Review Article

Therapeutic implications of how TNF links apolipoprotein E, phosphorylated tau, α-synuclein, amyloid-β and insulin resistance in neurodegenerative diseases

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While cytokines such as TNF have long been recognized as essential to normal cerebral physiology, the implications of their chronic excessive production within the brain are now also increasingly appreciated. Syndromes as diverse as malaria and lead poisoning, as well as non-infectious neurodegenerative diseases, illustrate this. These cytokines also orchestrate changes in tau, α-synuclein, amyloid-β levels and degree of insulin resistance in most neurodegenerative states. New data on the effects of salbutamol, an indirect anti-TNF agent, on α-synuclein and Parkinson’s disease, APOE4 and tau add considerably to the rationale of the anti-TNF approach to understanding, and treating, these diseases. Therapeutic advances being tested, and arguably useful for a number of the neurodegenerative diseases, include a reduction of excess cerebral TNF, whether directly, with a specific anti-TNF biological agent such as etanercept via Batson’s plexus, or indirectly via surgically implanting stem cells. Inhaled salbutamol also warrants investigating further across the neurodegenerative disease spectrum. It is now timely to integrate this range of new information across the neurodegenerative disease spectrum, rather than keep seeing it through the lens of individual disease states.

Abbreviations
AD, Alzheimer’s disease; APOE, apolipoprotein E; Aβ, amyloid-β; DAMPs, damage-associated molecular patterns; FTD, frontotemporal dementia; HMGB1, high-mobility box 1 protein; IR, insulin resistance; IRS-1, insulin receptor substrate 1; PAMPs, pathogen-associated molecular patterns; PD, Parkinson’s disease; Pin-1, peptidyl prolyl1 isomerase; PRRs, pattern recognition receptors; P-tau, phosphorylated tau; T2DM, type-2 diabetes mellitus; TBI, traumatic brain injury; TLR, toll-like receptor
Introduction

Neuroinflammation is gaining traction in explaining most neurodegenerative diseases. The proteins amyloid-β (Aβ) and tau, respectively, visible in brain sections as plaques and neurofibrillary tangles, have long been the hallmark cerebral histological findings for a diagnosis of Alzheimer’s disease (AD). In the absence of serious competitors, the amyloid theory rapidly took the lead as the most promoted actual cause of this condition, with early spectacular transgenic mouse experiments (Janus et al., 2000) leading directly to large human trials, ensuring that for many years the aim of almost all effort towards developing a treatment for AD involved Aβ removal. Despite all this expenditure, the past decades of focusing on the amyloid theory are now widely accepted to have been unrewarding. As reviewed 8 years ago (Clark et al., 2010), this theory unaccountably continued to dominate long after publication that the ability of Aβ to inhibit long-term potentiation (LTP; Wang et al., 2005; Rowan et al., 2007) in mouse hippocampal slices depends on downstream activity of TNF, a key pro-inflammatory cytokine by then well-known in the disease pathogenesis literature (Clark et al., 2004). These key observations (Wang et al., 2005; Rowan et al., 2007), as well as evidence that Aβ is an agonist of toll-like receptor 2 (TLR2) and TLR4 (Reed-Geaghan et al., 2009), were largely ignored, even though the inflammatory theory of AD had been well-aided by this time (Lee et al., 2007). More recently, 3,6'-dithiothialidomide, a new TNF-α synthesis inhibitor, was reported to attenuate the effect of i.c.v. injection of Aβ42 on hippocampal neurogenesis and memory deficits (Russo et al., 2012). In addition, microglial activation, the primary cerebral source of pro-inflammatory cytokines, has proved to coincide with neuronal loss (Wright et al., 2013), and synaptic deficits have been prevented by inhibiting TNF production (Cavanagh et al., 2016), in each case this happened before amyloidosis was evident.

Furthermore, research on the genotypic variants of the apolipoprotein E (APOE) gene (Lynch et al., 2001; Vitek et al., 2009) and on the effects of stimulating a receptor expressed on myeloid cells 2 (see references Ulland et al., 2017 and Ulrich et al., 2017 for recent reviews) has drawn attention towards the primacy of the inflammatory theory of neurodegenerative diseases. Hence, it is now seen as a research focus that promises to develop well, with practical consequences. An early report of side effects observed during the first experimental therapeutic TNF infusions in tumour patients 40 years ago, when the future of this cytokine was thought to lie in this field (Sherman et al., 1988; Spriggs et al., 1988), is worth recalling. Although these authors did not specifically study brain function, they reported unintended side effects that included lethargy, loss of recent memory and aphasia, as often seen in stroke, traumatic brain injury (TBI), Parkinson’s disease (PD) and AD, soon after they commenced treatment with TNF.

More recent milestones have been passed, with three large retrospective studies being consistent with the centrality of TNF in the development of AD and PD. In brief, the first two were a lower AD incidence in a longitudinal study of the chronic s.c. use of anti-TNF biologicals to treat rheumatoid arthritis (Chou et al., 2016), and the reduced development of PD in a population chronically treating asthma with inhaled salbutamol, its well-established indirect anti-TNF properties seemingly unappreciated by the authors (Mittal et al., 2017). More recently, systemic anti-TNF therapy of inflammatory bowel disease has also been associated with a highly significant 78% reduction in the onset of PD (Peter et al., 2018). All three of these reports are extremely significant events for researchers concerned with finding practical treatments for AD and PD, since they demonstrate, for the first time, that chronically reducing just one parameter, cerebral TNF levels, can alter the frequency of onset of these two important neurodegenerative states. Clearly, these outcomes render agents with TNF neutralizing properties, as well as the innate or conferred capacity to enter the brain, prime molecules of interest in developing therapy for these two presently intractable neurodegenerative conditions. These studies of course inevitably carry the caveat that these patients are not normal populations but already bear the burden of a chronic cytokine excess. Nevertheless, the general experience regarding any two chronic inflammatory states is that they predispose, not protect, against each other. In passing, we also note that these systemic injections tend to be assumed to act via removing systemic TNF. It is conceivable, from experience with perispheral administration, that the smaller amounts that manage to enter the CSF are more active. We feel it is now timely to integrate this new information into a review of the larger picture, rather than keep seeing it through the lens of individual neurodegenerative diseases in isolation.

For clarity, we note that the term TNF-α, still commonly seen in new literature, became an obsolete synonym for TNF some years ago. It is a relic from the short period, a decade after TNF was first described, when lymphotoxin (LT) had been renamed TNF-β. Accordingly, TNF became TNF-α. Subsequently, LT was divided into subgroups separate from TNF. Thus, the terms TNF-β and TNF-α had no further purpose and were officially discarded at an annual international TNF conference. Accordingly, the TNF field has long reverted to the original term, and we use it in this text.

Toll-like receptor dependency of chronic inflammatory diseases

The implications of the failure to help patients by removing cerebral Aβ have finally begun to drive home the message that, until the pathogenesis of AD is clearly understood, and research interest in lowering amyloid consequently declines, researchers will remain ill-equipped to advise on successfully treating this disease (Karran and De Strooper, 2016). We have recently (Clark and Vissel, 2015) reviewed the literature demonstrating that increased Aβ, soluble or not, does not cause direct damage but is merely one of the pro-inflammatory cytokine-inducing damage-associated molecular patterns (DAMPs) that are agonists of toll-like receptors (TLRs) on or in most cells, including throughout the brain. In particular, Aβ fits the pattern of being one of the secondary, or cytokine-inducible, DAMPs that induce the cytokines that induce them, thus generating increased severity as well as chronicity. Other TLRs and functionally similar pattern recognition receptors (PRRs) recognize pathogen-associated molecular patterns (PAMPs) present on the surface of, for example, the microbes now widely agreed to be sometimes associated with AD (Itzhaki et al., 2016). This is entirely
consistent with the relationship between total infectious burden and PD (Bu et al., 2015) (Figure 1).

Although excess TNF can be a prime mover in inflammatory responses, at physiological levels, this cytokine is vital to the signalling involved in normal brain function, being required for essentials such as normal transmission via modulating excitatory neurotransmission (Pickering et al., 2005), homeostatic synaptic scaling (Stellwagen and Malenka, 2006) and LTP (Cumiskey et al., 2007). Remarkably, as well as controlling pathogens via innate immunity, these cytokines, when excessively increased, also cause disease (Clark, 1987; Clark and Rockett, 1994; Clark et al., 2004). Compared to the rest of the body, the brain develops negligible tolerance to continuing production of TNF (Steinshamn and Waage, 1987; Clark and Rockett, 1994; Clark et al., 2004). Compared to the rest of the body, the brain develops negligible tolerance to continuing production of TNF (Steinshamn and Waage, 2000; Qin et al., 2007). Logically, therefore, the affected brain is particularly likely to develop chronic disease if these cytokines are generated in the brain in chronic excess in either infectious or non-infectious conditions. Such illnesses are now referred to as chronic, or non-resolving (Nathan and Ding, 2010), inflammatory diseases. Exploration of the interplay of cellular mediators, particularly cytokines allied to TNF, that binds the worlds of brain physiology, innate immunity and neurodegenerative disease into a single conceptual entity is expanding spectacularly at present (Ahmed et al., 2018; Rankin and Artis, 2018; Wendeln et al., 2018).

To paraphrase Fernandez et al. (2008) from a decade ago, what matters is not whether a particular danger signal or PRR is acting. Instead, it is whether the total sum of their activity and persistence, and thus the chronic level of pro-inflammatory cytokines, including the IL-1β and TNF they induce, are sufficient and chronic enough for homeostasis to be lost, at which point they initiate and drive neurodegenerative disease within neural circuits. The literature on IL-1β in neurodegenerative disease is much less developed than that of TNF, but the advent of the first specific anti-human IL-1β biological, canakinumab (Rondeau et al., 2015), may well change this. As in a recent example (Calderon-Garciduenas and de la Monte, 2017) that discusses a mix that includes inflammation, obesity and air pollution, the likelihood of AD onset depends on the critical mass of relevant signalling inputs being present. Importantly, these same PAMP and DAMP-induced cytokines are required for many normal physiological functions that fail because homeostasis is lost (Figure 1). This is in part why removing soluble Aβ or its plaque, until recently the goal of many large clinical trials (Salloway et al., 2014), cannot, of itself, be expected to retard sporadic human AD disease progression. As we have summarized (Clark and Vissel, 2015), cytokines generated by other secondary DAMPs, S100 proteins (Foell et al., 2007) and high-mobility group box 1 protein (HMGB1) (van Zoelen et al., 2009), are still present to continue to induce cytokines such as TNF. Not unexpectedly, removing Aβ was successful in mouse transgenic models designed to generate artificially high levels of Aβ (Janus et al., 2000). Since these mice can be expected to have merely physiological levels of these other secondary DAMPs known to be increased in human AD, the artificially induced Aβ is what creates the critical mass in these animals.

**Therapeutic ambition is best focused on very early indicators of disease**

Clearly, any indicator of neurodegenerative disease likely to be a successful therapeutic target will be among those reliably present preclinically, so the condition can be nipped in the bud. Here, we address the interactions of four such indicators: pro-inflammatory cytokines, alterations within insulin receptor (InsR) components, insulin resistance (IR) itself and the cis isomer of phosphorylated tau (P-tau). All appear before frank illness and are, therefore, much more likely to

**Figure 1**

An illustration of how a range of chronic external stimuli that present DAMPs or PAMPS to various TLRs on different cerebral cellular components and thus induce TNF and similar cytokines. These in turn generate P-tau, α-synuclein (α-Syn) and Aβ, proteins known to have the capacity to be secondary DAMPs (i.e. induced by TNF, and also act as a TLR agonist, thereby inducing more TNF). Clinical manifestations and therefore diagnoses vary, but the broad edifice, we argue, rests on a foundation of chronic pro-inflammatory cytokines generated in this manner.
be underlying pathogenic mechanisms than subsequent symptoms or signs. Regarding TNF and IL-1β, plasma levels of clusterin (apolipoprotein J), are intimately associated with the onset, progression and severity of AD (Thambisetty et al., 2010). These authors employed a novel and impressive proteomic neuroimaging paradigm that allowed them to show that clusterin increases 10 years earlier than fibrillar Aβ deposits occur. Unfortunately, the authors refer only to the amyloid chaperone function of clusterin and seem to have been unaware of its role as an acute phase protein (Hardardottir et al., 1994) and, therefore, a marker of inflammation. A subsequent meta-study reports that CLU, the clusterin gene, is the second highest of a list of the 15 top-rated genes linked to AD on the Alzgene web-based collection (Ogliati et al., 2011). This forms an impressive link between inflammatory cytokines and the primary instigation of AD. Likewise, a dysfunctional change in insulin receptor substrate 1 (IRS-1) that leads to insulin resistance, and therefore glucose hypometabolism, has been shown to be present for up to 10 years before AD onset (Kapogiannis et al., 2017).

**Insulin resistance**

**Insulin resistance in systemic and neurodegenerative diseases**

Long-known as an important regulator of blood glucose, insulin is also, on much evidence, a signalling molecule crucial for normal brain function. Malfunction of this aspect of brain physiology in neurodegenerative diseases, typically arising through cerebral IR caused by insulin receptor dysregulation, has been widely researched and reviewed (de la Monte and Wands, 2008; Talbot and Wang, 2014). As reviewed previously (Clark et al., 2012), excess levels of TNF mediate the development of cerebral IR and consequent glucose hypometabolism, overactive GSK-3 and tau hyperphosphorylation. In essence, this constellation of changes comprises the main components of the inflammatory theory of neurodegenerative disease. For example, a downward spiral of degeneration, including acquired epilepsy (Samokhina et al., 2017), is regarded as being strongly contributed to by this glucose hypometabolism (Zilberter and Zilberter, 2017). In addition, and as we discuss below, much recent knowledge of tau biology allows this protein, as is Aβ, to be appreciated as part of the inflammatory theory of this disease.

**Increased TNF causes insulin resistance**

The basic science spanning immunity and metabolism largely accepts that chronic pro-inflammatory cytokines cause the cerebral IR that is instrumental to co-existing cognitive and metabolic impairments in various diseases (see Chawla et al., 2011 for an extensive review). This consensus includes a chronic excess of anti-inflammatory cytokines promoting insulin sensitivity. Indeed, the prototype TNF inducer, bacterial wall LPS, reproduces the IR seen in human sepsis within 7 h of its administration (Carlson, 2004). Feinstein et al. (1993) appear to have been the first to argue that TNF exerts a major part of its anti-insulin effect by interrupting insulin-stimulated tyrosine phosphorylation. This concept has been repeatedly investigated, initially in adipocytes, with TNF strongly inhibiting insulin-stimulated glucose uptake (Hotamisligil et al., 1994). Soon afterwards, now over 20 years ago, this cytokine proved to cause IR through inhibiting signalling by IRS-1 (Hotamisligil et al., 1996). In addition, infliximab, the first commercial, specific anti-TNF biological agent, was shown to improve insulin signal transduction in muscle, liver and hypothalamus in obese diabetic mice. In doing so, it restored the activity of insulin-induced insulin receptor IRS1, receptor substrate-2 tyrosine phosphorylation and Akt and forkhead box protein O1 (FOXO1) serine phosphorylation (Araujo et al., 2007). Intracerebral infliximab has also been reported to improved insulin signal transduction through IRS-1 (Arruda et al., 2011). IRS-1 has since been shown to be abnormally phosphorylated, accounting for IR, in post-mortem brains from patients with tauopathies, including AD (Yarchoan et al., 2014).

A landmark 2011 study compared frontal cortex activity of the insulin–P13K–Akt signalling pathway in type 2 diabetes mellitus (T2DM) and AD in brains during autopsy (Liu et al., 2011). Not only were the same in-principle changes found in T2DM and AD brains but insulin signalling apparently contributed to the observed hyperphosphorylation of tau. This approach to understanding IR in neurodegenerative diseases has been continued and refined, particularly in the hands of Bomfim et al. (2012), Talbot et al. (2012) and Talbot and Wang (2014). Similar recent studies into the cognitive impairment in a post-sepsis mouse model (Neves et al., 2018) showed the same detailed IR pathophysiology, including changes surrounding IRS-1 and Akt, as well as a positive response to a glucagon-like protein-1 mimetic that reverses IR, as reported in AD in this study. In particular, infliximab completely blocks the Aβ-induced inhibition of IRS-1, the insulin receptor component discussed below in a tau context (Bomfim et al., 2012). As noted earlier, it is now undisputed that TNF is an essential step in this brain pathophysiology, setting the scene for a series of novel observations in tau biology, as described below. Sometimes, this is couched in terms of Aβ directly provoking increased tau pathology (Karran and De Strooper, 2016), which unfortunately obscures the essential intermediary roles of TNF and IR.

**Reduced neurogenesis, via insulin resistance, in neurodegenerative diseases**

It has been clear, since a seminal publication in 2003 (Ekdahl et al., 2003), that inflammation is detrimental to neurogenesis in the adult human brain. As we have reviewed previously (Clark et al., 2012), the clock genes that set cells’ rates of division are inhibited by increased levels of TNF or IL-1β (Cavadini et al., 2007). Among these are the period genes, Per1, Per2 and Per3 and the central, interconnecting, response element clock gene, rev-erba. Many such genes have been demonstrated to be regulated by insulin (Tahara et al., 2011), including in the progenitors of adult neurogenesis in the hippocampus (Moriya et al., 2007; Borgs et al., 2009; Kimiwada et al., 2009). Therefore, the reduced neurogenesis seen in the subventricular zone is plausibly caused by IR in T2DM (Bachor et al., 2017), PD and AD, which share cerebral IR (Talbot et al., 2012; Aviles-Olmos et al., 2013), and thus its...
consequences, one of which is inhibited neurogenesis (Haughey et al., 2002; Marxreiter et al., 2013).

**TNF causing tau phosphorylation by initially inducing insulin resistance**

A logical corollary of the above is that induction of IR by TNF rationalizes the link between this cytokine and tau phosphorylation, with IR as an intermediate step. *In vitro* generation or addition of TNF has been reported to promote tau phosphorylation, and TNF neutralization to reduce it (Gorlovoy et al., 2009). Likewise, i.c.v. administration for 3 days of infliximab to APP/PS1 transgenic mice reduced tau phosphorylation (Shi et al., 2011). It also reduced amyloid plaque, presumably because of the capacity of excess TNF to enhance promoter activity of the Aβ (APP) gene (Ge and Lahiri, 2002). The intermediary role of GSK-3 in these steps is discussed in our 2012 review (Clark et al., 2012).

**APOE**

**Effects of APOE genotype on peripheral compared to cerebral inflammation**

While discussing hyperphosphorylated tau (or P-tau, often written simply as tau when the context is clear), it is appropriate to introduce the influence of APOE proteins on our understanding of neurodegenerative diseases. Briefly, the relevant APOE gene is polymorphic, with three major alleles, APOE-e2, APOE-e3 and APOE-e4, carriers of the latter possessing the best-known genetic susceptibility to many neurodegenerative diseases (Strittmatter et al., 1993). As reviewed previously (Tai et al., 2015), APOE4 is the greatest genetic risk factor for AD, increasing the risk by up to 12-fold compared to APOE3, with APOE4-specific neuroinflammation being an important component of this risk. Reports on the influence of APOE genotypes in neuroinflammation are more fragmentary, since *in vivo* models are a challenge. In brief, LPS induced pro-inflammatory cytokines from microglia *in vitro* in a APOE4 > APOE3 > APOE2 pattern (Maezawa et al., 2006b), whereas the APOE order was reversed to APOE2 > APOE3 > APOE4 when astrocytes were examined (Maezawa et al., 2006a). Adding to the complexity one might encounter in a functioning brain, these authors also found that dendrites of hippocampal neurons damaged by i.c.v. LPS regenerated successfully in an APOE2, but not in an APOE4, environment. Tai et al. (2015) have systematically summarized the field, including their recent studies in which they discuss a more complex set of interactions than previously described in this setting. This involved amplification of detrimental TLR receptor pathways, suppression of the beneficial anti-inflammatory cytokine IL-4 and loss of positive functions of APOE2 protein when APOE4 is generated instead. They propose that these studies point towards an *in vivo* pro-inflammatory effect of APOE4 in the neurodegenerative diseases, chiefly by influencing receptor signalling pathways.

**Pro-inflammatory interaction between APOE4 and tau**

Interest in the interactions between APOE and tau has a long history (Strittmatter et al., 1994). Recent impressive data on this topic in a brain injury context (Cao et al., 2017) are entirely compatible with the reasoning in the above paragraphs. So too is research into a mouse tauopathy model, derived from transgenic mice overexpressing the frontotemporal dementia (FTD) tau mutation P301S tau on a background of the various APOE genotypes (Shi et al., 2017). These authors reported that co-culturing P301S tau-expressing neurons with APOE4-expressing mixed glial cells resulted in a significantly higher level of TNF secretion and markedly reduced neuronal viability compared with these same neurons co-cultured with APOE2 or APOE3 glial cells. Moreover, mice generating APOE4 protein exhibited greatly enhanced brain atrophy and neurodegenerative change. This effect was independent of Aβ, a link previously championed for many years. Thus, APOE4, in all likelihood, has a strong pro-inflammatory effect in the brain as well as peripherally.

**New insights in tau biology – cis/trans isomerism, DAMP activity and insulin resistance control**

Discussion of the *cis/trans* forms of tau requires a synoptic preamble about Pin-1, a peptidyl-prolyl *cis/trans* isomerase. As reviewed previously (Lim and Lu, 2005), Pin-1 binds to and isomerizes specific pSer/Thr-Pro motifs and, in a novel regulatory mechanism, catalytically induces conformational changes following phosphorylation. Pin-1 is reported to minimize the accumulation of the pathogenic *cis* pT231-tau conformation by converting it to the non-pathogenic *trans* form (Nakamura et al., 2012). Through hippocampal Pin-1 being oxidized and largely inactivated in the AD brain (Sultana et al., 2006), the pathogenic (see next paragraph) *cis* P-tau form increases. In a similar vein, two single nucleotide polymorphisms of Pin-1, which were in linkage disequilibrium and combined to form haplotypes, increased the risk of developing AD (Segat et al., 2007). For these reasons, impaired Pin-1 has been argued to be one of the driving forces for the initiation and progression of AD.

This development in tau biology explains much and has now given tau a considerably firmer foothold within the literature on neurodegenerative disease pathogenesis. Two additional advances have further strengthened the case for its relevance. First, it is now evident that the harmfulness of P-tau resides in the *cis*, as distinct from the *trans*, conformation of the molecule (Nakamura et al., 2013b). The anti-*cis* form antibody that this group developed has been used to argue the case for this P-tau variant being an early driver of neurodegeneration in human AD (Nakamura et al., 2013a) and in human TBI as well as in a mouse model of TBI (Kondo et al., 2015). Additionally, this antibody has proved to be therapeutically useful in this TBI model (Albayrak et al., 2016). Second, an unrelated set of recent observations leads to the conclusion that at least one form of P-tau, seen in FTD patients, P301L, can act as a DAMP in a mouse tauopathy model, enhancing the signalling message for the production of TNF and IL-1β (Cook et al., 2015). Similarly, while investigating the hippocampal infiltration of CD38 T cells – also seen in FTD – in another tauopathy model, at the part of the mouse lifespan when deficits and tau pathology are maximal,
others (Laurent et al., 2017) reported an up-regulation of TLR2, CD68 and TNF, all of which are associated with activation of innate immunity, in the hippocampus.

New TNF-based insights

Insights from the recognition of the A1 astrocyte subset

Microglia and astrocytes both become reactive during neuroinflammation, and knowledge about the interactions of these cells, as well as the cytokines and other molecules they release when in this state, is still limited. Five years ago, a novel line of reasoning in astrocyte biology began with the discovery that LPS, as distinct from ischaemia, induces an increase in the astrocyte subtype, later termed A1. These cells, in which some 50% of gene expression is different from in the A2 subtype, have been demonstrated to be detrimental, rather than protective, in the mouse brain (Zamanian et al., 2012). Arguably, they are part of a spectrum of astrocyte subtypes (Liddelow and Barres, 2017). Generation of these detrimental A1 astrocytes (Liddelow et al., 2017; Liddelow and Barres, 2017) requires the joint action of TNF, IL-1α and complement component 1q, and they release an as yet unidentified toxin(s) that causes in vitro apoptosis of neurons and oligodendrocytes, as well as of axotomized neurons in vivo.

Hence, introducing an anti-TNF specific biological into the brain that is generating many of these noxious astrocytes would be a constructive start in reducing the formation of this harmful subtype. Ideally, it could even be administered in conjunction with a neutralizer of the as yet unidentified toxin released by A1 astrocytes, which are present in damaged regions in AD, PD, amyotrophic lateral sclerosis and multiple sclerosis brains (Liddelow et al., 2017). Indeed, these authors have drawn from these lines of evidence to propose that any treatment that would prevent the formation of A1 astrocytes or reduce their effects can reasonably be predicted to increase new synapse formation (through reducing the release of harmful complement components), reduce neurodegeneration and stimulate spontaneous remyelination. Thus, from this initial post-LPS observation (Zamanian et al., 2012), a narrative is beginning to emerge that provides an additional rationale for reducing the excess cerebral TNF present in neurodegenerative diseases. It is yet to be determined whether this novel astrocyte subtype operates in parallel with the apparent capacity of TNF of microglial origin to cause apoptosis of neurons directly (Burguillos et al., 2011; Kaur et al., 2014) or is an essential downstream component for this process.

Insights from infectious disease

Clearly, discovering causes of disease is retarded by artificial barriers within medical research. Clinical versus non-clinical, systemic versus cerebral and non-infectious versus infectious are examples. When clinical features and markers overlap, ignoring these barriers is surely the only way to stand far enough away from the minutiae to see a big enough picture to gain a therapeutically useful perspective. Fortunately, our initial collaboration, while working on haemoprotozoa, with the group who first identified TNF in their tumour research (Carswell et al., 1975) gave us a bigger picture from the start. As reviewed previously (Clark, 2007a; Clark, 2007b), they helped us to pioneer expanding TNF towards the pathogenesis of malaria and sepsis disease (Clark, 1978; Clark et al., 1981). In this earlier work, we also assayed for, and theorized about, what came to be called IL-1β. As the concept of proinflammatory and anti-inflammatory cytokines evolved, TNF proved to be near the top of a cascade of the former, with anti-TNF, in the hands of arthritis researchers, inhibiting IL-1 production as well as neutralizing TNF (Brennan et al., 1989).

In addition, recombinant TNF, but not IL-1β, became readily available as a research tool. We focused on TNF thenceforth, although for many years, only in a cerebral context when a systemic infectious disease influenced brain function, as in malaria (Clark et al., 1989). We were quite oblivious to the work of others who were, at this time, far-sightedly arguing the case that IL-1 was responsible for the astrogliosis central to AD and Down syndrome (Griffin et al., 1989). Since TNF is extremely pleiotropic, it has proven to be a very useful avenue to understanding physiology and the pathophysiology of disease. For example, research into the roles of this cytokine has allowed us to understand why systemic infectious diseases caused by protozoa, bacteria and viruses can include strong CNS components. In tropical Africa, falciparum malaria provides an excellent example of a systemic sepsis-like inflammatory disease that may include an acute encephalopathy, in this case termed cerebral malaria. Once this acute disease has subsided and the pathogen cleared, a chronic state termed the post-cerebral malaria syndrome may develop (Idro et al., 2005). This condition can exhibit long-term cognitive impairments, including deficits in memory, attention, visuospatial skills, language and executive function (Carter et al., 2005; Boivin et al., 2007; John et al., 2008a; Kihara et al., 2009) and aggressive behaviour (Idro et al., 2010). As we have reviewed previously (Clark et al., 2010), the literature links TNF with aggression. Similar cerebral consequences, not yet as closely studied as the above, can follow severe sepsis (Iwashyna et al., 2010; Lazosky et al., 2010; Jacob et al., 2011). The pathogenesis of the post-cerebral malaria syndrome is considered to be consistent with the work of D’Mello et al. (2009), who demonstrated that peripheral TNF can pass through the blood–brain barrier and stimulate microglia to proliferate by generating chemokines that mediate the recruitment of TNF-generating monocytes into the brain.

Post-cerebral malaria syndrome correlates with CSF levels of TNF (John et al., 2008b) and has been likened to acquired cerebral palsy (Holding and Snow, 2001; Carter et al., 2005; Idro et al., 2010). Notably, through its neutralization with etanercept, TNF has been incriminated in a rat model of cerebral palsy (Aden et al., 2010). Moreover, glutamate excitotoxicity, a TNF-induced phenomenon we have explained (Clark and Vissel, 2016) through the combined effects of this cytokine enhancing glutaminase (Takeuchi et al., 1993) and inhibiting glutamate re-uptake proteins (Fine et al., 1994; Carmen et al., 2009), has been documented in a mouse model of cerebral malaria (Miranda et al., 2010). This model has recently been reported to be highly sensitive to treatment with the glutamine analogue 6-diazo-5-oxo-L-norleucine, a glutaminase inhibitor (Gordon et al., 2015). This agent is, therefore, plausibly applicable to non-

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infectious neurodegenerative states in which cerebral TNF levels are raised. Likewise, cerebral orexin depletion induced by excessive cerebral TNF in malaria is proposed to cause the coma in cerebral malaria and may be implicated in the poor sleep patterns, cognition and motor control in certain neurodegenerative states (Clark and Vissel, 2014). It has recently been demonstrated that intranasal orexin reverses both the coma of experimental post-cardiac arrest and the cardiac arrest-induced increases in mRNA for inflammatory cytokines (Modi et al., 2017).

Insights from lead toxicity

The harmful public health implications of lead (Pb²⁺) exposure are well recognized and, as recently discussed (Taylor et al., 2011), have been campaigned against, with incomplete success, for over a century (Turner, 1909). From the beginning, this knowledge included an awareness of an associated encephalopathy, and parallels with AD started to be published over 40 years ago (Niklowitz and Mandybur, 1975). More contemporary reviews describe these manifestations in some detail, including negative effects of Pb²⁺ on intelligence, learning, memory, executive function, processing speed, language, visuospatial skills and affect (Mason et al., 2016), glutamate release, LTP and synaptic plasticity, increased amyloid precursor protein and increased Aβ production, initially using peripheral cells (Guo et al., 2011). Hypomethylated DNA, whether in lead-poisoned literature. As we have previously summarized (Clark and Vissel, 2013), the background for this unanticipated change to proceed along the same kinase pathway when either HMGB1 and Aβ are increased, as has been reported (Cheng et al., 2004), signalling for cerebral TNF regulation to proceed along the same kinase pathway when either LPS or Pb²⁺ is the initiator.

Insights from recent α-synuclein literature

α-Synuclein, a product of one of the three known snc genes, is widely known in basic biology. It was first identified in the torpedo fish (Maroteaux et al., 1988) and has more recently studied roles in frog embryology (Wang et al., 2011). α-Synuclein is also present in its soluble form in normal human macrophages, T cells, beta cells, NK cells and monocytes (Shin et al., 2000), and has a significant role in innate immunity (Beatman et al., 2015; Stolzenberg et al., 2017). Historically, neurodegenerative diseases have been categorized by which of several proteins are produced in unusually high amounts, those relevant to this section of this text being termed the synucleopathies. While the archetypal example is PD, this protein has been correlated closely with AD outcomes (Larson et al., 2012; Korff et al., 2013) and has been described in both TBI (Mondello et al., 2013; Acosta et al., 2015) and Pb²⁺ toxicity (Zhang et al., 2012). As well as in the brain, α-synuclein also has a predilection for forming in the gut wall (Natale et al., 2011; Cersosimo et al., 2013). Additionally, it is strongly induced by H5N1 influenza virus (Jang et al., 2009), which is a strong PAMP (Geeraedts et al., 2008), and therefore TNF generator.

Several strands of research have begun to develop in the relationship between α-synuclein and TNF over the last 5 to 10 years. They co-exist with a general increased interest in inflammation within the PD research world (Ferger et al., 2004; Bartels and Leenders, 2007; Cebrian et al., 2014). First, for motives unassociated with TNF, the β₂-adrenoceptor agonist, albutamol (a synonym for salbutamol) was studied in two small open trials in PD patients, some years apart (Alexander et al., 1994; Uc et al., 2003). Next, with dependence on original concepts from 1995 (Ignatowski and Spengler, 1995), salmeterol, another β₂-adrenoceptor agonist, was reported to reduce levels of cytokines such as TNF and also to reduce dopaminergic neurotoxicity in vitro and in vivo (Qian et al., 2011). A short-acting equivalent, salbutamol, was subsequently shown to share this anti-TNF activity (Romberger et al., 2016; Keranen et al., 2017). This agent, brain-penetrant when inhaled, is a widely used asthma medication. Importantly, in a recent 11-year study in over 4 million Norwegians, it was associated with significantly reduced α-synuclein levels and associated risk of developing PD (Mittal et al., 2017). As a control, the use of the β₂-adrenoceptor antagonist, propranolol, was monitored in this population for some years, as well as used in vivo and in vitro experiments, and was found to have the opposite effect on PD incidence. Although not mentioned by these authors, this outcome is entirely consistent with the capacity of salbutamol to reduce TNF, as noted above. This provides evidence for chronically enhanced levels of this cytokine, conceivably aided by the cascade of chemokines and cytokines it induces, to increase α-synuclein levels. This outcome also sits strikingly alongside α-synuclein possessing agonist activity for TLR2 (Kim et al., 2013), that is, being a TNF-inducing DAMP. Accordingly, a considerable literature shows that this protein, particularly in its aggregated state, induces TNF (Alvarez-Erviti et al., 2011; Beraud et al., 2013; Hoffmann et al., 2016). Thus, as for S100 proteins, HMGB1 and Aβ in an AD context (Clark and Vissel, 2015), it seems clear that α-synuclein can function as a secondary, or positive feedback DAMP (de Haan et al., 2013) (Figure 1). As such, it further enhances levels of the cytokines that induced it in the first place, thus increasing its presence, as well the concentration of these harmful cytokines. Among other consequences, excitotoxicity, acknowledged to be present in PD

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(Ambrosi et al., 2014), can ensue (Clark and Vissel, 2016). Equally importantly, these developments will open minds to the likelihood of salbutamol, given its anti-TNF properties, plus the increasing awareness of excess TNF in the pathogenesis of such conditions as post-stroke syndromes, TBI and AD, as being a plausible treatment for these other clinical variants within the neurodegenerative disease stable.

**Insights from the basic similarities of certain neurodegenerative states**

Superficially, post-stroke syndromes and TBI develop very differently than do PD and AD. Clinically, their origins seem a world apart: not a gradual onset over years, as with AD or PD, but typically absent one day and dramatically present the next. But this does not necessarily mean a fundamentally different mechanism is operating. Abruptness in onset is what one would expect from an ischaemic event(s) in a highly oxygen-dependent site, or from instantaneous external trauma. Also, while AD and PD continue to worsen as the months pass, post-stroke syndromes and TBI generally do not. Yet histology and laboratory assays identify all these conditions as a close-knit group. Like PD and AD, post-stroke syndromes and TBI both exhibit enhanced TNF production (Taupin et al., 1993; Cui et al., 2012), increases in tau (Ilhle-Hansen et al., 2017; Kulbe and Hall, 2017), IR (Brooks et al., 1984; Mowery et al., 2009), α-synuclein (Impellizzeri et al., 2016; Kim et al., 2016) and Aβ (Lee et al., 2005; Acosta et al., 2017). One study (Simpkins et al., 2009) collected much relevant data, reporting, for example, that some 70% of brains of 55 patients who died within 24 h of head injury had Aβ precursor protein accumulations, with the earliest detectable at 2 h of survival (McKenzie et al., 1996).

Also, these conditions predispose to one another, for example, stroke to AD (Henon et al., 2001) and TBI to PD in older individuals (Gardner et al., 2015), with a more recent study (Camacho-Soto et al., 2017) finding the link to be stronger during the prodromal period. Similarly, TBI predisposes to AD (Fleminger et al., 2003). As with AD and PD, post-stroke syndromes and TBI also manifest a predisposition to be more severe in APOE4 individuals (Eramudugolla et al., 2014; Das et al., 2016). Another set of observations transgressing these traditional clinical divisions concerns the ability of SB623 stem cells, which manifest an anti-TNF activity (see below) being efficacious for the PD model generated by injecting methylphenyltetrahydropyridine (MPTP) (Tate et al., 2017) and in post-stroke patients (Steinberg et al., 2016b).

It is also illuminating to recall here, as we have discussed earlier in this text, that AD (Chou et al., 2016) and PD (Mittal et al., 2017; Peter et al., 2018) have been inadvertently reduced in incidence when patients were treated with anti-TNF agents, on a grand scale, for another purpose. It therefore seems most plausible that post-stroke syndromes and TBI, AD and PD eventually result in similar clinical outcomes through the effects of increased levels of TLR agonists, chronically excessive TNF generation, and thus cellular and cytokine activity that is clinically recognized as post-TNF P-tau, IR, α-synuclein and Aβ activity. Logically, therefore, what sets post-stroke syndromes and TBI apart, in a pathophysiological sense, from AD and PD is simply where, and at what rate, this excess TNF is initially produced.

**Therapeutic implications of these insights**

The financial interest of the pharmaceutical industry in anti-TNF biologicals is enormous. The gross income from Humira (adalimumab), Enbrel (etanercept) and Remicade (infliximab) seen on the graph at https://www.forbes.com/sites/matthewherper/2015/07/29/the-top-drug-launches-of-all-time/#46db4cd6f512 succinctly demonstrates that this class of agents is the most commercially successful therapeutic agents of recent decades. It is difficult to doubt, from this observation as well as the number of biosimilars becoming available, that they can be remarkably efficacious. For two decades, this class of drug has been approved, and commonly used, to treat a number of non-cerebral disease states, which is what this graph depicts. Considering the number of people afflicted with neurodegenerative diseases, these totals have the potential to much more than double.

Evidence of the usefulness of infliximab in a small open trial on rheumatoid arthritis (Elliott et al., 1993) was successfully expanded to formal, identical protocol testing within a year (Elliott et al., 1994). Testing and adoption across clinical specialty boundaries followed in due course, fairly soon encompassing psoriasis and Crohn’s disease. Once TNF also began to appear in the literature on the pathogenesis of neurodegenerative disease, it seemed perfectly reasonable, to those with a broad interest in roles of TNF in disease pathogenesis, that a similar story would soon unfold in these non-infectious chronic cerebral disease states. It was therefore scientifically unaccountable to see the use of another anti-TNF biological, etanercept, for a neurodegenerative disease, AD, attracting negligible neutral or positive comment, but much strong scepticism, on Alzforum, and unprecedented industrial-scale criticism on the web. Remarkably, this negativity persisted throughout a 2006 AD pilot study (Tobinick et al., 2006), 2008 case reports (Tobinick and Gross, 2008) and subsequent invited reviews on its logic (Tobinick, 2009; Tobinick, 2010; Tobinick, 2018). Nowadays, however, the general perception has mellowed, the UK Alzheimer’s Society seeing an anti-TNF approach as their main research interest (https://www.alzheimers.org.uk/research/our-research/research-projects/understanding-whether-drugs-rheumatoid-arthritis-can-reduce-risk-alzheimers-disease).

In these earlier studies, initially in AD but subsequently mainly in post-stroke syndromes, etanercept was administered by a novel route (Tobinick and Vega, 2006; Tobinick, 2016) into Batson’s plexus (the cerebrospinal venous system) plus a short period head-down tilt (Trendelenburg position) to overcome its large molecular size and take advantage of the valveless nature of this vascular system (the perispinal route). A proposal was made from Southampton to replicate this perispinal approach in a formal trial, but in the event, both etanercept and placebo were administered s.c. (Butchart et al., 2015). From the limited information available in this text, published in a journal owned by the American Academy of Neurology (AAN), this Southampton trial can appear to have had a completely negative outcome. Unfortunately, this is often misleadingly quoted as though it had replicated, and negated, the original technique of 9 years earlier (Tobinick et al., 2006; Tobinick and Vega, 2006), in which treatments were administered via Batson’s plexus. However, other positive and significant outcomes of the Southampton trial are presented and discussed in the first author’s PhD thesis (Butchart, 2017), which covers outcomes of this trial more
extensively, is consistent with enough s.c. administered etanercept having entered the brain to have had some significant clinical effects. These extended data are consistent with a report, drawn from a particularly large database over a long period, of s.c. chronic use of anti-TNF biologicals to treat rheumatoid arthritis significantly reducing AD incidence (Chou et al., 2016).

In the current absence of funding for a controlled replication of the use of the perispinal route, studies of treating post-stroke syndromes and TBI with etanercept administered by this route continue to appear as case reports (Tobinick, 2011; Tobinick et al., 2012; Tobinick et al., 2014), with the 2012 publication involving over 600 cases. Unaccountably, this approach, and therefore controlled trials, has been actively discouraged by the AAN through issuing a Practice Advisory notice that, unusually, attracted a rebuttal editorial (Clark, 2017). As noted, such clinical advice ultimately needs to be based on observation by AAN members, which remains absent after years of invitations. Also, this Advisory, in the face of the literature and related FDA approvals, profoundly over-states the toxicity of etanercept.

The prospect of routine perispinal anti-TNF therapy for post-stroke syndromes is greatly strengthened by another treatment, from the literature effectively anti-TNF, that has had a strikingly similar outcome to etanercept in an open trial (Steinberg et al., 2016b). The rationale for this approach began when human marrow stromal cells provided useful therapy in a rat model of stroke in 2002 (Li et al., 2002). Some years later (Liu et al., 2009), rat mesenchymal stem cells were shown, when introduced into a cerebral ventricle in a rat stroke model, to significantly improve function while enhancing production of the anti-inflammatory cytokine **IL-10** and decreasing TNF levels. These studies, and others, laid the groundwork for the above open trial, with a positive outcome, of surgically transplanting SB623 stem cells into brains of patients suffering from post-stroke syndromes (Steinberg et al., 2016b). Evidently this generates essentially the same outcome, and from the literature for the same reasons, as does perispinal etanercept (Tobinick, 2011; Tobinick et al., 2012). This is consistent with data from experimental PD, in which both SB623 cells (Tate et al., 2017) and an anti-TNF agent (Ferger et al., 2004) have attenuated the

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**Figure 2**

A visual comparison of complexity of methods designed to generate similar clinical improvements in post-stroke syndromes by reducing cerebral TNF. To date, both have been done in open trials only. Illustration adapted from ‘Head anatomy anterior lateral views’; Patrick J. Lynch; illustrator; C. Carl Jaffe; MD; cardiologist Yale University Center for Advanced Instructional Media; Creative Commons Attribution 2.5 Licence 2006.
Conclusions

In conclusion, the logic of treating neurodegenerative diseases through reducing chronically increased cerebral levels of TNF is becoming a competitive field and rapidly gaining credibility. As discussed in this text, the links between TNF and APOE4 predisposition, P-tau, a-synuclein, AjI and IR in these diseases have now generated a compelling literature on harmful sequences of events that can disappear or be reduced to the degree to which homeostasis can return once excess TNF is therapeutically removed. This degree is governed by the proportion of reversible dormancy compared to permanent damage this excess TNF has caused in that patient’s neural circuits. In effect, we have argued here that the ubiquity of excess cerebral TNF in post-stroke syndromes, TBI, PD and AD appears to have gathered all these clinical descriptors under the one pharmacological roof.

Unfortunately, treatments that pass the test of being logical, can, through poor communication delaying consensus on the details of a condition’s pathophysiology, be long-delayed. This does not need to be so: malarial researchers do not, and may never, agree on the pathogenesis of the encephalopathy termed cerebral malaria (Clark and Rockett, 1994), but this did not prevent quinine providing a reasonably successful therapy through killing the PAMP-generating parasite. Indeed, through the centuries before malaria was realized to be an infectious disease, quinine was equally successful while thought to work through reducing fever. Similarly, gaps still exist in the PD literature, such as precisely how a-synuclein aggregates, and why its capacity to harm eventually focuses on dopaminergic neurons (Mor et al., 2017).

Hence, however scientifically important it is to fully understand details of pathophysiology, these may plausibly be resolved in parallel with finding a useful treatment through applying what is already known. Most advances arise from logical small open trials on re-positioning medication, such as etanercept, that is already approved for a number of related conditions and very widely used. Indeed, this is already what is happening with etanercept, SB623 cells and salbutamol, as discussed in this review. In the same vein, much is not yet known about the detailed pathogenesis of rheumatoid arthritis, Crohn’s disease and psoriasis, yet their anti-TNF treatment is, overall, a success. This is despite these diseases being much more dissimilar clinically than post-stroke syndromes, TBI, PD and AD. What is now decades of experience in treating these three unalike peripheral diseases thus provides valuable experience for the neurodegenerative disease world. It therefore now seems valid to suggest that enough is now known about the pathophysiology of mainstream versions of these neurodegenerative conditions to foster comparisons in outcomes and costs between the virtues of treating patients by injecting specific anti-TNF biologicals perispinally (Tobinick et al., 2006; Tobinick et al., 2012), achieving the same end by injecting into the brain cells that generate FGF2 (Steinberg et al., 2016b) and administering salbutamol (Mittal et al., 2017). Variants of each condition may respond only slightly, but this is no less true of, for example, rheumatoid arthritis. As antagonists of other pro-inflammatory cytokines show more promise, they may well join the list of rational target molecules.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander et al., 2017a,b,c)

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Author contributions

I.A.C. proposed the scope of the review. Both authors were involved in planning and editing the manuscript, blending their complementary expertise. Both authors read and approved the final manuscript.
Conflict of interest

The authors declare no conflicts of interest.

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