Movies of cell growth explain skin graft success and may help understand cancer

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How to maintain healthy skin and heal wounds is an intricate problem. Maintaining the skin requires exactly the right number of cells to divide to replace those shed from the skin surface. Too many cell divisions can lead to cancer, whereas too few will result in ulcers. Wound healing needs a short burst of cell production to fill the gap in the skin. Latest research shows that all dividing skin cells can flip between two probability game modes and so have the potential to both maintain and heal skin, challenging the view that only rare stem cells matter.

Understanding the rules of the games not only explains how skin maintains itself and heals wounds, but also shows how skin grafts work and suggests how changes to the rules could lead to cancer.

Watching high definition movies of human skin cells dividing in real time showed they play two types of dice game, for maintenance or wound repair. In the maintenance game, the odds are balanced between production and shedding, with a 50:50 chance of a daughter cell going on to divide or stopping division and migrating to the skin surface. These probabilities keep the skin in balance. However, cells next to a wound temporarily switch to the repair game, in which the odds of producing dividing cells are nine times higher, ensuring rapid healing.

"This research demonstrates that dividing human skin cells can switch their behaviour between these two modes of maintenance or repair, challenging the longstanding view that skin renewal and healing relies on a special population of stem cells," says Dr Phil Jones, senior group leader at the Wellcome Trust Sanger Institute and MRC Cancer Unit, University of Cambridge.

To carry out the investigation of skin turnover, researchers took live imaging movies of more than 3,000 human skin cells dividing in culture. The images showed that single cells expanded exponentially in repair mode until they had produced multi-layered sheets of cells, after which the behaviour switched to maintenance mode. However, this is only half the story.

"By scratching sheets of cells in the balanced mode and observing cells next to the scrape, we saw that they changed into wound healing mode until the scratch was closed again," says Dr Joanna Fowler, an author of the paper from the Sanger Institute. "The cells could switch backwards and forwards between the two states as required, proving that the behaviours were reversible."

Skin loss due to burns or ulcers that won't heal can be fatal and skin graft surgery is used to replace burnt or damaged skin. Sheets of skin can be grown from very small skin patches in the laboratory, and this can save the lives of patients with serious burns.

"As plastic surgeons, we have been growing sheets of skin from burns patients to save lives for decades. A single skin cell can create a patch of one centimetre diameter or more, and many of these together can make a whole sheet. However until now we couldn't explain how this worked," says Dr Amit Roshan, first author and Cambridge Cancer Centre Clinical Research Fellow at MRC Cancer Unit, Cambridge. "This research explains how skin cell cultures expand, and could lead to further improvements in wound healing in the clinic."

The cells appeared to sense when their neighbours were missing, flipping from maintenance to wound healing behaviour: once they were surrounded by cells again, they flipped back. Inhibiting a cell signalling protein ROCK2 kinase prevented cells in expanding mode flipping back into balanced mode, indicating that cell signalling was required to make the switch. In further corroboration of the two mode games, the investigators found differences in gene expression between wound healing and balanced populations of cells.

"These findings have great implications for understanding cancer, where cells have too many dividing daughters. Mutations could change the rules of the game and load the dice in favour of dividing cells, leading to cancer." Says Dr Phil Jones, "The knowledge that all dividing skin cells are the same but can switch their behaviour will help us understand how DNA changes associated with cancer alter cell behaviour."

More information: Human Keratinocytes have two interconvertible modes of Proliferation. *Nature Cell Biology*, dx.doi.org/10.1038/ncb3282

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