How the brain eats itself

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The brain is the basis of the self. We may imagine it to be a relatively unchanging structure, but recent research has shown that the brain is in fact continuously changing its microstructure, and it does so by ‘eating’ itself. The processes of eating things outside the cell, including other cells, is called phagocytosis. In the brain, phagocytosis is performed by a particular type of cell called microglia, which can ‘eat’ neurons (nerve cells) or the connections between neurons (synapses). Microglia engulf neurons and synapses during development in order to sculpt the neural circuits of the brain. Into adulthood, they continue to eat synapses, pathogens and debris in order to shape memory, stop infections and clear accumulating rubbish from the brain. However, too little synaptic pruning by microglia during development may lead to autism; whilst too much eating of synapses during adolescence may contribute to schizophrenia. Too little phagocytosis of debris and protein aggregates or too much eating of synapses and neurons may cause neurodegeneration. A whole host of problems have recently been blamed on excessive phagocytosis in the brain, including aspects of obesity, aging and even sleep deprivation. In this article we will review the evidence, outline what biochemistry can contribute and discuss how to stop the brain eating too much of itself.

Decoding the phagocytic code

First the ground rules: how do microglia know what to eat? Phagocytosis is regulated by a phagocytic code – a kind of cannibal’s etiquette. Phagocytes, such as microglia, need phagocytic receptors on their surface to both detect and trigger engulfment of their targets. Whether a target cell is eaten by a phagocyte is determined by the target cell’s surface expression of: i) ‘eat-me’ signals, ii) opsonins and iii) ‘don’t-eat-me’ signals (Figure 1).

The most common ‘eat-me’ signal is the phospholipid phosphatidylserine, which is normally found exclusively on the inner side of the cell membrane. However, when cells are activated, stressed or dying they expose phosphatidylserine on the outer surface of their membrane. The molecule can then be detected by phagocytes, via binding to receptors, such as TREM2, and this interaction encourages eating of the cell.

Opsonins are normally soluble, extracellular proteins that, when bound to the surface of a cell, encourage phagocytes to eat that cell. Traditional opsonins include IgG antibodies and complement factors C1q, C3b or C4. But MFG-E8, GAS6, calreticulin, galectin-3 and APOE can also act as opsonins by binding simultaneously to phosphatidylserine or sugars on target cells, and to phagocytic receptors on phagocytes.

Most of our cells have ‘don’t-eat-me’ signals, such as CD47 or cell surface sialylation, that engage respectively, SIRPα or SIGLEC receptors on phagocytes to inhibit phagocytosis. Removal of sialylation from the cell surface (desialylation) or loss of CD47 enables phagocytosis.

How a phagocyte responds to these signals depends on which receptors it expresses to detect the signals, and which opsonins it releases. Microglia have long and dynamic processes that constantly survey their environment for: ‘eat-me’ signals, ‘don’t-eat-me’ signals, opsonins and inflammatory signals. However, when microglia become ‘activated’ by inflammatory signals, they migrate to the site of inflammation, release opsonins, upregulate phagocytic receptors and become highly phagocytic, in order to eat pathogens, damaged brain tissue and protein aggregates.

Microglia eat the brain into shape during development

The brain of an adult human consists of roughly 100 billion neurons that form about 60 trillion synaptic connections with other neurons. Surprisingly, however,
during development twice as many neurons are generated, which then try to wire up the brain with trillions of further connections. Neurons that form an insufficient number of connections or insufficiently active connections, do not get fed necessary quantities of growth factors via these connections, and as a result, these neurons die by apoptosis. These apoptotic neurons, which expose phosphatidylserine, then become phagocytosed by microglia. Apoptotic neurons are eaten when half dead, but neuronal precursor cells are eaten alive to keep their numbers in check. In addition, synaptic connections that are not used to transmit signals are removed by a process of synaptic pruning, which is partly carried out via microglial phagocytosis of the inactive synapses (Figure 2), tagged by the complement factors C1q and C3b. Mice lacking these opsonins or complement receptor 3 (CR3, the microglial phagocytic receptor that detects C3b) fail to remove less active synapses, leading to impairment in certain neuronal circuits. Mice lacking a receptor for a signalling protein called fractalkine, which is required to recruit microglia to synapses, also fail to remove weak synapses, and develop autism-like behaviour, as do mice lacking the phagocytic receptor TREM2. The implication is that autism is caused by insufficient synaptic pruning during development, which results in an excess number of synaptic connections that then overload the brain.

Rett's syndrome is a genetic brain disorder that causes some similar traits to autism, but also causes severe movement and coordination problems. However, mouse models with the mutation causing this syndrome show excessive microglial engulfment of synapses. In humans, there is a late phase of synaptic pruning in adolescence, and recent evidence suggests that excessive microglial phagocytosis of synapses during this phase causes schizophrenia. Variants of the complement C4 genes are strongly linked to schizophrenia, and C4 mediates synaptic pruning, at least in mice.

Trouble in the adult and aged brain

A growing number of health conditions are being linked to activation of microglial phagocytosis. Chronic sleep deprivation causes cognitive dysfunction in humans, and in mice it increases phagocytosis of synapses by microglia – one of many reasons to ensure you get sufficient sleep! Obesity can also result in cognitive decline in humans. Studies conducted in mice found that diet-induced obesity resulted in loss of memory and synapses, increased microglial activation and increased synaptic proteins within microglia, implying that microglia were phagocytosing synapses. This idea was further supported by the finding that the deficits were prevented by inhibiting microglial activation, microglial phagocytosis or microglial recruitment to synapses.

Viral infections of the brain, such as HIV, can cause long-term damage, and West Nile virus infection of
the brain has been shown to cause cognitive damage in mice as a result of microglial phagocytosis of synapses, prevented by C3 knockout.

Aging results in reduced memory and cognitive function and is accompanied by brain shrinkage (atrophy) of 0.5–1.0% per year after the age of 60, primarily due to loss of white matter and synapses, rather than neurons. In mice, loss of memory with age is accompanied by loss of synapses in the hippocampus (an area central to memory), and knockout of opsonin C3 prevents synaptic and memory loss. Similarly, knockout of the phagocytic receptor TREM2 prevents synaptic loss with age, suggesting this loss is due to microglial phagocytosis of the synapses.

Alzheimer's disease is characterized by amyloid plaques, tau tangles, microglial activation, synaptic loss, neuronal loss and brain atrophy. Microglia may slow this process by phagocytosing both the plaques themselves and the beta amyloid that forms them. Microglia have a general garbage-disposal role in the brain, eating any rubbish accumulating in the extracellular space, including protein aggregates and cellular debris. However, the microglia associated with amyloid plaques appear to be ineffective at eating the plaques, possibly due to senescence. And senescent microglia, which are poor at phagocytosing, accumulate with age and neurodegeneration. This suggests the possibility that insufficient microglial phagocytosis of amyloid or debris may contribute to the disease. This is supported by Genome Wide Association Studies (GWAS), which show that Alzheimer's is linked to genes regulating microglial phagocytosis, including APOE, TREM2 and CD33.

The above suggests that Alzheimer's disease may be related to insufficient microglial phagocytosis. However, other studies suggest that synapses and neurons may be lost as a result of too much microglial phagocytosis. In amyloid mouse models of the disease, synapses are lost and phagocytosed by microglia, and synapse loss and memory loss are prevented by inhibiting or knocking out C1q, C3 or CR3, suggesting that synapses are lost as a result of excessive microglial phagocytosis of complement-tagged synapses. Neuronal loss in amyloid models is also prevented in C3 knockout mice. Recently, neurons with TAU tangles have been found to be phagocytosed alive by microglia. Additionally, excessive microglial phagocytosis has been suggested to contribute to other neurodegenerative diseases, such as Parkinson's disease, as blocking microglial phagocytosis can prevent neuronal loss in mouse models.

**How to stop the brain eating itself**

How can we prevent too much microglial phagocytosis in the diseases and conditions outlined above? Our lab looks at the signals regulating the interactions between neurons and microglia during microglial phagocytosis of neurons, in order to find ways of preventing excessive phagocytosis. We found that microglial phagocytosis of live neurons often involves stressed neurons reversibly exposing phosphatidylycerine, which is then bound by the opsonin MFG-E8, which then activates the vitronectin receptor (VNR) on microglia to trigger phagocytosis of the stressed neurons. Alternatively, the phosphatidylycerine-exposed neurons bind the opsonin GAS6, which then triggers the phagocytic receptor MER tyrosine kinase (MERTK) on microglia. Thus, we could prevent neuronal loss after stroke in mice by knockout of MFG-E8 or MERTK. Additionally, we could prevent loss of neurons in mice

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**Figure 2. Neurophagy:**

Glia eating live neurons or neuronal parts. Neurophagy was discovered by the neuropathologist Georges Marinesco in the 1890s when examining patient brains, and observing glial cells apparently phagocytosing neurons.
infected with endotoxin by blocking VNR or knockout of MERTK. This suggests that blocking VNR or MERTK could be the solution in some conditions. We also found that galectin-3 could act as an opsonin for MERTK, and knockout or inhibition of galectin-3 could prevent neuronal loss after brain trauma – so galectin-3 inhibitors could be a treatment option in other conditions. However, the long-term blocking of MERTK or VNR might not be advisable as they mediate the phagocytosis of cellular debris.

Another option is to target the microglial P2Y6 receptor, required for microglial engulfment of neurons, as this does not seem to be involved in the phagocytosis of dead cells or debris. We have found that P2Y6 knockout mice are protected in models of neuroinflammation, Parkinson's disease, Alzheimer's disease and aging, so we are trying to find a drug to block this receptor, in the hope that it might be used to prevent excessive microglial phagocytosis of neurons. The other attractive target to prevent excessive microglial phagocytosis is CR3, but there is currently no way to block this in the brain. Importantly, we have to keep in mind that microglial phagocytosis plays many beneficial roles in the brain, so the specificity of how we target this process is crucial.

**Conclusion**

The brain eats itself to: create itself during development, maintain itself during adulthood and destroy itself with age. We need to learn how to block the latter without disrupting the former.

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**Further reading**


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Guy Brown is Professor of Cellular Biochemistry at the University of Cambridge, and heads a lab working on the roles of microglia in neuroinflammation and neurodegeneration. The lab was the first to show that inflamed microglia could eat live neurons, and so blocking phagocytosis could prevent neurodegeneration in culture and in vivo. Current research involves the roles of TREM2, CD33, APOE, CRT, P2Y6, P2Y12 and GAL-3 in neuroinflammation and neurodegeneration.

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