also been suggested that the difference in precious-metal abundances between Earth and the Moon was caused by a drop in the flux of impacts during the period between 4.5 billion and 4.1 billion years ago[11], just after the Solar System formed. These models generally assume that the Moon retained about half of the mass that was transferred to it by impactors.

Using millions of computational impact simulations, Zhu and colleagues examined the fraction of impactor mass that could be retained by planetary bodies. The authors simulated impacts at different velocities (10–20 km per second), and at low angles (20°) to high angles (80°) with respect to the body's surface (Fig. 1). They found that material from larger impactors is less effectively retained than that from smaller counterparts, and that high-angle impacts deliver a larger mass fraction to the body than do low-angle impacts.

In the case of Earth, these results imply that the retention of impactor mass is generally high for all but the most glancing impacts with the most massive objects. For the Moon, which has a mass only about 1% of that of Earth, the shallower the angle of impact, and the more massive the impactor, the greater the likelihood that material would be lost, never reaching the Moon's surface or passing into its interior. Using crater diameters[12] to establish the frequency and size of impactors striking the Moon, Zhu *et al.* discovered that impactor-mass retention probably changed modestly over time, and that the average retention was about 20%, which is around three times lower than previous estimates.

Inefficient retention of material from objects striking the Moon partially offsets the difference between the theoretically and geochemically determined Earth–Moon input-mass ratios. Zhu and colleagues then argue that about 50% of late-accretion input mass was lost to the Moon's deep interior or core before 4.35 billion years ago, and that this loss explains any remaining discrepancy. Later, once the Moon had cooled, late-accretion input mass was distributed into the lunar mantle and crust. The authors further suggest that as many as 300 impact craters of more than 300 km in diameter might have existed on the Moon, but that fewer than 30% of these craters are preserved today owing to impact-derived erosion or to gradual subsidence (viscous relaxation) of the earliest craters in the hot lunar crust.

The suggestion of inefficient mass retention from glancing impacts negates the requirement for the proposed temporally varying impact fluxes[11]. However, the idea that precious metals were lost to the Moon's deep interior or core before 4.35 billion years ago is more problematic. Without evidence from craters for the impact flux to the Moon at that time, geochemistry is the only valid test of this idea. Loss of precious metals to a metallic core can lead to these elements being separated (fractionated) from one another[13]. However, this chemical effect has not so far been detected in rocks from the lunar interior[3,4]. Furthermore, low precious-metal abundances estimated for the lunar mantle make it difficult to envisage how such fractionation signatures could have been erased by further late accretion.

Zhu *et al.* also assume that the penetration of impactors through the lunar crust, which is about 40 km thick[14], would lead to all retained impactor material entering the mantle. But, in reality, this material would pollute both the crust and the mantle. Finally, because only a relatively small number of lunar rocks have been analysed, models such as the authors' that can reproduce precious-metal abundances in the Moon through simulations have limited resolution.

Nevertheless, the new models will be of value in understanding the evolution of planetary bodies, especially Mars. Current estimates for late-accretion input mass expressed as a function of total body mass are 0.02%, about 0.5% and up to 0.7% for the Moon[4], Earth[2] and Mars[15], respectively. The estimate for Mars has been explained by early formation of the planet relative to Earth and the Moon, in addition to a constant input-mass flux in the Solar System's first 50 million to 100 million years[15], and impacts involving massive objects[5,16].

Extrapolation of Zhu and colleagues' models would suggest that Mars, which has a mass only about 11% of that of Earth, retains less material from large impactors than does Earth. Assuming that the two bodies were subjected to a similar number of glancing impacts, these models would imply that Mars had a proportionally greater late-accretion flux than did Earth. The combination of geochemistry and formation models will undoubtedly continue to improve our understanding of how Earth and its nearest neighbours came to be. ■

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NEUROSCIENCE

T cells inhibit neural stem cells in old brains

Age-dependent changes in their environment can impair stem cells' function. The finding that T cells infiltrate the brains of aged mice and cause dysfunction of neural stem cells reveals a potential therapeutic target. SEE ARTICLE P.205

ALLISON M. BOND & HONGJUN SONG

In a healthy adult, tissue-specific stem cells replenish damaged tissue and sustain plasticity (the addition of new cells) in organs. In two regions of the adult brains of most mammals (the subventricular zone of the lateral ventricles and the dentate gyrus of the hippocampus), neural stem cells generate new neurons, which contribute to brain plasticity and cognition[1]. However, there is still debate over whether new neurons are commonly generated in the adult human brain. The proliferation of neural stem cells in mammals decreases with age, resulting in a reduction in the number of new neurons formed over time, and the mechanism underlying this change is poorly understood[2]. On page 205, Dulken *et al.*[3] examined how changes in the microenvironment of neural stem cells in the brains of old mice affect stem-cell proliferation.

Stem cells in an old brain are dysfunctional and are less likely to divide than are young stem cells[4]. However, the intrinsic properties of neural stem cells remain stable — both young and old neural stem cells have a similar potential to differentiate and proliferate *in vitro*[5]. Stem cells are located in a specialized microenvironment called a niche, which consists of molecules and other cells that interact with

stem cells to support their division, survival and function. Age-associated changes in the neural-stem-cell microenvironment have not been well characterized: thus, an unanswered question is whether changes in this microenvironment might drive age-related stem-cell dysfunction.

Dulken *et al.* investigated how ageing affects different cell types in the neural-stem-cell niche in the subventricular zone of the adult mouse brain. The authors used a technique called single-cell RNA sequencing to examine gene expression in individual cells in this niche in young and old mice. They observed genome-wide differences between the young and old animals in the gene-expression patterns of endothelial cells and of cells called microglia and oligodendrocytes.

The authors also observed that immune cells called T cells — specifically, a class of T cell that expresses the protein CD8 — were present in old but not young brains (Fig. 1). Imaging analysis revealed that these T cells were in close proximity to neural stem cells. The authors also found that, in old human brains, T cells infiltrated an area that is equivalent to the region of the mouse brain that was infiltrated by T cells. These findings raise the possibility that T cells affect ageing stem cells. This discovery is intriguing because a healthy brain is surrounded by a boundary called the blood–brain barrier, which tightly regulates what can enter the brain[6], and immune cells in the bloodstream do not normally cross this barrier[7].

The authors found that, compared with T cells in the bloodstream, T cells in the ageing mouse brain make higher levels of a protein called interferon-γ, which is a type of immune signalling molecule called a cytokine. Cytokine production is a hallmark of T cells that have become activated, which occurs when they recognize a fragment of a protein called an antigen. Dulken and colleagues report that neural stem cells express the receptor for interferon-γ, which suggests that interferon-γ might be used for signalling between T cells and neural stem cells. When analysed using single-cell RNA sequencing, a subpopulation of the old neural stem cells was found to express exceptionally high levels of genes that are expressed in response to interferon-γ signalling. And when the authors monitored the ability of these high-responding cells to divide *in vivo*, they found that the cells proliferated less than did the neural stem cells that had a low response to interferon-γ *in vivo*.

To test the hypothesis that interferon-γ can decrease the proliferation of neural stem cells, Dulken and colleagues used a technique that enabled T cells to enter the brains of young mice. This T-cell influx was accompanied by an increase in the interferon-γ response of neural stem cells and a decrease in their proliferation. The authors also cultured neural stem cells from young mice *in vitro* in the presence or absence of T cells. When cytokines that induce T-cell secretion of interferon-γ were added to these cultures, the neural stem cells co-cultured with T cells proliferated less than did those cultured in the absence of T cells. The impaired proliferation in the presence of T cells could be prevented by an antibody that blocked interferon-γ signalling. Dulken and colleagues' work is consistent with a model suggesting that the microenvironment of neural stem cells in the aged brain is infiltrated by T cells that release interferon-γ, which is sufficient to inhibit neural-stem-cell proliferation.

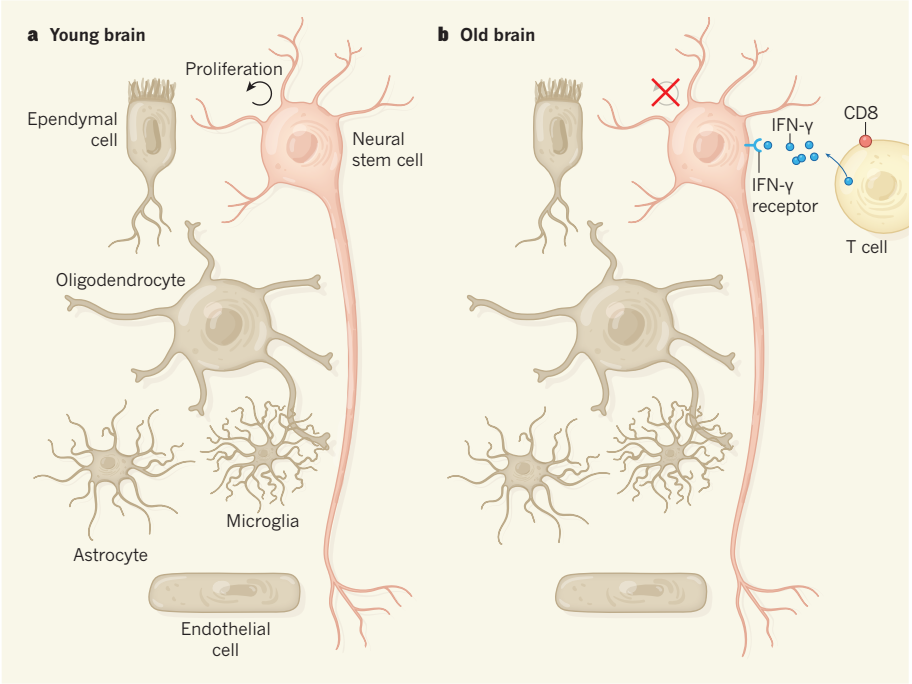

Figure 1 | T cells inhibit the proliferation of neural stem cells in old brains. Dulken *et al.*[3] studied changes in the aged mouse brain to try to understand why there is a decline in the proliferation of neural stem cells as animals age. **a**, In a young healthy mouse brain, one population of proliferating neural stem cells resides in a specialized microenvironment called a niche that contains other types of cell (including ependymal cells, endothelial cells, astrocytes, oligodendrocytes and microglia) and signalling molecules (not shown) that can regulate neural-stem-cell function and proliferation. **b**, Dulken and colleagues report that, in the brains of old mice, immune cells called T cells, of a type that expresses the protein CD8, infiltrates the neural-stem-cell niche. These T cells secrete a signalling protein called interferon-γ (IFN-γ). The interferon-γ receptor is present on the surface of neural stem cells, and the activation of this interferon-γ signalling pathway in neural stem cells inhibits their proliferation.

The authors' evidence for the previously unsuspected infiltration of T cells into an aged brain raises the question of what mechanism is responsible for this invasion, and whether signals in the ageing brain might recruit T cells to the brain. Future studies should determine which antigens the infiltrating T cells recognize. T cells that express the protein CD4 in the bloodstream outside the brain have a role in regulating the formation of new neurons in the young dentate gyrus[8] through an unknown mechanism, and it would be interesting to learn whether T cells that express CD8 infiltrate the old dentate gyrus to inhibit stem-cell proliferation. Would blocking interferon-γ in the aged brain increase stem-cell proliferation and the generation of new neurons, and would this also improve cognition? Many such fascinating questions remain to be investigated.

Dulken and colleagues' work adds to a growing body of evidence that points to interactions between immune cells and stem cells as a cause of age-related decline in tissue function[9]. Perhaps therapies can be developed to target the immune system as a way of combating ageing-related stem-cell deficits throughout the body. ■

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