The dual role of Tumour Necrosis Factor in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder currently affecting approximately 50 million people, with an extraordinarily large burden of disease on society, Research has been primarily focused on amyloid-beta, one of the hallmarks of AD, but has so far failed to yield treatment options that have passed clinical trials. With the advent of more modern assays, other aspects of AD, such as formation of Tau neurofibrillary tangles and the involvement of neuroinflammation can be more thoroughly investigated, opening up potential avenues for treatment. In particular, tumour necrosis factor, a master cytokine, has been shown to be correlated to earlier onset and faster progression of AD. In this review, multiple mechanisms and pathways relating to TNF, the therapeutical targets they present, and current treatments are discussed. While research into these subjects have not yet yielded a cure, there is evidence that the onset and progression of AD can be slowed, provided it is detected at an early enough stage.

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History and mechanism of Alzheimer's disease

Approximately 100 years ago, Alzheimer's disease (AD) was first characterized in a patient by Alois Alzheimer. One of many presenile dementias, AD continues to have one of the greatest burdens of disease in the world, with approximately 50 million affected individuals and possessing the number 5 spot on the list of causes of death worldwide in 2016. Comparing the number of cases to data from 1990 reveals that in slightly over 20 years, cases have approximately doubled. (*GBD 2016 Dementia Collaborators, 2019).* Extrapolating with these numbers, we can expect more than 100 million affected individuals by 2050.

What makes AD and other forms of dementia contribute so severely to the burden of disease is their gradual progression of neurodegeneration, characterized by problems with memory and language, leading to impairment of day-to-day function, eventually requiring near-constant care.

Despite its increasingly prevalent role in the global burden of disease, significant details of the pathology and its progression are still unknown. There is significant evidence that synapse loss (*Scheff and Price, 2001)* and axonal degeneration (*Raff et al., 2002)* are responsible for neurodegeneration in AD, brought on by accumulation of abnormal amyloid-ß (Aß) protein and abnormal function of microtubule-associated protein Tau *(Mandelkow & Mandelkow, 1998*).

Amyloid-ß in Alzheimer's disease

Current research indicates that formation of Aß plaques is the result of a loss of balance in several Aß related functions; production, clearance and aggregation. Aß consists of peptides produced by proteolytic cleavage of Amyloid-ß Precursor Protein (APP). While the exact function of APP and Aß is yet unclear, they are strongly evolutionarily conserved, hinting at their importance (*Selkoe, 1989)*. Proteolytic cleavage of APP is achieved by a set of protease complexes known as α, ß and γ-secretase complexes. Serial cleavage by ß-secretase followed by γ-secretase results in formation of Aß peptides *(Hutton & Hardy, 1997)*. Different cleavage sites result in different Aß peptides, of which Aß42 has been shown to be especially highly present in AD brains, including in early-onset disease *(Iwatsubo et al., 1994)*. Accordingly, mutations correlated with a disposition for familial AD in APP and the secretase complexes, particularly proteins in the γ-secretase complex known as presenilin-1 (PS1) and presenilin-2 (PS2), have been shown to skew Aß peptide production towards Aß42 *(Scheuner et al., 1996)*. Interestingly, recent research has proven the existence of a coding mutation in the APP gene that reduces the amount of amyloidogenic peptides produced, leading to a protective effect against AD *(Jonsson et al., 2012)*. ß-secretase 1 (BACE1) has also been shown to be involved in the production of Aß42, with BACE1-deficient neurons showing strongly diminished Aß42 production, highlighting it as a key protein and potential therapeutic target *(Cai et al., 2001)*.

Clearance of Aß is orchestrated through multiple mechanisms; proteolytic degradation is performed by neprilysin, as proven by a marked increase in Aß40 and Aß42 in neprilysin-deficient mice *(Iwata et al., 2001)*. Normal clearance pathways such as lysosomal autophagy *(Bendiske and Bahr, 2003)* and the proteasome *(Marambaud et al., 2005)* have also been shown to play their role in clearing Aß. The last major player in Aß clearance consists of chaperone molecules, primarily the apolipoprotein E (ApoE) protein. In particular, mutations in the ε4 allele have been shown to be linked to an increase disposition for AD *(Strittmatter et al., 1993)*. On the other hand, the ε2 allele is linked to a lower disposition for AD *(Corder et al., 1994).* The exact mechanism by which these mutations achieve their detrimental or protective effect is still poorly understood.

Higher-than-usual production or lower-than-usual clearance of Aß leads to an increase in aggregation. Not just does this result in a higher amount of Aß monomers, but these monomers also assemble into dimers, and subsequently larger oligomers. These soluble oligomers have

been shown to form intracellularly *(Walsh et al., 2000)*, and only assemble into insoluble fibrils, and subsequently the characteristic Aß plaques in the extracellular space. It is here that the primary pathogenic role of Aß42, the longest Aß peptide, can be found, as it is uniquely suited for seeding these plaques by nature of its carboxy terminus *(Jarrett et al., 1993)*. While Aß plaques have long been viewed as the primary hallmark of AD, there is ongoing debate about whether the plaques are pathogenic. It has been shown that the smaller, soluble oligomers are actively pathogenic, causing dendritic spine loss *(Koffie et al., 2009)* and neuritic dystrophy *(Knowles et al., 1999)*. A likely explanation for damage to tissue near plaques is that plaques serve as a reservoir of biologically active oligomers, further supported by the presence of biologically active dimers and oligomers in the core of plaques *(Shankar et al., 2008)*.

While it is undeniable that Aß deposited in the extracellular space plays a key role in AD pathology, however, it is not the sole hallmark of AD.

Tau in Alzheimer's disease

The other primary hallmark of AD is the presence of intracellular deposits of the microtubule associated protein Tau. Normal functioning Tau stabilizes neuronal microtubules, which are key in the homeostasis of neurons through regulating intracellular transport and maintaining cell polarity *(Drewes et al., 1998)*. It has been shown that Tau achieves its function through the establishing of gradients, both of Tau as a protein, with concentration of Tau being nearly 10-fold higher in the distal half of the axon compared to the proximal half *(Black et al., 1996*), but also by formation of a gradient of Tau phosphorylation, which is highest in the proximal part of an axon, rather than at the growth cone *(Mandell and Banker, 1996)*. Together, these findings further support a role for Tau and its phosphorylation in neuronal development.

Normal phosphorylation of Tau can achieve a variety of effects, including the release of Tau from microtubules after phosphorylation at Ser262 or Ser214 by a microtubule-affinity-regulating kinase (MARK). Hyperphosphorylation of Tau has been shown to play a major role in the formation of intracellular neurofibrillary tangles, which take the form of aggregates of paired helical filaments, which are insoluble, as opposed to the normally very soluble Tau protein. While it stands to reason to excessive detachment of Tau from microtubules is necessary for production of paired helical filament aggregates, the aforementioned phosphorylation by MARK has been shown to also provide a protective effect against the formation of paired helical filaments *(Schneider et al., 1999)*.

For a long time, it was debated whether Aß plaques or Tau neurofibrillary tangles were responsible for the damage associated with AD, but recent research has shown that hyperphosphorylation of Tau and the subsequent formation of neurofibrillary tangles is a downstream effect of Aß deposition *(Hardy et al., 1998)*, and that presence of Aß42 fibrils in fact plays a major role in the formation of neurofibrillary tangles *(Götz et al., 2001)*. Aß fibrils in general have been shown to induce Tau phosphorylation, which in excess leads to accumulation of Tau neurofibrillary tangles *(Busciglio et al., 1995)*. On top of that, recent evidence suggests that Aß aggregation without the formation of Tau neurofibrillary tangles leads to reduced neurotoxicity *(Roberson et al., 2007)*, opening another therapeutic avenue of approach.

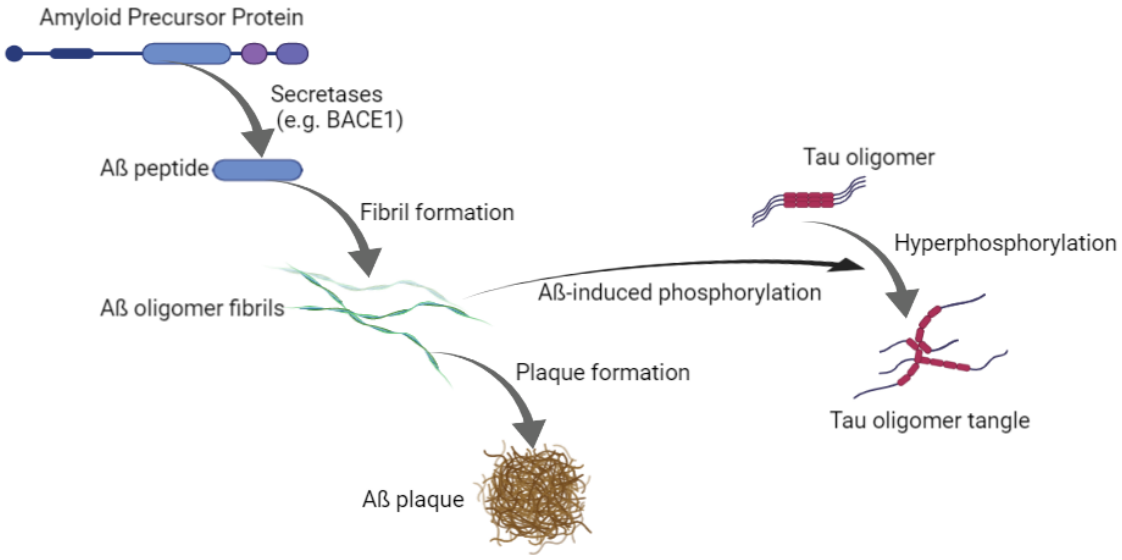

Figure 1. Overview of formation of primary Alzheimer's Disease hallmarks. Amyloidogenic processing of Amyloid Precursor Protein (APP) by secretase proteins causes formation of oligomers, eventually resulting in formation of plaques. Amyloid-beta fibrils have been shown to play a role in phosphorylation of Tau, speeding up the process of Tau oligomer tangle formation. Created using Biorender (BioRender.com).

One of the interesting features of Tau pathology in AD is that it has been shown to spread throughout the brain, specifically through brain networks, in a process that is enhanced by the presence of Aß *(Vogel et al., 2020)*. The same research shows that the entorhinal cortex, a part of the brain that is regarded as an interface between the hippocampus and the neocortex, is one of the hotspots for Tau accumulation, which corresponds with the type of neurodegeneration that AD is famous for.

While Aß aggregation and Tau pathology and their related damage to neurons and synapses are the established hallmarks of AD, there is another less well-investigated factor in neurodegeneration in patients with AD.

Neuroinflammation in Alzheimer's disease

With the rise of more convenient quantitative assays for protein levels, more and more evidence is starting to crop up for the involvement of neuroinflammation in the progression of AD. Both Aß fibrils *(Webster et al., 1997)* and Tau neurofibrillary tangles *(Shen et al., 2001)* have been shown to activate the classical complement pathway, leading to cell lysis. Microglia, functioning as the brain's macrophages, are responsible for the production of complement proteins, with production of complement proteins in AD brains being significantly increased compared to normal brains *(Yasojima et al., 1999)*.

The same microglia and astrocytes have been found to accumulate in the vicinity of Aß plaques, expressing several key cytokines and chemokines, including IL-1ß, IL-6 and Tumour Necrosis Factor (TNF) *(Benzing et al., 1999)*. While it is possible to assume this is an attempt at clearing the aberrant protein plaques, it has been shown microglia are incapable of phagocytizing the Aß aggregates in the presence of the inflammatory cytokines *(Koenigsknecht-Talboo and Landreth, 2005)*.

IL-1 has been shown to be specifically upregulated in neuritic Aß plaques compared to non-neuritic plaques, hinting at a role in the transformation of a plaque to its neuritic state *(Griffin et al., 1995)*. IL-1 normally possesses a trophic function through activation of S100ß, a neurite growth-promoting cytokine, which is also elevated in AD brains *(Marshak et al., 1992)*. It has been proposed that the overexpression of IL-1 in microglia near non-neuritic Aß plaques leads

to excessive neurite growth as result of S100ß activation, which in turn ends up turning the initial plaque neuritic. This theory has been termed the cytokine cycle *(Griffin et al., 1998)*.

Along the same lines, upregulation of the pro-inflammatory cytokine IL-6 has been shown in AD brain compared to normal brains *(Bauer et al., 1991)*, along with one of its products, the potent protease inhibitor alpha-2-macroglobulin. Inactivation of proteases is bound to lead to a decrease in protein clearing, and indeed it has been shown that soluble IL-6 receptor can modulate processing of APP *(Ringheim et al., 1998)*, and thus contribute to formation of Aß plaques. It has been reported that mutation in the C allele of IL-6, which reduces IL-6 activity, also leads to delayed progression of AD *(Papassotiropoulos et al., 1999)*. However, there is also evidence that IL-6 has beneficial effects, such as improving neuron survival *(Hama et al., 1991)* and providing an immunosuppressant effect through activation of the hypothalamic-pituitary-adrenal axis (*Mastorakos et al., 1993)*.

It is important to realize the incredible depth to the signaling, both positive and negative, of these molecules, which is more evident in TNF than any other molecule.

TNF signalling

TNF, initially named TNF-α, is a 26 kDa transmembrane protein *(Carswell et al., 1975)* that exists as a homotrimer *(Tang et al., 1996)*. At the time of discovery, it was noted for its production in response to endotoxin, and subsequently named for its ability to kill tumor cells. It quickly became clear however, that TNF exists in more than one form; the initially discovered transmembrane TNF (tmTNF) can be cleaved ADAM17, also known as TNF-alpha-converting enzyme (TACE) *(Black et al., 1997)*, to release a soluble TNF (solTNF) from the cell membrane. solTNF is a 17 kDA protein *(Shirai et al., 1985)* that also forms homotrimers *(Wajant et al., 2003)*. The solTNF monomers consist of two antiparallel ß-pleated sheets with antiparallel ß-strands, forming a ß-structure that is a hallmark of the TNF family *(Bazan, 1993)*.

Not only are both tmTNF and solTNF their own molecules with separate functions, there are also two separate TNF receptors. Tumour Necrosis Factor Receptor 1 (TNFR1), also known as CD120a, is expressed on most cell types, while Tumour Necrosis Factor Receptor 2 (TNFR2), also known as CD120b, is primarily expressed in immune cells. The main difference can be found in their intracellular domains and the corresponding function; TNFR1 contains a death domain *(Tartaglia et al., 1993)* that is silenced by a Silencer of Death Domain (SODD) protein *(Jiang et al., 1990)*, while TNFR2 contains a domain responsible for binding TNF-receptor associated factors (TRAFs) *(Varfolomeev and Ashkenazi, 2004)*. While this sets up a simple dichotomy of TNFR1 being responsible for activation of cell death pathways and TNFR2 for signal transduction, the truth is significantly more complicated. For example, TNFR1 has been shown to induce inflammation, tumour necrosis and apoptosis, as would be expected, but also cell proliferation and stimulation of differentiation *(Liu et al., 1996)*. With such varying potential outcomes of TNFR1 activation, looking at the ligand-receptor interactions can provide a starting point for figuring out the complex TNF system.

Experiments in search of the binding affinity of solTNF and tmTNF to TNFR1 and TNFR2 lead to an interesting set of evidence; solTNF forms a much more stable interaction with TNFR1 than with TNFR2, leading to prolonged activation of the receptor *(Grell et al., 1998)*. Inversely, tmTNF has been shown to be the primary activating ligand for TNFR2 *(Grell et al., 1995)*, though tmTNF is still also an activator for TNFR1. Note that a stronger, more stable interaction with one type of TNF does not mean that binding with the other type is impossible or even useless.

TNF manages its role as a master-cytokine by interacting with other powerful pathways, most important among which are the NF-κB pathway, JNK pathway and the P38-MAPK pathway.

TNF activation of the NF-κB pathway

The Nuclear Factor kappa-light-chain-enhancer of activated B-cells (NF-κB) pathway comprises a set of transcription factors that affect proliferation, apoptosis/cell survival and inflammation, particularly in response to infection and cellular stress *(Oeckinghaus & Ghosh, 2009)*. In their default state, they are bound to a set of proteins from a matching inhibitor protein family, the I-κB proteins, which ensures native NF-κB dimers remain in the cytoplasm *(Perkins, 2000)*. Activation of NF- κB results from induction of degradation of I-κB by phosphorylation, followed by phosphorylation of the NF-κB domains. The proteins responsible for the phosphorylation and subsequent activation of I-κB and NF-κB is known as the I-κB kinase (IKK) complex. This complex consists of two I-κB kinases (IKK1 and IKK2) *(Mercurio et al., 1997)*, heat shock protein-90 (Hsp90) and the Hsp90-associated cdc37 protein *(Chen et al., 2002)*, and an essential regulatory protein NF-κB Essential Modulator (NEMO) *(Yamaoka et al., 1998)*.

It has been shown that presence of TNF causes rapid activation of NF-κB, needing low receptor occupancy and occurring within minutes after binding *(Hohmann et al., 1990)*. It has been shown that IKK-2 deficient mice are relatively deficient in TNF-induced I-κB phosphorylation *(Tanaka et al, 1999)*, while involvement of IKK1 is still under review. Ligand binding to TNFR1 causes the SODD protein to disassociate from TNFR1 complexes, allowing the now-revealed death domain of TNFR1 to interact with the adaptor protein Tumour necrosis factor receptor type 1-associated death domain protein (TRADD) *(Hsu et al., 1995)*, which then forms a basis to bind TRAF2 as well as the death domain-containing serine-threonine kinase receptor-interacting kinase (RIP) *(Hsu et al., 1996a)*. There is evidence that TRAF2 is responsible for recruiting of IKK complexes, while RIP is responsible for the actual activation of the IKK complex through interaction with NEMO *(Devin et al., 2000)*.

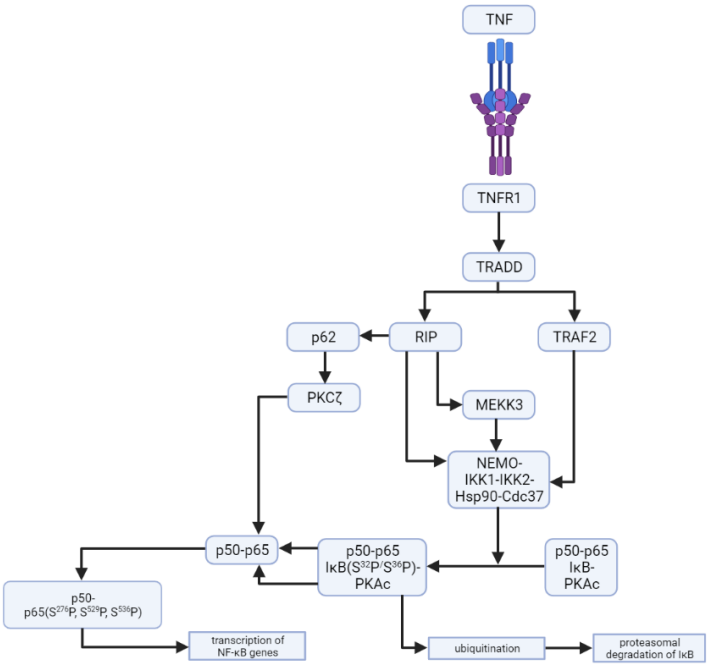

Figure 2. Overview of activation of NF-κB by TNFR1. Signalling through adaptor molecule TRADD allows for both RIP and TRAF2 to interfere with the IKK-complex, inducing activation of NF-κB units p50 and p65, while also inducing proteasomal degredation of inhibitor IκB. Adapted from *Wajant et al., 2003* using BioRender (BioRender.com).

While this interaction is enough to cause activation of NF-κB susceptible pro-survival genes, there is evidence for additional routes affected by the system. TRADD has been shown to interact with Fas-associated protein with death domain (FADD) *(Hsu et al., 1996b)*, a critical part of a death-inducing signaling complex (DISC) together with caspase-8 and -10 *(Yeh et al.,*

1998). In accordance with the obvious pro-apoptotic effect of the activation of caspase-8, it has been shown that depletion of TRAF2, the alternative binding partner for the TRADD complex, causes cells to become more susceptible to induction of apoptosis through TNF *(Weiss et al., 1998)*. Another possible factor is the recruitment of antiapoptotic proteins cellular inhibitor of apoptosis protein (cIAP) 1 and 2 by TRAF2 *(Shu et al., 1996)*, which have been shown to interfere with caspase-8 activation *(Wang et al., 1998)*. One of the possible causes of depletion of TRAF2, and subsequent sensitization to apoptosis, is through the activation of TNFR2, letting TNFR2 play a role in induced apoptosis without possessing its own death domain *(Grell et al., 1999)*.

Altogether there is plenty of evidence showing that while activation of NF-κB by TNF generally leads to a protective function, the way the pathways are set up make it possible to have the opposite effect entirely as well.

TNF activation of the JNK & p38-MAPK pathways
Two other pathways that have been shown to be activated follow TNF receptor binding are the Jun N-terminal kinase (JNK) pathway and the p38-MAPK pathway, both related to mitogen-activated protein kinases.

Activation of the JNK pathway through TNF has been shown to proceed through the adaptor protein TRAF2 *(Reinhard et al., 1997)*, Further downstream, the phosphorylation of JNK and subsequent activation is reliant on two dual specificity mitogen-activated protein kinase kinases (MKKs), MKK7 and MKK4, with MKK7 being essential, and MKK4 supporting the activation of JNK, but not activating it by itself *(Tournier et al., 2001)*. Recent evidence has shown that mixed lineage kinase 3 (MLK3) is the link between TRAF2 and MKK4/MKK7 *(Sondarva et al., 2010)*. Aside from TRAF2-MLK3-MKK4/7, there is evidence for additional mechanisms of activation of JNK induced by TNF; germinal center kinases (GCKs) provide additional activation of MAP-kinases, such as through mitogen-activated protein kinase kinase kinase (MEKK) 1 *(Chadee et al., 2002)*, which has a downstream effect on MKK7, and thus activation of JNK. Binding of TNFR1 has also been shown to induce interaction of apoptosis signal-regulating kinase 1 (ASK1) with TRAF2 through generation of reactive oxygen species (ROS), influx of which can be sensed through the antioxidant-sensitive mechanisms of ASK1 *(Gotoh and Cooper, 1998)*. ASK1 can then activate MKK7, once again leading to JNK activation.

Activation of JNK through any of the aforementioned pathways has two distinct outcomes; JNK has been shown to have pro-apoptotic functions, both through interaction with the transcription factor AP-1 *(Tournier et al., 2002)*, but also through its ability to phosphorylate and thus inactivate anti-apoptotic protein Bcl-2 *(Yamamoto et al., 1999)*. However, as with NF-κB, the opposite effect can also be achieved, as JNK has been shown to protect against apoptosis during neuronal development *(Kuan et al., 1999)*.

Many of the pieces named in the JNK pathway activation sequence also play a role in the activation of the p38-MAPK pathway, with evidence of involvement for TRAF2 *(Yuasa et al., 1998)* and ASK1 *(Ichijo et al., 1997)*. Activation of p38 through the MAPK cascade has been shown to increase IL-1 and IL-6 production, though the exact mechanism is not yet resolved. These examples all serve to sketch the far-stretching and multipurpose role of TNF signaling in inflammation, providing an abundance of potential therapeutic targets.

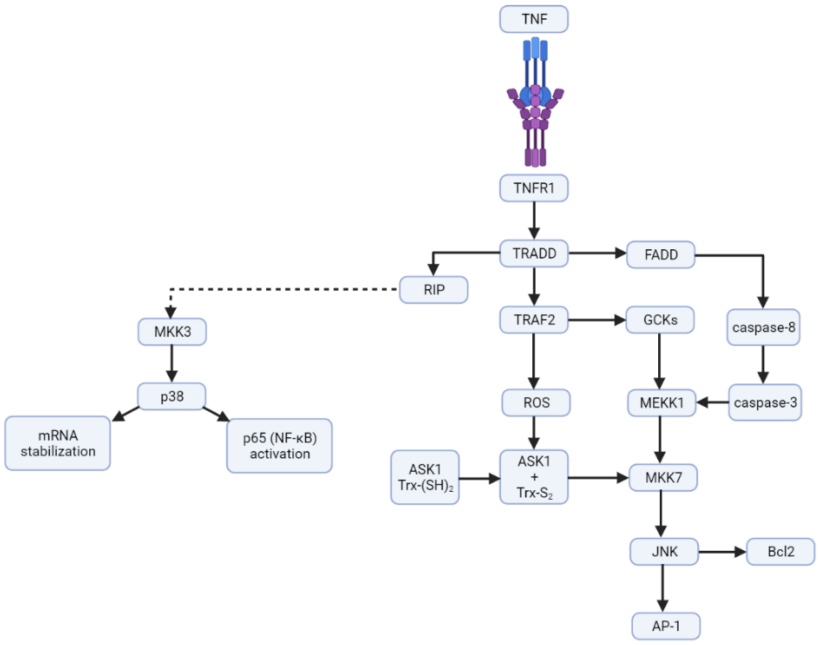

Figure 3. Activation of p38 and JNK pathways by TNFR1. Signaling through adaptor molecule TRADD activates RIP and subsequently MKK3-p38 through a poorly elucidated mechanism. Signaling through death domain adaptor protein FADD activates a caspase cascade, interacting with mitogen-activated kinases to activate JNK. Adapted from *Wajant et al., 2003* using BioRender (BioRender.com).

TNF in Alzheimer's disease

With the abundance of evidence for a role of neuroinflammation in AD, and the incredibly pluripotent role of TNF therein, it is to be expected the TNF plays a direct role in a variety of processes, protective or harmful. Example include that serum TNF is increased in AD patients *(Alvarez et al., 2007)*, a symptom that has been shown to correlate with an increased rate of cognitive decline *(Holmes et al., 2009)* and that genetic changes in TNF are positively correlated to AD *(Collins et al., 2000)*.

This is backed up by evidence that expression of TNFR1 is increased in AD-brains, while TNFR2 expression is decreased *(Cheng et al., 2010)*. The same research also shows that TNF is more likely to bind TNFR1 in AD-brains, and that interestingly, there is no significant difference in mRNA distribution of TNFR1 and TNFR2 between AD and non-demented brains.

Further evidence for the link between TNF and AD has been found in TNFR2 knockout murine brains, which showed a substantial decrease in Aß-plaques, with APP levels not being significantly different. It was shown that BACE1 activity, and thus generation of Aß42, was increased in TNFR2 knockout mice, and the opposite was shown as well; overexpression of TNFR2 reduces BACE1 amount and activity, leading to healthier APP processing *(Jiang et al., 2014)*. A role for TNFR1 in the same system has also been implicated, as deletion of TNFR1 resulted in a decrease in BACE1 activity, which has been shown to be a result of BACE1 promotor activity modulation through the NF-κB pathway by TNFR1 *(He at al., 2007)*. While both TNFR1 and TNFR2 have been implicated in the NF-κB pathway, there is evidence that the method of activation has important implication. Sustained activation of NF-κB through binding of TNFR2 has been shown to provide protection against glutamate excitotoxicity as a result of activation of a PI3K-dependent PKB/Akt phosphorylation upstream of NF-κB *(Marchetti et al., 2004)*. On the other hand, the same research shows that binding of TNFR1 induces a much more short-lived activation of NF-κB.

Further evidence for the role of TNF in maintaining a healthy brain is that TNFR2 is mandatory for correct oligodendrocyte differentiation, but not for proliferation or survival through regulation

of the expression of microRNAs in the brain. Further evidence for the importance of TNFR2 can be found in experimental models of experimental autoimmune encephalomyelitis (EAE) in mice, where the beneficial effects of inhibiting soluble TNF were not reproduced in TNFR2 negative mice *(Madsen et al., 2016)*.

With the amount of evidence that TNFR1 is involved in negative processes in the pathology of AD, it stands to reason that therapies to interfere with TNF would be trialled in order to combat AD. However, again, evidence surfaced that a healthy amount of nuance is required.

TNF blockage as treatment

With the abundance of evidence for the detrimental effects of TNF and its role in the formation of AD, a first generation of blanket TNF treatments was developed and trialled. A prime example is the fusion protein etanercept. This fusion protein consists of two extracellular soluble-TNF binding domains combined with the Fc fragment of human immunoglobulin G1, which lets the receptor fragment stay in the bloodstream for longer. Thus, etanercept functions as a decoy receptor, decreasing occupancy of the normal functional TNFR1 and TNFR2 *(Marotte and Cimez, 2014)*.

While etanercept is still commercially available and used against a variety of disorders, such rheumatoid arthritis, trials of its use against AD have come with a variety of warning signs. As could be expected from disabling the broad inflammatory function of TNFR1 and protective functions of TNFR2, a trial with etanercept was stopped due to a significant increase of infections in the etanercept cohort compared to the placebo cohort, with no significant changes in cognition and behaviour or global function *(Butchart et al., 2015)*. In fact, there is evidence of a patient developing symptoms of psychosis after treatment with etanercept, with the symptoms showing improvement once treatment was halted *(Atigari and Healy, 2014)*. This serves as further evidence for earlier findings of increased infections and also increased demyelination as a result of TNF antagonist use, mimicking the effects of autoimmune diseases *(Prinz, 2011)*. Incidences reported to the Food and Drug Administration Adverse Event Reporting System showed no incident with TNF inhibitor usage as its definitive cause, but 71.3% of reported incidents was deemed to be a possible result of TNF inhibitor usage *(Deepak et al., 2013)*.

Besides etanercept, there are two other licensed anti-TNF drugs, both of which are monoclonal antibodies; infliximab and adalimumab. While they see use in the treatment of inflammatory-mediated conditions, they largely share the same profile of problems as etanercept *(Mpofu et al., 2005)*. There is still some space for the investigation of these compounds, as evidenced by the case report of a patient with rheumatoid arthritis that responded to etanercept after infliximab failed to provide a sufficient effect *(Buch et al., 2004)*.

Targeting TNFR1

As it became clear that more selective targeting of the TNF system, and especially TNFR1, was required, focus shifted towards use of more precisely targeted therapies, such as monoclonal antibodies. One of the first therapies to attempt this avenue is a humanized version of a TNFR1 antibody fragment, converted into a full IgG1 antibody known as ATROSAB. ATROSAB has been shown to selectively inhibit the TNFR1 receptor and subsequently inhibit TNF-mediated cell death and NK-κB induced IL-6 and IL-8 release, reducing inflammatory burden *(Zettlitz et al., 2010)*.

Another promising example of such a targeted TNFR1 therapy is Xpro1595, a dominant-negative TNF variant that inactivates native solTNF homotrimers by inducing sequestration *(Steed et al., 2003)*. Though it needs to be present in excess of the normal amount of TNF, it was shown to significantly attenuate TNF-induced caspase activity, and again reduced TNF-mediated inflammation in murine models.

Targeting TNFR2
Ameliorating the negative effects of TNFR1 is only one approach to a complex system. With TNFR2's proven protective and even essential function in a healthy brain, there is a clear role for promoting TNFR2 activity over TNFR1.

Research with a constructed TNFR2 selective agonist has shown to provide tmTNF mimetic activity, and worked to provide protection against oxidative stress induced cell death, with the protection relying on the PI3k-PKB/Akt pathway *(Fischer et al., 2011)*. As discussed earlier, TNFR2 plays a role in tissue differentiation and regeneration as well, making it all the more suitable as a target in neurodegenerative diseases; it is however also worth remembering that TNFR2 activation can have detrimental effects as well, which an aggressive activation push might accelerate.

With that in mind, the most promising strategy is composed of simultaneous use of a TNFR1 antagonist and a TNFR2 agonist. Evidence shows that combining the administration of ATROSAB with a specific TNFR2 agonist injected into the magnocellular nucleus basalis of a murine acute neurodegeneration model showed significant protection of the brain against cell death, as well as reverting memory impairment that resulted from the neurodegeneration. The same evidence once again highlighted the importance of TNFR2 activation, as replacing the TNFR2 agonist with a TNFR2 antagonist blocked any positive effect of the treatment *(Dong et al., 2016)*.

It is worth noting that the blood-brain-barrier poses an obstacle in the administration of antibody-based TNF treatments in human patients, as under physiologic conditions they are unable to cross the blood-brain-barrier. However, there is evidence that injury to the central nervous system increases permeability, making it possible for antibodies to cross in certain pathologies *(Williams et al., 2014)*. In order to be effective outside of increased blood-brain-barrier permeability, antibodies have been engineered that are capable of being transported across the blood-brain-barrier under physiologic circumstances *(Yu et al., 2011)*. The earlier-mentioned use of TNF mimetics should also function through the blood-brain-barrier, as TNF functions as master cytokine under normal circumstances.

While it is clear that there is a role for the manipulation of TNF in pathologies that involve inflammation, there is also no doubt to the risks involved with the complexities of the TNF system and its targets. If other treatment options provide the same benefits with without risk, it stands to reason that they would be preferred over TNF-based treatments.

Other Alzheimer's disease treatments
At the time of writing, the primary treatment for AD is simply supportive care of both family and professional caretakers. Drug-wise, cholinesterase inhibitors and a glutamate antagonist are prescribed and have been shown to at least slow neurodegeneration in the first year of treatment, but a lack of treating the actual cause of neurodegeneration means that cognitive decline is inevitable *(Scheltens et al., 2021)*.

There has been an attempt to vaccinate against Aß42, which had generally positive results as far as Aß plaque clearance *(Nicoll et al., 2006)* and slowing of cognitive decline *(Hock et al., 2003)* is concerned; however, this vaccination in trials also resulted in T-lymphocyte meningoencephalitis in some patients *(Orgogozo et al., 2003)*, serving as a reminder that our knowledge is still insufficient.

While there is plenty of ongoing research into finding a cure for AD, there has been a disproportionate focus on the role Aß in AD, with a severe lack of promising results so far. With the focus shifting away from solely Aß, more and more Tau and neuroinflammation-related drug should be expected to appear in trials.

Further supporting the case for focus on the role of neuroinflammation in AD is evidence that long-term usage of nonsteroidal anti-inflammatory drugs (NSAIDs) reduces the risk and age-of-onset of AD *(in 't Veld et al., 1998)*. However, it is important to realize that formation of AD risk factors (e.g. Aß-plaques) occurs long before noticeable neurodegeneration; hence, there is a need for more robust early screening for AD.

Beside TNF, there has been recent interest in the role of triggering receptor expressed on myeloid cells-2 (TREM2), a protein that is closely associated with AD risk factor ApoE and that has been suggested to be responsible for microglia activation *(Gratuze et al., 2018)*, fitting in the same scope as TNF treatment, but with a more focused target. However, it is likely to still suffer from the same problems as development of TNF drugs, as inhibiting microglia activation increases the risk of infections, and it still requires much earlier screening against AD risk factors, though ApoE is an increasingly interesting prospect.

Overall, while a large amount of trials for AD drugs exist, the majority of them are focused on treating hallmarks that happen down the line in AD, such as Aß and Tau pathologies. The aforementioned problem of these problems happening long after initiation of AD pathology means that it is very unlikely for any of these drugs to prove to be a "magic bullet" to reduce AD disease burden.

Another problem is the fact that trials for AD drugs are still very uncommonly performed in humans. A vast majority of the research stems from murine models, often induced with certain aspects of long-term AD brain (e.g. APP-transgenic mice) which are not indicative of the complete response as it would be in humans, especially considering the gradual progression of AD.

Conclusion

Despite years of research into AD, only a fraction of potential risk factors, and thus solutions, has been investigated. While heavy focus has been put on Aß in the past, development of more advanced and convenient assays is paving the way for research into the more complex systems of neuroinflammation. The TNF pathway, as demonstrated, has a wealth of possible therapeutical targets to investigate in the fight against AD.

It seems likely that a more carefully selected target than either TNF, TNFR1 or TNFR2 will provide the best outcome, as crosstalk and interplay can lead to entirely different effects, with even the generally-protective TNFR2 being capable of inducing apoptosis under certain circumstances. Still, it is worth keeping in mind that AD is undoubtedly one of the most devastating diseases, both on a personal and a burden of disease level. Side effects such as increased infection rate, while dangerous, might still be preferable if the protection against or reversal of AD can be achieved to a significant extent.

While it is possible that no cure, that is to say a method by which neurodegeneration can be reverted, can be found, there is more than enough evidence that at least the onset and severity of AD can be ameliorated. This however relies on a robust, non-invasive detection method that is currently lacking. More research and trials with biomarkers can hopefully one day provide a robust early-detection system, though the progressive nature of the disease means that acquiring data takes times.

Despite the grim atmosphere as a result of failed trials around Aß treatment, more and more is being discovered about AD, the brain, and the many involved pathways. With the development of more modern assays and models, we can expect more patient trials as targets are discovered. Hopefully, this will ensure that in the future, AD and its immense burden on society can be eliminated.

List of abbreviations

Aß (Amyloid-ß)
AD (Alzheimer's Disease)
ApoE (Apolipoprotein E)
APP (Amyloid-ß Precursor Protein)
ASK1 (Apoptosis signal-regulating kinase 1)
BACE1 (ß-secretase 1)
DISC (Death-induced signalling complex)
FADD (Fas-associated protein with death domain)
GCK (Germinal center kinase)
Hsp90 (Heat shock protein 90)
IKK (I-κB kinase)
JNK (Jun N-terminal kinase)
MARK (Microtubule-affinity-regulating kinase)
MEKK (Mitogen-activated protein kinase kinase kinase)
MLK (Mixed lineage kinase)
MKK (Mitogen-activated protein kinase kinase)
NEMO (NF-κB Essential MOdulator)
NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B-cells)
PS1 (Presenilin 1)
PS2 (Presenilin 2)
RIP (Receptor interacting kinase)
ROS (Reactive oxygen species)
SODD (Silencer of Death Domain)
solTNF (Soluble TNF)
TACE (TNF-alpha-converting enzyme)
tmTNF (Transmembrane TNF)
TNF (Tumour Necrosis Factor)
TNFR1 (Tumour Necrosis Factor Receptor 1)
TNFR2 (Tumour Necrosis Factor Receptor 2)
TRADD (Tumour necrosis factor receptor type 1-associated death domain protein)
TRAF (TNF-receptor associated factor)
TREM2 (Triggering receptor expressed on myeloid cells-2)

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