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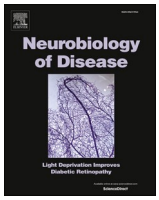

Review

Inflammation in dementia with Lewy bodies

Jay Amin [a,b,*], Daniel Erskine [c], Paul C. Donaghy [c], Ajenthan Surendranathan [d], Peter Swann [d], Amy P. Kunicki [a,b], Delphine Boche [a], Clive Holmes [a,b], Ian G. McKeith [c], John T. O'Brien [d], Jessica L. Teeling [e], Alan J. Thomas [c]

[a] Clinical Neurosciences, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, UK
[b] Memory Assessment and Research Centre, Southern Health NHS Foundation Trust, Southampton, UK.
[c] Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, UK
[d] Department of Psychiatry, University of Cambridge, UK
[e] School of Biological Sciences, Faculty of Environmental and Life Sciences, University of Southampton, UK

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ABSTRACT

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative cause of dementia, behind Alzheimer's disease (AD). The profile of inflammation in AD has been extensively researched in recent years, with evidence that chronic peripheral inflammation in midlife increases the risk of late-onset AD, and data supporting inflammation being associated with disease progression. In contrast, our understanding of the role of inflammation in DLB is less developed. Most research to date has examined inflammation in related disorders, such as Parkinson's disease, but there is now a growing range of literature examining inflammation in DLB itself. We present a review of the literature in this field, exploring a range of research methodologies including those quantifying markers of inflammation in cerebrospinal fluid, peripheral blood, post-mortem brain tissue, and using neuroimaging and preclinical data.

Our review reveals evidence from PET imaging and peripheral blood analysis to support an increase in cerebral and peripheral inflammation in mild or prodromal DLB, that dissipates with disease progression. We present evidence from post-mortem brain tissue and pre-clinical studies that indicate α-synuclein directly promotes inflammation, but that also support the presence of AD co-pathology as an important factor in the profile of neuroinflammation in DLB. We propose that specific markers of inflammation may play a sentinel role in the mild stage of the disease, particularly when combined with AD pathology.

We advocate further examination of the profile of inflammation in DLB through robust longitudinal studies, to enhance our understanding of the pathogenesis of the disease. The goal should be to utilise future results to develop a composite biomarker to aid diagnosis of DLB, and to potentially identify novel therapeutic targets.

1. Introduction

Dementia with Lewy bodies (DLB) accounts for between 4 and 7% of clinical cases of dementia, but the presence of Lewy body pathology is as high as 21% in autopsy series (Vann Jones and O'Brien, 2014; Schneider et al., 2012; McAleese et al., 2021). DLB is characterised by a combination of clinical features including recurrent complex visual hallucinations, cognitive fluctuations, motor symptoms of parkinsonism and rapid eye movement sleep behaviour disorder (RBD). This symptom profile is associated with poorer prognosis and higher caregiver distress in DLB compared to Alzheimer's disease (AD) (Mueller et al., 2017; McKeith et al., 2017). It is therefore imperative that we better our understanding of the underlying mechanisms behind the onset and progression of DLB.

The defining pathological features of DLB are the presence of Lewy bodies and Lewy neurites in the brain, consisting primarily of alpha-synuclein (α-synuclein). There is, however, significant overlap of neuropathological features between DLB, AD and Parkinson's disease (PD) (Hansen et al., 2019). This overlap has been shown to affect the clinical phenotype of DLB, with patients showing higher tau pathology at autopsy demonstrating fewer core clinical features of DLB (Ferreira et al., 2020). In community samples there is considerable under-

* Corresponding author at: Memory Assessment and Research Centre, Clinical Trials Facility, Tom Rudd Unit, Moorgreen Hospital, Botley Road, Southampton SO30 3JB, UK.
E-mail address: jay.amin@soton.ac.uk (J. Amin).

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diagnosis of DLB (Kane et al., 2018), in addition to delays in accurate diagnosis (Galvin et al., 2010). Improving our understanding of the aetiology of DLB will guide the development of biomarkers to improve diagnostic accuracy.

Increasing evidence supports a key role for inflammation in the aetiology and progression of AD, the most common cause of dementia (Heneka et al., 2015). Our understanding of whether inflammation is important in DLB is not yet established and has primarily relied on extrapolation of data from other alpha-synucleinopathies such as PD and PD dementia. However, there is an increasing focus on defining the profile of cerebral and peripheral inflammation in DLB, which may help our understanding of disease pathogenesis including whether this differs from other neurodegenerative diseases. Modulation of immune mechanisms in DLB could lead to novel therapeutic strategies for the disease.

Our aim is to review current evidence describing the profile of inflammation in DLB. The electronic databases of PubMed and Web of Science were searched to select publications relevant to this topic, utilising search terms including "inflammat*", "Lewy", "microglia*", "synuclein*", and "dementia". This search was restricted to papers published in English in peer-reviewed journals until October 2021. Reference lists of relevant articles, including previous review articles on this topic, were searched to identify further appropriate studies. Articles reporting on clinical studies were selected for inclusion if they included a DLB group.

We now present an overview of the evidence identified that describes the profile of inflammation in DLB, categorising studies into sections on cerebrospinal fluid, peripheral blood, neuroimaging, post-mortem brain tissue and pre-clinical.

2. Inflammation in cerebrospinal fluid

Alterations in the concentration of cytokines in the cerebrospinal fluid (CSF) provides a useful insight into neuroinflammatory processes within the brain in DLB, particularly due to the interaction between cerebral inflammatory cells and degenerating neurons. There have been several reports on cytokine concentrations in the CSF of patients with DLB.

Procalcitonin, a marker of bacterial infection, has been found to be raised in the CSF of DLB patients compared to controls, without a concomitant rise in plasma levels, although this was in a sample of only 8 DLB patients and requires replication (Ernst et al., 2007). Wennstrom and colleagues examined CSF levels of interleukin-6 (IL-6) in 29 patients with DLB, 45 patients with AD and 36 controls, and found that IL-6 levels were significantly lower in DLB patients compared with both AD and control groups (Wennstrom et al., 2015). CSF IL-6 concentration in DLB correlated negatively with cognitive test scores (Mini Mental State Examination, MMSE) and positively with CSF α-synuclein levels. By contrast, a study which compared 25 patients with DLB to 33 patients with AD and 46 age matched controls concluded that there were no significant differences in IL-6 or IL-1beta (IL-1β) between groups (Gomez-Tortosa et al., 2003).

Different immune responses are likely to occur for Lewy body and Alzheimer's pathologies. YKL-40 (also known as chitinase 3-like 1) is a glycoprotein expressed by glial cells (Bonneh-Barkay et al., 2012) and, despite increased levels being found in AD (Craig-Schapiro et al., 2010), it has been reported not to be elevated in the CSF of patients with established and prodromal DLB compared to controls (Morenas-Rodríguez et al., 2019). Similarly, soluble triggering receptor expressed on myeloid cells 2 (TREM2) and progranulin, both markers of inflammation, were also not elevated. DLB patients with a CSF profile consistent with co-existing AD pathology did exhibit higher levels of YKL-40 (Morenas-Rodríguez et al., 2019), suggesting co-morbid AD may drive secretion of YKL-40 from glial cells in such patients.

A cross-sectional study including 23 people with DLB examined CSF tumour necrosis factor alpha (TNF-α), interferon gamma (INF-γ), induced protein 10 (IP-10), IL-10, and IL-8 immunoassays as nominal markers of the activity of different immune cell populations. No differences were found in the CSF in DLB for any inflammatory marker compared to controls (Hu et al., 2019). The authors reported that IL-8 concentration was higher in AD than in controls, again suggesting the peripheral immune profile in DLB is different to AD.

In summary, there have only been limited studies exploring CSF levels of inflammatory markers to date. One of these studies indicates that the profile of inflammation in CSF changes as DLB progresses, and others suggest that the nature of that profile may be different to that found in AD. However, findings to date have not been consistently reproduced and so there remains a need for adequately powered, confirmatory studies examining CSF markers of inflammation in DLB.

3. Inflammation in blood

Examination of blood-based biomarkers offers a less invasive method of exploration of the immune system in dementia. There is growing evidence of alterations in the peripheral immune system in DLB, although the nature and significance of these changes has yet to be determined.

Plasma cytokines in DLB and AD were assessed by King and colleagues (King et al., 2018) at both the prodromal and established dementia disease stages, but changes were only detected in the prodromal (or mild cognitive impairment, MCI) groups. Patients in both MCI with Lewy bodies (MCI-LB) and AD MCI groups had significantly higher levels of multiple cytokines (IL-1β, IL-2, IL-4, and IL-10), than the control or dementia groups. Furthermore, both MCI groups had lower concentrations of plasma TNF-α than the control or dementia groups. Lower concentrations of IL-1β, IL-2 and IL-4, and higher levels of IL-6 and TNF-α, were associated with greater severity of cognitive impairment across all patient groups and with parkinsonism in the DLB and MCI-DLB groups (King et al., 2018). In a separate report on longitudinal follow-up of the same cohort, several cytokines showed highly significant reductions over time: IL-1β, IL-2, IL-4, IL-6, IL-10 and INF-γ. Of these, IL-1β, IL-2, IL-4, IL-10 and INF-γ had positive correlations with Addenbrookes cognitive examination – revised (ACE-R) scores, showing an association between falling cytokine concentrations and worsening cognition (Thomas et al., 2020). Since these changes in cytokine concentrations with progressing disease in DLB include pro-inflammatory (*e.g.* IL-1β) and anti-inflammatory (*e.g.* IL-4 and IL-10) markers, it remains uncertain as to whether this result signifies immune suppression or exhaustion with disease progression.

A novel study combined peripheral cytokine measurements with positron emission tomography (PET) imaging of amyloid (using the PiB ligand) and microglial activation (using the PK-11195 ligand for the translocator protein, TSPO), and found raised macrophage inflammatory protein 3 (MIP-3), IL-2, and IL-17A, with decreased IL-8, in the serum of 19 patients with DLB compared to controls, but no correlation between microglial activation or amyloid deposition with peripheral cytokine levels (Surendranathan et al., 2018). Although a link between central and peripheral inflammation was not found in this study, larger sample sizes will be required to detect possible associations.

One study examined peripheral lymphocyte subsets using flow cytometry, comparing 31 DLB patients with 31 AD patients and 31 controls (Amin et al., 2020a). Lower proportions of CD4+ helper T cells and CD19+HLA-DR+ activated B cells were found in DLB patients compared to those in the AD (but not the control) group, suggesting that DLB may be characterised by impaired proliferation and/or reduced activation or exhaustion of T helper and B cells. Serum cytokines were also recorded to be significantly different in DLB patients in this study, with IL-6 higher in DLB than in controls, in contrast to the relative reduction reported in one CSF study noted earlier. Detectable IL-1β levels were found to be more frequently present in DLB than both control and AD patients. However, none of the cytokine concentrations or lymphocyte subsets correlated with the severity of clinical features of DLB in this cross-sectional study (Amin et al., 2020a).

An exploratory study which included both probable and possible DLB patients investigated correlations between cytokines and both cognitive and neuropsychiatric symptoms, finding modest positive correlations between IL-6 and baseline Alzheimer's disease assessment scale–cognitive subscale (ADAS-COG) scores, and between serum TNF-α and neuropsychiatric inventory (NPI) total score (Clough et al., 2015). TNF-α and IL-6 were also, together with monocyte chemoattractant protein-1 (MCP-1), found to be elevated in a more recent report of 16 patients with DLB, compared to controls (Usenko et al., 2020).

In summary, there is accumulating evidence to suggest an early inflammatory response in the blood in DLB. IL-1β and IL-6 are the cytokines most consistently raised in DLB and may be highest in the prodromal stages of disease. IL-1β is part of the IL-1 family and is mainly pro-inflammatory in nature, with a key role in innate immunity. IL-6 is a pivotal cytokine in the immune response and is a therapeutic target for several inflammatory diseases, with involvement in nearly all aspects of the immune system including neutrophil recruitment to sites of infection and shaping the T cell response. Determining a precise role for IL-6 in DLB will be more likely in studies that undertake more comprehensive immune profiling to identify the balance between immune activation, regulation, and suppression. Longitudinal studies examining IL-6 and other immune markers will also be useful to determine changes as the disease progresses. Despite clear alterations to peripheral cytokines and lymphocyte subsets in DLB, there are still conflicting findings and all but one study was cross-sectional, meaning that the significance of these findings remain uncertain.

4. Inflammation using brain imaging

In vivo brain imaging has the potential to allow the investigation of inflammatory processes at an early disease stage and, like blood and CSF analysis, permits correlation with disease progression. Several magnetic resonance imaging (MRI) and PET modalities have been suggested as potential measures of neuroinflammation (Stefaniak and O'Brien, 2016). The most studied of these is TSPO PET.

TSPO is a mitochondrial membrane protein associated with cholesterol transport. Whilst TSPO is expressed in neuronal, endothelial and glial cells, its expression in microglia and astrocytes is significantly greater than other cells, and neuronal expression of TSPO is minimal (Gui et al., 2020). TSPO PET ligands have been developed as markers of microglial cells *in vivo* and applied to a range of neurological disorders (Kreisl et al., 2020).

Two studies have reported increased TSPO ligand binding in DLB using ^{11}C-PK11195 (Surendranathan et al., 2018; Iannaccone et al., 2013). The first study found that six DLB participants (MMSE 24 ± 3.9) had greater ^{11}C-PK11195 binding compared with controls in nearly all subcortical and cortical brain regions examined (Iannaccone et al., 2013). A larger study of 19 DLB cases (MMSE 21.9 ± 4.5) divided cases into mild (ACE-R score > 65) and moderate/severe (ACE-R score ≤ 65) groups, and found increased ^{11}C-PK11195 binding in the mild DLB group in the inferior and medial temporal gyri, fusiform gyrus, putamen, inferior frontal gyrus and cuneus (Surendranathan et al., 2018). In contrast, binding in moderate/severe DLB was generally lower than in controls, with significantly lower values found in the caudate nucleus. This evidence suggests that increased microglial cell activity may be specific to early disease in DLB. ^{11}C-PK11195 binding in both the caudate and cuneus was strongly correlated with ACE-R score ($r = 0.83$ and 0.77, respectively). The neuroanatomical pattern of TSPO changes in DLB is distinct from that seen in other degenerative diseases like AD and frontotemporal dementia.

The effect of comorbid AD pathology on inflammatory process in DLB is open to investigation using PET imaging. No correlation was observed between ^{11}C-PiB amyloid PET and ^{11}C-PK11195 in 16 DLB cases (Surendranathan et al., 2018). However, in four cases of Lewy body dementia (three DLB and one PD dementia), a positive correlation was observed between ^{18}F-AV1451 tau PET and ^{11}C-PK11195 binding (Mak et al., 2021). The importance of this observation remains to be determined.

There has been no investigation of TSPO ligand binding in MCI-LB to date and, most critically, no investigation of the relationship between TSPO ligand binding and disease progression in DLB. Novel PET ligands are in development that bind to other potential microglial sites or to astrocytes (Boche et al., 2019). MRI measures of diffusivity such as free water are also under investigation as proxy measures of neuroinflammation. These modalities have not yet been studied in DLB. Development of PET α-synuclein ligands is in process (Korat et al., 2021), and would allow a valuable insight into the *in-vivo* relationship between neuropathology and neuroinflammation in DLB.

5. Inflammation in post-mortem brain tissue

Autopsy studies allow direct examination of neuroinflammation but largely examine later stage disease, which may bear little relevance to early-stage processes. Most work in this field has focused on the number and profile of microglial cells, the innate immune cells of the central nervous system. Microglia are highly dynamic cells that display a range of phenotypes in response to their microenvironment (Nimmerjahn et al., 2005), and which can be detected by examining cell surface markers using immunohistochemistry (Boche et al., 2013). In AD, microglia have been consistently shown to be activated (Heneka et al., 2015; Hopperton et al., 2018), but the specific profile of microglia in DLB has yet to be conclusively determined.

Numerous studies have examined the number of activated microglia in DLB. Two small studies immunostaining brain tissue for human leukocyte antigen – antigen D related (HLA-DR) have shown increased numbers of HLA-DR+ microglia in several regions of the DLB cortex compared with controls (Mackenzie, 2000; Imamura et al., 2005), although each study examined only five DLB cases. In contrast, one study showed that this marker was unchanged in eight DLB cases compared to controls, with the DLB cases selected to exclude significant concomitant AD pathology (Shepherd et al., 2000).

Further studies have utilised a range of other markers of microglial activation, with little evidence to support this being present in the DLB brain at post-mortem. Ionised calcium-binding adapter molecule 1 (Iba1) is a microglial marker (example of immunostaining in Fig. 1), and has been shown to be unchanged in the hippocampus of five cases of DLB compared to nine controls, although cluster of differentiation 68 (CD68)-positive microglia were increased in DLB (Streit and Xue, 2016). The authors suggested that the lack of upregulation of Iba1 on microglia, in conjunction with an absence of morphological evidence of activated cells, means that it was unlikely that significant microglial activation was present in their DLB cases (Streit and Xue, 2016). In support of this, the number of microglia expressing Iba1 and CD68 in the hippocampus has been shown to be no different in 12 DLB cases compared with either controls or AD (Bachstetter et al., 2015). Protein immunoreactivity for Iba1 and HLA-DR has also been examined in the pulvinar, with no difference found between DLB and controls (Erskine et al., 2018a). Furthermore, transcriptomic analysis of post-mortem cortical and subcortical brain tissue in DLB has also failed to demonstrate significant microglial activation (Erskine et al., 2018a; Rajkumar et al., 2020).

A range of microglial markers were examined in a large cohort of 29 controls and 30 DLB cases, selected to exclude significant concomitant AD pathology. The authors showed that multiple markers of microglial activation, including Iba1, CD68 and HLA-DR, were present in the temporal lobe at levels no different in DLB compared with controls, consistent with the absence of microglial activation in DLB in late stage disease (Amin et al., 2020b). Immunolabeling of YKL-40 was also performed in this study and showed no difference between DLB and controls (Amin et al., 2020b), as reported before (Llorens et al., 2017). However, this study did demonstrate increased cortical recruitment of T lymphocytes in DLB, consistent with a prior study (Castellani et al., 2011), supporting a potential role for adaptive immunity in the disease.

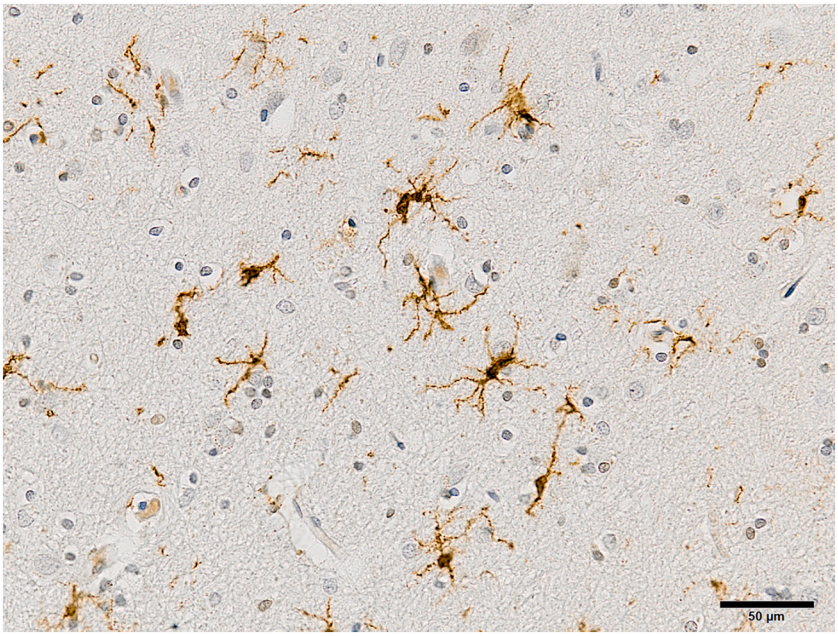

Fig. 1. Illustration of human brain tissue from a DLB case, immunolabelled with Iba1. Multiple microglia with ramified processes observed in the grey matter of the temporal lobe. Haematoxylin counterstaining. Magnification x20. Scale bar = 50 µm.

Exploration of the relationship between cerebral inflammation and adaptive immunity, particularly in early DLB, is warranted.

Astrocytes are glial cells that can also exhibit inflammatory phenotypes (Giovannoni and Quintana, 2020), but to date only one study has reported on the profile of these cells in DLB at post-mortem. The astrocytic marker glial fibrillary acidic protein (GFAP) was shown to be elevated in the pulvinar region in DLB (Erskine et al., 2018a), using both mRNA and histological analysis, a finding that warrants further investigation into this cell type in DLB.

TSPO, used as a marker of microglia in PET studies, at *post mortem* has been shown to be no different in DLB to control cases (Xu et al., 2019). As TSPO is expressed in both microglia and astrocytes, post-mortem investigation is required to understand the cellular correlates of TSPO PET ligand binding. This has not yet been reported in DLB.

Overall, the literature to date suggests a lack of significant microglial activation in DLB in post-mortem human brain tissue. Whilst it is reasonable to conclude that brain tissue collected at post-mortem is reflective of the end-stage of disease, this is not always the case. Examination of post-mortem brain tissue from DLB patients who die early in the course of their dementia is of interest, particularly to determine whether the profile of inflammation may differ compared with late disease. Concomitant AD pathology and neurodegeneration are also likely to be important factors that determine the profile of neuroinflammation in DLB. Most post-mortem work to date in this field has been limited by low case numbers, a narrow range of markers or sampling a small region of the brain. Investigation of multiple cortical and subcortical brain regions across a spectrum of DLB cases, including studying innate and adaptive immune components, will enhance our knowledge of the different factors that may contribute to neuroinflammation in DLB.

6. Basic biology of inflammation in DLB

The relationship between disease processes in DLB and inflammation has been difficult to identify, in part due to the lack of cell and animal models that specifically model DLB. Therefore, we have included studies that evaluate the direct effect of α-synuclein on immune cells and have omitted studies that have used models that directly model PD, such as selective accumulation of α-synuclein in the nigrostriatal pathway or neurotoxin-based models of nigrostriatal degeneration.

Mice injected intracerebrally with 3 µg of fibrillar α-synuclein mount a robust immune response, including increased levels of IL-1β mRNA, implying a direct association between α-synuclein and inflammation (Couch et al., 2011). Mice overexpressing α-synuclein under the ubiquitous *Thy-1* promoter accumulate α-synuclein in widespread brain regions, albeit at a slower rate when compared to intracerebral injection. These mice manifest robust inflammatory changes evidenced by altered to microglial morphology and phenotype, with increased TNF-α and toll-like receptor (TLR) 1, 4 and 8 expression in the nigrostriatal pathway, which is subject to neurodegeneration (Watson et al., 2012). To determine whether α-synuclein induces inflammation independent of neuronal loss, one study euthanised rats at different time-points following injection with α-synuclein aggregates and demonstrated that numbers of microglial cells were closely associated to the proportion of cells with aggregated α-synuclein and preceded cell loss, suggesting a direct link between intraneuronal α-synuclein accumulation and inflammation (Duffy et al., 2018).

Cell culture studies offer a direct view of the impact of α-synuclein on the activation state of microglia and, by extension, innate immune response to α-synuclein pathology. Typically, such studies apply α-synuclein to cell culture media as a model of secreted α-synuclein, which has been demonstrated to occur in cells overexpressing α-synuclein and is enhanced by lysosomal impairment known to be implicated in Lewy body disease (Alvarez-Erviti et al., 2011; Erskine et al., 2021). Extracellular α-synuclein is internalised by cultured microglia where it induces NF-κB translocation to the nucleus as a marker of a pro-inflammatory phenotype, and downstream secretion of pro-inflammatory chemokines (Cao et al., 2012; Daniele et al., 2015; Fellner et al., 2013; Kim et al., 2013). Microglia exposed to α-synuclein *in vitro* also seem to prime microglia for inflammatory responses by secreting TNF-α, IL-1β, IL-6, CXCL1, MCP-1 and IFN-γ, and matrix metalloproteinases 3, 8 and 9 (Daniele et al., 2015; Fellner et al., 2013; Reynolds et al., 2008; Lee et al., 2010). The prion-like spreading of α-synuclein has become a prominent view in the α-synucleinopathy field as a driver of progression; and inhibition or depletion of microglia delays spreading, while activation of microglia using lipopolysaccharide (LPS) enhances the spreading of α-synuclein into unaffected neurons in mice (George et al., 2019). Therefore, *in vitro* studies of cultured microglia

have demonstrated that they can internalise extracellular α-synuclein, inducing a pro-inflammatory phenotype that may promote the spread of α-synuclein. This may be particularly important during α-synuclein deposition in early DLB.

The observation that peripheral immune markers are particularly elevated in early-stage DLB suggests factors present early in disease may be more prone to stimulating an immune response. The protein α-synuclein undergoes a shift from a soluble monomer or tetramer under normal physiological conditions, to increasingly large and insoluble multimers in disease conditions (Outeiro et al., 2019). An early stage of α-synuclein accumulation is its aggregation into soluble oligomers that may precede fibril formation. These soluble oligomers of α-synuclein appear to be particularly prone to spreading *via* prion-like mechanisms and may have enhanced toxicity compared to insoluble fibrils (Ingelsson, 2016). Thus, at the earliest stages of DLB there may be an overabundance of oligomers relative to fibrils, which shifts in favour of fibrils with disease progression (illustrated in Fig. 2).

Oligomeric α-synuclein may stimulate an immune response based on its direct antagonism of TLR2 receptors (Kim et al., 2013), priming effect on TLR4 receptors (Hughes et al., 2019), and activation of the nucleotide-binding oligomerisation domain (NOD)-like receptor (NLR) family pyrin domain-containing 3 (NLRP3) inflammasome in human microglia (Trudler et al., 2021). However, the effect of oligomeric α-synuclein on immune responses may be less direct and mediated through α-synuclein oligomer-induced neuronal apoptosis, as oligomeric α-synuclein has previously been demonstrated to induce caspase activation in cultured neuroblastoma cells (Cascella et al., 2021). The apoptotic cascade involves either the mitochondria-mediated intrinsic pathway or death receptor-mediated extrinsic pathway, but in either case the end-result is DNA fragmentation, loss of cell membrane integrity and preparation of the cell for phagocytosis (Singh et al., 2019). However, whilst oligomeric α-synuclein appears to associate with pro-inflammatory signalling by activating TLRs, the effect of apoptosis appears to lead to an anti-inflammatory immune response (Maderna and Godson, 2003). Therefore, the activation of both pro- and anti- inflammatory markers in early stage DLB may be the result of the direct effect of α-synuclein oligomers on TLRs combined with an indirect effect mediated through apoptotic cell death.

There is less evidence regarding the involvement of the adaptive immune system in DLB, though as microglia can activate CD4+ and CD8+ T cells, it seems likely that the previously described activation of microglia by α-synuclein will also impact T cell activation (Cardinale et al., 2021). The role of aggregated gastrointestinal α-synuclein and the migration of antigen-specific adaptive immune cells into the brain also warrants further investigation.

Although α-synuclein is typically conceptualised as a synaptic protein, an emerging body of *in vitro* and *in vivo* work has demonstrated that α-synuclein has anti-microbial properties and is upregulated during active infection (Beatman et al., 2015; Park et al., 2016; Tomlinson et al., 2017). Critically, α-synuclein-null mice have increased mortality and worse progression when challenged with a variety of viral encephalitis-causing agents, implying that α-synuclein may fulfil an important function in host defence and may explain its remarkable conservation across species (Tomlinson et al., 2017). Interestingly, central administration of the influenza viruses H1N1 and H5N1 can induce both microglial activation and deficits in proteostasis leading to the selective accumulation of α-synuclein, which aggregates in regions vulnerable to Lewy body formation and not those typically spared by Lewy body pathology, such as the cerebellum (Jang et al., 2009; Erskine et al., 2018b; Marreiros et al., 2020). Therefore, the identification of α-synuclein as an anti-microbial protein that is up-regulated during active cerebral or peripheral infection alongside activation of the brain's immune cells, may indicate that the relationship between the disease process thought to be central to DLB and inflammation reflects a third underlying variable of cerebral infection.

It is important to note that α-synuclein is not the only pathological protein deposit in DLB and Alzheimer-type pathology in the form of amyloid-β plaques and tangles of hyper-phosphorylated tau are typical concomitant features (Outeiro et al., 2019; Walker et al., 2017). Critically, AD-type pathology is typically more severe in DLB than PD, suggesting it also contributes to the disease process (Walker et al., 2019). Amyloid-β has been demonstrated to have anti-microbial properties and is upregulated in infectious states like α-synuclein (Lee et al., 2008; Gosztyla et al., 2018), and can also bind to microglial receptors like CD36, TLR4 and TLR6, leading to a pro-inflammatory phenotype and secretion of chemokines and cytokines such as MIP-1, TNF-α and IL-1β (El Khoury et al., 2003; Webers et al., 2020). Tau pathology is less studied in the context of inflammation, although cultured microglia exposed to truncated tau have morphological changes consist with activation and release pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α (Kovac et al., 2011). Furthermore, tau transgenic mice have elevated levels of activated microglia throughout the brain, and challenge with LPS leads to increased deposition of phosphorylated, pathogenic tau, implying a bi-directional relationship between tau and inflammation.

In summary, although it is difficult to establish the causative factors

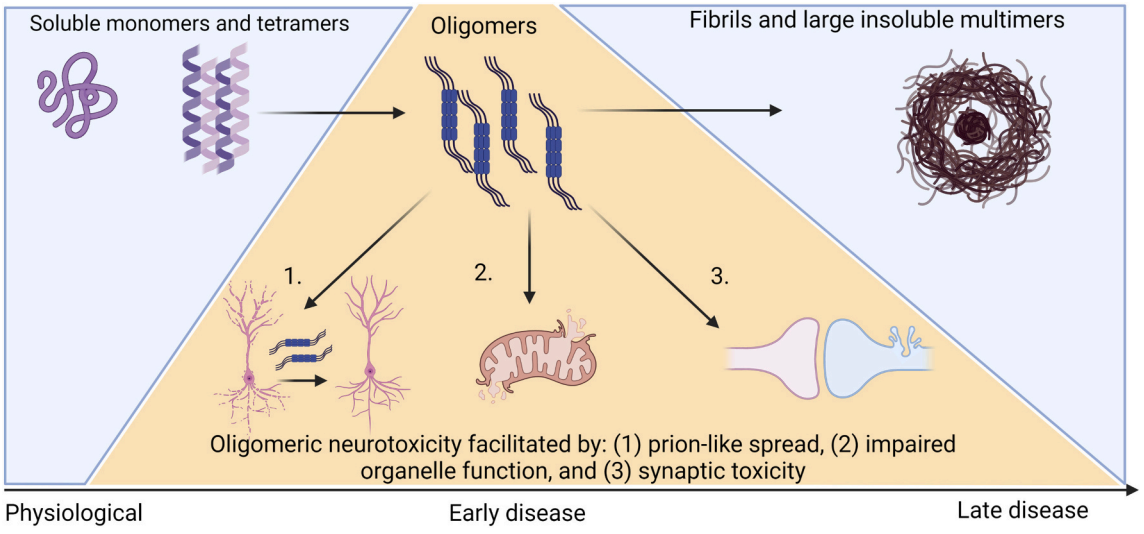

Fig. 2. Illustration showing the role that oligomeric alpha-synuclein may play in inducing inflammation in early dementia with Lewy bodies. Created with Biorender .com.

underlying inflammation in models of neurodegenerative diseases, there is compelling evidence that α-synuclein can induce inflammatory changes in immune cells, including microglia, and that these may have implications for spreading of α-synuclein and neuronal death, putative pathological processes in DLB. As α-synuclein is upregulated during active microbial infection in which there is also a marked immune response, and α-synuclein can induce inflammatory states and enhance α-synuclein propagation and neuronal loss, it is plausible to suggest that α-synuclein and inflammation may have a reciprocal relationship where each amplifies the other. Furthermore, AD-type pathology, which is a common concomitant feature of DLB, is also likely to influence inflammatory changes and may have an additive effect on cognitive and motor decline.

7. Discussion

We have presented an overview of changes to the immune system that have been reported in DLB using a range of research methodologies, as summarised in Fig. 3. Our review reveals a possible dynamic role of inflammation in DLB through the disease course and has identified several factors that span across different types of study, which may be key in enhancing our understanding of how inflammation changes in DLB.

Data from studies examining blood cytokines and PET imaging appear to support an increase in inflammation at the prodromal stage of DLB, which then decreases as cognition declines. This is consistent with post-mortem human brain tissue studies, which have failed to consistently demonstrate significant microglial activation in DLB. Overall, this implies that there is a peak of cerebral inflammation in mild DLB that then dissipates with disease progression. Several questions remain, however. Is this early peak in inflammation a physiological or protective response to the accumulating neuropathology in mild disease? Is this early peak associated with peripheral α-synuclein accumulation in the years prior to symptom onset in DLB, since *in vitro* evidence shows α-synuclein stimulates a neuroinflammatory response? Is the failure of microglial activation to persist into severe disease associated with the relative absence of severe neurodegeneration in DLB? How does the interplay between peripheral and cerebral inflammation affect pathogenesis, and what factors affect this communication? There are many hypotheses still to consider in this field, where future work would benefit from several methodological improvements.

Although evidence indicates that α-synuclein in DLB does itself drive inflammation and perhaps with a different neuroanatomical distribution, research from post-mortem brain tissue and pre-clinical research appears to show that the presence of AD co-pathology is also an important consideration when measuring neuroinflammation in DLB. Only limited PET imaging studies of inflammation have included measurement of amyloid and tau load, with no conclusive impression of its role in DLB to date. The interplay between α-synuclein deposition in DLB, AD pathology and microglial activation is a key area for future research. DLB cases included in post-mortem brain tissue work should aim to include a range of severity of AD pathology, whilst PET imaging studies can be used to measure cerebral amyloid and/or tau burden alongside microglial activation. Once PET ligands for α-synuclein are in use, this will allow investigation of the pathognomonic features of DLB and microglial activation in tandem, giving an insight into the relationship between the two. Furthermore, exploration of the relationship between neuropathological components of AD and DLB, and glial cells, in pre-clinical cell culture work will further enhance our knowledge of the precise role that concomitant pathology may play in the DLB brain. It is, however, clear from work in PD (covered elsewhere in this Special Issue) that a robust immune signal can be observed in α-synucleinopathies in the absence of AD co-pathology.

The relationship between neurodegeneration and neuroinflammation in DLB also warrants further attention. Cortical atrophy measured using structural brain imaging is less prominent in DLB compared with AD (Watson and O'Brien, 2012), with relative preservation of medial temporal lobe structures included as a supportive

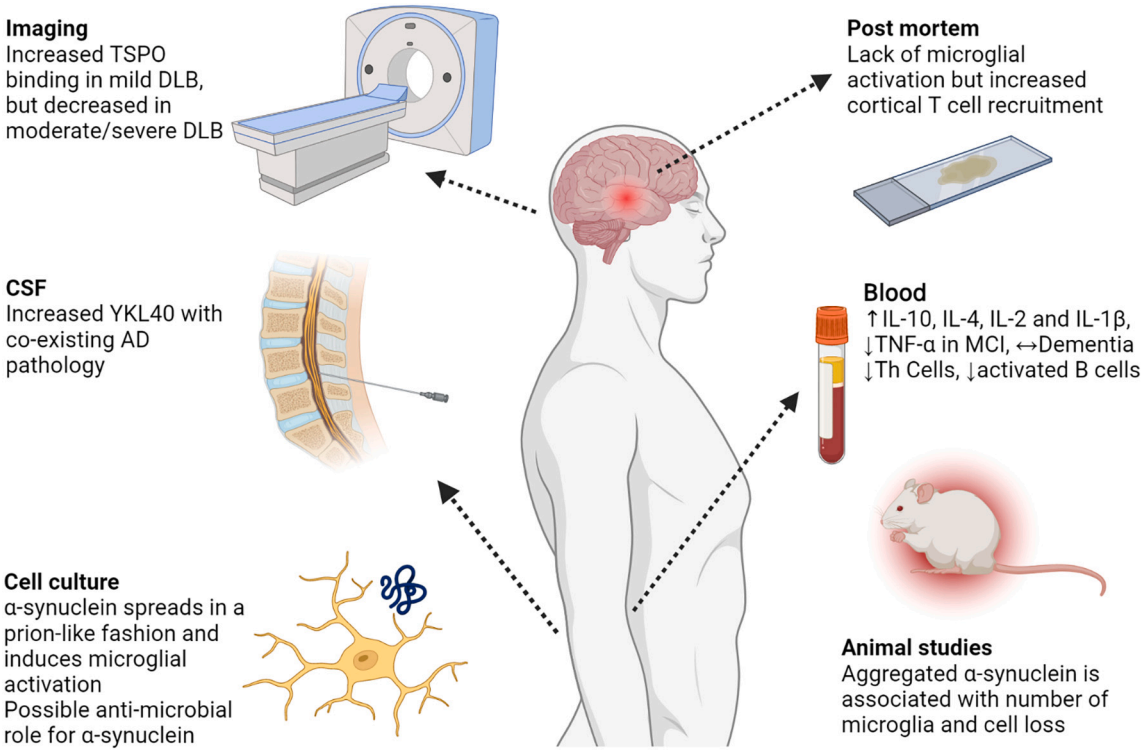

Fig. 3. Illustration showing the key findings from a range of research methodologies for the role of inflammation in dementia with Lewy bodies. TSPO – translocator protein; DLB – dementia with Lewy bodies; YKL-40 – chitinase-3-like protein 1; AD – Alzheimer's disease; IL – interleukin; TNF – tumour necrosis factor; MCI – mild cognitive impairment; Th – T-helper. Created with Biorender.com.

biomarker for the diagnosis of DLB (McKeith et al., 2017). The lack of prominent neurodegeneration in DLB is likely to be of relevance when considering the neuroinflammatory profile of the disease as it progresses. The microglial priming hypothesis of AD proposes that microglia already primed against neuropathological structures respond more robustly and show exaggerated production of pro-inflammatory cytokines in response to a peripheral inflammatory signal (for example a systemic bacterial infection), leading to increased phagocytosis and bystander neuronal damage (Perry and Holmes, 2014). The additive effect of AD pathology in addition to α-synuclein pathology in DLB has been shown to predict disease duration in a prospectively recruited post-mortem study of 49 patients with DLB (Ferman et al., 2018). It remains unclear, however, whether the differing profiles of neurodegeneration between AD and DLB is a cause or consequence of disease-specific neuropathological and inflammatory profiles. Further work is needed to examine the localisation and spread of neuropathology in DLB, and its relationship with neurodegeneration and neuroinflammation with disease progression.

There is mounting attention towards the role of inflammation in DLB, yet much of the existing data are limited by factors including small sample size, an absence of longitudinal studies and lack of reproducible findings. To improve reproducibility of research findings in this field we propose that CSF and blood (including serum and peripheral blood mononuclear cells) are collected prospectively and repeated over time in large collaborative longitudinal studies, which incorporate standardised methodologies of sample collection and processing. Zhou et al. have highlighted the critical importance of standardising methodological factors when assessing cytokine concentrations, including consistency in the timing of phlebotomy to limit the effect of diurnal variation, and ensuring that serum samples are processed under the same conditions (Zhou et al., 2010). In addition, specific immune pathways are difficult to determine with assessment of single cytokines that often have multiple roles, which in themselves may change in response to the microenvironment. A more robust evaluation of peripheral inflammation in DLB would involve combining such longitudinal studies with flow cytometry, targeted transcriptomics and proteomics, and PET imaging to truly gauge how innate and adaptive immune components respond to the underlying neuropathology over time. Measurement of markers of AD pathology and neurodegeneration (using structural brain imaging and serum neurofilament light, for example) could also be incorporated to measure potential confounders.

Genome wide-association studies (GWAS) have consistently identified inflammation-related genes as key factors in the aetiology of AD (Zhang et al., 2015). However, GWAS in DLB have not yet shown any such polymorphisms as being significant in DLB (Guerreiro et al., 2018), although larger scale studies are underway to investigate this. There remains a possibility that inflammation may not necessarily be a key aetiological factor in DLB, but it may play a sentinel role in the mild stage of disease. Exploration of potential interactions between peripheral infections and onset of DLB, along with work examining a possible anti-microbial role for α-synuclein, will help to clarify this.

We advocate further examination of inflammation in DLB, with a view to enhancing our knowledge of the pathogenesis of the disease. Consistent findings of alterations in immune components could aid the development of a diagnostic biomarker for DLB. Due to the presence of neuroinflammation in many neurodegenerative diseases any diagnostic biomarker is likely to need to be composite, perhaps with the inclusion of disease-specific markers of neuropathology. There is also the potential to identify novel immune targets for intervention, which are likely to be most effective in early disease. We have identified several methodological factors to guide robust future work in this field.

Declaration of Competing Interest

JOB has acted as a consultant for TauRx, Eisai, Novo Nordisk, Biogen and GE Healthcare and received grant support from Avid/Lilly, Merck and Alliance Medical.

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