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REVIEW

Amyloid β: one of three danger-associated molecules that are secondary inducers of the proinflammatory cytokines that mediate Alzheimer's disease

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This review concerns how the primary inflammation preceding the generation of certain key damage-associated molecular patterns (DAMPs) arises in Alzheimer's disease (AD). In doing so, it places soluble amyloid β (Aβ), a protein hitherto considered as a primary initiator of AD, in a novel perspective. We note here that increased soluble Aβ is one of the proinflammatory cytokine-induced DAMPs recognized by at least one of the toll-like receptors on and in various cell types. Moreover, Aβ is best regarded as belonging to a class of DAMPs, as do the S100 proteins and HMBG1, that further exacerbate production of these same proinflammatory cytokines, which are already enhanced, and induces them further. Moreover, variation in levels of other DAMPs of this same class in AD may explain why normal elderly patients can exhibit high Aβ plaque levels, and why removing Aβ or its plaque does not retard disease progression. It may also explain why mouse transgenic models, having been designed to generate high Aβ, can be treated successfully by this approach.

Abbreviations

AD, Alzheimer's disease; BACE1, β secretase; DAMP, damage-associated molecular pattern; EOAD, early onset human AD; HMGB1, high-mobility group box 1; LOAD, late onset human AD; PAMP, pathogen-associated molecular pattern; PD, Parkinson's disease; POCD, post-operative cognitive dysfunction; TLR, toll-like receptor

Tables of Links

TARGETS	
Catalytic receptors[a]	**Enzymes**[b]
TLR4	Dnmt1, DNA methyltransferase 1
TLR7	α secretase (ADAM10)
TLR9	BACE1, β secretase

LIGANDS	
Amyloid β	Lead
Cadmium	LPS
Exendin-4	Mercury
GLP-1, glucagon-like peptide-1	Thalidomide
IL-1	TNF

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2013/14 ([a,b]Alexander *et al.*, 2013a,b).

Introduction

Despite its dominance of the publications on the pathogenesis of Alzheimer's disease (AD), the amyloid theory is yet to provide any positive clinical outcome, and still contains uncertainties. Others (Castellani and Smith, 2011; Mullane and Williams, 2013; Castello *et al.*, 2014) have extensively summarized the amyloid theory and the difficulties it has encountered. These include the presence of abundant amyloid in sections from many cognitively normal older brains, and the failure, to date, of being able to replicate in humans, the anti-amyloid immunotherapy that performed well in mice. Recently, we (Morris *et al.*, 2014) extensively reviewed the complexities, inconsistencies and controversies that have now surrounded the amyloid theory, and discussed the bias of preclinical AD models towards the amyloid hypothesis. We also illustrated how extensive data cited in support of the amyloid hypothesis, including genetic links to disease, can be interpreted independently of a role for amyloid β (Aβ), and summarized the case for the validity of the argument for proinflammatory cytokines having a central role, and therefore being a valid pharmacological target. Here we expand this section of our recent review (Morris *et al.*, 2014) by going back to the roots of our understanding of innate immunity while still providing a role for Aβ. For this role of Aβ to become clear, we first consider the cytokine output of the innate immune system, and the pathogen-associated molecular pattern (PAMP) and damage-associated molecular pattern (DAMP) terminology that allows a workable framework for describing how this output is triggered through this primitive, but ever present, immune system recognizing its surroundings.

The immune system, for decades concerned with adaptive immunity against pathogens, is now, through innate immunity, recognized as being allied to the inflammatory response. This has brought together the basis of the pathogenesis of infectious disease, sterile inflammatory states such as AD and Parkinson's disease (PD), and also stroke and traumatic brain injury (TBI) (Arvin *et al.*, 1996; Tarkowski *et al.*, 2003; Esiri, 2007; Clark *et al.*, 2010; Eikelenboom *et al.*, 2011; Howcroft *et al.*, 2013). The general perception of inflammation as a complex interaction of cellular responses orchestrated by chemokines and cytokines rightly includes TNF and IL-1. But being termed proinflammatory cytokines often leads this closely linked pair to be regarded simply as biomarkers for the presence of inflammation, whereas their pleiotropy includes many roles in all tissues, including such diverse roles as physiological cerebral transmitters, particularly in brain homeostasis (Stellwagen and Malenka, 2006; McAfoose and Baune, 2009), which is otherwise unrelated to inflammation. As recently reviewed (Clark and Vissel, 2014), TNF and IL-1 closely mimic each other, and occur together, but for various reasons, including that anti-TNF antibody also reduces IL-1 (Brennan *et al.*, 1989), TNF dominates the literature.

The ubiquity and importance of TNF in biology, innate immunity and disease

The polypeptide TNF is arguably the centrepiece of the mammalian innate immune system. Yet it is extremely well preserved in phylogeny, huTNF recognizing and being very widely recognized, even by corals (Quistad *et al.*, 2014). The ubiquity of TNF in biology is demonstrated by the presence of many more entries in PubMed than any other proinflammatory cytokine, let alone Alzheimer's or Aβ. It is one of the pillars of normal physiology, including metabolism. The fundamental roles of lower concentrations of TNF and related cytokines in normal physiology, involving all organs but not least in the brain (Vitkovic *et al.*, 2000a,b), nowadays outnumber references to their proinflammatory and immunological roles. For instance, TNF and IL-1β are released during physiological neuronal activity and, as reviewed (Marin and Kipnis, 2013), play a crucial role in regulating the strength of normal synaptic transmission. TNF, of itself rather than through the inflammatory cascade it can trigger, is also involved in normal transmission via modulating excitatory neurotransmission (Pickering *et al.*, 2005), trafficking of AMPA receptors (Ferguson *et al.*, 2008), homeostatic synaptic scaling (Stellwagen and Malenka, 2006), long-term potentiation (Cumiskey *et al.*, 2007) and

maintaining normal background levels of neurogenesis (Bernardino *et al.*, 2008). Mitochondrial function depends on TNF (Sanchez-Alcazar *et al.*, 2000), as does regulation of the neurotransmitter, orexin (Zhan *et al.*, 2011), which, as recently reviewed in a brain disease context (Clark and Vissel, 2014), controls sleep, motor control, focused effort, appetite and water intake. TNF also regulates neuronal type 1 inositol trisphosphate receptors, which are central to neuronal Ca^{++} homeostasis, and thus the ionic signalling cascades on which normal function of these cells depends (Park *et al.*, 2008). Likewise, glycine receptors, which are structurally related to GABA receptors and have a similar inhibitory role, are influenced by proinflammatory cytokines (Chirila *et al.*, 2014). Clearly, all these functions are susceptible to TNF and/or IL-1 being outside their homeostatic range.

Yet TNF is much more than normal physiology. An awareness of TNF began with its detection in the serum of mice receiving Gram-negative bacterial endotoxin, that is, LPS, several weeks after they were infected with Bacillus Calmette–Guérin (BCG), an attenuated strain of *Mycobacterium bovis*. On transfer to mice bearing transplanted sarcomas, this novel protein caused necrosis of these tumours as effectively as did LPS, but contained no LPS (Carswell *et al.*, 1975). The argument that excessive TNF and IL-1 both controlled pathogens and generated disease was first put forward, in collaboration with Carswell, with respect to malaria (Clark *et al.*, 1981) and sepsis (Clark, 1982). Excessive production of TNF and related cytokines was soon recognized as mediating the rapid response of non-specific, or innate, immunity against malaria parasites, and subsequently many other pathogens, as well as the pathogenesis of the diseases these organisms induce (Clark *et al.*, 1981; Rook *et al.*, 1987; Clark and Cowden, 1989; Raziuddin *et al.*, 1994; Peper and Vancampen, 1995; Arsenijevic *et al.*, 1997; Bhutta *et al.*, 1997; Nakane *et al.*, 1999). TNF has also key roles in physiological functions (see later). Its control over insulin signalling, reviewed in an AD context (Talbot and Wang, 2014), will extend greatly its known influence in the brain and elsewhere, in both normal and disease states (Chiu *et al.*, 2008; Chiu and Cline, 2010).

Cloning of TNF (Aggarwal *et al.*, 1985) and LPS protection experiments based on this technology (Beutler *et al.*, 1985) produced data consistent with the above predictions. Thus, the groundwork on these cytokines mediating disease was in place before the first proposal that TNF and IL-1 were associated with inflammation (Nawroth *et al.*, 1986). Soon rTNF, when trialled against tumours in patients (Sherman *et al.*, 1988; Spriggs *et al.*, 1988), caused side effects that mimicked not only the disease seen in influenza and malaria but also the aphasia seen in stroke and AD. As we have discussed previously (Clark *et al.*, 2010), proinflammatory cytokines are enhanced very early in AD. For example, using a novel high-sensitivity proteomic neuroimaging technique, increased plasma levels of clusterin (apolipoprotein J), proved to be intimately associated with onset, progression and severity of AD (Thambisetty *et al.*, 2010). Increased clusterin follows even slightly enhanced levels of proinflammatory cytokines such as TNF and IL-1 (Hardardottir *et al.*, 1994). For all these reasons, it is essential to appreciate what generates TNF in AD. The recognized steps of TNF generation in innate immunity, and thence disease, are discussed next.

What controls the TNF response in innate immunity and disease?

The earlier observations tie together much diverse physiology and disease pathogenesis, so pose many important questions. For example, why should the same array of functionally related primitive cytokines, dominated by TNF, be generated in strikingly different circumstances? Our interest in this question arose from trying to understand spectacular protective outcomes of systemic exposure of mice to a then inexplicably wide array of agents, infectious and otherwise, weeks prior to infection with haemoprotozoan parasites (Clark *et al.*, 1976; 1977; Clark, 1979a,b). Intriguingly, such protection was functionally related to the onset of the non-specific systemic disease, akin to that seen in bacterial and viral infections, caused by these parasites (Clark *et al.*, 1981). At a major symposium in 1989, within the topic of the evolution of immune recognition, Janeway (1989) offered the argument of a primitive ability, retained in humans, of effector cells to recognize what he termed a range of 'pathogen-associated molecular patterns' on or secreted by infectious agents. The name stuck, and the now-familiar acronym PAMP, came into use. Five years later this concept was incorporated into a proposal that the immune system may have evolved to distinguish between danger and non-danger, as distinct from self and non-self (Matzinger, 1994; 2002; Gallucci and Matzinger, 2001). These authors saw PAMPs as a type of DAMP, and part of an overall damage-associated scheme (Seong and Matzinger, 2004). Hence, a disparate collection of signals triggering the same functional outcome fits within a framework that encompasses their ability to trigger the release of proinflammatory cytokines, with the capacity to kill pathogens through innate immunity, but also, in excess, to cause disease.

Thus, infectious agents provide triggers, collectively termed PAMPs, for release of TNF, and the rest of the proinflammatory cytokine cascade. Other triggers, either of host origin or exogenous, and usually termed damage-associated molecular patterns, or DAMPs, ultimately function in the same way as PAMPs. In effect, host function is inadvertently harmed in lieu of often non-existent pathogens. Others have elected, with commendable simplicity, to use the term alarmins to encompass both PAMPs and DAMPs (Oppenheim *et al.*, 2007; Chan *et al.*, 2012). Activation occurs when they are seen by the pattern recognition receptors (PRRs) (Janeway, 1989), the toll-like receptors (TLRs) (Poltorak *et al.*, 1998) being one of the best described PRRs families. Many PAMPs and DAMPs important in instigating disease onset are seen by TLR4, on the cell surface, and others, typically those arising from modified RNA and DNA, are recognized intracellularly by TLR9, on the endoplasmic reticulum. In either case the outcome is very similar from a disease pathogenesis perspective. TLRs were well summarized recently in a myocardial context (de Haan *et al.*, 2013), a text that also notes that DAMPs can be usefully divided into the constitutive and inducible, or secondary, groupings used here.

PAMPs implicated in chronic neuroinflammatory diseases

A key precursor of the present concept of PAMPs was the insight gained by early experience with the functional subtleties of BCG, which led to the original awareness that TNF exists, as outlined earlier. BCG is a pathogen, albeit attenuated, so by definition a source of PAMPs, and LPS is a PAMP derived from Gram-negative bacterial cell walls. Patients convalescing from typhoid (Neva and Morgan, 1950) and malaria (Rubenstein *et al.*, 1965) are tolerant to LPS, whereas chronic, non-resolving infections, such as caused by BCG in mice, cause a LPS-sensitive state (Suter *et al.*, 1958). A now historic set of experiments on this post-BCG LPS-sensitive state in Lloyd Old's laboratory, as recently recounted (Carswell-Richards and Williamson, 2012), led to the isolation of a peptide they termed TNF (Carswell *et al.*, 1975). This proved to be an invaluable tool in understanding details of a wide range of physiology, as well as innate immunity.

Acute severe infectious diseases, as well as sterile conditions such as stroke and TBI, can be forerunners to delirium, a transient AD-like condition associated with acute proinflammatory signals, and aptly described as the extreme end of the sickness behaviour spectrum (Cunningham and Maclullich, 2013). From an exceptionally large dataset, dementia, a related longer lasting state, proved to be more common in patients with more systemic infections, that is, exposure to PAMPs (Dunn *et al.*, 2005). Another comprehensive study found the rate of cognitive decline in AD to be higher in patients who experienced more systemic inflammatory events associated with increased serum levels of TNF (Holmes *et al.*, 2009). Likewise, others have recently compiled an intriguing overview of the influence of pathogenic microbes and the largely gut-located microbiome on the pathogenesis of AD and other chronic CNS disease (Hill *et al.*, 2014). As they note, new technologies now allow the balance between pathogens and homeostatic commensals to be monitored. The work on *Helicobacter pylori* (Alvarez-Arellano and Maldonado-Bernal, 2014), including the reported beneficial effects of its eradication on 5 year survival in AD (Kountouras *et al.*, 2010), is a specific example. Clearly, these groups' studies are readily expressed in PAMP terminology. Consistent with the accepted multifactorial origins of AD, any of these PAMPs, or the DAMPs discussed below, can also be expected to increase the rate of cognitive decline through influencing TLR-dependent production of TNF and similar CNS-active cytokines (Figure 1).

MicroRNAs (miRNA) and mitochondrial DNA (mtDNA)as DAMPs in AD

Many miRNAs, small non-coding RNAs, are increased in the CSF and plasma in AD (Lukiw, 2007; Cogswell *et al.*, 2008; Lukiw *et al.*, 2012b; Alexandrov *et al.*, 2014). This down-regulates complement factor H, a repressor of the innate immune response (Lukiw and Alexandrov, 2012a), thus enhancing this response, a key contributor to AD pathogenesis. As reviewed (Alexandrov *et al.*, 2014), miRNA146a is

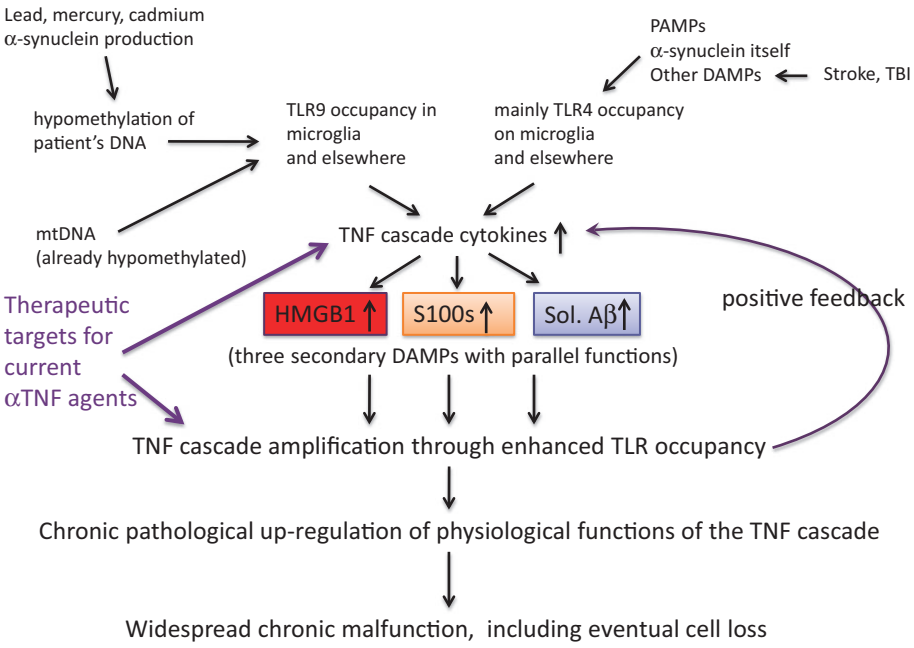

Figure 1

Late onset AD (LOAD). A representation of the array of DAMPs and PAMPs that, through triggering TLRs, can initiate release of proinflammatory cytokines. These cause changes that include enhancement of HMGB1, S100 proteins and soluble forms of Aβ in late onset AD, three secondary DAMPs that independently further enhance levels of the cytokines that induced them. Thus, chronic functional change and damage occurs within the brain.

up-regulated in the anatomical regions of the brain affected by AD, but not in the thalamus and brain stem of the same brain, and is induced by IL-1 and TNF, as well as by Aβ42 peptides, which act as DAMPs to induce TNF (Rowan *et al.*, 2007). In addition, let-7, one of the most abundant of the hundreds of the miRNAs expressed in the human brain, and increased in the CSF in AD, has been reported to act, through activating TLR7, a reliable TNF trigger (Lehmann *et al.*, 2012). These authors also observed that introducing let-7b into the CSF of mice resulted in neurodegeneration in intact, but not TLR7-deficient, mice. Intrauterine transfection with TLR7 restored activity.

Circulating mtDNA increases with age, which is associated with AD and PD, and the degree of increase is a familiar trait (Pinti *et al.*, 2014). mtRNA is increased in human plasma soon after trauma (Lam *et al.*, 2004), and has a bacterial DNA-like capacity to act as a danger signal, being similarly hypomethylated, and therefore sensed by TLR9 (Zhang *et al.*, 2009). This is in keeping with its pathogen ancestry (Margulis and Chapman, 1998; Emelyanov, 2001) identifying it as a PAMP that has evolved into a DAMP, but normally harmless provided that it remains in the mitochondrion, without access to TLR9. It is considerably more sensitive to oxidative stress than is mammalian nuclear DNA (Strand *et al.*, 2014). Oxidatively degraded mtDNA is a particularly aggressive DAMPs, proposed to participate in neurodegenerative processes (Mathew *et al.*, 2012). Others have reported that occupancy of several TLRs simultaneously enhances oxidative stress (Lavieri *et al.*, 2014), consistent with this increased DAMP potency of mtDNA.

Increased CSF levels of mtDNA have recently been correlated with severity in paediatric TBI cases (Walko *et al.*, 2014). It is yet to be investigated whether mtDNA variants associated with AD and PD (Coskun *et al.*, 2012) differ in their degradation rates. Likewise, uncertainty still surrounds CSF levels of mtRNA in AD. They have been argued to be reduced (Podlesniy *et al.*, 2013), but other have proposed that technical error has left the question unresolved (Sondheimer *et al.*, 2014).

Toxic metals and excess α-synuclein production generating DAMPs in AD

In brief, the evidence is consistent with lead (Pb) turning mammalian nuclear DNA into a DAMP. As discussed elsewhere (Clark and Vissel, 2013), Pb hypomethylates DNA that then recognizes TLR9, and generates TNF (Guo *et al.*, 1996; Cheng *et al.*, 2006). Fetal exposure to Pb also leads, via chronic TNF generation, to amyloid deposition later in life (Basha *et al.*, 2005; Bihaqi *et al.*, 2011). As reviewed (Wang *et al.*, 2008), the case for epigenetic involvement in the pathogenesis of AD is well known: any discernible inheritance of late onset AD is non-Mendelian, concordance rates in monozygotic twins are low and levels of folate and homocysteine in the AD brain fit abnormal methylation homeostasis. Others have independently expanded these concepts in AD (Mastroeni *et al.*, 2010; 2011; Bakulski *et al.*, 2012; Bihaqi *et al.*, 2012) and PD (Iraola-Guzman *et al.*, 2011; Kaut *et al.*, 2012).

We (Clark and Vissel, 2013) have also discussed the publications on mercury and cadmium which show that lead is not the only contaminant metal associated with DNA hypomethylation (Hanna *et al.*, 2012; Goodrich *et al.*, 2013), an inflammatory response (Gardner *et al.*, 2009; Olszowski *et al.*, 2012), and Aβ accumulation (Song and Choi, 2013; Notarachille *et al.*, 2014). We also summarized the implications of increased intraneural levels of soluble α-synuclein in human AD brains being a much better correlate with cognitive impairment than are levsl of the soluble forms of Aβ or phosphorylated tau (Larson *et al.*, 2012). The actual process of generating excessive α-synuclein hypomethylates the DNA of the cell producing it (Desplats *et al.*, 2011). These authors examined the intracellular location of α-synuclein as well as of Dnmt1, the major DNA methylation enzyme, in neurons from PD and dementia with Lewy bodies brains, and reported a cytoplasmic, rather than nuclear, location of this protein in neurons that overexpress it. Crucially, this cytoplasmic α-synuclein sequestered Dnmt1, reducing its levels by almost 50% in the nucleus, where it normally keeps DNA highly methylated. Consequently, a 30% decrease in local global DNA methylation occurred. Hence, the events leading up to increased soluble α-synuclein (Larson *et al.*, 2012) give DAMP activity to this DNA, leading to up-regulation of proinflammatory cytokines when sensed by TLR9.

High-mobility group box 1 (HMGB1), S100 proteins and Aβ: three potent secondary DAMPs

Certain DAMPs incriminated in generating neuroinflammatory disease can themselves be induced by proinflammatory cytokines of infectious or sterile origin. They may therefore be termed secondary DAMPs (de Haan *et al.*, 2013), and can also be regarded as positive feedback DAMPs, being further generated by the proinflammatory cytokines they themselves induce. This would thereby perpetuate and worsen disease, as happens in AD. Some mediators such as HMGB1 are constitutive in cells and, before they encounter the TLRs or other PRRs that enable them to display their proinflammatory potential, require relocating from their usual physiological niche by proinflammatory cytokines (Wang *et al.*, 1999b) or by tissue damage. HMGB1 is a non-histone nuclear protein that, when extracellular, functions as a proinflammatory cytokine generator (Andersson *et al.*, 2000), exacerbating inflammation. It is released in sepsis (Wang *et al.*, 1999a; Andersson and Tracey, 2003), malaria (Alleva *et al.*, 2005) and influenza (Alleva *et al.*, 2008), and on recognition by TLR4 and the receptor for advanced glycation end products (RAGE) enhances inflammation through inducing cytokines such as TNF (van Zoelen *et al.*, 2009). HMGB1 is essential to the chain of events that mediates cognitive impairment in sepsis survivors (Chavan *et al.*, 2012) and memory impairment (Mazarati *et al.*, 2011). It is released during trauma (Cohen *et al.*, 2009), and involved in post-operative cognitive dysfunction (POCD) (He *et al.*, 2012). When injected i.c.v. HMGB1 worsens, and anti-HMGB1 monoclonal antibody ameliorates, infarction in experimental cerebral ischaemia in rats (Liu *et al.*, 2007). Recently, HMGB1 has proved to be a long-lasting component

of the inflammatory response of stroke (Schulze *et al.*, 2013). Increased extracellular HMGB1 has a well-documented involvement in a range of chronic inflammatory CNS states, including AD (Fang *et al.*, 2012).

The S100 proteins are constitutive calcium-binding molecules present in cytoplasm, where they have homeostatic roles, but when released to the extracellular compartment they operate as proinflammatory danger signals, that is, as DAMPs. They are induced (Yen *et al.*, 1997) and released extracellularly by proinflammatory signals, for instance from astrocytes by TNF (Edwards and Robinson, 2006), and therefore are also pro-inflammatory (Ryckman *et al.*, 2003; Simard *et al.*, 2013). S100B is increased in the CSF in the early stages of AD (Peskind *et al.*, 2001), and S100A9 and S100A12 are enhanced in autopsy brains of both familial and sporadic AD (Shepherd *et al.*, 2006). S100 proteins are well represented in the publications on TBI, stroke and PD. For example, S100B is increased in CSF of paediatric TBI cases (Berger *et al.*, 2002), as are mtDNA and HMGB1 (Walko *et al.*, 2014), as discussed earlier. It is regarded as a DAMP in PD (Sathe *et al.*, 2012). Indeed, as discussed (Foell *et al.*, 2007), the S100 proteins are standard DAMPs, by the same criteria as are HMGB1 and mtDNA.

The soluble Aβ proteins, a term encompassing a range of oligomers, are normally present in cells (Selkoe *et al.*, 1996; Ghiso *et al.*, 1997). They have various physiological functions including synapse elimination in brain development (Wasling *et al.*, 2009) and in the normal hippocampus (Puzzo *et al.*, 2011). Although when in excess soluble Aβ is often regarded as the initiator of AD, it is not specific to this condition, being documented in lead exposure (Basha *et al.*, 2005; Bihaqi *et al.*, 2011) and in post-stroke patients (Lee *et al.*, 2005). As reviewed recently (Knowles *et al.*, 2014), many more proteins than previously suspected are inherently unstable, and can therefore misfold. Such prefibrillar states, analogous to Aβ oligomers, can be expected to allow PRRs to sense chemical groupings not normally accessible to the cellular environment, and therefore merit investigation as DAMPs in disease pathogenesis (Stefani and Dobson, 2003). To date some 50 conditions, including AD and the spongiform encephalopathies, have been associated with such aggregations (Chiti and Dobson, 2006; Knowles *et al.*, 2014). Indeed, the finding that this phenomenon was common to these two diseases apparently inspired the idea of Aβ plaques causing AD. As recorded (Schnabel, 2011), this recognition of the histological similarities of scrapie prions and plaque in AD (Prusiner *et al.*, 1983; Prusiner, 1984; Masters, 1985) arose from the meeting of like minds who saw similarities between histological features as implying similar function. The idea received encouragement from the ability of products of the amyloid cascade to kill neurons directly (Yankner *et al.*, 1989), with its scope eventually widening to encompass a direct capacity to impair synapse function (Beyreuther *et al.*, 1993). Coming at a time when AD research needed direction, these ideas quickly dominated the field, and still have formidable momentum, despite increasing criticism and repeated trial failure. Once it became evident that the plaque formed from aggregated Aβ was inert in terms of disease pathogenesis (Holmes *et al.*, 2008), the focus of amyloid research transferred to the soluble oligomers of this peptide.

Nevertheless, as the progenitor of amyloid plaque, soluble Aβ has a front-row seat in the experimental world of AD pathogenesis, with HMGB1 and the S100s well to the rear. The built-in bias towards Aβ in the transgenic APP-based models (below) has also muddied the waters. Soluble Aβ has been referred to as a constitutive DAMP (Shichita *et al.*, 2012), because when enhanced it exacerbates levels of proinflammatory cytokines, mainly through activating TLR4 (Reed-Geaghan *et al.*, 2009; Stewart *et al.*, 2010; Vollmar *et al.*, 2010). It is, without doubt, also generated to excess in the various infectious diseases in which amyloid plaque is histologically evident, such as neuroborreliosis (Miklossy *et al.*, 2006), cerebral *Chlamydia* infections (Little *et al.*, 2004) and HIV dementia (Soontornniyomkij *et al.*, 2012). Important cerebral functional consequences of Aβ-induced inflammation have been documented for some time (Wang *et al.*, 2005; Rowan *et al.*, 2007), and new data continue to emerge (Lourenco *et al.*, 2013).

Clearly, Aβ production is controlled by proinflammatory cytokines, as well as generating them. Studies on the secretases have, as reviewed (Gandy, 2005; Zhang and Song, 2013), demonstrated this. For example, genetically inhibiting TNF signalling (He *et al.*, 2007), or administering thalidomide, an inhibitor of TNF (He *et al.*, 2013), reduces both β secretase (BACE1) and Aβ load. TNF also up-regulates BACE1 (Yamamoto *et al.*, 2007; Zhao *et al.*, 2011) and γ secretase (Liao *et al.*, 2004), another secretase variant involved in Aβ enhancement. Moreover, a 3,6 dithio variant of thalidomide, which inhibits TNF production, prevents (Gabbita *et al.*, 2012) and reverses (Tweedie *et al.*, 2012) disease in mouse models of AD. Likewise, glucagon-like peptide-1 (GLP-1), which has several mimetics in routine clinical use against type 2 diabetes mellitus, enhances α secretase (ADAM10) (Ohtake *et al.*, 2014). This shifts the cleavage of the amyloid precursor protein away from the Aβ producing β-secretase pathway and towards the growth-signalling pathway, reducing the brain levels of Aβ. Data generated 10 years ago with exendin-4, a GLP-1 mimetic (Perry *et al.*, 2003), are consistent with this. The GLP-1 mimetics have been well reviewed as plausible AD treatments (Greig *et al.*, 2004; Holscher and Li, 2010) and have complex functions that can broadly be described as anti-inflammatory, including, as recently reviewed (Clark *et al.*, 2012; Clark and Vissel, 2013), countering the insulin resistance generated by an inflammatory milieu. These mimetics protect against (McClean *et al.*, 2011) and reverse (McClean and Holscher, 2014) experimental AD, and are in clinical trials (NCT01255163, NCT01843075).

POCD as an illustrative microcosm

As discussed, the inflammation-induced, inflammation-generating nature of these three secondary DAMPs provides parallel positive feedback mechanisms operating to enhance the original inflammatory cascade in AD (Figure 1). Post-surgery patients provide a convenient example of how the big picture has been missed. Transient delirium is common in intensive care units, and is, as noted earlier, an extreme manifestation of the sickness behaviour caused by systemic inflammation (Cunningham and Maclullich, 2013). A characteristic of post-surgery patients, particularly the more

elderly, is the persistent self-propagating inflammatory syndrome, in which case it is referred to as POCD, with changes analogous to those seen in AD (Newman *et al.*, 2007; Steinmetz *et al.*, 2009). Indeed, in some studies the conversion rates to dementia are up to 70% in patients who are 65 years or older (Vanderweyde *et al.*, 2010).

The publications on POCD show how a field can be obscured by focusing on individual jigsaw pieces rather than constructing the wider picture. For example, at least three groups have explored both inflammatory cytokines and HMGB1 in POCD (Terrando *et al.*, 2010; He *et al.*, 2012; Lin *et al.*, 2014). Notably, all three groups considered HMGB1 in isolation from S100s or Aβ. Likewise, while others (Linstedt *et al.*, 2002; Rohan *et al.*, 2005; Leiendecker *et al.*, 2010; Li *et al.*, 2012; Lili *et al.*, 2013) showed increased S100s in POCD, two of these co-assaying for an inflammatory cytokine (Li *et al.*, 2012; Lili *et al.*, 2013), and none for HMGB1 or Aβ. In the same vein, others have published on Aβ in POCD (Xie and Tanzi, 2006; Ji *et al.*, 2013; Reinsfelt *et al.*, 2013; Xu *et al.*, 2014), but few discuss inflammatory cytokines (Ji *et al.*, 2013; Reinsfelt *et al.*, 2013), and none, so far as we are aware, co-investigated HMGB1or S100s. All this is consistent with the concept, based on mouse studies (Terrando *et al.*, 2010), of preventing POCD by pre-emptively treating at-risk surgical patients with anti-TNF antibody.

The bias built into transgenic AD models and caused by injecting soluble Aβ

Could mouse transgenic models, which encouraged the argument that anti-amyloid immunotherapy approaches were ready for human trials (Janus *et al.*, 2000; Morgan *et al.*, 2000), have led researchers astray? The same question mark may hang over the impressive outcome in which ultrasound scanning, rather than passive or active antibody, was recently used to remove Aβ and restore normal function in another mouse strain commonly used as an AD model (Leinenga and Gotz, 2015). Because these genetically modified mouse strains overexpress human AβPP and therefore Aβ, any other secondary DAMP, such as HMGB1 or S100s, would become relatively insignificant (Figure 2), allowing Aβ removal, by whatever method, to be sufficient to block the secondary DAMP step in the pathogenesis pathway. Whereas these mouse models are an argument in favour of anti-amyloid immunotherapy for early-onset human AD (EOAD), which is characterized by mutations that lead to high Aβ expression (Kowalska, 2003), the same does not hold for the much more common, sporadic, late onset form of the disease, in which there is no reason to presume, as in mouse models and EOAD, that secondary DAMP function is dominated by Aβ rather than shared with HMGB1 and S100 proteins.

It has become common practice (Maurice *et al.*, 1996; Kim *et al.*, 2014) to strengthen the amyloid case by transiently reproducing aspects of AD by injecting soluble Aβ into experimental animals. As with transgenic mice, such experiments have limited relevance to the clinical disease without HMBG1 and S100 proteins, the other two secondary DAMPs we have discussed, being brought into the equation.

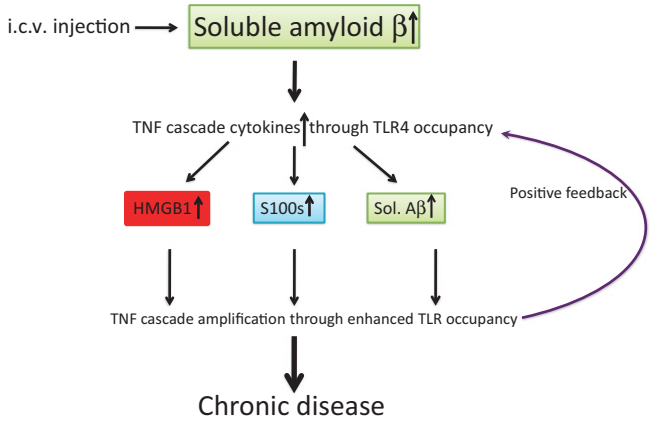

Figure 2
Model of AD induced by i.c.v. injection of Aβ in mice. Partial mimicry of LOAD, but the pathway is artificially biased towards of an end result that is Aβ dependent, and therefore responds to therapy that reduces a TNF cascade that was initially induced by the injected Aβ.

Total PAMP plus DAMP determines outcome

We have made the case that PAMPs and DAMPs may start the chain of proinflammatory events leading to the pathogenesis of the chronic neurodegenerative diseases, including being incorporated into the AD pathogenesis pathway. A most prescient publication has proposed a damage signal hypothesis of AD pathogenesis in which long-term activation of the innate immune system was central (Fernandez *et al.*, 2008). In essence, the authors reasoned that what matters is not whether a particular danger signal is present, but whether the total sum of their activity and persistence, and thus the chronic level of the proinflammatory cytokine they induce, are sufficient to initiate and drive neurodegenerative disease. Although much more is known nowadays about the range of possible DAMPs, including the presence of Aβ in their ranks, the idea that the danger signals discussed earlier all converge to provide harmful levels of the same proinflammatory cytokines (Fernandez *et al.*, 2008) still rings true. Our awareness of the details of outcomes when a number of TLRs are activated simultaneously is, however, still in its infancy (Rosenberger *et al.*, 2014).

Aβ in perspective

One consequence of the prolonged enthusiasm for Aβ has been a relative ignorance in this field of the other secondary DAMPs, such as HMGB1 and S100s, which are increased in AD but remain little tested in this context. Until all three are given equal consideration, there seems little rationale for implying that Aβ is more potent than the other two. Nevertheless, plaque is certainly an instructive histological footprint from which to infer long-term DAMP activity by soluble Aβ. For example, the presence of excessive plaque in the absence of cognitive loss (Schmitt *et al.*, 2000) may indicate

that few if any other PAMPs or DAMPs were up-regulated in that individual. Hence increased Aβ alone may, in this circumstance, have been insufficient to raise the net load of proinflammatory cytokines above threshold required for disease onset. If, on the other hand, HMGB1 and the S100s – as well as other inflammation-enhancing DAMPs of which we are as yet unaware – are plentiful, immunotherapeutically removing soluble Aβ, no matter how diligently or on how grand a scale, as in recent random trials (Doody *et al.*, 2014; Salloway *et al.*, 2014), is unlikely to be helpful to AD patients because the contributions from other secondary DAMPs ensure that the total proinflammatory cytokine load remains high enough to maintain illness.

We propose that, as one of the secondary DAMPs able to further enhance inflammatory cytokine levels, soluble Aβ has a middle-ranking role in AD pathogenesis, no more or less essential than those of HMGB1 or the S100 proteins. This questions the continuing stream of literature assuming oligomer versions of Aβ are the primary initiators of AD pathogenesis, either implying direct harmfulness or acting via the proinflammatory cytokines it induces. As noted earlier, even the post-Aβ proinflammatory cytokine step is still often omitted from the AD pathogenesis narrative, even though the capacity of Aβ to act as a DAMP, a link first recognized in 2005 (Wang *et al.*, 2005), is now clear. As noted earlier, Aβ is recognized by various TLRs (Reed-Geaghan *et al.*, 2009; Stewart *et al.*, 2010; Vollmar *et al.*, 2010) and the field is continuing to expand (Lourenco *et al.*, 2013). Particularly telling recent evidence is that etanercept, the anti-TNF agent used off-label via an apparent i.c.v. equivalent route for treating AD and stroke (Tobinick and Vega, 2006a; Tobinick *et al.*, 2006b; 2012), has been reported to prevent memory deficits caused by administering Aβ to mice i.c.v. (Detrait *et al.*, 2014). Notably, publications ignoring the effects of post-Aβ TNF includes new evidence on GABA from reactive astrocytes impairing memory in mouse models of AD (Jo *et al.*, 2014). TLR4s, which sense Aβ, are on astrocytes (Gorina *et al.*, 2011) and oligomeric Ab induces high levels of TNF in these cells (White *et al.*, 2005).

Even so, understanding the secondary DAMP character of Aβ, in line with that of HMGB1 and the S100 proteins, requires an awareness that the proinflammatory cytokines that mediate the harm caused by Aβ had also been instrumental in inducing Aβ (Liao *et al.*, 2004; He *et al.*, 2007; 2013; Yamamoto *et al.*, 2007; Zhao *et al.*, 2011). Given these shared positive feedback functions of HMGB1, S100 and Aβ for proinflammatory cytokines, it is intriguing to consider the history of AD research priorities, and the number and influence of consequent publications, if either or both of these other two DAMPs, as well as Aβ, had left histologically spectacular plaques as a persistent footprint of their past formation.

Parallel circumstances in related conditions

This review is not complete without noting the parallel world within the publications on the AD-related conditions, stroke and TBI (Hua *et al.*, 2007; Cohen *et al.*, 2009; Hyakkoku *et al.*, 2010; Su *et al.*, 2011; Tsai *et al.*, 2011; Shichita *et al.*, 2012). Indeed, a narrative largely parallel to ours could be constructed, focusing on either stroke or TBI, with a similar degree of reference to the other two neurodegenerative states as all three conditions are now described in terms of the innate immunity cytokines and have an appreciable body of publications on HMBG1, S100 proteins and Aβ. Thus, the best way to advance rational treatment of this close knit trio of neurodegenerative conditions seems to be to focus on what they have in common, despite their disparate clinical origins. As reviewed (Clark and Vissel, 2013), a range of studies point to efficacy of anti-TNF agents and GLP-1 mimetics, which, as TNF induces insulin resistance, ameliorate consecutive harmful steps in those brain disease states with excess TNF, whatever their traditional, clinically based, disparate nomenclatures.

In summary, a clear perspective on the role of soluble Aβ in AD is most rationally gained by visualizing it in the company of other secondary DAMPs, such as HMBG1 and S100 proteins, rather than in isolation. When this is performed, the presence of high amyloid levels in many cognitively normal older brains, and the failure to replicate in humans the anti-amyloid immunotherapy, successful in transgenic mice, can be better understood.

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Conflict of interest

The authors declare that they have not any conflict of interest.

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