

# DNA damage to stem cells is central to ageing

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DNA damage is a major mechanism behind the loss of adult stem cells over time, according to a *Nature* paper by Oxford University researchers and international colleagues.

The finding has implications for the use of adult stem cells in transplantation and, more broadly, for understanding the process of ageing itself, since stem cells are essential for repairing and regenerating tissue.

An adult stem cell is a cell that has not yet differentiated (specialised): it can become any one of various cell types. Adult stem cells can differentiate to yield the major specialised cell types of whatever tissue or organ they are found in. They also renew themselves. This makes them crucial for long-lived multicellular organisms like animals, which depend on tissue replenishment from adult stem cells for their continued existence.

Stem cells must be maintained throughout life with a minimum of mutations to their DNA, since these mutations could stop the stem cell working or even kill it. Professor Richard Cornall from the University of Oxford and colleagues studied stem cells that generate blood, found in bone marrow.

In order to establish the importance of DNA damage and repair, they looked at a mouse which lacked an enzyme crucial for DNA repair (DNA ligase IV, or 'Lig4').

The Lig4 enzyme repairs so-called ‘double-strand breaks’: breaks in the DNA double helix caused by oxidation and radiation that we are exposed to all the time. In the mice lacking Lig4, repairs were inefficient, and the DNA of the stem cells became damaged much faster, leading to loss of stem cells.

‘As we get older, it is known that our capacity to regenerate blood and other cells diminishes,’ says Professor Cornall. ‘In the mouse without Lig4, this process was accelerated. This shows how important DNA repair is in slowing down the loss of stem cells. In other words, DNA damage can be an important mechanism in tissue ageing.’

The findings have implications for the process of ageing itself. ‘It has been suggested that accumulation of DNA damage, leading to loss of adult stem cells, is a principal mechanism behind ageing,’ says Professor Cornall. ‘Our findings lend weight to that theory.’

He adds: ‘Our findings also imply that inherited or environmental factors that increase oxidative DNA damage may be key determinants of the rate of tissue ageing.’

The findings are also important for the use of adult stem cells in transplants. The success of cultivating and transplanting stem cells, for example for use in leukaemia patients, will depend on how often DNA breaks occur and how well they are repaired.

Source: University of Oxford

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