CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140222

Project Title:
Direct Roles for RB and E2F1 in DNA Repair

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

The retinoblastoma (RB) gene was the first tumor suppressor to be cloned almost 30 years ago. It is now known that RB is mutated not only in retinoblastomas but also in other cancers, including cancers of the bone and lung. Moreover, the RB protein is functionally inactivated in many cancers through other mutations or by the action of viruses, as is the case in most cervical cancers. Taken together, loss of RB function occurs in most tumors and is considered a hallmark of cancer. The RB protein binds to and inhibits the activity of the E2F1 transcription factor. E2F1 regulates the expression of genes important for cell proliferation and RB is widely believed to function as a tumor suppressor by inhibiting E2F1 and blocking the expression of these growth-promoting genes. RB also regulates the activity of other transcription factors and current models suggest that these activities may also contribute to tumor suppression by RB. The current RB-E2F1 paradigm does not include functions beyond their abilities to regulate gene expression. However, preliminary data from our laboratory demonstrates that E2F1 and RB accumulate at sites of DNA breaks and directly contribute to efficient DNA repair. We have developed two unique knock-in mouse models that will allow us to separate the roles of E2F1 and RB in regulating gene expression from their functions in DNA repair. These knock-in mouse models will be used to establish the physiological relevance of E2F1 and RB activities at sites of DNA damage for maintaining genome integrity and suppressing cancer. This proposal seeks to significantly expand our understanding of RB biology to include functions for RB and E2F1 at sites of DNA damage that promote DNA repair in the context of chromatin. Establishing new roles for RB and E2F1 in DNA repair will open up new therapeutic opportunities for the treatment of cancers with RB mutations or other disruptions in the RB-E2F1 pathway.