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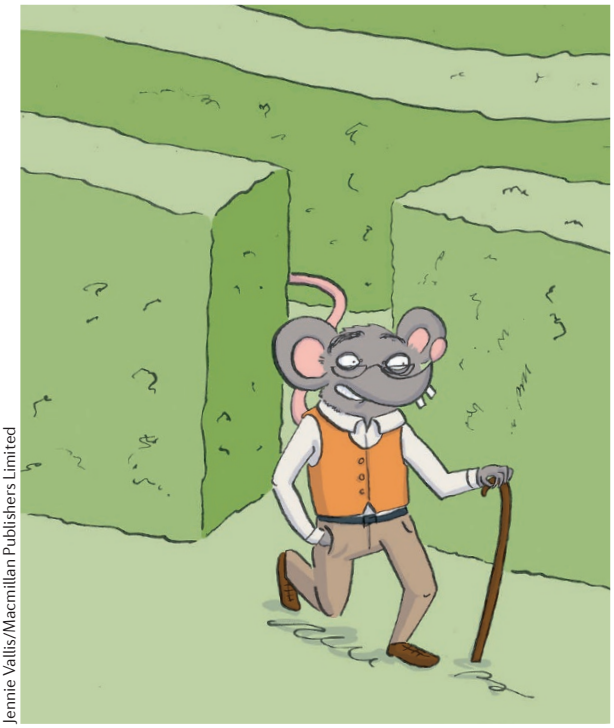
AGEING

A youthful reminder

In rodents, the introduction of blood from young to old animals can reverse some of the negative effects that ageing exerts on CNS function, including detrimental changes in hippocampal function. However, it is not known which molecules found in young blood exert such effects or whether human plasma could also elicit such functional restoration. Wyss-Coray and colleagues now show that systemic administration of plasma from human umbilical cord counteracts the effects of ageing on long-term potentiation (LTP) and hippocampal-dependent cognitive function in mice. They also identify tissue inhibitor of metalloproteinase 2 (TIMP2) as a key molecule in plasma that confers these effects.



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To examine the effects of human plasma on brain function in old mice, the authors systemically delivered plasma obtained from umbilical cord, young individuals or elderly people to aged, immunodeficient animals, which could receive multiple plasma infusions without mounting a detrimental immune response. Cord plasma, but not the other plasma samples, increased the number of dentate gyrus cells exhibiting expression of FOS, a marker of neuronal activation.

To confirm whether this effect could be elicited in the presence of an intact immune system, the authors delivered a single injection of plasma to wild-type mice in which FOS expression induced the expression of a fluorescent reporter. Using this approach, they detected cord plasma-induced FOS expression in the dentate gyrus and CA1. Together, these gene expression data suggest that treatment of old mice with human cord plasma induces neuronal activity in the hippocampus.

Next, the authors examined hippocampal LTP in immunodeficient mice treated with human plasma. Cord plasma markedly increased LTP in old but not young mice following treatment. Moreover, cord plasma-treated aged animals performed better in two hippocampus-dependent memory tasks — the Barnes maze and contextual fear conditioning — than untreated aged mice. Thus, human umbilical cord plasma improves neuronal functioning and cognition in aged mice.

The authors switched their attention to identifying factors underlying the restorative effects of human cord plasma in mice. They compared protein changes in young versus old human plasma with age-dependent changes in mouse plasma. Cluster analyses revealed a list of youth-associated plasma proteins; the top entries from this list — which included TIMP2 — were then systematically assessed in old mice for their ageing-countering effects.

Treatment with recombinant TIMP2 increased FOS expression in the dentate gyrus of old wild-type mice. Furthermore, systemic TIMP2 treatment for 2 weeks markedly improved the performance of such animals in the Barnes maze and in contextual memory recall. Last, TIMP2 treatment increased LTP at dentate gyrus synapses, as measured in hippocampal slices from old mice. These results suggest that TIMP2 may, at least in part, be responsible for the beneficial effects of human cord plasma in old mice. In support of this hypothesis, the authors found that old mice treated with TIMP2-immunodepleted human cord plasma failed to see the same improvements in memory function as those animals treated with TIMP2-containing cord plasma.

Together, these data indicate that plasma from human umbilical cord, like blood from young mice, can counteract the ageing-related decline in hippocampal function in old mice, and that TIMP2 is a key factor conferring these effects.

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