Peer-reviewed version available at Pharmaceutics 2020, 12, 880; doi:10.3390/pharmaceutics12090880

Review

Drugs Modulating CD4+ T Cells Blood-Brain Barrier Interaction in Alzheimer's Disease

Norwin Kubick[1], Patrick C. Henckell Flournoy[2] Ana-Maria Enciu[3], Gina Manda[3] and Michel-Edwar Mickael[4,5]

[1]Institute of Biochemistry, Molecular Cell Biology, University Clinic Hamburg-Eppendorf, Hamburg, Germany
[2]PM research center, Kaggeholm, 178 54 Ekerö, Stockholm, Sweden
[3] Victor Babes national institute of pathology, București 050096, Romania
[4]Bevill biomedical sciences research building, UAB Birmingham, AL 35294-2170
[5] Institute of Genetics and Animal Breeding of the Polish Academy of Sciences, ul. Postepu 36A, Jastrzębiec, 05-552 Magdalenka, Poland
* Correspondence:orresponding author Michel.edwar77@gmail.com

Abstract

The effect of Alzheimer's disease (AD) medications on CD4+ T cells homing has not been thoroughly investigated. Alzheimer's disturbs the life of at least five million persons in the USA. CD4+ T cells could both exacerbate and reduce AD symptoms. Regulating CD4+ T cells homing to the leaky blood-brain barrier (BBB) constitutes a new hope for enhancing AD prognosis. Alzheimer's drugs such as Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (Razadyne) and memantine are known to play an important part in regulating the neurotransmitters mechanisms. However, little is known about the effect of these drugs on CD4+ T cells homing. In this review, we focus on current and new drugs that could modulate CD4+ T cells interactions with the BBB in AD.

Key words

Alzheimer, Blood brain barrier, CD4+ T cells, migration, medication

Background

T cells infiltration affects Alzheimer's disease prognosis

Exploiting T cells infiltration in AD requires solving the T cells paradox [2]. It is difficult to localize T cells invading the brain during AD brains in the area of amyloid plaques. It was also reported that these T cells do not proliferate near the area of the plaques [3]. However, amyloid β -reactive T cells were produce pro-inflammatory cytokines thus contributing to prolonged inflammatory response in AD. Data also suggests that depletion of hippocampal T cells infiltration in tau-driven AD mouse models decreased spatial cognitive impairments [4]. Interestingly, the drug bexarotene [5] a retinoid X receptor agonist [6] that causes apoptosis in T cells seemed to reverse the course of AD [18]. Conversely, AD-prone mice deficient in lymphocytes show a larger degree of growth of amyloid β plaques in the brain [7]. The solution of this paradox could be related to the variability of the impact of various T cells subpopulations on AD. Alterations in the levels of various subpopulations of T cells were identified in the Alzheimer patients blood. Overall there was a rise in the frequency of CD4+ cells including FoxP3+, FoxP3-, Th9, and Th17 subpopulations [8] [9] [10]. Conversely, a decrease in the level of CD8+ was observed [11]. However, the exact role of T cells subpopulations is still not clear [12]. Specific T cells subpopulations could be performing an anti-inflammatory function by producing neurotrophic factors that protect neurons by stimulating the phagocytosis activity by resident macrophages (e.g., microglia) and thus help to reduce amyloid β deposition [13]. Th2 was reported to have a protective effect against AD [14] with an ability to induce the promotion of Aβ 1-42 autoantibodies [15]. Moreover, temporary reduction of regulatory T cells numbers shortened the time before the APPPS1 showed reduction in their congtive abilities [2]. Additionally, increasing the frequency of regulatory T cells by peripheral IL-2

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injection augmented microglia numbers that are specifically targeting plaque and enhanced cognitive abilities in APPPS1 mice [2]. Conversely, Th1 cells through the production of IFNγ had a negative impact by augmenting microglial activation as well as increasing in amyloid-β as well as exacerbating cognitive abilities in an AD mouse model [16]. Taken together, these reports suggest that manipulation of specific T cells subpopulations infiltration of the brain could prove critical for enhancing AD prognosis.

Investigating the effect of AD medications on CD4+ T cells homing is critically needed

Understanding the impact of known and new AD drugs on T cells homing to the blood-brain barrier is crucial for battling this disease [8]. Amyloid-β vaccines peptide yielded hopeful outcomes in AD mouse models. However, severe side effects was reported. These serious side effects were attributed to increase in recruitment and infiltration of CD4+ T cells [17]. The BBB is a protective boundary that regulate the passage of various substances to and from the brain, including lymphocytes. [18]. The main building block of the BBB is known as a neurovascular unit (NUV). The NUV consists of endothelial cells, astrocytes, microglia, and pericytes (Figure 1). Compelling examination suggests that each element of the NUV is uniquely influenced by AD pathologies [15][19][20]. There seems to be a malicious feedback loop between Aβ buildup and NUV damage throughout AD development [21] [22]. This cycle could be one of the leading causes of the dysregulated effect of CD4+ T cells in AD [21]. Currently, there are four primary Alzheimer's drugs; Donepezil, Rivastigmine, Galantamine and memantine [23]. In this review, we will discuss their impact on the interactions between various CD4+ T cells subpopulations and the NUV components. Next, we will explore CD4+ T cells-linked cytokines and the drugs related to them. Finally, we will cover new and repurposed drug designs that could be beneficial for regulating $CD4^+$ T cells infiltration.

Main text

i) T cells endothelial interactions in AD

Little is known about the difference in interaction between endothelial cells and the various CD4+ T cells subpopulations. However, it could be safe to assume that in AD, endothelial cells experience converse modifications that facilitate T cells migration. These changes could be summarized in two aspects. The first is the reduction of the expression of the proteins responsible for the BBB high structural integrity. This is manifested in the reduction of TJ proteins, occludin, claudin5, and ZO1 (Figure 2) [22]. Additionally, β-amyloid seems to impair Wnt/β-catenin signaling at the blood–brain barrier [24]. Furthermore, endothelial GLUT1 deficiency leads to cerebral microvascular degeneration and acceleration of Aβ pathology in the amyloid mice model [47]. The second aspect is the increase in adhesion molecules responsible for T cells homing in AD-like mouse models [3]. Also, increased frequency of T cells together with an increase in endothelial adhesion molecules such as ICAM1 and VCAM1 as well as alpha integrin levels was reported in AD mice [3] [25]. In

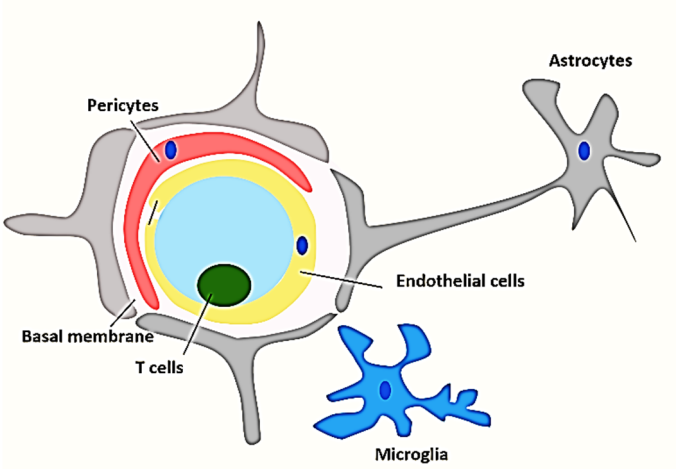

Figure 1. NUV interaction with T cells. NUV is composed of astrocytes, endothelial cells, microglia and pericytes. In AD, NUV become leakier giving the opportunity for an increase in T cell infiltration.

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addition higher frequency of adhesion molecules known to be expressed on leukocytes such as E-selectin and Icam1 were also reported [40]. Besides, PECAM1 is elevated in AD patients [26].

Effect of known AD drugs on T cells proliferation and homing

In general, classical AD drugs seem to attenuate CD4+ T cells proliferation. Donepezil is a safe drug with mild side effects that acts by inhibiting the breakdown of the neurotransmitter acetylcholine [27]. It is reported to have some enhancements on cognitive abilities. However, no improvements were present on patient self-assessed quality of life. Donepezil is a cholinergic inhibitor and is transported across the BBB by choline transporter [28]. In an interesting study, Agnieszka Jóźwik et al. found that soluble β-amyloids were unable to stimulate the proliferation of $CD4^{+}CD28^{+}$ T cells isolated from blood of patients who were administered donepezil [29]. Rivastigmine is another cholingeric inhibitor as it exercises its activity on acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). This drug is highly selective for the hippocampus and cortex. It also exerts positive influence on cognitive abilities [30] [31]. Interestingly, it was shown that administration of rivastigmine resulted in reduction of T cells proliferation in AD patients' blood [32]. However, rivastigmine was reported to induce a high incidence of gastrointestinal and visual adverse side effects [33] [34]. Whether these side effects are related to T cells inhibition is an open question. Galantamine is a competitive cholinesterase inhibitor that also allosterically modulates nicotinic acetylcholine receptors [35]. Unfortunately, it is associated with numerous side effects [36]. Galantamine seems to reduce T cells proliferation, in certain disease such as diabetes [37]. However, its effect on T cells homing in AD is not yet known. Furthermore, administration of memantine lead to a significant reduction of memory T cells of (e.g. CD45RO+ CD4+) in the blood. This could be a double edge sword as memantine can control unbalanced CD4+ T cells infiltration in AD, but may also increase the infection rate [38]. Regrettably, the information covering the difference in the impact of these drugs on CD4+ T cells subpopulations homing is scarce, however vital that could be.

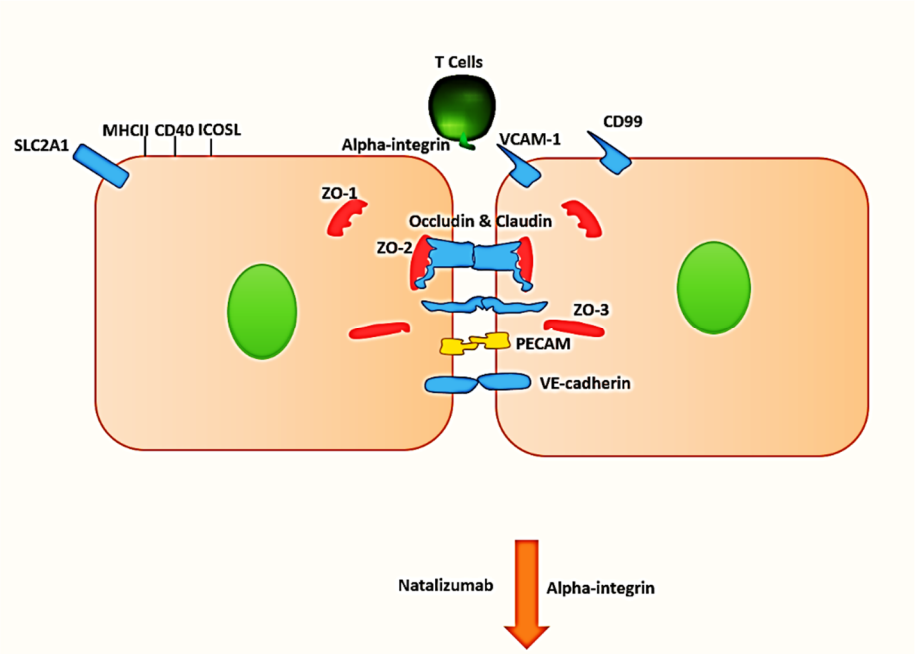

Figure 2. Endothelial cells interaction with T cells in AD. T cells migration could be dominantly paraceullar. Increase in the number of VCAM and alpha integrin has been reported.

Drug strategies that can manipulate CD4+ T cells-endothelial cells interaction

Several interactions between CD4+T cells and endothelial cells could be exploited in order to manipulate CD4+ T cells migration to the brain. These interactions include; regulating CD4+ T cells adhesion mechanisms, manipulating BBB physical characteristics, regulating CD4+ T cells activation and employing drugs with known BBB crossing ability.

(i) Blocking proinflmmatory CD4+ T cells subpopulations adhesion could constrain deposition, hyperphosphorylation, and enhance congtive function [26]. Selective blockade of integrinα4β1, by monoclonal antibodies such as natalizumab, is now employed as first-line therapy in MS [39]. Natalizumab limits the migration of pathogenic lymphocytes into CNS, thus reducing local inflammation. It would be interesting to investigate its impact on AD patients [40].

(ii) In certain phases of AD, it could be beneficial to increase adherence of Tregs to the BEC. It has been reported that, through using genetically engineered mesenchymal cells that co-express both selectin and its ligand, targeted delivery to CNS inflammatory sites was achieved [41]. Manipulating the endothelial layer adherence could also be done using salvianolic acid which was reported to reverse the decrease of TJ proteins induced by spinal cord injury [42].

(iii) Another innovative method is increasing CD4+ T cells activation through mast cell-derived exosomes. It has been demonstrated that exosomes associated with mast cells have the ability to activate B and T cells [43]. Because exosomes can escape the BBB, they can function as APC outside the CNS. The effect of this process on AD progression is not yet known.

(iv) Manipulating the physical characteristics of the endothelial layer constitutes another strategy. This approach could be achieved by employing radiotherapy, nanoparticles, electric fields, and lasers [96].

(v) Additionally, several drugs that are known to pass through the endothelial layer could be used to manipulate CD4+T cells homing. These drugs include ebitaride and peptide 001-C8, which are known to cross the BBB through adsorptive-mediated transcytosis [44]. However, their impacts on T cells and AD prognosis are still not known. Several drugs that could cross the BBB through saturable transport such as diamine polyamines and leptin have also not been investigated [44].

ii) CD4+ T cells interactions with astrocytes

CD4+ T cells and astrocytes in AD

Future research is needed to unravel more details about the interaction between CD4+ T cells and astrocytes in AD [45]. Astrocytes are critical in clearing Aβ deposition. Additionally, astrocytes can also contribute to neuronal protection by restricting the access of Aβ deposits to them [45]. This could be one of the reasons, behind astrocytes activation and accumulation during AD [45]. Whether the change in astrocytes function observed in AD is related to T cells interaction remain an open question. The interaction between CD4+ T cells and astrocytes can take more than one form. (I)The first form covers the influence that astrocytes exert on T cells. It was reported that astrocytes could present Aβ to Th2 cells that are specific for this antigen [46]. After they become activated these Th2 cells acquire a regulatory ability and were shown to suppress proinflammatory CD4+ helper T cells such as Th1 and Th17 cells [46]. Furthermore, the Aβ could upregulate the production of IL-6 and IL-8 in astrocytes [47] [48]. Interestingly IL-6 inhibit Th1 and Treg differentiation while increasing Th2 and Th17 differentiation (Figure 3) [49] [50]. Furthermore, it was shown that amyloid-β induces PGE2 production in astrocytes [51] providing further evidence for a role of PGE2 pathway in astrocytes influencing CD4+ T cells function. Glutamate's effects on T cells is a function in its concentration showing higher inhibition abilities in case of upregulation of its concentration [52]. It could be hypothesized that, the dysregulation of NMDA receptors in

astrocytes caused by amyloid-β could influence T cells function. It is essential to note that the pathological levels of glutamate produced by over stimulation of NMDA receptors in neurons and astrocytes is reduced with the use of MK801 and memantine. However, their effect on T cells homing in AD is not yet known. Glucose uptake by astrocytes seems to increase in Alzheimer [53], whether this influence T cells homing is still not known. (II) Effect of T cells on astrocytes. Aβ-specific Th1 or Th17 cells can only cause a small increase in MHC-II and CD86 levels on astrocytes. However, they can significantly increase the phosphorylations of STAT1 and STAT3 in glial cells. This observation proposes that lymphocytes specific for Aβ may stimulate astrocytes [83] [84]. Nevertheless, further experiments are justified to shed more light on these fascinating interactions.

Effect of classical AD drugs on CD4+ interactions with astrocytes in AD

Further in vitro and in vivo studies are critically needed to assess the effect of classical AD drugs on CD4+ T cells relationship with astrocytes in AD. Donepezil was shown to have positive influence on astrocytes through damping their reaction [56]. Donepezil effect on the glutamate-GABA axis, PGE2 pathway, and on T cells polarization is not yet apparent. Rivastigmine significantly enhanced GLT-1 protein expression in the brain thus it could be affecting glutamates transport to the brain [57]. Galantamine attenuates amyloid-β deposition and astrocytes activation [58]. Astrocytes stimulated with LPS or TNFα resulted exhibited a rise in proinflammatory chemokines levels (such as CXCL10 and CCL20). Interestingly this proinflammatory response was eliminated by utilizing memantine [59][60]. However, little is known about its impact on different CD4+ T cells-astrocytes interaction.

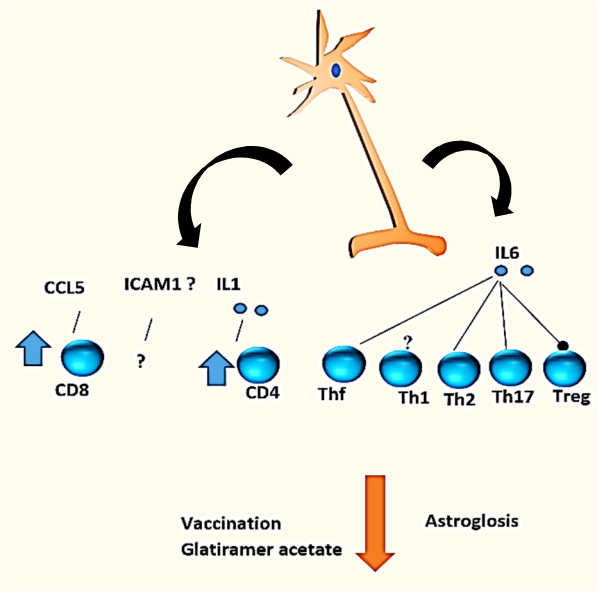

Figure 3. Astrocytes can regulate T cell differentiation in T cells. Several pathways have been reported to modulate T cells by astrocytes including IL-1 and IL-6 in AD.

Effect of repurposed drugs on CD4+ T cells-astrocytes relationship

Glatiramer acetate (GA) competently controls the induction of STAT1 and STAT3 in glial cells, as well as brain-resident immune cells [54]. Furthermore, it was reported that immunization of APPPS1 mice by GA protected cognitive abilities, decreased amyloid-β plaque burden and inflammation [61]. Moreover, T cell-based vaccination in conjunction with glatiramer acetate reduced plaque formation and cognitive deterioration. The vaccination exercised its influence by reprograming microglia into a CD11c+ IGF1+ phenotype. However, the effect of GA on the interaction between astrocytes and CD4+ T cells infiltrating the brain during AD is still hidden [62].

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iii) CD4+ T cells interaction with microglia

CD4+ T cells and microglia relationship in AD

In the context of AD, several reports have shown that a significant cross-talk between CD4+ T cells and microglia takes place either directly or through the release of cytokines [63][64]. Th2 seems to have an anti-inflammatory effect on microglia. Reports have shown that, Th2 cells specific for amyloid-β are capable of switching the cytokines production into an anti-inflammatory response by down regulating TNFα, and IL-2 levels as well as decreasing microglia activation (Figure 4) [15]. However, there are still unsolved paradoxes. For example, it was demonstrated that Th1 cells can stimulate microglia and enhance amyloid β clearance [15]. Conversely, it was claimed that Th1 could exacerbate the AD pathological conditions through the release of IFNγ [15]. Hence, the exact role of Th1 in AD has not been determined. Furthermore, reduction of Tregs, amplified the quantity of Aβ load, augmented microglia responses and diminished glucose metabolism [63]. Treatment with IL-2 increased the number of regulatory T cells and was associated with an amplified microglia frequency, and repaired cognitive abilities in APPPS1 mice [65] [66] [67]. Nevertheless, the exact interaction between Th17 and microglia is still not clear (supplementary table 1).

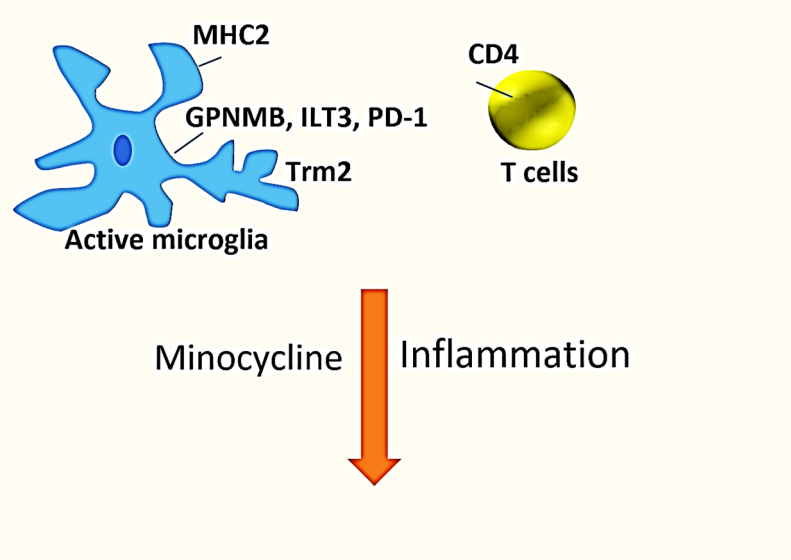

Figure 4. Microglia regulation of T cells. Microglia can both act as APC and modulator through its MHC2, GPNMB, ILT3, and PD-1.

Effect of classical AD drugs on microglia-T cells actions

The impact of traditional AD drugs on CD4+ T cells interaction with microglia is still not fully understood. Donepezil can inhibit microglial activation in vitro, however, the clinical drug dose and the in vitro concentration of the drug are different [68]. Rivastigmine reduced microglia and T cells activation and decreased pro-inflammatory cytokines (TNF-alpha, IFNγ, and IL-17) in EAE. [69]. However, its effect on microglia in AD is not yet apparent. Galantamine and memantine treatment could reduce microglial activation in vitro. Nevertheless, how these two drugs could affect CD4+ T cells has not been yet investigated [70][71].

Drugs that could influence microglial- CD4+ T cells interaction

One of the main drugs that could influence microglial- CD4+ T cells crosstalk is Minocycline. This drug was reported to act on both T cells and microglia and decrease IFNγ release in the central nervous system without impairing the Aβ phagocytosis. Extensively documented in animal AD models as having anti-inflammatory properties, it has been tested in 2018 for safety, tolerability, and pharmacokinetics in normal, healthy volunteers (ClinicalTrials.gov identifier (NCT number): NCT02802631).

iv) CD4+ T cells interaction with pericytes

CD4+ T cells interaction with pericytes in AD

AD pathology is characterized by cerebrovascular pericytes degeneration. This could lead to increasing Aβ deposition and angiopathy development as well as reducing Aβ40 and Aβ42 clearance [20] [22]. Furthermore, deficiency in pericytes decreases BBB integrity and increase permeability [72][73]. Interestingly pericytes could recruit neutrophils through a CXCL8 pathway [74][75]. In another study, LPS-treated pericytes upregulated the levels of cell adhesion molecules such as VCAM1 which in turn, increased adhesion of lymphocytes to pericytes (figure 5) [76]. However, there is not any study that systemically investigated pericytes interaction with different CD4+ T cells yet.

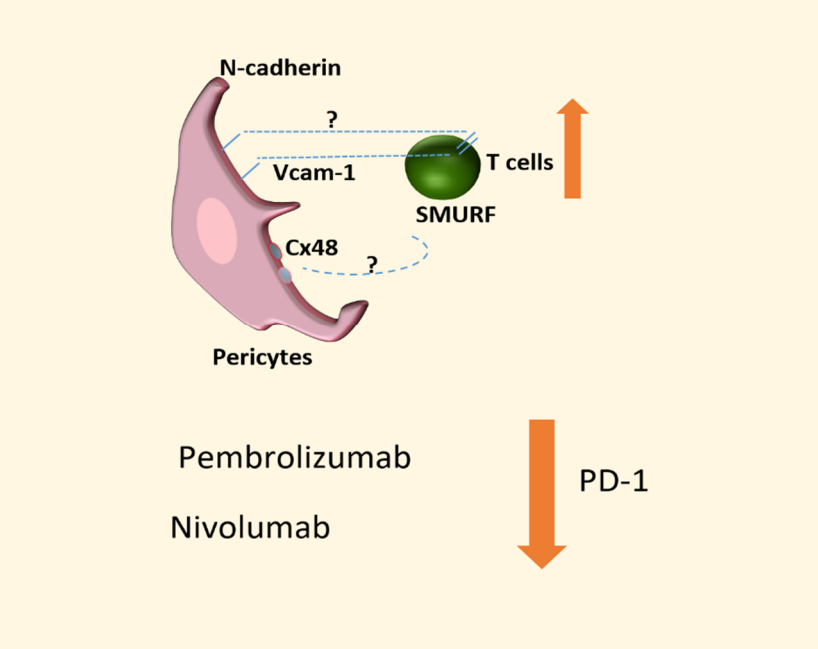

Figure 5. Few drugs have been designed to modulate pericytes – T cell interaction. N-cadherin has also been reported to expressed by T cells. Cadherins are known to form strong adhesive homodimer [67]. We can speculate about the existence of N-cadherin homodimers between T cells and pericytes that can regulate T cell migration into the brain. Pericytes selectivity is also regulated through gap junctions built of connexin-43, connecting the cytoplasm of the two cells types. Interestingly C×43 is expressed by thymic Treg cells progenitors where it plays a role in supporting Treg development. CX43 has also been reported to interact with SMURF2. SMURF2 which is an E3 ubiquitin ligase is highly expressed in healthy mouse T cells. Pembrolizumab and Nivolumab have the ability to regulate PD-1 pathway in AD.

Drugs that could influence pericytes CD4+ T cells interaction

Drug targeting of pericytes is a promising field. Targeting PD-L1 increased anti-inflammatory macrophages [77] leading to improvement of cognitive functions. However, the effect of blocking PD1 on CD4+T cells-pericytes interactions is not yet known. Additionally, it is worth emphasizing that the effect of classical AD drugs on T cells-pericytes interaction has not been yet investigated.

Drugs influence on CD4+ T cells cytokines is not well documented

One important aspect of CD4+ T cells infiltration of the brain in AD is the effect of various cytokines produced by CD4+ T cells in vivo. CSF from AD patients included both pro and anti CD4+T cells differentiation cytokines [15][78]. Additionally, CD4+ T cells associated cytokines are closely linked to risk of AD [78]. Proinflammatory cytokines, have also been shown to cause neurofibrillary tangle formation [79]. Furthermore, Fibrillar amyloid has been shown to bind NLRP3, one of the pattern recognition receptors that induce IL-1β production [80]. NLRP3 inhibitors decrease cerebral amyloid-β and enhanced cognitive function [81]. Paradoxically, overexpression of proinflammatory cytokines reduces amyloid β plaque [15]. Even more overexpression of anti-inflammatory cytokines, such as IL-4, IL-13, and TGF-β1, has also been revealed to decrease deposition of amyloid-β [82]. Immunohistochemical reports have demonstrated that TGF-β2 is localized in reactive astrocytes while microglia is found in the

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extracellular plaque [15]. Also, TGF-β1 and TGF- β2 upregulation have been reported in AD patients CSF [83]. TGF- β2 could decrease microglial and astrocytes reaction to amyloid β deposition [15]. Furthermore, anti-inflammatory cytokines activate microglia, and increase the levels of ARG1 [15]. ARG1 overexpression could reduce tau phosphorylation [84]. These observations emphasize the role of CD4+ T cells cytokines in both worsening the diseases status and the fight against it. The question arises how different drugs targeting AD affect and get affected by cytokines associated with CD4+ T cells. Systematic studies are crucially needed to decipher the effectiveness of AD medication in light of CD4+ T cytokines role.

Nonsteroidal anti-inflammatory drugs (NSAIDs) effect on T cells homing in AD

One crucial drug design approach that can manipulate CD4+ T cells related cytokines is the use of NSAIDs. ibuprofen, indomethacin, and diclofenac usage is linked to decrease in reduction of Aβ-42. However NSAIDs do not slow down the progression of AD [85]. Inetretsingly, NSAIDs can activate PPARγ [85] [86]. Indomethacin and ibuprofen were reported to increase PPARγ in glial cells and decrease amyloid β deposition [87] [88]. The TOMMORROW study (https://clinicaltrials.gov/ct2/show/NCT01931566) aimed to evaluate the effect of pioglitazone (agonist of PPARγ) on prevention of AD. However, the approach is not yet successful [15]. Neglecting the unique impact of cytokines on CD4+ T cells polarization while employing specific NSAIDs could be a contributing factor for these trials failure. In particular, it could be essential to investigate the effects of NSAIDs on the TH17/Treg axis.

v) New and upcoming drug designs that could benefit AD prognosis.

Peripheral T cells population modifiers drugs used to regulate T cells in AD

Monoclonal antibodies such as alemtuzumab decreased peripheral T cells count of both CD4+ and CD8+ [89]. However, its effect on AD patients is not yet known. Another types of peripheral modulators include Sphingosine-1-Phosphate receptor (S1PR). S1PR limits lymphocytes traffic and decreases their peripheral count, mainly by confining them into lymph nodes [90]. Several S1PR agonists (ponesimod, siponimod, amiselimod, and ozanimod) are currently tested in MS clinical trials [91]. SEW2871 administration prevented cognitive abilities in Alzheimer's rat model, indicating the S1P1R signaling pathway could be a new therapeutic target [92]. Additionally, selective inhibition of proinflammatory phenotypes of CD4+ T cells Bromodomain and extra-terminal domain (BET) protein can block Th1/Th17 differentiation from CD4+ naïve cells [93][94]. It was reported that jq1 which is a known BET-Bromodomain inhibitor decreases inflammation and tau phosphorylation in Alzheimer mice model [95].

Checkpoint blockade as a putative regulator of CD4+ T cells homing in AD

Targeting PD-1 has been proposed as a possible mechanism of modulating the course of neurodegenerative diseases. This strategy was shown to releases self-reactive T cells from immune tolerance mechanisms [96]. When applied in the context of AD, inhibiting the PD-1 pathway induced an IFNγ signaling pathway, increasing the frequencies of $CD45^{high}$ $CD11b^{+}$ cells [97]. In cascade, this increased clearance cerebral amyloid-β plaques and improved cognitive performance. However, it is worth noting that this strategy could not be used to target AD on its own [97].

CD4+ T cells repolarization as a drug design strategy

One of the innovative approaches toward exploiting CD4+ T cells in treating AD is cellular reprogramming. Various CD4+ T cells subpopulations influence AD prognosis differently. Amyloid-β -specific CD4+ T cells polarized in vitro to three main CD4+ T cells population (e.g., Th1, Th2 and Th17), were adoptively transferred to APPPS1 mice. Assessment of the animals indicated that Th1 cells upregulated microglial activation, amyloid-β deposition and impaired

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cognitive function [16]. Thus, manipulating cytokines responsible for T cells repolarization could constitute an alternative therapy for AD. However, this approach is hindered by the change in the pathogenicity of CD4+ T cells subpopulations during the phases of the disease. Further experiments are needed to shed more light on the possibility of overcoming this significant obstacle.

Conclusion

The future for enhancing therapeutic and preventative measures for AD could lay in manipulating CD4+ T cells interaction with the BBB. Designing drugs that target interactions between CD4+ T cells and each of the NUV members could prove critical in enhancing the prognosis of this disease. However little is known about CD4+ T cells brain migration beyond the role of endothelial cells. Extensive experiments are needed to investigate the different impacts various CD4+ T cells subpopulations have in AD. In the context of drug design, in particular, there is a vital urge for understanding the effect of known and existing drugs on various T cells subpopulations. Additionally, new AD medications have to take into consideration the important contribution made by various CD4+ T cells subpopulations into the dynamics of the disease.

List of abbreviations

AD Alzheimer's disease

BBB Blood brain barrier

BEC Brain Endothelial Cells

CNS central nervous system

COX2 Cyclooxygenase-2

FoxP3 Forkhead Box P3

ICAM1 Intercellular Adhesion Molecule 1

IFNγ Interferon gamma

IL-2 Interleukin-2

IL-6 Interleukin-2

NLRP3 PYD domains-containing protein 3

NSAIDs Nonsteroidal anti-inflammatory drugs

PD-1 Programmed cell death protein 1

PECAM1 Platelet endothelial cell adhesion molecule 1

S1PR Sphingosine-1-Phosphate receptor

TGF-β Transforming growth factor beta

TJ tight junctions

TNFα Tumor necrosis factor alpha

VCAM1 Vascular cell adhesion protein 1

ZO1 Zonula occludens-1

Declarations

Competing interests

The authors would like to declare no competing interests.

Funding

This review was partially supported by the REDBRAIN European funding.

Authors' contributions

All authors contributed equally.

Acknowledgements

We would like to thank Professor *Macrious Abraham & Professor Mary Joachim* for his visionary directions.

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