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STEM CELLS

‘Cheating’ cell death

> “bulge stem cells resist DNA damage-induced cell death by upregulating BCL-2 and downregulating p53”

Adult stem cells self-renew in tissue over long periods of time, so they are at great risk of accumulating DNA damage. How they sense and respond to DNA damage was unclear, but this study identifies the mechanism that makes bulge stem cells, which reside in a specialized microenvironment in the epidermis, markedly resistant to DNA damage.

The authors examined the effects of DNA damage on bulge stem cells by administering ionizing radiation to 7-week-old mice. Irradiation caused cell cycle arrest and apoptosis in both epidermal cells and bulge stem cells, but bulge stem cells showed reduced and undetectable apoptosis 12 and 24 hours after irradiation, respectively. This was not caused by quiescence, induction of senescence or premature differentiation, so another mechanism must operate.

To investigate this further, the authors assessed the mRNA and protein levels of the anti-apoptotic B cell lymphoma 2 (BCL-2) and found that they were higher in bulge stem cells than other epidermal cells. Moreover, bulge stem cells from BCL-2-deficient mice had increased levels of apoptosis, indicating that bulge stem cells resist apoptosis, at least in part, by expressing higher levels of BCL-2. They also examined the levels of the tumour suppressor protein p53, which is activated following DNA damage and induces apoptosis. They found that p53 was transiently stabilized after DNA damage but downregulated to barely detectable levels in bulge stem cells 24 hours after irradiation. Furthermore, bulge stem cells from mice with decreased expression of MDM2, a negative regulator of p53, showed a marked increase in apoptosis 24 hours after irradiation, confirming that bulge stem cells resist apoptosis, at least in part, by downregulating p53 expression.

The downregulation of p53 and consequent decline in apoptosis might be caused by rapid clearance of DNA lesions. Indeed, in bulge stem cells, phosphorylated histone H2AX (which marks DNA damage-induced foci) disappeared faster and p53-binding protein 1 (which enhances p53 transcription) was less abundant than in other epidermal cells. Bulge stem cells also showed reduced DNA damage compared with control cells and increased rates of non-homologous end joining (NHEJ), which suggests that they repair DNA lesions more quickly by upregulating this pathway. This is mediated by DNA protein kinase (DNA-PK), a key protein in the NHEJ pathway; bulge stem cells had increased DNA-PK nuclear expression and activity, and a decrease of DNA-PK augmented apoptosis and abolished the enhanced DNA repair activity following ionizing radiation treatment.

Together, these findings show that bulge stem cells resist DNA damage-induced cell death by upregulating BCL-2 and downregulating p53 owing to enhanced repair of DNA damage by DNA-PK-mediated NHEJ. Further studies will be required to determine whether this feature is specific to bulge stem cells or whether it also applies to other stem cell types.

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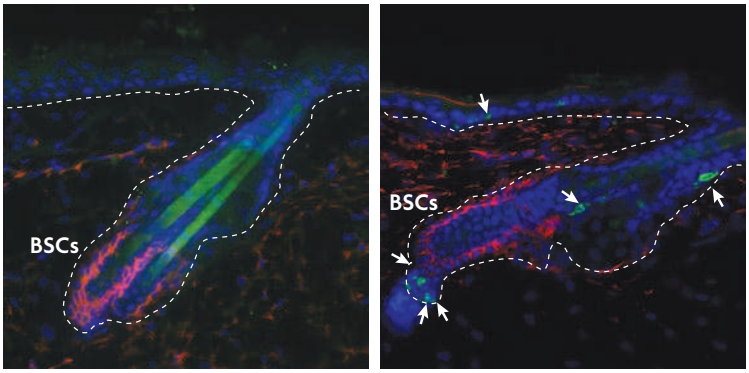
ORIGINAL RESEARCH PAPER Sotiropoulou, P. *et al.* Bcl-2 and accelerated DNA repair mediates resistance of hair follicle bulge stem cells to DNA-damage-induced cell death. *Nature Cell Biol.* **12**, 572–582 (2010)



Skin sections of control mice (left) and mice with 5 gray of irradiation 24 hours earlier (right). Stem cells are labelled in red for expression of CD34 and dead cells are labelled in green (and indicated by arrows) for caspase 3 activation; nuclei are stained in blue. The dashed line outlines the epidermis. BSCs, bulge stem cells. Image courtesy of C. Blanpain, Université Libre de Bruxelles, Brussels, Belgium.