CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170146

Project Title:
B cell receptor signaling intersects with angiogenesis in diffuse large B cell lymphoma

Award Mechanism:
Individual Investigator

Principal Investigator:
Aguiar, Ricardo

Entity:
The University of Texas Health Science Center at San Antonio

Lay Summary:

Angiogenesis, the development of new vessels to support tumor grown, is a cancer hallmark. In diffuse large B cell lymphoma (DLBCL), a common and aggressive cancer type, angiogenesis is associated with poor outcome. However, we know little about the contribution of the lymphoma cell to this abnormal vessel development, and clinical trials that tested classical anti-angiogenic agents in DLBCL were negative. Thus, a better understanding of the proangiogenic role of the lymphoma cell will facilitate the development of new treatment strategies that target the tumor and its supporting microenvironment.

DLBCL is also driven by constitutive activation of B cell receptor (BCR) signals. Earlier, we showed that genetic or pharmacological depletion of the enzyme phosphodiesterase 4B (PDE4B) terminates BCR activity, and inhibits the growth of BCR-dependent lymphomas. Interestingly, in non-cancer models, PDE4B also modulates angiogenesis. Therefore, we tested whether the interplay between PDE4B and the BCR found in lymphoma cells could influence angiogenesis in the tumor microenvironment. Using a novel mouse model, and a FDA-approved PDE4 inhibitor in vivo, we found that targeting PDE4B suppresses the BCR, blocks angiogenesis and improves the survival of mice harboring B cell lymphoma.

Here, to bring these findings closer to a successful clinical initiative, we will need to define: a) the signaling circuitry that mediates PDE4B proangiogenic role in lymphoma; b) the relative contribution of the tumor and endothelial cells to this process; c) the benefit of combining PDE4 and BCR-related inhibitors as anti-lymphoma and anti-angiogenesis agents. When this study is completed, we will have validated the hitherto unsuspected link between BCR signaling and angiogenesis in DLBCL, and laid out the groundwork for the implementation of rationally developed clinical trials that uses FDA-approved agents to attack the lymphoma cell and its microenvironment