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Pregnancy Induces Persistent Changes that Potentiate Apoptotic Signaling and Responses to DNA Damage

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A full-term pregnancy reduces the lifetime risk of breast cancer by up to 50%. This effect is mediated, in part, by p53-dependent pathways. Gene expression profiling was used to investigate the mechanisms that alter apoptotic responses to DNA damage in the mammary gland. Radiation-induced responses in BALB/c-*Trp53*+/+ and BALB/c-*Trp53*-/- mice identified 121 genes that were altered by radiation and p53 status (p53-IR). To determine the effect of parity, mice were mated, force-weaned and mammary glands were allowed to involute for 21 days (parous) and compared with age-matched nulliparous mice. Gene expression profiles were determined in mammary tissues from nulliparous (N), parous (P), irradiated nulliparous (N-IR) and irradiated parous (P-IR) mice. The p53-IR gene signature did not differ among the N-IR and P-IR groups indicating that transcriptional activity of p53 was not altered by parity. However, expression profiles of apoptosis-related genes differed significantly in the parous group. The alterations in parous mammary tissues was accompanied by over-representation of biological processes that included “signal transduction” (*e*=1.69E-05). Within this set, Wnt signaling was especially pronounced (*e*<0.001). As TGFβ signaling has been implicated in multiple studies of parity-induced changes and Wnt5a was shown to be responsive to TGFβ, these genes were selected for epigenetic analysis. Primary mammary epithelial cells were isolated from N and P mice to determine patterns of active (H3K4me3) and repressed (H3K27me3) chromatin. Chromatin immunoprecipitation (ChIP) showed a 4-fold increase in the ratio of H3K4me3/H3K27me3 in parous mammary epithelium by qPCR. This was confirmed in preliminary ChIPseq experiments which identify global changes in chromatin.

Parity-regulated genes collaborate with p53-dependent targets, which act as a “switch”, to elicit apoptosis following ionizing radiation. The epigenetic states of the parity-regulated genes *Tgfb2* and *Wnt5a* provide a mechanism for the persistent alterations in gene expression and apoptosis in parous mammary epithelial cells.

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