Regulation of Annexin A2 by Ionizing Radiation in Human Skin Equivalent Culture: Does A Nuclear Annexin A2-Protein Kinase C Epsilon Complex Contribute To Reduced Cancer Risks At Low Dose Exposures?

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Annexin A2 (AnxA2) is known to be silenced in a number of tumor types and has previously been shown to be responsive to low dose ionizing radiation. In the current study, we ask whether the nuclear localization of AnxA2 is affected by low dose radiation and whether this activity is linked to protein kinase C epsilon (PKCε), a known oncogene. We demonstrate that nuclear translocation of AnxA2 in response to X-radiation (10-200 cGy) is increased in both experimental human skin tissue and murine progenitor cell model systems. Oncogenic protein kinase C epsilon (PKCε) is a nuclear binding partner of AnxA2, and the levels of phospho-PKCε increase in experimental human skin after exposure to the epigenetic carcinogen 12-O-tetradecanoylphorbol-13-acetate (TPA). Transgenic manipulation of murine progenitor cells demonstrates that PKCε levels are increased in nuclear extracts from AnxA2 silenced cells (using shRNA), relative to vector controls, suggesting that AnxA2 contributes to PKCε nuclear export, thereby reducing its oncogenic potential. Furthermore, we demonstrate that low dose irradiation reduces the focus forming potential of mouse progenitor cells when exposed prior to treatment with either epidermal growth factor or TPA. In order to determine how silencing AnxA2 alters transcriptional programming we compared the radiation transcriptome in AnxA2-deficient and vector control cells using whole genome mouse microarrays. These data demonstrate that the silencing of AnxA2 significantly alters the cellular response to radiation,

which may be relevant to AnxA2-deficient cancer phenotypes. These observations implicate AnxA2 in an adaptive mechanism during the response to ionizing radiation and raise the possibility that induction of AnxA2 may reduce oncogenic potential through PKCε.