Reprogramming the Brain's Cleaning Crew to Mop Up Alzheimer's Disease

Summary: *Using CRISPR gene editing, researchers were able to control microglia and reverse their toxic state associated with Alzheimer's disease, and put them back on track.*

Source: UCSF

The discovery of how to shift damaged brain cells from a diseased state into a healthy one presents a potential new path to treating Alzheimer's and other forms of dementia, according to a new study from researchers at UC San Francisco.

The research focuses on microglia, cells that stabilize the brain by clearing out damaged neurons and the protein plaques often associated with dementia and other brain diseases.

These cells are understudied, despite the fact that changes in them are known to play a significant role Alzheimer's and other brain diseases, said Martin Kampmann, PhD, senior author on the study, which appears Aug. 11 in *Nature Neuroscience*.

"Now, using a new CRISPR method we developed, we can uncover how to actually control these microglia, to get them to stop doing toxic things and go back to carrying out their vitally important cleaning jobs," he said. "This capability presents the opportunity for an entirely new type of therapeutic approach."

Leveraging the Brain's Immune System

Most of the genes known to increase the risk for Alzheimer's disease act through microglial cells. Thus, these cells have a significant impact on how such neurodegenerative diseases play out, said Kampmann.

Microglia act as the brain's immune system. Ordinary immune cells can't cross the blood-brain barrier, so it's the task of healthy microglia to clear out waste and toxins, keeping neurons functioning at their best. When microglia start losing their way, the result can be brain inflammation and damage to neurons and the networks they form.

Under some conditions, for example, microglia will start removing synapses between neurons. While this is a normal part of brain development in a person's childhood and adolescent years, it can have disastrous effects in the adult brain.

Over the past five years or so, many studies have observed and profiled these varying microglial states but haven't been able to characterize the genetics behind them.

Kampmann and his team wanted to identify exactly which genes are involved in specific states of microglial activity, and how each of those states are regulated. With that knowledge, they could then flip genes on and off, setting wayward cells back on the right track.

From Advanced Genomics to a Holy Grail

Accomplishing that task required surmount fundamental obstacles that have prevented researchers from controlling gene expression in these cells. For example, microglia are very resistant to the most common CRISPR technique, which involves getting the desired genetic material into the cell by using a virus to deliver it.

To overcome this, Kampmann's team coaxed stem cells donated by human volunteers to become microglia and confirmed that these cells function like their ordinary human counterparts. The team then developed a new platform that combines a form of CRISPR, which enables researchers to turn individual genes on and off—and which

Kampmann had a significant hand in developing—with readouts of data that indicate functions and states of individual microglia cells.
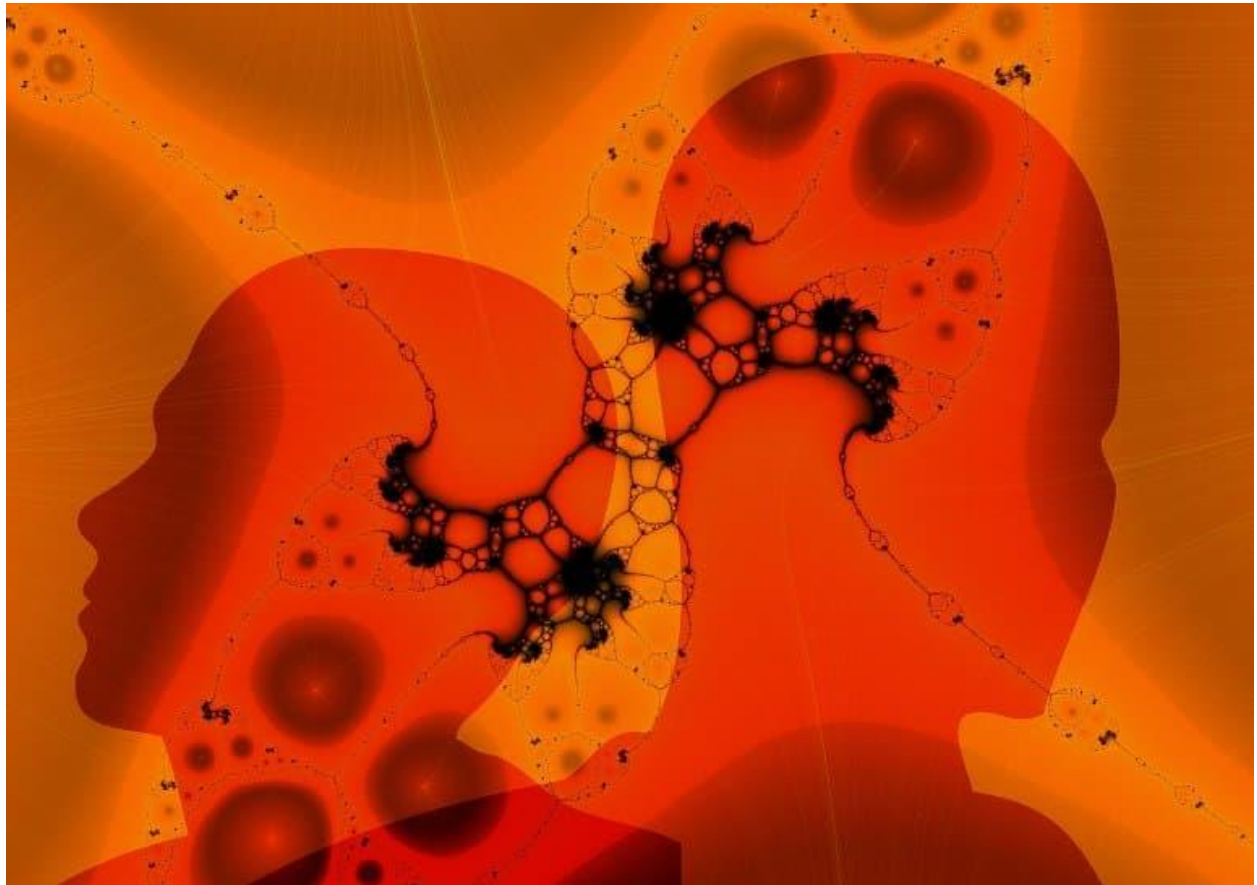
The research focuses on microglia, cells that stabilize the brain by clearing out damaged neurons and the protein plaques often associated with dementia and other brain diseases. Image is in the public domain

Through this analysis, Kampmann and his team pinpointed genes that effect the cell's ability to survive and proliferate, how actively a cell produces inflammatory substances, and how aggressively a cell prunes synapses.

And because the scientists had determined which genes control those activities, they were able to reset the genes and flip the diseased cell to a healthy state.

Armed with this new technique, Kampmann plans to investigate how to control the relevant states of microglia, by targeting the cells with

existing pharmaceutical molecules and testing them in preclinical models. He hopes to find specific molecules that act on the genes necessary to nudge diseased cells back to a healthy state.

Kampmann said that once the right genes are flipped, it's likely that the "repaired," microglia will resume their responsibilities, removing plaques associated with neurodegenerative disease and protecting synapses rather than taking them apart.

"Our study provides a blueprint for a new approach to treatment," he said. "It's a bit of a holy grail."

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May 12, 2022

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About this Alzheimer's disease and gene editing research news

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Abstract

A CRISPRi/a platform in human iPSC-derived microglia uncovers regulators of disease states

Microglia are emerging as key drivers of neurological diseases. However, we lack a systematic understanding of the underlying mechanisms.

Here, we present a screening platform to systematically elucidate functional consequences of genetic perturbations in human induced pluripotent stem cell-derived microglia.

We developed an efficient 8-day protocol for the generation of microglia-like cells based on the inducible expression of six transcription factors. We established inducible CRISPR interference and activation in this system and conducted three screens targeting the 'druggable genome'. These screens uncovered genes controlling microglia survival, activation and phagocytosis, including neurodegeneration-associated genes.

A screen with single-cell RNA sequencing as the readout revealed that these microglia adopt a spectrum of states mirroring those observed in human brains and identified regulators of these states. A disease-associated state characterized by osteopontin (SPP1) expression was selectively depleted by colony-stimulating factor-1 (CSF1R) inhibition.

Thus, our platform can systematically uncover regulators of microglial states, enabling their functional characterization and therapeutic targeting.