

Category: Recent scientific data

**TGF $\beta$  mediates persistent gene expression changes in mouse mammary gland after low dose ionizing radiation exposure.**

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Ionizing radiation (IR) is a known breast carcinogen that increases risk starting at doses above 0.5 Gy, which is encompassed in the range of diagnostic and therapeutic exposures. In addition to its carcinogenic action as a DNA mutagen, IR activates the cytokine TGF $\beta$ 1 in the stroma of the mouse mammary gland, which then signals to alter extracellular composition and mediate epithelial cell fate. Microarray expression profiling has revealed distinct gene expression changes elicited by high or low doses of IR. We examined if an acute whole body low dose (0.1 Gy) would elicit a detectable gene expression program in the mammary gland. 10 week-old wildtype and *Tgf $\beta$ 1* +/- Balb/c littermates were injected with an estrogen and progesterone mixture to synchronize estrus two days before irradiation. At 1 or 4 weeks post-radiation inguinal mammary glands were harvested for RNA extraction and genome-wide microarray profiling. Herein we report that an acute whole body dose of 0.1 Gy elicits persistent changes in hundreds of genes that are evident at least until 4 weeks after exposure, and that TGF $\beta$ 1 levels modulate a distinct gene expression program in response to IR. Altered genes include those suggesting epithelial differentiation, stromal remodeling, and stress. Consistent with this role of TGF $\beta$ 1 in gene expression changes, we have previously shown that acute low dose IR can increase frequency and shorten latency of tumors resulting from unirradiated *Trp53 null* mammary fragments transplanted into mammary glands of syngeneic wildtype Balb/c mice that were previously irradiated with 0.1-1.0 Gy, but only in *Tgf $\beta$ 1* wild type hosts. Identical transplants into haplo-insufficient *Tgf $\beta$ 1* +/- mice nullified the promotion (Nguyen et al. submitted). Together, these data suggest that IR, a known environmental carcinogen, has dual actions as a mutagen and significantly via the host. Furthermore, TGF $\beta$ 1 is a key mediator of the mammary response to radiation exposure both in preneoplastic states and in tumorigenesis. *This work is supported by funding from the NIEHS to MHBH and DOD BCRP pre-doctoral fellowship to DHN.*