Mechanisms and Actions of Ionizing Radiation as a Breast Carcinogen

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Ionizing radiation is one of very few exogenous exposures are known to increase breast cancer risk. Both human and experimental animal data suggest that there are additional poorly understood factors associated with aging or other life events that are permissive of, or actively promote, carcinogenesis. For example, Land et al. conducted a nested case-control study (Land et al., 1994) in which sophisticated statistical modeling indicated that early first birth, multiple births and long cumulative lactation history protect not only against breast cancer *per se*, but against radiation-induced breast cancer in this population. Thus, while radiation exposure increases breast cancer risk, these events are unlikely to be sufficient as evidenced by the long latency (approximately 40 years) between exposure and disease, and the observation that subsequent tissue and reproductive processes can modify risk. A more mechanistic understanding of the cellular and molecular events that occur over a woman's lifetime is necessary to understand the increased risk of breast cancer in populations exposed during puberty.

Mammary gland stem cells have been hypothesized to be the primary targets in the etiology of breast cancer, and have been implicated as targets for carcinogenesis in several model systems. Thus the identification of the stem and progenitor populations of mammary gland is of critical to understanding not only the mammary gland, but also the genesis of cancer (Reya et al., 2001). The regenerative capability of mammary gland stem cells is astounding; a single mammary gland stem cell is predicted to be capable of generating 10^{12}-10^{13} progeny (Smith and Chepko, 2001). We hypothesize that exposure to a carcinogen, such as ionizing radiation, during puberty may alter the characteristics and regulation of the niche for putative mammary stem cells and thereby affect their long term potential to become neoplastic.

This talk will review the molecular determinants of epithelial lineages, how the mouse mammary gland responds to radiation exposure and studies of irradiated normal human epithelial cells in culture. Understanding ionizing radiation as a prototypic carcinogen will allow us to compare other putative environmental carcinogens and assess their role in breast cancer initiation and progression.

References

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