CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP100695

Project Title:
Self-Antigen Dependence of Chronic Active B-Cell Receptor Signaling in the Activated B-Cell Type of Diffuse Large B-Cell Lymphoma

Award Mechanism:
Individual Investigator

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

Lay Summary:

B-cell non-Hodgkin's lymphoma (B-NHL) is an uncontrolled proliferation of a single B-cell clone, that like normal B cells has a unique B-cell receptor (BCR) sequence. In normal immune responses, foreign antigen binds to the BCR on B-cell clones whose BCR sequences recognize it, causing them to proliferate and secrete antibody (soluble BCR) against the antigen. B-cell proliferation normally stops when the antigen is cleared, just as other mechanisms normally eliminate B-cell clones that recognize self-antigen and could cause autoimmune diseases like lupus. More than just indicating clonal origin, however, the BCR in B-NHL may drive proliferation as in normal B cells: we recently discovered that in ABC-DLBCL, a type of B-NHL that responds poorly to standard therapy, tumor cells require BCR expression and BCR-derived growth signals. Enzymes transmitting these signals are therefore therapeutic targets in ABC-DLBCL, but the question remains: What activates the BCR in ABC-DLBCL? Using ABC-DLBCL cell lines, we will test the hypothesis that self-antigen is responsible for continuous BCR activity. Since antigen can be almost any molecule and is difficult to identify directly, we will address this hypothesis indirectly by: 1) Showing that ABC-DLBCL lines require their particular BCR sequence for survival. Using novel techniques for genetic manipulation, we will replace antigen binding sequences of the BCR gene with corresponding sequences from non-BCR-dependent lines. If ABC-DLBCL lines die without their native antigen-binding BCR sequence, it will strongly imply BCR activation by a self-antigen. 2) Showing that peptides (short protein sequences) can bind and inactivate the BCR of ABC-DLBCL lines. Screening techniques can find antigen-mimicking peptides that bind to a BCR, and may bind without activating it. If such peptides are lethal to ABC-DLBCL lines expressing their target BCR, it will imply a specific antigen that they have displaced by competition, and suggest new, highly-specific therapies for ABC-DLBCL.