Award ID:
RP100502

Project Title:
The Role of Net1 in the Cellular Response to Ionizing Radiation in Breast Cancer

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas Health Science Center at Houston

Lay Summary:

The use of ionizing radiation (IR) is an integral component of breast cancer treatment for virtually all patients who receive breast conserving surgery and in most patients with locally advanced breast cancer treated with mastectomy. IR is also commonly used to treat breast cancer patients with inoperable primary tumors, in metastatic disease, and as a palliative treatment in very advanced local recurrences in the bone and elsewhere. However, despite the wide use of IR therapy, resistance to IR commonly occurs within tumor populations, resulting in cancer recurrence. Our current work has identified the RhoA activating protein Net1 as a novel regulator of cell survival following exposure to IR. In the proposed research, we will identify the molecular mechanism for how Net1 controls DNA damage and survival responses in breast cancer cells. These findings will allow us to determine whether targeting Net1 or its regulatory proteins is a suitable way to sensitize human breast cancer cells to IR therapy. We will also develop a transgenic mouse that lacks the Net1 gene within its mammary glands. This work will provide a unique model to study the role of Net1 in mammary gland development, as well as in the maintenance and function of the adult mammary gland. We will then use explanted breast epithelial cells from Net1 knockout mice to ascertain whether normal mammary epithelial cells also require Net1 for protection from IR. These studies will provide a necessary understanding of how Net1 contributes to IR responses in normal breast epithelial cells relative to breast cancer cells. Taken together, this work will allow us to quantitatively assess the utility of targeting Net1 in breast cancer cells to increase the efficacy of IR therapy.