

News & views

Ageing

Immune-cell shutdown harms old brains

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Immune cells called macrophages have been found to shut down major metabolic pathways during ageing. Restoring metabolism in these cells is sufficient to alleviate age-associated cognitive decline in mice.

Immune cells called macrophages are found in almost every tissue, and are crucial for maintaining organ health and providing a first line of defence against disease-causing organisms. The energy demands of macrophages increase drastically when they are activated, and so they rebalance or enhance their two main energy-producing metabolic pathways (glycolysis and oxidative phosphorylation) to quickly fuel an effective immune response¹. Writing in *Nature*, Minhas *et al.*² report that macrophages shut down these metabolic pathways during ageing, severely compromising macrophage function and, in turn, brain health. This work has implications not only for the preservation of brain health during ageing, but also for conditions such as Alzheimer's disease or sepsis, in which similar maladaptive macrophage states could be common.

As we age, chronic, low-grade inflammation develops in most people³. One inflammatory signalling protein whose levels rise not only during ageing⁴ but also during neurodegenerative disease⁵ is prostaglandin E₂ (PGE₂). Minhas *et al.* set out to investigate whether PGE₂ might cause age-associated changes in macrophages. Interestingly, the authors found increased production of PGE₂ in human and mouse macrophages themselves – both in the brain and elsewhere in the body (the periphery). This led to the activation of PGE₂'s receptor protein EP2 in the cells, which in turn resulted in suppression of oxidative phosphorylation and glycolysis. The resulting energy-deficient state both limited the beneficial functions of macrophages and increased inflammation.

To determine whether these changes could cause age-associated cognitive dysfunction, the authors examined a mouse strain in which EP2 receptor levels were reduced exclusively

in macrophages in the body and brain, and treated mice with an EP2 inhibitor. Strikingly, EP2 inhibition restored macrophage metabolism to youthful levels in both settings, reducing inflammation in the periphery and brain, and alleviating cognitive decline (Fig. 1). These results indicate that (at least in mice) macrophage dysfunction during ageing affects brain health, and that normal cell function can be

restored by reversing metabolic shutdown in the cells.

Minhas and colleagues went on to dive deeper into the metabolic rewiring of aged macrophages. They found that such macrophages favoured energy storage in the form of glycogen (a large glucose polymer) over the use of glucose for energy production through glycolysis or oxidative phosphorylation. Although glycogen normally serves as a fuel reserve, aged macrophages did not seem to use this reserve, despite their energy-deficient state.

It is unclear why aged macrophages store extra glycogen, but dendritic cells, a related cell type, use their glycogen stock to fuel their earliest inflammatory responses⁶. Therefore, it is conceivable that aged macrophages increase glycogen storage so that they can mount a stronger immune response during acute inflammatory activation. In line with this idea, aged microglia (brain macrophages) are well known to be primed – that is, to respond more strongly to inflammatory insults than do young microglia⁷. Minhas and co-workers did not directly analyse whether microglial priming is enabled by increased glycogen stores.

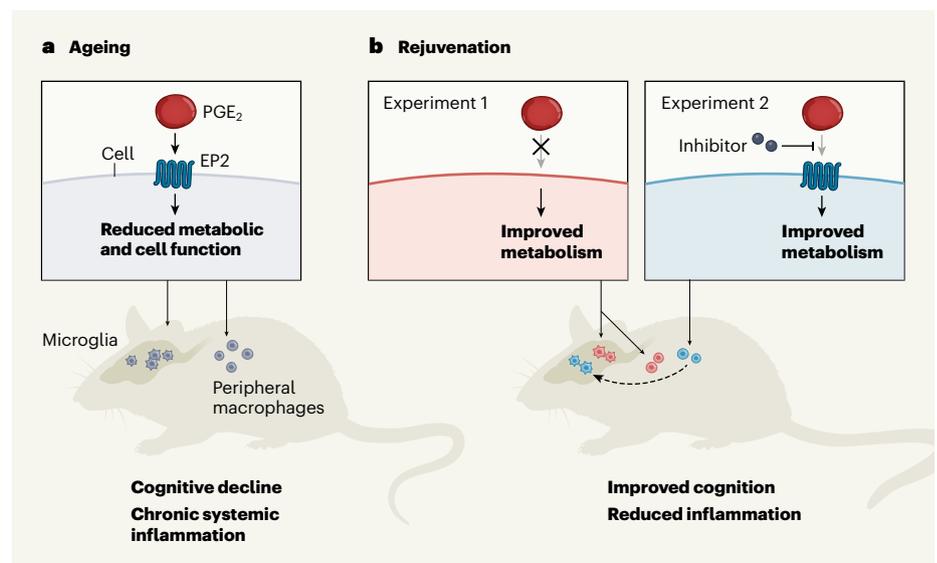


Figure 1 | Reversing metabolic shutdown in aged macrophages. Immune cells called macrophages are found throughout the body (the periphery) and in the brain, where they are called microglia. **a**, Minhas *et al.*² report, that during ageing, peripheral macrophages and microglia produce more of the protein prostaglandin E₂ (PGE₂), which binds to EP2 receptors on the cells' membranes. They demonstrate that activation of this signalling pathway leads to metabolic dysfunction in the cells, and so to systemic chronic inflammation and cognitive decline. **b**, The authors inhibited the EP2 receptor in two ways. First, they used a genetic approach to reduce levels of EP2 in both macrophages and microglia. Second, they inhibited the receptor pharmacologically – but only in the periphery. Under both conditions, EP2 inhibition improved metabolic function in peripheral macrophages and microglia, reducing inflammation and restoring cognitive ability. The mechanism by which peripheral inhibition of EP2 leads to changes in microglia is unknown (dashed arrow).

However, this possibility would certainly be worth investigating, because some evidence suggests that exacerbated immune responses in the aged brain contribute to neurodegenerative disease⁷.

Notably, there is also evidence for a role of microglial metabolic dysfunction in brain disease, particularly in Alzheimer's disease. The risk of developing Alzheimer's increases several-fold in people who carry mutations in the microglial receptor protein TREM2. In mice, TREM2 deficiency causes breakdown of microglial metabolism and exacerbation of Alzheimer's pathology⁸. Furthermore, chronic exposure of microglia to aggregated amyloid- β protein, a hallmark of Alzheimer's disease, leads to the breakdown of oxidative phosphorylation and glycolysis in these cells in mice⁹. In both cases, enhancing microglial metabolism leads to less-severe Alzheimer's pathology in the mouse models.

In sepsis (a condition that results from excessive inflammation in response to infection), PGE₂ levels also increase⁹ and long-term cognitive deficits often develop⁷. Here, macrophages enter a state called immune paralysis, which is also characterized by suppression of both oxidative phosphorylation and glycolysis¹⁰. Thus, the cellular shutdown of macrophages during sepsis or during ageing and neurodegenerative disease might be

a response to excessive or chronic immune stimulation, respectively. This adaptation would be beneficial from an evolutionary perspective because it would protect an organism from a hyperactive immune response that could cause tissue damage. However, in the context of an ageing organism, it seems to predispose the brain to dysfunction or even degeneration. Whether macrophage immune states are indeed similar across these different conditions remains to be investigated.

Another intriguing aspect of Minhas and colleagues' study is the finding that, even when EP2 inhibition was limited to the periphery in aged mice (using a substance that cannot enter the brain), brain inflammation was reversed and cognitive function restored (Fig. 1). This corroborates previous findings that immune signals generated outside the brain can affect microglia¹¹, and that stimulation of immune cells outside the brain can partially restore the metabolism and function of peripheral macrophages after sepsis¹⁰ and of microglia in mouse models of Alzheimer's disease⁹. Thus, a growing body of evidence indicates that, in mice, macrophages remain responsive to immune stimulation even during disease and ageing.

The next challenges will be to demonstrate that this macrophage plasticity is also retained towards the end of the considerably longer

human lifespan, and that the PGE₂-EP2 pathway is relevant for human brain ageing and disease. Moreover, the immune signals that induce initial microglial shutdown or restore microglia to a youthful state in aged animals remain unknown. Their identification could lead to therapeutic approaches to combat a range of diseases.

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