Small Molecule Stabilization of the CARD11 G-quadruplex Represses Transcription: Developing a Therapeutic Target for Diffuse Large B-Cell Lymphoma

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Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous malignancy characterized by the uncontrolled growth of abnormal B-cells in the lymphatic system. The activated B cell (ABC) subtype presents the main challenge to overcoming the oncogenic defects that lead to the diseases' aggressive nature. CARD11 (caspase recruitment domain-containing protein 11), often activated through the signaling of the B cell Receptor (BCR), is a critical scaffold molecule and its recurrent gain-of-function mutations are frequently found in chemoresistant DLBCL. This study aimed to investigate the potential value of CARD11 as a therapeutic target for DLBCL by examining the stability of DNA secondary structures (G-quadruplexes/G4s) within this gene. G-quadruplex structures act as barriers to transcription factors, RNA polymerases, and other proteins involved in gene expression. After stable G-quadruplexes were identified within the guanine-rich CARD11 promoter region, small molecules from the National Service Center (NSC) were screened using the fluorescence resonance energy transfer (FRET) technique for their ability to stabilize G-quadruplexes. Using qPCR, it was determined that G4 stabilization led to repression of CARD11 transcription and subsequent reduction in other crucial oncogenes in DLBCL with known G4 structures (BCL2 and MYC). Additionally, 752 compounds from a natural library were tested using FRET assays to identify natural compounds that stabilized the CARD11 G4 structure (using a 5°C threshold). These findings highlight that stabilizing the CARD11 promoter G4 structures inhibits DLBCL growth by silencing CARD11 gene expression and downstream oncogenic signals from the BCR.

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