Study provides insight into how dying neurons control eating behaviors of the brain microglia

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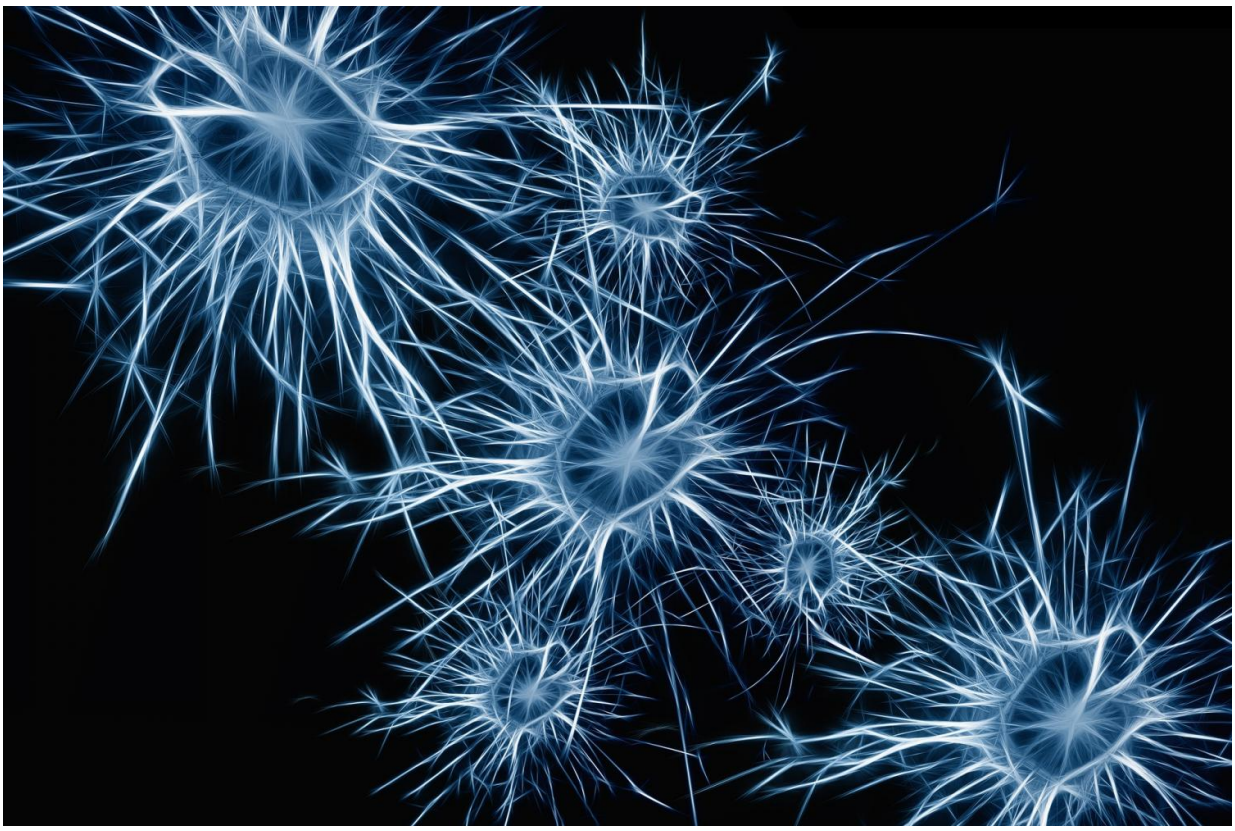

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A new Mount Sinai study, published July 23 in the journal *Nature Neuroscience*, provides important insight into how microglia, cells that

form a branch of the immune system inside the brain, go about their job of clearing out dying and non-functional neurons—and how they sometimes mistakenly attack healthy neurons, an event that can play a role in neurodegenerative diseases like Alzheimer's and Parkinson's diseases.

The functionality of neurons, highly sensitive cells, begins to decline as a person ages. When neurons die, they don't die unnoticed; they activate their neighbors, the microglia. The ability to clear biological debris makes microglia both a friend and foe of the brain. Microglia are friends as long as they clear the dying neurons but do not affect healthy cells, but foes when the reverse happens.

The new research conducted at the Icahn School of Medicine at Mount Sinai revealed that microglia clearance activity in different brain regions goes hand in hand with the natural rate of neuronal degeneration/death. The research team also discovered that the highly calibrated response of microglia to neuronal cell death is governed by the gene regulatory protein complex polycomb repressive complex 2 (PRC2), which silences the microglia clearing program in the absence of dying neurons, and that if PRC2 is inactivated, the microglia can mistakenly attack healthy neurons.

Specifically, the research team found that microglia in the cerebellum, a brain region important in regulating motor learning and balance, display a distinct clearance phenotype characterized by the engulfment and catabolism of cells and cellular debris. This feature of cerebellar microglia matches the existence of cell death in the cerebellum, where neuronal numbers start declining during adolescence. Conversely, they found microglia in the striatum and cortex display a homeostatic surveillance phenotype, aligned with low rates of neuronal death in those brain regions. These brain-region-specific differences in neuronal degeneration suggest the possibility that microglia may fine-tune their

clearance activity in accordance with the load of cell debris.

"Our study shows that microglia in different regions of the brain display different capacities to 'eat' or remove dying cells," says Anne Schaefer, Ph.D., Associate Professor of Neuroscience and Psychiatry and Co-Director of the Center for Glial Biology at the Icahn School of Medicine at Mount Sinai. "We found that if the eating behavior is turned on inappropriately in the absence of cell death, it can impair the function of adjacent neurons and lead to cellular changes frequently associated with neurodegenerative diseases such as Alzheimer's disease. The study also provides evidence that PRC2, a protein complex that silences a given gene's expression, restricts the expression of genes that support clearance activity. "

The team found that the non-eating phenotype of microglia in the striatum and cortex is established with the help of PRC2, which keeps genes involved in eating at bay. But if PRC2 is inactivated, the microglia's eating behavior is switched on aberrantly in the absence of dying cells or debris. With nothing left to clear, microglia turn to healthy neurons and induce changes frequently associated with neurodegenerative diseases.

"Our research indicates that microglia eating behavior requires tight regulation and could be dangerous to neurons if there are factors that interfere with these mechanisms." says Pinar Ayata, Ph.D., Postdoctoral Fellow in the Departments of Neuroscience and Psychiatry at the Icahn School of Medicine at Mount Sinai. "Our work may help to shed light on how environmental factors that can deregulate epigenetic mechanisms, such as stress and changes in metabolism, may contribute to neurodegenerative disorders."

"There is a possibility that regional differences in microglia function may underlie some of the known brain region-specific susceptibilities to

neurodegenerative disorders," adds Dr. Schaefer. "It also raises the possibility that 'training' microglia eating behaviors may help to establish a condition that supports microglia clearance activity without damaging neurons."

More information: Pinar Ayata et al, Epigenetic regulation of brain region-specific microglia clearance activity, *Nature Neuroscience* (2018). DOI: 10.1038/s41593-018-0192-3

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