CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170496

Project Title:
Targeting a Growth and Survival Pathway in Bone Tumor Cells.

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
Texas A&M University System Health Science Center

Lay Summary:

Of the 700,000 newly diagnosed cancers per year in the US, about 40% will eventually affect bone. Bone cancer, or malignant bone disease (MBD), frequently causes catastrophic bone damage in the form of tumor-filled osteolytic bone lesions (OLs). OLs cause fracture, chronic pain, and provide a robust environment for tumor growth, thus reducing the probability of survival.

MBD is typically treated by drugs that kill tumors and slow bone loss. Even with these treatments, OLs frequently fail to heal, continually supporting tumor survival while selecting for drug-resistant tumor cells.

MBD tumors secrete proteins called Wnt inhibitors (WI) that inhibit the repair of OLs. Of the known WIs, Dickkopf-1 (Dkk-1) is most commonly involved with MBD. Blockade of WI activity (especially Dkk-1) is a potentially promising OL repair therapy, but we have made a remarkable additional discovery that further increases the significance of targeting WIs in MBD: Tumor-derived Dkk-1 also accelerates proliferation and enhances survival of tumors.

In this work, we established that Dkk-1 upregulates an enzyme called aldehyde dehydrogenase1a1 (ALDH1A1). Through its detoxifying properties, ALDH1A1 increases the tumor's resistance to environmental stresses that occur during exposure to therapy and metastasis. We therefore propose that therapeutic inhibition of Dkk-1 and other WIs could inhibit tumor survival as well as repair OLs, thus raising the attractive possibility of a single agent that targets both the tumor and its microenvironment.

Therefore, our goal is to establish (i) how Dkk-1 upregulates ALDH1A1 in human bone tumor cells and ii) examine how this knowledge can be employed to develop novel bone-preserving and anti-tumor strategies for MBD.

Successful completion of this study will increase our understanding of a mechanism that plays a key role in both tumor survival and bone destructive capacity in MBD, raising the possibility of a new generation of multi-purpose therapies.