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Immunological signatures in frontotemporal lobar degeneration

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Abstract

Purpose of review: Over the last year, research into the immunological and inflammatory signatures of frontotemporal lobar degeneration (FTLD) has accelerated greatly. Herein, we highlight recently proposed roles of brain-resident microglia as well as peripheral myeloid cells in frontotemporal dementia (FTD)-spectrum disorders.

Recent findings: Recent unbiased genetic, transcriptomic and proteomic surveys using human data confirm significantly altered immune-function genes as well as transcript and protein modules associated with inflammatory and immune function. Beyond human studies, novel animal models indicate important roles for both microglia and monocytes, and central involvement of genes such as *Trem2*, *Apoe* and *Tbk1*.

Summary: The importance of neuroinflammatory activity in FTD pathophysiology is unambiguous, but whether this activity is primarily beneficial or detrimental remains unclear, with variable results reported for distinct disease paradigms and types of pathology. Going forward, it will be crucial to determine which types of microglial and peripheral myeloid responses are favorable, in response to which specific protein pathologies, and at which point in disease course.

Keywords

frontotemporal dementia; neurodegeneration; immune system; inflammation; microglia; monocytes; myeloid

Introduction

Frontotemporal dementia (FTD) represents one of the most common forms of dementia in people under 65 years of age and occurs due to progressive neurodegeneration of the frontal and temporal lobes of the brain (i.e., frontotemporal lobar degeneration [FTLD]). Diagnoses along the FTD spectrum are clinically and pathologically diverse. FTD patients are divided clinically into those with predominant changes in behavior and personality (bvFTD) or

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Conflicts of interest

None

language (primary progressive aphasia [PPA], which is subdivided into semantic variant [svPPA] and nonfluent variant [nfvPPA]). In some individuals, FTD presents with aspects of motor neuron disease or amyotrophic lateral sclerosis (FTD-MND or FTD-ALS). Related Parkinsonian disorders on the FTD spectrum include corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP).

FTLD is characterized pathologically by aggregated forms of the proteins TDP-43, tau, or, less commonly, FET (FUS, EWS, TAF15). Although the majority of individuals diagnosed with FTD have an apparently sporadic form of disease, a significant fraction (perhaps 40% of cases; [1,2]) have a family history of dementia or other neurodegenerative disease, and an estimated 10–30% of cases are inherited in an autosomal-dominant fashion [1–3]. Intense study of the genes implicated in familial forms of FTD suggests that immunological and inflammatory mechanisms are likely to play a central role in disease pathogenesis.

Research into the immunological signatures of FTD has accelerated rapidly over the last few years, but early suggestions of immune system involvement date to the early 2000s [4,5]. Microglia, the brain-resident macrophages, have been implicated by human genetics as crucial players in Alzheimer's disease (AD; reviewed in [6]), and emerging research suggests that microglia may be equally important in FTLD pathogenesis. In this review we highlight important findings from the last year that illuminate immunological mechanisms and signatures in FTD-spectrum disorders and models of FTLD. We begin by focusing on recent human studies, including genetic and proteomic analyses, human cell culture models, and clinical observations. We then consider important advances in our understanding of immunological responses in mouse models relevant to FTLD. Collectively, results from the past year suggest not only that brain-resident microglia, but also peripheral myeloid cells, show significant alterations in FTD. Diverse myeloid cell populations therefore warrant further investigation and may represent promising targets for therapeutic intervention in FTD-spectrum disorders.

I. Human studies

Overlapping genetic architecture between FTD and disorders of the immune system

Recent work systematically assessing the genetic overlap or pleiotropy between FTD-spectrum disorders and diseases of the immune system has identified a striking number of shared risk loci [7]. In particular, loci within the *HLA* region on chromosome 6 appear to be a major driver of the overlapping genetic architectures of FTD and immune-mediated disorders such as rheumatoid arthritis and ulcerative colitis. Interestingly, although the FTD genome-wide association study (GWAS) data used for the pleiotropy analysis were based on sporadic FTD, many of the identified pleiotropic genes were found to be differentially expressed in post-mortem brains from individuals with autosomal-dominant FTLD caused by pathogenic *GRN* mutations (i.e., *GRN*+ FTLD). Consistent with their previously established association with immune-mediated diseases, the majority of these *HLA*-associated genes were predominantly expressed in microglia within the brain. An important caveat of this finding and similarly designed analyses is that differential expression of *HLA*-region genes could reflect differences in microglial abundance (determined by survival and

proliferation) and/or activation state in FTLD brains. Clarification of this issue will be an important aspect of future research.

CXCR4 in FTD-spectrum disorders

The chemokine receptor CXCR4 is well known for its roles in immune function, HIV infection, and neuronal migration during brain development, but was only recently implicated in FTD-spectrum disorders. Using GWAS-driven pleiotropy analysis, recent studies have identified *CXCR4* as a shared genetic risk factor between the FTD-spectrum disorder PSP and Parkinson's disease (PD), as well as between PSP and CBD [8,9]. Beyond this, *CXCR4* expression appears to be dysregulated in FTD, PSP, and PD as well as in a mouse model of tauopathy [8]. Although this study's findings are consistent with the FTD–immune-disorder pleiotropy analysis described above, CXCR4 also functions in neural development [10], and this function could be equally germane to FTD pathobiology given recent work implicating neurodevelopmental processes in bvFTD [11].

Inflammatory protein dynamics in the FTLD brain

A recent unbiased mass spectrometry-based proteomic study identified protein modules significantly altered in postmortem frontal cortex from patients with ALS, ALS-FTD and FTLD associated with TDP-43 pathology (FTLD-TDP; [12]). Using weighted co-expression network analysis, the authors identified significant increases in modules expressed primarily by microglia and astrocytes in FTLD. In particular, an RNA-splicing module that was significantly enriched for microglial proteins was altered in FTLD and correlated with TDP-43 pathology. Beyond changes in RNA-splicing proteins, an inflammation-associated protein module that was increased in FTLD also showed significant up-regulation in frontal cortex of carriers of pathogenic *C9ORF72* repeat expansions with ALS but without evidence of dementia. This suggests that the identified inflammatory changes associated with FTLD-TDP are also associated with pathogenic *C9ORF72* expansion even in the absence of overt cortical pathology or dementia symptomatology. Thus, at the proteomic level, there is strong evidence for changes in microglial function in ALS and FTLD that is associated with the presence of TDP-43 pathology and/or pathogenic *C9ORF72* repeat expansion (which results in TDP-43 pathology).

Monocytes in the blood and CSF in FTD

Beyond the increasingly appreciated role of brain-resident microglia in neurodegenerative disorders, circulating monocytes may also influence neurodegeneration-associated processes. Moreover, alterations in monocyte number, subtype and/or activation state may reflect analogous changes in brain microglia. It is thus important to understand whether monocytes are altered in FTD, both in the circulation and CSF. A recent study addressing these questions in detail found that the proportion of $CD14^+$ monocytes (relative to total leukocytes) was elevated in CSF specifically in PPA (n = 25) [13]. Conversely, non-classical $CD14^+/CD16^+$ monocytes were significantly increased in number and in proportion to total monocytes in blood specifically in bvFTD (n = 32). Interestingly, all FTD subtypes also showed suggestive increases in non-classical monocytes in the CSF as well. Though these results need to be replicated in independent cohorts, the possibility that monocytes, a

population of myeloid cells much more accessible than microglia, may show alterations in FTD is exciting and warrants further investigation.

Myeloid cell expression profiling in human brain

A recent large-scale comparison of brain myeloid cell expression profiles in mouse models of inflammation and neurodegeneration as well as human AD has identified both commonalities and important differences [14]. In particular, gene expression modules identified as specific to LPS treatment (as opposed to those identified in models of neurodegeneration) or associated with neutrophil and monocyte expression showed significant up-regulation in AD in the fusiform gyrus and temporal cortex, regions impacted early in disease; this differential expression was mostly not observed in neurodegeneration models. As mentioned above, these expression changes could reflect alterations in cellular composition and/or activation state.

It will be important to determine if similar myeloid-associated expression changes are observed in pathologically affected regions in FTLD. As a preliminary way to address this question, we tested genes from the 'neutrophil/monocyte' expression modules from Friedman et al. 2018 [14] for differential expression in (i) the *MAPT* P301L tauopathy model [15], (ii) the human cortex in *GRN*+ FTLD [16], and (iii) fusiform gyrus [14] and temporal cortex [17] in human AD. Intriguingly, we found that 8/16 genes available for analysis showed differential expression in P301L mice when grouped by P301L status and brain region (Figure 1, a–f), suggesting that the neutrophil/monocyte modules may also be relevant to FTLD-tau. While such changes were not observed in isolated hippocampal myeloid cells from 12-month-old P301L mice [14], the changes we observed in P301L may be attributable to analyzing multiple brain regions across the mouse lifespan and the use of bulk tissue rather than isolated myeloid cells. We also found that selected genes altered in the P301L model were differentially expressed in *GRN*+ FTLD cortex (Figure 1g). *CCND2*, encoding cyclin D2, showed significant decreases in cortical expression in the *MAPT* P301L model, in *GRN*+ FTLD, and in both AD datasets (Figure 1b, g, h). These findings suggest that differential expression of neutrophil/monocyte-associated genes may be a feature not only of AD, but also of FTLD-tau and FTLD-TDP.

Beyond the neutrophil/monocyte gene set, newly generated gene expression data from *MAPT* P301L and P301S tauopathy models in [14] suggest that a common set of neurodegeneration-associated myeloid genes are up-regulated in both tau and non-tau transgenic models of neurodegeneration, providing additional support for the notion that the human FTLD-tau brain may show myeloid-cell changes analogous to those observed in AD.

II. Mouse models relevant to FTLD

The past year has seen numerous advances in our understanding of immunological signatures relevant to FTLD from a variety of novel mouse models, including those modulating the function or expression of *Trem2*, *ApoE*, *Tbk1*, and *TARDBP* (encoding TDP-43). Emerging results from the study of peripheral myeloid cells in models of CNS injury and inflammation suggest that this population of cells is worthy of intensive investigation in the context of neurodegeneration.

TREM2

In humans, the R47H variant of the microglial receptor TREM2 increases risk for AD by approximately 3-fold [18,19], and a recent meta-analysis indicates that this variant may similarly increase risk for FTD [20]. Evidence suggests that the R47H allele is hypomorphic [21–23]; individuals heterozygous for R47H may therefore have insufficient TREM2 function. To date, most attempts to model the effects of *Trem2* deficiency in mice have relied on complete loss of *Trem2* (e.g., see [24]). Strikingly, however, a recent study using the *MAPT* P301S tauopathy model has found that *Trem2* haploinsufficient mice show evidence of exacerbated phospho-tau pathology in the cortex, as well as augmented deposition of a pathological conformer of tau in both hippocampus and cortex [25]. Intriguingly, complete loss of *Trem2* did not exacerbate tau pathology relative to that observed in *Trem2* wild type mice, suggesting that partial loss of Trem2 function is particularly detrimental in the context of tauopathy. It remains to be determined precisely how complete loss of Trem2 results in milder tau pathology relative to that observed in Trem2 haploinsufficient mice, although the strikingly altered gene expression pattern [25,26] and metabolism [27] of *Trem2*-null microglia likely underlies this phenomenon.

ApoE

The *APOE4* allele is the most potent known risk factor for late-onset AD, and recent genetic pleiotropy analysis indicates that it is also a risk factor for FTD [28]. Despite the clear pleiotropic effects of ApoE on multiple human brain cell types [29], a recent study has found that *Apoe* is expressed at very high levels in murine microglia (at the 99th percentile of all microglial transcripts) [30]. Furthermore, microglial *Apoe* expression is significantly up-regulated by both aging and the presence of mutant *APP/PS1* or *MAPT* transgenes [30], and this up-regulation appears to depend on signaling through *Trem2* [31]. Given that ApoE is a ligand for TREM2 [32,33], it appears that secreted ApoE may augment its own expression in microglia (either in an autocrine or paracrine manner) via TREM2 signaling [34], ultimately inducing a disease-associated microglial gene expression program [30,31].

A human *APOE4* knock-in (KI) allele has recently been reported to exacerbate tau pathology and neurodegeneration in *MAPT* P301S transgenic mice, relative to both E2 and E3 KI alleles and *Apoe* knockout (KO) mice [35], suggesting that the *E4* allele exerts a toxic gain of function. Moreover, this study demonstrated that *E4* KI microglia displayed an augmented inflammatory response to LPS treatment, and P301S^{+} *E4* KI mice showed greater numbers of activated microglia in the cortex and hippocampus relative to *E2* or *E3* KI mice or *Apoe* KO mice. Taken together, recent work on ApoE suggests that it potently modulates microglial function with important consequences for aging and neurodegeneration.

Microglia-mediated recovery from disease in a model of TDP-43 pathology

Pathologically proven FTLD-TDP cases are thought to occur on a spectrum with ALS, and a portion of FTLD-TDP cases develop subtle motor symptoms or concurrent ALS. Recent findings from mouse models of ALS with TDP-43 pathology may therefore inform shared pathophysiologic processes in FTLD-TDP. Until very recently, it was widely assumed that microgliosis exacerbated or even drove the development of TDP-43 pathology. On the

contrary, Spiller and colleagues elegantly illustrated that microgliosis is a critical step in the recovery of motor function after suppressing expression of a nuclear localization-defective form of TDP-43 [36]. Moreover, microglia-mediated recovery after TDP-43 insult was specific to CNS-derived microglia rather than infiltrating macrophages. Taken together, these findings suggest that enhancing the microglial response to neurodegenerative processes, rather than suppressing it, may prove key in the prevention or treatment of FTLD with TDP-43 pathology.

Along similar lines, pathogenic mutations in the autophagy regulator TBK1 can cause FTLD-TDP [37,38], and recent findings in mice indicate that partial loss of *Tbk1* is associated with both TDP-43 pathology and augmented CNS inflammation [39]. In the case of TBK1 haploinsufficiency, neuroinflammation (mediated by the kinase RIPK1) has been interpreted to be detrimental. Clearly, much remains to be understood regarding the effect of microglial activation even in the context of TDP-43 pathology.

Peripheral myeloid cells in models of neurodegeneration

The role of the peripheral immune system in promoting, inhibiting, or otherwise regulating neurodegenerative processes remains unclear. A recent report (described above) suggests it plays no role in TDP-43 clearance in mice [36]. By contrast, other recent work in traumatic spinal cord injury suggests there is a robust interaction between monocyte-derived macrophages (MDMs) and resident microglia, with MDMs decreasing microglial phagocytosis and preventing damage secondary to acute and chronic inflammation [40]. Despite the apparent lack of effect of MDMs in a model of TDP-43 proteinopathy, it remains to be determined whether MDMs or MDM–microglia communication regulate pathobiology in human FTLD. Regardless, MDM migration into the CNS remains a topic of interest given recent work showing that a failed MDM response to TGF-β precipitates demyelinating disease in mice [41]. In this context, failure to respond to TGF-β in the CNS could serve as both a nidus for incipient neurodegeneration and provocation for ongoing inflammation following monocyte recruitment into the CNS.

An emerging role for IL-33 in FTLD-like pathology?

Despite a lack of direct evidence for involvement in FTD, the cytokine IL-33 appears to be potentially involved in regulating tau pathology, with promising evidence from *Il33* KO mice. IL-33 plays a prominent role in the response to CNS injury and is expressed by mature oligodendrocytes and gray-matter astrocytes [42]. IL-33-deficient mice have prominent aggregations of insoluble, hyper-phosphorylated tau in cerebral cortex and hippocampus with corresponding cognitive deficits [43]. Of note, *Il33* KO mice also demonstrate abundant intra-neuronal vacuolation, suggesting abnormal lysosomal function. Recent findings indicate that astrocyte-secreted IL-33 regulates microglial synapse engulfment during neural development [44], thus potentially connecting a developmental role for microglia to later-life tau pathology. Finally, a recently identified loss-of-function variant in human *IL33* (0.65% frequency in Europeans) [45] that reduces eosinophil numbers and protects against asthma may be useful in future human studies on IL-33 and risk for tauopathy given that such *IL33* mutations may also increase risk for a human CNS phenotype similar to that reported in mice.

Conclusion

In this review we provided a focused summary and analysis of recent advances involving immunological signatures salient to FTD. We began with advances in human genetics, which indicate a striking level of genetic overlap between FTD and immune-mediated disorders. From genes we moved to an unbiased survey of proteins altered in FTD-spectrum disorders, which identified modules of microglial and inflammatory proteins that are up-regulated along the FTD-ALS spectrum.

Beyond microglia, we discussed recent findings indicating that monocytes may be up-regulated in the CSF in nfvPPA, while non-classical $CD16^{+}$ monocytes may increase in the blood in bvFTD. New transcriptional profiling data from human AD brain indicates substantial similarities with expression profiles derived from mouse models of neurodegeneration, but one striking difference appears to be a putative neutrophil/monocyte expression module altered preferentially in human AD. Given the recent finding that specific populations of monocytes may be altered in FTD and our analyses presented in Figure 1, it will be important to further explore neutrophil/monocyte-related gene expression profiles in independent FTLD cohorts.

Moving on to mouse studies, we discussed a new model of TREM2 haploinsufficiency that more closely mimics the hypomorphic R47H allele that increases risk for AD and FTD. Trem2 haploinsufficiency in mice appears to specifically exacerbate tau pathology, suggesting that partial loss of TREM2 function in humans may endow microglia with a unique, detrimental phenotype that promotes tauopathy. Beyond TREM2, the past year has witnessed a renaissance in our understanding of ApoE biology. While it is clear that ApoE can exert cell-autonomous and non-cell-autonomous effects on neurons, astrocytes and microglia, it is also apparent that ApoE drives a gene expression program downstream of TREM2 and in response to aging and neurodegeneration. The E4 allele of ApoE, now implicated as an FTD risk factor by pleiotropy analysis, has recently been shown to exacerbate tau pathology independent of its effects on amyloid pathology, and also promotes the presence of activated microglia in models of tauopathy.

Moving forward, the most important questions to address include determining whether microglial responses are generally beneficial or detrimental with regard to FTLD pathology, whether the nature of the response depends on the type of pathology (e.g., TDP-43 vs. tau), and whether the response changes over the course of disease. Beyond microglia, there are preliminary suggestions that peripheral myeloid cells may show significant alterations in FTD, just as there are now hints that some non-microglia myeloid cells may be present in the AD brain. It will thus be crucial to determine which additional immune cell populations are most relevant in FTD. Work from mouse models indicates that, at least in some contexts, activation of microglia in the context of ongoing TDP-43 pathology may have a profound, beneficial effect. The next few years of research are likely to greatly enhance our understanding of immunological mechanisms in FTLD and related forms of neurodegeneration.

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Key points

- Recent genetic, transcriptomic and proteomic studies indicate altered immune system function in FTD-spectrum disorders.
- Emerging evidence suggests that, beyond brain-resident microglia, peripheral myeloid cells may also be altered in FTD.
- Mouse models relevant to FTD suggest important roles for *Trem2*, *Apoe* and *Tbk1* in regulating microglial function and the neuroinflammatory response.

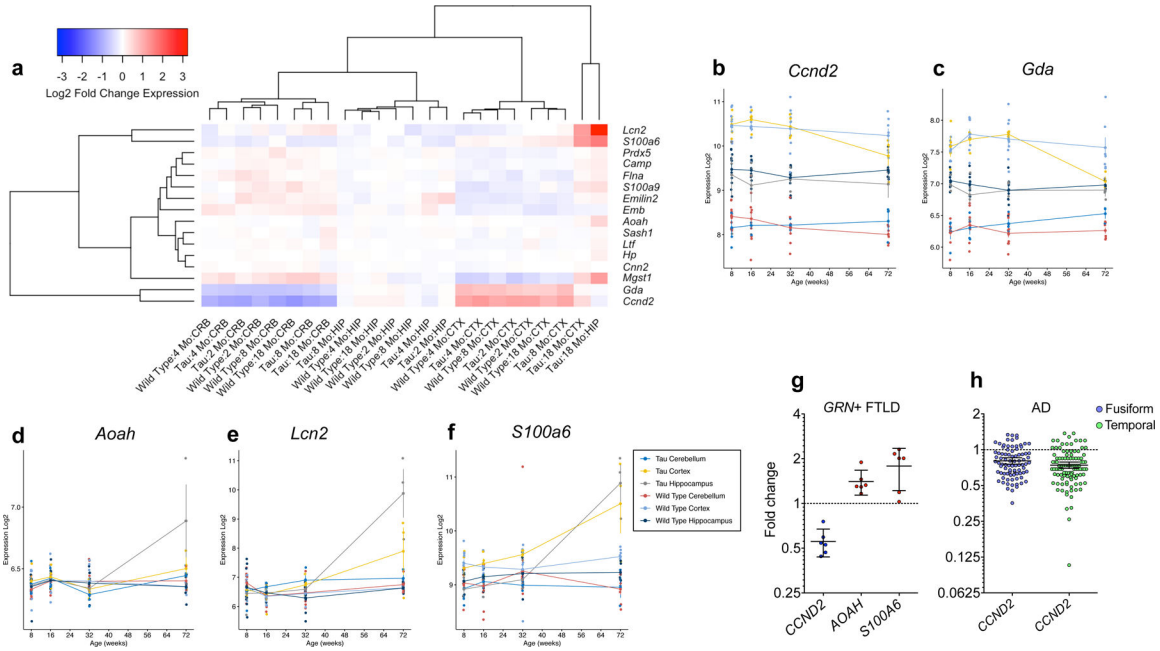

Figure 1. Neutrophil/monocyte expression module genes show differential expression in a model of FTLD-tau, in human *GRN*+ FTLD, and in human AD.

Heatmap and line plots depict neutrophil/monocyte gene module [14] expression changes in P301L transgenic mice relative to wild type mice across lifespan (data from [15]; http://www.mouseac.org; GSE64398). (**a**) Average fold change in expression for each of the 16 myeloid genes with data available is depicted by heatmap. Tissue type (i.e., cortex, hippocampus, or cerebellum) was the predominant grouping when organized by columns, followed by tau status and age, with the exception of 18-month-old P301L hippocampus and cortex, which were categorized separately (far right on heatmap). Fold change in expression was calculated for each group (e.g., cerebellar tissue from 4-month-old wild type mice) relative to average expression for each gene. (**b-f**) Expression profiles are shown for selected genes that were differentially expressed over mouse lifespan when grouped by P301L status, tissue type, and age ($p_{raw} < 0.05$ by ANOVA). (**b,c**) *Ccnd2* and *Gda* (encoding cyclin D2 and guanine deaminase, respectively) were expressed most highly in cortex and hippocampus in P301L mice and showed decreased expression at 18 months in P301L cortex. (**d-f**) *Aoah*, *Lcn2*, and *S100a6* (encoding Acyloxyacyl hydrolase, Neutrophil gelatinase-associated lipocalin, and S100-A6 [Calcyclin], respectively) were remarkable for increased expression during aging in P301L cortex and/or hippocampus. (**g,h**) Fold change in expression was calculated for each gene relative to its average expression level in the control group. (**g**) *CCND2*, *AOAH*, and *S100A6* were determined to be differentially expressed in human *GRN* + FTLD cortex using the Brain Myeloid Landscape (BML) tool ($p_{adj} < 0.05$; [14]; http://research-pub.gene.com/BrainMyeloidLandscape). To independently confirm these changes, we performed secondary statistical analysis on the *GRN*+ FTLD cortex data ([16]; GSE13162), including age, sex, and postmortem interval as covariates. Consistent with the primary analysis, at least one microarray probe for each of these genes showed significant differential expression (*CCND2*, $p_{raw} < 0.004$; *AOAH*, $p_{raw} < 0.02$; *S100A6*, $p_{raw} < 0.0002$). (**h**) *CCND2* was further analyzed for differential expression in human AD brain using BML,

and was found to be significantly decreased in fusiform gyrus ($p_{adj} < 0.05$; [14]; GSE95587) and temporal cortex ($p_{adj} < 0.0001$; [17]; GSE15222). Error bars represent 95% confidence intervals.