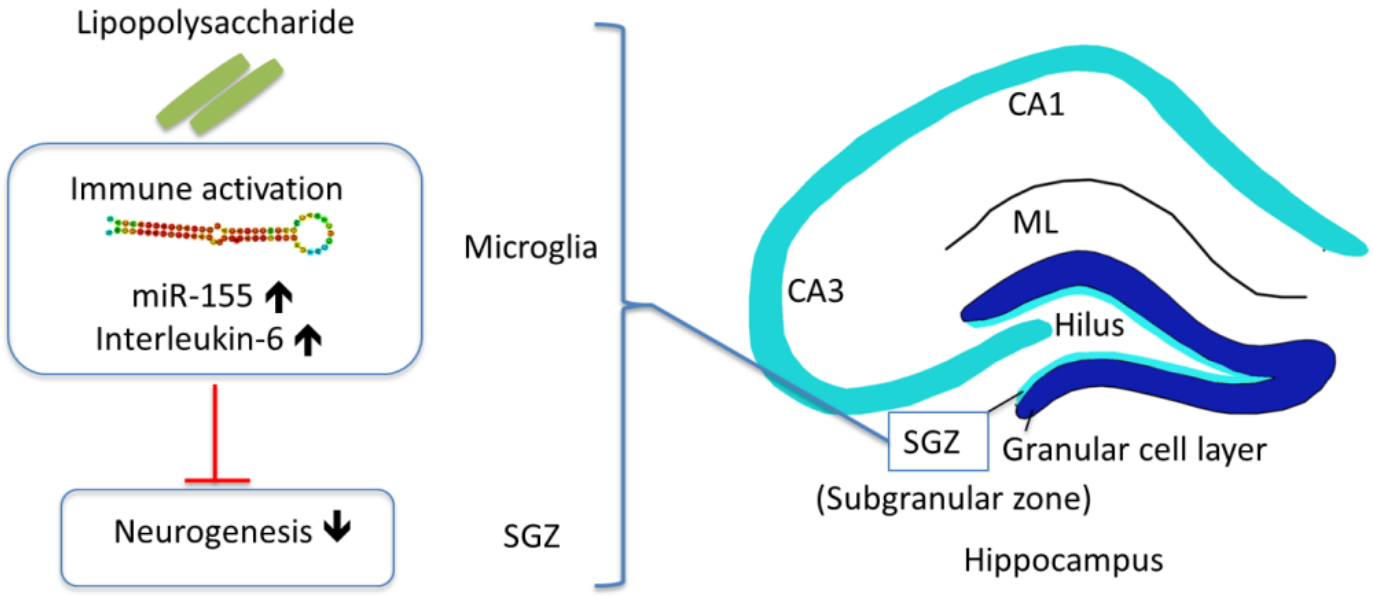
A small RNA, microRNA-155, “micromanages” inflammation and renewal of neurons in the brain

The immune system is like a silent army, protecting the body from enemy viruses and bacteria. Inflammation is part of this response, acting to eliminate pathogens and initiate tissue repair.

Most of the time, our immune systems silently fight off invaders; however, excess inflammation can be damaging. Inflammation in the brain leads to abnormal neural development and regeneration, yet little is known about how inflammation causes these neurogenic abnormalities. microRNAs are small genetic molecules that regulate the expression of other genes, thereby helping to orchestrate most biological processes in humans and animals. They are known to control inflammatory responses throughout the body. We investigated the role of a specific microRNA, miR-155, in regulation of the inflammatory response in the brain.



A clue pointing towards miR-155 is its presence at high levels in the central nervous system of patients with inflammation-related disorders, including multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS; also called Lou Gehrig’s disease), and Down syndrome. Recent studies have shown that suppression of miR-155 is beneficial for reducing disease progression in animal models of ALS and MS, suggesting that its high expression may be a causative factor for brain damage.

How does inflammation affect the adult brain? The adult brain is not static, and actually has the ability to renew neurons (neurogenesis) and make new connections. The hippocampus, a structure important for learning and memory, is one of few brain areas where neurogenesis happens in adults. During the immune response, signaling molecules called cytokines are released from

immune cells to mediate inflammation. Some cytokines, such as interleukin-6 (IL6), alter neurogenesis. We showed that when adult mice were treated with an inflammation activator (lipopolysaccharide, a component of bacteria), neurogenesis was decreased in the hippocampus. We found that this is mediated by IL6 production from microglia, the brain's immune cells, and miR-155 is essential for the IL6 production. Since neurogenesis is thought to support learning and memory, these changes could be detrimental for adult brain function, and could lead to abnormal brain development in children.

Using genetically altered mice lacking miR-155, we found that miR-155 mediates the decrease in neurogenesis and increase in microglia in response to lipopolysaccharide (see figure). Genetic expression of higher levels of miR-155 reproduced the suppressed neurogenesis and enhanced inflammation seen in the mouse brain treated with lipopolysaccharide. Our results show that miR-155 is a key molecule for inflammation-mediated suppression of neurogenesis in the adult brain.

This study proves the fundamental role of miR-155 in the brain's response to inflammation, and may be a promising therapeutic target for neuroinflammatory diseases. Currently, we are investigating if pharmacologic interventions of the miR-155 pathway correct hippocampal neurogenesis in animal models of neurologic disorders.

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Publication

miR-155 Is Essential for Inflammation-Induced Hippocampal Neurogenic Dysfunction.
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