CANCER STEM CELLS

Symmetry is key

There is increasing evidence that the development and growth of many tumours is sustained by a small subset of cells, the cancer stem cells (CSCs). However, the characteristics that distinguish CSCs from normal stem cells (SCs) are largely undefined. In a paper recently published in *Cell*, Pier Giuseppe Pelicci and colleagues establish that mammary CSCs divide differently from normal mammary SCs and implicate p53 as a master regulator of this process.

Cells from the mammary glands of wild-type and *Erbb2* transgenic mice were grown in suspension culture (mammospheres) followed by limiting dilution and transplantation into cleared fat pads of syngeneic mice. The authors found that the proportion of cells with SC qualities was higher in cultures from ERBB2 mammospheres than in wild-type cultures. This increase was also seen following the transplantation of cells explanted directly from ERBB2-expressing mammary tumours when compared with normal mammary glands.

Why are there more cells with SC-like qualities in mammary glands expressing ERBB2? SCs can undergo symmetrical cell division, which increases the SC population by generating two daughter SCs, and asymmetrical cell division, which allows self-renewal and differentiation by producing a progenitor cell as well as a daughter SC. By staining primary mammary cells with a membrane-specific fluorescent dye that segregates in daughter cells following cell division, and so decreases in intensity, the authors were able to track the number of cell divisions and to isolate cell subsets with high, intermediate or low staining patterns: low staining represented the most frequently dividing cells. Culturing these subsets in mammospheres, followed by limiting dilution and transplantation assays, identified that there was an increased frequency of self-renewing divisions in ERBB2 CSCs. By staining with a cell polarity marker, NUMB, the authors then demonstrated that although the wild-type cells divided only asymmetrically, ERBB2 CSCs could divide both asymmetrically and symmetrically. ERBB2 CSCs also had a higher replicative potential than normal SCs. Therefore, the divisions of CSCs are not only more frequent than their normal counterparts, but are also unrestricted and more often symmetrical.

Similar to ERBB2 CSCs, SCs from *Trp53*-null mammary glands were found to divide symmetrically and to increase in number over time. Although p53 was not mutated in the ERBB2 tumour mammospheres, the authors demonstrated that its activity was decreased. Restoration of p53 activity in these cells by Nutlin 3 (an inhibitor of MDM2) re-established asymmetrical growth, decreased their replicative potential and reduced the growth of transplanted mammospheres *in vivo*. The size of spontaneous tumours in ERBB2 mice treated with Nutlin 3 was also reduced, a result that was attributed to decreased self-renewal of CSCs as there were no anti-proliferative or apoptotic effects detected.

Although the mechanisms have not yet been elucidated, these results identify a new role for p53 in the control of symmetrical SC divisions and suggest that the reactivation of p53 might be useful in treating tumours with wild-type *TP53* alleles and attenuated p53 signalling.

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ORIGINAL RESEARCH PAPER Cicalese, A. *et al.* The tumour suppressor p53 regulates polarity of self-renewing divisions in mammary stem cells. *Cell* **138**, 1083–1095 (2009)