STEM CELLS

Insights into breast cancer heterogeneity

Increasing evidence indicates that breast tumours are sustained by a population of cancer stem cells (CSCs). In a recent study published in *Cell*, researchers led by Pier Paolo Di Fiore report the purification and molecular characterization of normal human mammary stem cells (hNMSCs) from cultured mammospheres, and provide evidence supporting a model in which breast tumour heterogeneity is a reflection of the number of CSC-like cells in the tumour.

To isolate putative stem cells on the basis of their functional characteristics the authors stained human mammosphere cultures with a fluorescent marker, PKH26, which labels quiescent cells but not proliferating cells as it is lost by dilution. They recovered PKH26-positive ($PKH26^{POS}$) cells by fluorescence-activated cell sorting. Unlike PKH26-negative ($PKH26^{NEG}$) cells, $PKH26^{POS}$ cells formed both basal and luminal cells in two-dimensional differentiation assays, were able to re-establish mammary development in the cleared fat pads of immunocompromized mice and possessed other characteristics expected of hNMSCs.

By comparing microarray expression profiles of $PKH26^{POS}$ cells with $PKH26^{NEG}$ cells, a gene signature for hNMSCs was identified and some of the newly identified stem cell genes could be used as markers to accurately isolate hNMSCs from normal human mammary glands. Meta-analyses of published breast cancer gene data sets revealed a correlation between the expression of several candidate signature genes and the state of tumour differentiation. Poorly differentiated tumours expressed higher levels of genes in the hNMSC gene signature compared with well-differentiated tumours.

Does the heterogeneity of breast cancers reflect their CSC-like content? Di Fiore and colleagues indeed showed that CSC-like cells isolated from poorly differentiated tumours using markers from the hNMSC signature set formed mammospheres in culture and tumour xenografts more efficiently than normal hNMSCs or CSC-like cells isolated from well-differentiated tumours.

Recently, this group also showed that CSCs more often divide symmetrically to produce daughter stem cells rather than asymmetrically to produce one stem and one progenitor cell. Together with the findings in this study, the authors present a model for mammary tumorigenesis

in which oncogenic mutations in stem cell populations determine the frequency at which CSCs will skip asymmetric divisions. This will influence the number of stem cells in the tumour with resulting changes in the pathological features of the tumour.

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ORIGINAL RESEARCH PAPER Pece, S. *et al.* Biological and molecular heterogeneity of breast cancers correlates with their cancer stem cell content. *Cell* **140**, 62–73 (2010)