Y. Alvin Huang, MD PhD (Brown University, USA)

ABSTRACT

Title:
The signaling function of CHI3L1/YKL-40 in neuroinflammation and Alzheimer's disease

Background:
Chitinase-3-like protein 1 (CHI3L1, or YKL-40) is an important regulator of immunity and, in the brain, is primarily secreted by activated astrocytes and heralds a neurotoxic inflammatory state. While it has been well known as a high-profile biomarker for Alzheimer's disease (AD) and inflammatory brain conditions such as aging and CNS autoimmune disorders, the biological role of CHI3L1 in neuroinflammation and AD pathogenesis remains to be elucidated. Here, we sought to define the signaling mechanism whereby CHI3L1 governs inflammatory neurotoxicity and neurodegeneration for future translation into much-needed therapeutic.

Method:
We used a combination of in-vitro and in-vivo tools to recapitulate and manipulate CHI3L1 secretion in neuroinflammation, including i) cultures of primary mouse astrocytes and neural stem cells (NSCs), and iPSC-derived cultures of human neurons, astrocytes and microglia; and ii) established mouse models of Chi3l1/Chil1 conditional knockout and overexpression and autoimmune-mediated astrocytopathy hallmarked by CHI3L1 induction. For the functional outputs of CHI3L1 manipulations in the context of neuroinflammation and neurodegeneration, we focused on analyzing cellular features of inflammatory toxicity and neurodegeneration in NSCs and neurons.

Results:
We first confirmed the induction of CHI3L1 and neuroinflammatory features in cultured astrocytes activated by well-characterized pro-inflammatory stimuli, including the cytokine IL-1β and the autoantibody targeting astroglial protein aquaporin 4 (AQP4 IgG; as in the CNS autoimmune disorder neuromyelitis optica, NMO). Strikingly, astrocyte-secreted CHI3L1 inhibited proliferation and neuronal differentiation of NSCs, and enhanced Aβ production, tau phosphorylation and apoptosis in differentiated neurons in vitro. In vivo, we analyzed brain tissues from mice overexpressing CHI3L1 or receiving stereotaxic transfer of AQP4 IgG, and observed a significant reduction in adult hippocampal neurogenesis and defective learning behaviors; such in-vivo defects, of note, can be rescued by CHI3L1 depletion in astrocytes. We further characterized the molecular mechanism of CHI3L1 by identifying the receptor and downstream pathway in NSCs. Mechanistically, CHI3L1 engages the CRTH2 receptor and dampens β-catenin signaling, which is critical for neurogenesis. Finally, we showed that this CHI3L1/CRTH2/β-catenin cascade can be targeted to restore neurogenesis and ameliorate cognitive deficits resulting from neuroinflammation.

Conclusion:
Our findings provide the pioneering evidence for the biological role of CHI3L1 in the brain, departing from its long-regarded role as merely a biomarker. The discoveries we made here would be highly advantageous for the development of much-needed therapeutics to prevent neuroinflammatory toxicity in AD and relevant brain disorders.