Discovery identifies new RX target for age-rleated macular degeneration and Alzheimer's

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For the first time, researchers at LSU Health New Orleans have shown that a protein critical to the body's ability to remove waste products from the brain and retina is diminished in age-related macular degeneration (AMD), after first making the discovery in an Alzheimer's disease (AD) brain. The research team, led by Walter Lukiw, PhD, Professor of Neurology, Neuroscience and Ophthalmology at LSU Health New Orleans Neuroscience Center, also discovered a key reason, identifying a new treatment target. The paper, microRNA-34a-mediated down-regulation of the microglial-enriched triggering receptor and phagocytosis-sensor TREM2 in age-related macular degeneration, was published March 7, 2016, online at in the journal, *PLOS ONE*.

During their normal day-to-day operation, the brain and retina produce relatively large quantities of waste products, which have to be cleared away so that they do not clog up the delicate parts of the thinking and visual system. Part of the waste disposal system consists of a very special waste-sensing transmembrane protein located in highly specialized cells called microglial cells found in the brain and retina. This waste-sensing protein in microglial cells is known to scientists as the "triggering receptor expressed in microglia," or TREM2 protein.

In this work, the researchers examined human AD-affected brain and AMD-affected retina, the retina of aging 5xFAD transgenic animals and microglial and other brain and retinal cells in culture.

"We have discovered that in age-related degenerative diseases of the brain, such as Alzheimer's disease, and the retina, such as age-related macular degeneration, there is a lowered and insufficient amount of TREM2 protein, and this may be in part responsible for the inability of the brain and retina to clear away their end-stage waste products," notes Dr. Lukiw, who is also the Bollinger Professor of Alzheimer's Disease at LSU Health New Orleans.

These waste products consist chiefly of amyloid—misfolded proteins, small various remnants of the innate immune system, small, very sticky toxic proteins and prominently, a 42-amino acid amyloid protein called Aβ42 peptide. Because they cannot be properly removed, the waste products accumulate in the brain and retina and contribute to the progressive appearance of insoluble lesions called senile plaques in the brain and drusen in the retina. These lesions ultimately contribute to episodes of age-related inflammatory degeneration.

"We have also discovered that an excessive amount of a small piece of ribonucleic acid (RNA) called microRNA-34a, or miRNA-34a, is in part responsible for insufficient TREM2 protein," adds Dr. Lukiw. "These scientific findings further indicate that getting rid of the excessive miRNA-34a to restore normal TREM2 abundance may provide a highly effective therapeutic strategy for the treatment of both degenerative diseases of the brain, such as Alzheimer's disease, and progressive diseases of the retina, such as age-related macular degeneration."

More information: Surjyadipta Bhattacharjee et al. microRNA-34a-Mediated Down-Regulation of the Microglial-Enriched Triggering Receptor and Phagocytosis-Sensor TREM2 in Age-Related Macular Degeneration, *PLOS ONE* (2016). DOI: 10.1371/journal.pone.0150211