynx defective-1

APOE = Apolipoprotein E

APP = Amyloid precursor protein

AICD = APP intracellular domain

Aβ = β-amyloid

BACE = β-site APP cleaving enzyme

C83 = C-terminal fragment consisting of 83 amino acids

C99 = C-terminal fragment consisting of 99 amino acids

CDK5 = Cyclin-dependent kinase 5

CHO = Chinese hamster ovary

CSF = Cerebrospinal fluid

FAD = Early-onset familial Alzheimer's Disease

HEK = Human embryonic kidney

IP-10 = Interferon γ-inducible protein 10

IFN-γ = Interferon-γ

IL = Interleukin

KO = Knockout

LOAD = Late-onset Alzheimer's Disease

MCP-1 = Monocyte chemoattractant protein-1

MIP-1α = Macrophage inflammatory protein 1-alpha

NFTs = Neurofibrillary tangles

NSAIDs = Non-steroidal anti-inflammatory drugs

Pen-2 = Presenilin enhancer-2

PPARγ = Peroxisome proliferator activated receptor γ

p-tau = Phosphorylated tau

PSEN = Presenilin

RANTES = Regulated on activation normal T-cell expressed and secreted

SPs = Senile plaques

sAPP = Soluble APP fragment

TACE = Tumor necrosis factor-α converting enzyme

TGF-β = Transforming growth factor-β

tg = Transgenic

TNF-α = Tumor necrosis factor-α

CONFLICT OF INTEREST

The authors declares no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

This work was financed by PIDC/DTP-PIC/5587/2014, Fundação para a Ciência e Tecnologia of the Ministério da Educação e Ciência, Feder funds through compete 2020. It was also supported by iBiMED (UID/BIM/04501/2013).

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