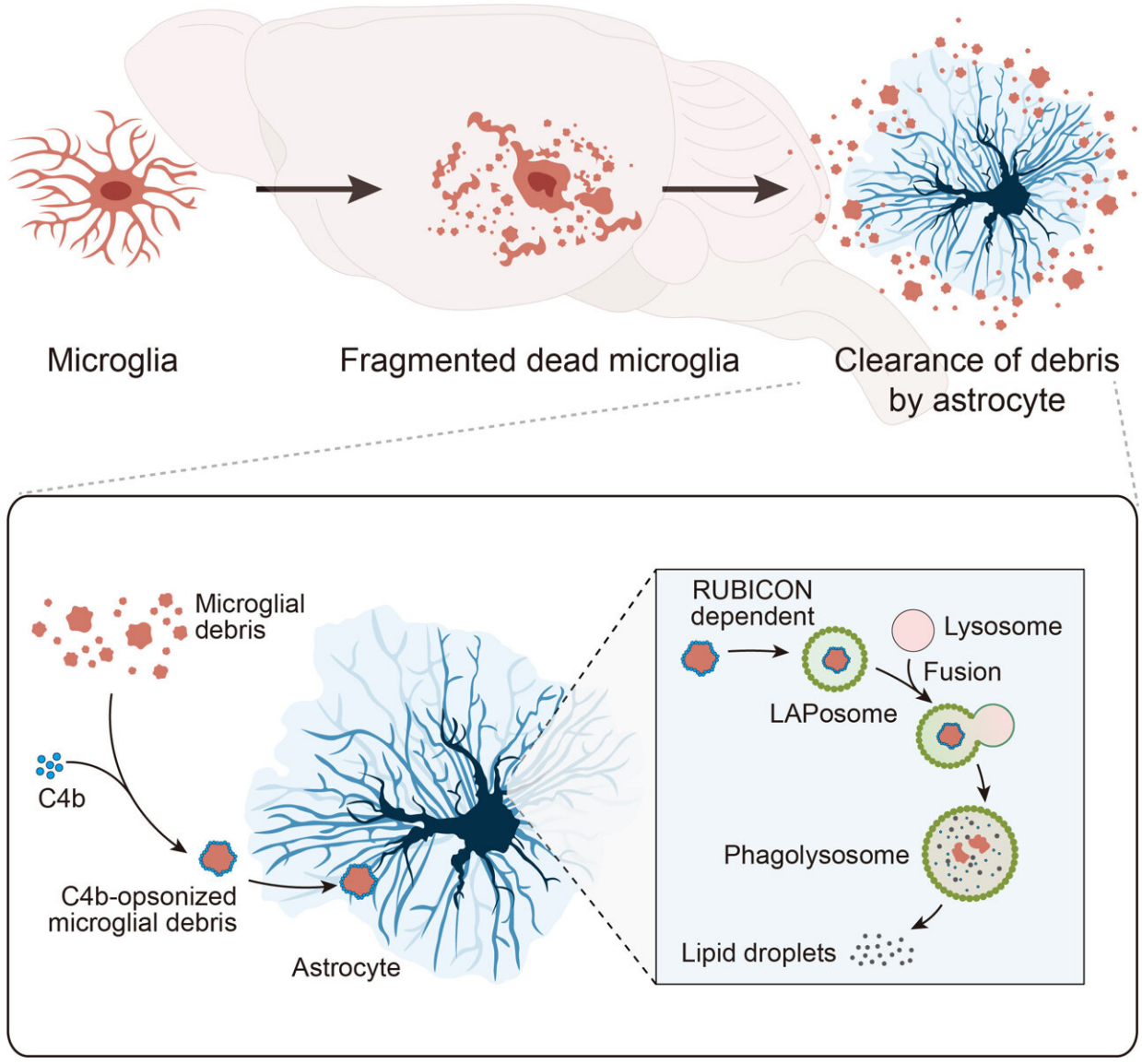
Part-time 'janitor' cell cleans up the nervous system when the normal janitors die

October 25 2022



The debris of microglia (professional phagocytes) is primarily engulfed by

astrocytes (nonprofessional phagocytes), which is facilitated by C4 opsonization. The phagocytosed debris is then degraded in astrocytes via RUBICON-dependent LAP, and microglial debris-containing LAPosomes subsequently fuse with lysosomes to form phagolysosomes, in which the debris is degraded. Credit: *Nature Communications* (2022). DOI: 10.1038/s41467-022-33932-3

Microglia are a type of immune cell that works as a "janitor" to the central nervous system that clears out dead cells and other debris. But when these janitor cells themselves die, other microglia don't do the cleaning up of their fallen brethren. So who does? Researchers have now identified the janitors of these janitors, helping explain how the nervous system maintains optimal conditions for functioning.

The findings were reported in a paper published in *Nature Communications*.

Microglia are the immune cells of the central nervous system, including the brain and retina. These cells, a type of phagocyte (or "cell eater") that acts in a similar way to a janitor in that it goes around clearing away or scavenging dead cells and excessive cells, pruning the spines of dendrites (the branch-like parts of neurons), and attacking invading pathogens.

And microglia themselves also die. The population of microglia is kept stable by the birth of new generations of microglia.

A great deal of research has been performed on the functions and mechanisms of microglia activity, but until now, it was not known how the body got rid of dead microglia. Microglia don't scavenge dead microglia.

This is important because if dead cells (of whatever type) are not

removed in a timely fashion, these accumulated cellular corpses can begin to interfere with the functioning of the central nervous system.

In a diseased central nervous system, the speed of microglial turnover ramps up dramatically. In the worst cases, as much as 95 percent of microglia can die and be replaced within just a few days. The microglia are not clearing away dead microglia, yet this massive microglia die-off does not result in massive microglia debris accumulation, or any detectable inflammatory responses to such debris.

"Something is sweeping away these dead microglia. But if the microglia aren't doing it themselves, what does?" said Bo Peng, a neuroscientist at Fudan University and corresponding author of the paper. "Put another way: Who is the janitor of the janitors?"

Finding out what mechanism is responsible is important because the clearing away of cellular debris is a key aspect of maintaining optimal homeostatic conditions (meaning the body's self-regulating process of maintaining the internal temperature, pressure, acidity etc., that are optimal for functioning).

So the researchers systematically studied the various cellular and molecular mechanisms underlying microglial debris removal.

In normal conditions of homeostasis, approximately 30 percent of the microglia in the brain turn over each year in humans and in mouse models, or 0.1 percent per day. This relatively slow turnover rate to some extent hinders researchers from studying the clearance of microglial debris. To overcome this obstacle, the researchers used a drug that is able to penetrate the brain and accelerate microglial cell death.

They also screened the major cell types in the brain—neurons, pericytes, endothelial cells, vascular smooth muscle cells, oligodendrocyte

precursor cells, oligodendrocytes, neural stem cells (NSCs), CNS border-associated macrophages (BAMs) and astrocytes—to see if they were responsible.

They concluded that none of these engulfed microglial debris. Instead, they found that it is the astrocytes that do the job. These are a type of glial cell, those non-neuronal cells in the nervous system that perform support work for the neurons.

The normal job of the star-shaped astrocyte glial cells is manifold: nutrient provision to nervous tissue, regulation of blood flow in the brain, and repair and scarring after infection or injury, amongst other tasks. But astrocytes are not normally involved in microglial work of clearing away cellular debris. This is 'part-time' work, taking over from the normal janitors.

They also found that the astrocyte's engulfing of microglial corpses is assisted by a group of extra-cellular proteins called opsonins—in this case "C4b" opsonins—that bind to the surface of cells or other substances and act as a sort of tag that labels them items that need to be eaten ('phagocytosed').

"Sort of like how a luggage tag tells airport workers where to send your bag, these C4B opsonins tell the astrocytes to come and take the dead microglial debris away," said Prof. Peng.

The engulfed microglial debris is then degraded by LC3-associated phagocytosis (LAP), a particularly efficient mechanism of ingestion and recycling of cellular components, and then fused with lysosomes, the cellular machinery that contains many different types of enzymes that can break down biomolecules, for further degradation.

In addition, the researchers found that astrocytic phagocytosis rates are

correlated with the speed of microglial turnover in both normal and diseased conditions. In other words, when something is not right with the amount of microglial turnover, the amount of astrocytic phagocytosis gets dialed up or down.

The next step, according to the researchers, is to find out how the central nervous system performs this dialing up or down to maintain the optimum microglial turnover rate.

More information: Tian Zhou et al, Microglial debris is cleared by astrocytes via C4b-facilitated phagocytosis and degraded via RUBICON-dependent noncanonical autophagy in mice, *Nature Communications* (2022). DOI: 10.1038/s41467-022-33932-3

Provided by Fudan University