CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170488

Project Title:
Mechanisms of Notch Dysregulation in Pediatric Osteosarcoma

Award Mechanism:
Individual Investigator Research Awards for Cancer in Children and Adolescents

Principal Investigator:
Lee, Brendan

Entity:
Baylor College of Medicine

Lay Summary:

Osteosarcoma (OS) is the most common primary bone cancer and occurs in adolescents and young adults. Among diagnosed OS patients, 15-20% present with lung metastasis at initial diagnosis and about 40% develop metastasis at a later stage. Current treatments including surgery and chemotherapy have increased survival rate to around 70%. However, the clinical outcome for metastatic OS remains poor. Our knowledge of the genetic causes of OS and mechanisms of OS progression and metastasis are still limited. Interestingly, we have shown that mice with chronically activated Notch1 (GOF) in bone cells develop spontaneous OS with a high level of genomic instability, which is a signature feature of human OS. Furthermore, we also found that Pum2, a RNA-binding protein, was drastically increased in tumors from the GOF Notch1 mice. Pum2 affects genomic instability by regulating multiple genes involved in genome surveillance, and has previously been implicated in tumorigenesis. Hence, it is important to understand the mechanisms through which Notch signaling activates Pum2 to regulate genome stability and how this contributes to the progression of OS. In addition, we have found that Notch1 is a novel downstream target of the tumor suppressive miRNA-34c (miR-34c). Overexpression of miR-34c in our OS mouse model increased survival and decreased lung metastasis. Furthermore, we found several miR-34c putative targets associated with lung metastasis in OS. Hence, by delineating the molecular network of the Notch upstream regulator miR-34c, we will identify novel target genes/pathways associated with OS metastasis. Overall, our study will broaden our understanding of: 1) what causes genomic instability in OS progression, and 2) how lung metastasis is regulated in OS. Also, our study will lead to identify novel therapeutic approaches that could improve the current management of OS.