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Preclinical breast cancer biology

105P LONG-TERM EFFECTS OF EARLY PREGNANCY ON THE GENE EXPRESSION AND PROPERTIES OF MAMMARY EPITHELIAL CELL SUBPOPULATIONS IN MICE

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The breast cancer protective effect of an early pregnancy is well established in humans and rodents, but the underlying mechanism is unclear. Since breast cancers are thought to originate from specific cell subpopulations of mammary epithelia, we studied the effect of early parity on the gene expression and properties of specific luminal and basal mammary cells in mice. Thereby, mammary epithelial cell subpopulations were isolated by flow cytometry from parous and age-matched nulliparous mice and investigated using unbiased genomics and bioinformatics, as well as in vitro colony formation and in vivo mammary gland reconstitution assays. The results of the transcriptome analysis showed an upregulation of differentiation genes and a pronounced decrease in the Wnt/Notch signaling ratio in basal stem/progenitor cells. This was associated with a downregulation of carcinogenic pathways and a strong reduction in the proliferation potential of this cell subpopulation in vitro and to a lesser extent in vivo, indicating that basal stem/progenitor cells are the main target of pregnancy. As a possible mechanism for reduced Wnt signaling in basal stem/progenitor cells, we found a 2-fold decrease in the expression of the secreted Wnt ligand Wnt4 in mammary cells from parous mice. This corresponded to a similar decrease in the progesterone receptor positive and Wnt4 secreting cells. Notably, Wnt4 partially rescued the in vitro proliferation failure of basal stem/progenitor cells, strongly suggesting a causal relationship between decreased Wnt4 secretion and parity-induced changes in the gene expression and properties of basal stem/progenitor cells in mice. In conclusion, our study shows that early parity induces differentiation and downregulates the Wnt/Notch signaling ratio and the in vitro and in vivo proliferation potential of basal stem/progenitor cells in mice. Thereby, our study not only delineates the long term effects of early parity, but it also paves the way for future studies examining whether inhibitors of Wnt signaling can be used to mimic the parity-induced protective effect against breast cancer.

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