CANCER

A glial contribution to 'chemobrain'

> astrocytes exposed to conditioned medium derived from MTX-treated microglia became more reactive

Persistent cognitive impairment following chemotherapy has a lasting detrimental effect on the quality of life of many individuals with and survivors of cancer; however, the underlying causes are poorly understood. Monje and colleagues have now developed a mouse model of chemotherapy-induced cognitive dysfunction that reveals a central role for microglia in the neurological changes associated with chemotherapy.

The effects of chemotherapy on cognition have been proposed to be linked to white matter defects. In support of this hypothesis, Monje and colleagues show that frontal lobe post-mortem tissue samples from individuals treated with chemotherapeutics contain fewer of the cells responsible for mediating myelination (oligodendrocytes and oligodendrocyte precursor cells (OPCs)) than do samples from control subjects. This prompted the authors to further investigate the effects of chemotherapy on oligodendrocyte lineage cells in a mouse model.

To mimic clinical chemotherapy regimes, the authors administered three consecutive weekly doses of a common chemotherapeutic agent, methotrexate (MTX), to juvenile mice. Using transmission electron microscopy, the authors revealed a decrease in myelin sheath thickness in the white matter of MTX-treated mice at 4 weeks after treatment, compared with control (saline-treated) mice. The authors also observed cognitive deficits reminiscent of those seen in patients treated with chemotherapeutics, including performance impairments in a novel object recognition task (NORT) that relies on attentional function.

Immunostaining of tissue samples from the mice 4 weeks or 6 months after the end of the MTX treatment revealed that — as observed in patients — there was a long-term decrease in proliferating OPCs in the white matter of MTX-treated animals compared with controls. This was accompanied by an increase in the number of non-proliferating 'late' OPCs and a decrease in the number of cells expressing markers of mature oligodendrocytes, suggesting that OPC differentiation is promoted by MTX but stalls before the cells reach maturity.

Next, the authors sought to unpick the mechanisms driving the altered OPC dynamics in MTX-treated mice. They found that OPCs derived from mice that had not been exposed to MTX suffered a similar fate to that of endogenous OPCs when transplanted into the brains of MTX-treated mice, including inappropriate differentiation. This suggested that the microenvironment of the OPCs has a role in driving their altered dynamics.

The authors hypothesized that interactions between OPCs and other cell types present in their microenvironment might be important in mediating the effects of MTX. They identified an increase in the numbers of activated microglia and reactive astrocytes in the white matter of the MTX-treated mice. Further investigation showed that MTX treatment could activate microglia directly in vitro and that astrocytes exposed to conditioned medium derived from MTX-treated microglia became more reactive.

These findings suggested that microglial activation might drive changes in astrocyte and OPC dynamics that lead to cognitive deficits in MTX-treated mice. To determine the importance of microglia for these effects, the authors fed MTX-treated mice with chow containing PLX5622, a drug that depletes microglia, beginning 1 week after the end of the MTX treatment. Treatment with PLX5622 protected against the effects of MTX on astrocyte reactivity, OPC proliferation, myelin sheath thickness and performance in the NORT, indicating that microglia are central to the deleterious effects of MTX on the white matter and associated cognitive function.

This study highlights the importance of the regulation of glial dynamics for healthy brain function and indicates that disruption of these dynamics may underlie the neurological dysfunction associated with chemotherapy. Although the precise mechanisms linking microglial activation to OPC dysfunction are unclear, these findings could point to new approaches for the prevention or alleviation of 'chemobrain'.

Katherine Whalley

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