Neuroinflammation is a pathological feature of several neurodegenerative diseases, including Alzheimer’s disease (AD) and amyotrophic lateral sclerosis (ALS), raising the possibility of common therapeutic targets. However, triggers of innate immune signaling in these disease processes remain elusive.

We previously established that cdsRNA, an established trigger of innate immunity, is spatially coincident with cytoplasmic phosphorylated TAR DNA-binding protein 43 (pTDP-43) inclusions, a pathologic hallmark of ALS and AD, in neurons of patients with C9ORF72-mediated ALS. Up to 50% of brains with AD pathology harbor cytoplasmic pTDP-43 aggregation. We also found that cdsRNA is spatially coincident with pTDP-43 inclusions in brain cells of patients with AD, a striking pathological similarity to ALS. Consistent with this finding, RNA sequencing analysis on AD patients further showed that type-I interferon signaling is significantly elevated in brain regions affected by AD.

Cytoplasmic inclusions of pTDP-43 may confer nuclear hypofunction of TDP-43, which increases expression of cryptic exons in STMN2 and UNC13A. Thus, we modified our machine-learning pipeline, DRIAD (Drug Repurposing In Alzheimer’s Disease), to incorporate cryptic exon detection as a proxy for pTDP-43 inclusions. Using DRIAD, we demonstrated that baricitinib and ruxolitinib (FDA-approved JAK inhibitors that block interferon signaling) show a protective signal only in cryptic exon-expressing brain regions. These results indicate that targeting JAK-mediated immune responses is not only relevant in ALS but also in the cdsRNA/pTDP-43-positive subset of AD.

We conducted a CRISPR screen in an in vitro model of cdsRNA-mediated death in differentiated human neural cells lacking microglia to identify genes whose ablation rescues the phenotype. Both the interferon receptor subunit IFNAR2 and the JAK family member TYK2 were top hits. Experimentally inhibiting the activity of IFNAR2 and TYK2 (using a blocking antibody and an FDA-approved inhibitor, respectively) rescued the cdsRNA-induced toxicity, validating these two hits and supporting further efforts to target this pathway. Together, these findings demonstrate the potential for brain-penetrant TYK2 inhibitors as drug candidates for some forms of AD, ALS, and potentially other incurable neurodegenerative diseases.