REPORT FROM:

Imagine Institute, the Institute of Brain & Spine

Alzheimer's disease (AD) is the most common neurodegenerative disease, but the underlying molecular and cellular events that lead to it are not completely understood. It is known that inflammation plays an important role, so our goal is to study the role of mast cells, a type of immune cells involved in inflammation. Mast cells can play both detrimental and protective roles in various pathological settings. Importantly, these cells have recently been suggested to play a role in neurodegenerative diseases and neuroinflammation, but their contribution to these processes is poorly understood. For example, mast cells are found in higher numbers around amyloid plaques in AD patients and possibly at an early stage, possibly even before other important cells and could therefore be considered as early responders.

Masitinib, a drug inhibiting mast cell functions, has been proven efficient (as an adjunct therapy) in AD in a phase II clinical trial. In an AD mouse model, masitinib had beneficial effects on learning. This result and others suggest that mast cells can, in specific conditions, be toxic for the neurons. Our lab has identified three gene families in mast cells with reported roles in neuropathological settings:

a. Insulin-regulated aminopeptidase (IRAP): We suggest that IRAP is a new regulator of the inflammatory response of mast cells. A chemical targeting of IRAP by a small molecule inhibitor reduced pro-inflammatory cytokine secretion upon mast cell activation in vitro and in vivo.
b. Epdr1 is a secreted protein that was found to be secreted/expressed in an IRAP-dependent manner. GWAS data analysis yielded that genetic variants of Epdr1 are associated with the risk of developing Alzheimer's disease. This data provides a strong rationale for the study of Epdr1 in mast cell-dependent inflammation and neurodegeneration.
c. Phospho-histidine kinases and phosphatases: Increased extracellular Nme1 has been detected both in vitro in a model of brain injury as well as in post-mortem cerebrospinal fluid (a model for neurodegeneration) suggesting that it could also be a marker or functional player in neurodegenerative diseases. Nme1 increased neuronal survival in an injury model suggesting a neuroprotective activity.

These findings, and our continued research, provide hope that a treatment for Alzheimer's disease is within reach.