Title

Regulation Of Mammary Stem/Progenitor Cells By P53 And Parity

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Abstract

Breast cancer is the most common tumor among women with inherited mutations in the p53 gene (Li-Fraumeni syndrome). The tumors represent the basal-like subtype which has been suggested to originate from mammary stem/progenitor cells. In mouse mammary epithelium, mammosphere-forming potential was increased with decreased dosage of the gene encoding the p53 tumor suppressor protein (*Trp53*). Limiting dilution transplantation also showed a 3.3-fold increase in the frequency of long-term regenerative mammary stem cells in *Trp53-/-* mice. The repression of mammospheres by p53 was apparent despite the absence of apoptotic responses to radiation indicating a dissociation of these two activities of p53. The effects of p53 on progenitor cells were also observed in TM40A cells using both mammosphere-forming assays and the DsRed-let7c-sensor. The frequency of long-term label-retaining epithelial cells (LRECs) was decreased in *Trp53-/-* mammary glands indicating that asymmetric segregation of DNA is diminished and contributes to the expansion of the mammary stem cells. Treatment with an inhibitor of γ-secretase (DAPT) reduced the number of *Trp53-/-* mammospheres to the level found in *Trp53+/+* cells. These results demonstrate that basal levels of p53 restrict mammary stem/progenitor cells. Notch is a target of γ-secretase suggesting that the Notch pathway is a therapeutic target to prevent expansion of this vulnerable pool of cells. The expansion of p53-deficient mammary stem/progenitor cells can also be reversed after the expression of C-terminal p53, suggesting that the C-terminal domains of p53 may be responsible for the regulation of mammary stem/progenitor cells self-renewal. In parous mammary gland, increased p53 responsiveness sensitized mammary stem/progenitor cells to ionizing radiation without affecting the self-renewal of these cells, which may be responsible for the parity-induced protection against breast cancer.

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