Cellular Physiology: Key to Survival

Any living organism requires nutrients to survive. From where do cells obtain their nutrients?

The following is provided for discussion purposes with qualified computational biology professionals to describe the mechanisms for creating nutrients and the ways in which cells "eat."

TREM-2 is part of the signaling for phagocytosis that is one of the means of transporting essential epigenetic factors into the cytoplasm. It has three forms; positive TREM1 (acetylation - "on"), negative TREM2 (methylation - "off") and TREM3 (transitional - "modulating").

TREM regulates the activities for endocytosis that allows "intake" from the surface of cells into the cytoplasm.

Quantum Computational Biology (QCB) modeling has identified, with near certainty, that extracellular autophagy (SOD3) based on histidine - arginine activity is critical for TREM to "cleave" elements to prepare them for transitioning into the cytoplasm where SOD1 can "feed" cells using endocytosis.

These activities would apply to all chronic diseases; not only Alzheimer's. In other words, mutation of autophagy can be the result of SOD3 and SOD1.

https://neurosciencenews.com/alzheimers-genetics-inflammation-14461/

'Crosstalk' between genes promotes brain

inflammation in Alzheimer's

NEUROSCIENCE NEWSJULY 11, 2019

Summary: *Findings could help in the development of treatments to prevent brain inflammation associated with Alzheimer's disease.*

Source: *Mass General*

A new study by scientists at Massachusetts General Hospital (MGH) offers clues about how to prevent inflammation of brain tissue, which promotes Alzheimer's disease (AD). The findings of this study online now and appearing in the September 4, 2019 print issue of the journal *Neuron*, could contribute to the development of new therapies for AD.

It's known that the brains of people with AD fill with deposits of damaged nerve cells and other proteins, known as amyloid plaques, as well as tangled formations of proteins called tau. "But if you just have plaques and tangles alone, you probably won't develop Alzheimer's disease for a long time, if at all," says neuroscientist Rudolph E. Tanzi, PhD, director of the Genetics and Aging Research Unit at MGH, and senior author of the Neuron study. Rather, explains Tanzi, it's the inflammation that occurs in response to plaques and tangles, or neuroinflammation, that is the primary killer of neurons, which leads to cognitive decline.

Tanzi's lab discovered the first gene associated with neuroinflammation in AD, known as CD33, in 2008. CD33 carries the genetic code for receptors found on microglia cells, which normally act as one of the brain's housekeepers, clearing away neurological debris, including plaques and tangles. In 2013, Tanzi and colleagues published their discovery that CD33 influences the activity of microglia: When the gene is highly expressed, microglia turn from housekeepers to neuron killers, sparking neuroinflammation.

Meanwhile, other investigators identified another gene, TREM2, which has the opposite effect of CD33: It shuts down microglia's capacity to promote neuroinflammation. In other words, says Tanzi, CD33 is the "on" switch for neuroinflammation, while TREM2 acts like an "off" switch. "The Holy Grail in this field has been to discover how to turn off neuroinflammation in microglia," says Tanzi.

In their most recent inquiry, Tanzi, neuroscientist Ana Griciuc, PhD, and their colleagues set out to discover how CD33 and TREM2 interact, and what role that "crosstalk" might play in neuroinflammation and the origin of AD. To do that, they posed a question: What happens when these critically important genes are silenced–individually and simultaneously?

To find answers, Tanzi and his team studied laboratory mice specially bred to have brain changes and behavior consistent with AD. The team began by observing and testing a strain of AD mice

that had their CD33 genes turned off. They discovered that these mice had reduced levels of amyloid plaque in their brains and performed better than other AD mice on tests of learning and memory, such as finding their way in a maze. However, when mice had both CD33 and TREM2 silenced, the brain and behavior benefits disappeared–which also happened when only a single TREM2 gene was quieted. "That tells us that TREM2 is working downstream of CD33 to control neuroinflammation," says Tanzi. That theory was bolstered by sequencing of microglia RNA, which indicated that both CD33 and TREM2 regulate neuroinflammation by increasing or decreasing activity of an immune cell called IL-1 beta and the cell receptor IL-1RN.

"We are increasingly realizing that to help Alzheimer's patients, it is most critical to stop the massive brain nerve cell death that is caused by neuroinflammation," says Tanzi.

"We now see that the CD33 and TREM2 genes are the best drug targets for achieving this goal."

The primary authors of the Neuron paper are Ana Griciuc, PhD, an assistant professor of Neurology at MGH and Harvard Medical School (HMS); and Rudolph Tanzi, PhD, vice-chair of the department of Neurology and director of the Genetics and Aging Research Unit at MGH, and the Joseph P. and Rose F. Kennedy Professor of Neurology at Harvard Medical School. Tanzi is also scientific advisor for and an equity stakeholder in AZTherapies, a Boston-based company that is testing a drug designed to reduce neuroinflammation called ALZT-OP1 in a phase III clinical trial.

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Abstract

TREM2 Acts Downstream of CD33 in Modulating Microglial Pathology in Alzheimer's Disease

Highlights
• Mitigation of Aβ pathology in 5xFAD;CD33 −/− mice is abrogated by knocking out TREM2
• Reduction of Iba1 + cells in 5xFAD;TREM2 −/− mice is not rescued by knocking out CD33
• CD33 and TREM2 knockout increase and reduce microglial activation, respectively
• Gene expression changes in 5xFAD;CD33 −/− microglia depend on the presence of TREM2

Summary
The microglial receptors CD33 and TREM2 have been associated with risk for Alzheimer's disease (AD). Here, we investigated crosstalk between CD33 and TREM2. We showed that knockout of CD33 attenuated amyloid beta (Aβ) pathology and improved cognition in 5xFAD mice, both of which were abrogated by additional TREM2 knockout. Knocking out TREM2 in 5xFAD mice exacerbated Aβ pathology and neurodegeneration but reduced Iba1 + cell numbers, all of which could not be rescued by additional CD33 knockout. RNA-seq profiling of microglia revealed that genes related to phagocytosis and signaling (IL-6, IL-8, acute phase response) are upregulated in 5xFAD;CD33 −/− and downregulated in 5xFAD;TREM2 −/− mice. Differential gene expression in 5xFAD;CD33 −/− microglia depended on the presence of TREM2, suggesting TREM2 acts downstream of CD33. Crosstalk between CD33 and TREM2 includes regulation of the IL-1β/IL-1RN axis and a gene set in the "receptor activity chemokine" cluster. Our results should facilitate AD therapeutics targeting these receptors.