Commentary

Syk and Yea Shall Find

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The article by Ghosh and Ghealen in the current issue of EBioMedicine provides new insights into the pathophysiology of the inflammatory system in Alzheimer’s disease (AD). The story describing the accumulation of aggregated proteins in the AD brain, including β-amyloid and tau protein, has been developing since Alois Alzheimer first identified neurofibrillary tangles with a silver stain more than 100 years ago. Classically, neuritic plaques composed of aggregated Aβ peptides accumulate in the neuropil, outside neurons and glia, while neurofibrillary tangles composed of aggregated tau accumulate within neurons. The localization of these proteins necessarily focused attention on neuronal dysfunction in AD.

However, all neurodegenerative diseases also suffer from a dysfunctional inflammatory response, but the biological basis of this response is largely unknown. The classic model for the inflammatory response posits the presence of two states: M1, a cytotoxic state, and M2, a regenerative state. This simple model describing M1 and M2 in AD was initially appealing but now appears to insufficiently describe the varied immunological states characteristic of the AD brain. This model appears to be inadequate because it omits the process of phagocytosis, which appears to play a very important role in AD.

Recent Genome-wide Association Studies have implicated triggering receptor expressed on myeloid cells 2 (TREM2) and CD33, both of which regulate microglial phagocytosis, in AD. The signaling pathway leading from TREM2 plays a key role in the article by Ghosh and Ghealen. TREM2 couples to TYRO protein tyrosine kinase binding protein (TYROBPs), which then recruits spleen tyrosine kinase (Syk) to the phosphorylated immunoreceptor tyrosine-based activation motif (ITAM) of TYROBP, and activates phagocytosis (N'Diaye et al., 2009). CD33 is also a risk factor for AD, but acts in opposition to TREM2. CD33 binds to Syk through its immunoreceptor tyrosine-based inhibitory motif (ITIM) domain and inactivates the phagocytic response of microglia. These studies suggest that TREM2 and CD33 play important reciprocal roles in regulating the phagocytic function of microglia in the CNS, with Syk acting as a downstream kinase that mediates the actions of TREM2 and CD33 on phagocytosis. However the actions of Syk in AD are poorly understood. In addition, little is known about how Aβ might affect Syk activity in microglia.

Enter the article by Ghosh and Ghealen, which highlights a surprising interaction between Syk and GTPase activating protein binding protein (G3BP), which binds RNA. RNA binding proteins are a fascinating group of proteins, several of which have already been genetically linked to motor neuron degenerative diseases, that regulate RNA metabolism in the nucleus and cytoplasm. While in the nucleus, RNA binding proteins regulate functions like RNA splicing and transcription. Upon translocation to the cytoplasm, they control the localization, transport and translational activity of mRNA. They do so through a unique mechanism mediated by reversible aggregation into macromolecular stress granules via low complexity, prion-like domains present in most RNA binding proteins. Normal physiological aggregation in the biology of RNA binding proteins suggests a provocative connection with the pathophysiology of neurodegenerative diseases, where pathological protein aggregation plays a prominent role.

Until now, pathological protein aggregation was thought to be limited to within neurons or to the extracellular space. In the current article, Ghosh and Ghealen highlight a pathological microglial response that occurs after Aβ treatment. They show that treating microglial cells with Aβ causes formation of persistent, abnormally large G3BP granules. The finding of large, potentially pathological G3BP granules is important because it expands the aggregation story from the classic pathology-associated aggregates of tau within neurons to include a potentially new type of pathological aggregate composed of G3BP. The presence of these large G3BP aggregates is consistent with studies from our group showing the presence of seemingly pathological accumulations of G3BP in brain samples from human cases with AD and both human and mouse cases of tauopathy (Vanderweyde et al., 2012, Vanderweyde et al., 2013).

Ghosh and Ghealen also make the striking observation that phosphorylated Syk translocates to G3BP granules after exposure to Aβ. This suggests a mechanism whereby chronic activation of Syk could cause microglial dysfunction by Syk sequestration. We still don’t know what is the binding partner of phosphorylated Syk in stress granules, and how Syk is recruited to them. Moreover, the downstream effects of Syk translocation to G3BP granules remain to be determined. The authors note that activated microglia show induction of pro-inflammatory cytokines by Aβ, including interferon gamma (IFN-γ), interleukin 1β (IL-1β) and monocyte chemoattractant protein 1 (MCP-1). These are...
all known to suppress Aβ degradation in microglia and macrophages after Aβ phagocytosis and enhance Aβ accumulation in mouse brains (Yamamoto et al., 2008, Yamamoto et al., 2005) (Yamamoto et al., 2007). This study sheds new light on upstream mechanisms of cytokine production upon Aβ stimulation of microglia, namely through the Syk-stress granule axis.

The work of Ghosh and Ghealen might also help to elucidate an important controversy in the inflammation field: why does the response of microglia to TREM2 inactivation differ between mouse models and human diseases? Loss of function mutations of TREM2 or TYROBP are linked to highly inflammatory Nasu-Hakola disease in human, whereas disruption of TREM2 in amyloid precursor protein (APP)-overexpressing mice, a model of AD, results in reduced inflammation and Aβ accumulation in mouse brain (Jay et al., 2015). One possibility is the species-specific heterogeneity in Syk-associated stress granule complex, which may have contrasting biological outputs dependent on their molecular configuration. In highlighting the interaction between Syk and G3BP granules, the work of Ghosh and Ghealin potentially opens a new chapter in our understanding of pathophysiological mechanisms of inflammation and microglia in AD, opening doors to novel therapies.

Conflicts of Interest

Benjamin Wolozin is co-founder and CSO of Aquinnah Pharmaceuticals, Inc.

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