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Title: "Pharmacological and Genomic Profiling Identifies Deregulation of Classical and Alternative NFκB Signaling in Mantle Cell Lymphoma"

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Statement of the Problem/Background:
Mantle cell lymphoma (MCL) is an aggressive malignancy characterized by an extremely poor prognosis, underscoring the need for novel therapeutic strategies.

Research Question/Hypothesis:
Large-scale pharmacological profiling identified a subset of mantle cell lymphoma (MCL) lines sensitive to the PKC inhibitor Sotrastaurin (STN). Subsequent analysis of a larger set of MCL lines identified STN-sensitive MCL lines and STN-insensitive MCL lines.

Research Design/Methods Used in the Investigation:
High-throughput RNA sequencing identified recurrent mutations in negative regulators of the alternative NFκB pathway in MCL cell lines and patient samples.

Results/Summary of the Investigation:
STN-sensitive MCL lines exhibited chronic activation of the CARD11-BCL10-MALT1 (CBM) complex and dependency on classical NFκB signaling. In contrast, STN-insensitive cell lines displayed activation of the alternative NFκB pathway. Cells containing mutations in negative regulators of the alternative NFkB pathway were sensitive to inhibition of NIK-NFκB signaling, identifying NIK as a new therapeutic target for MCL.

Interpretation/Conclusion of the Investigation:
These findings reveal a pattern of mutually exclusive activation of the CBM-NFκB or alternative NIK-NFκB pathways in MCL and provide critical insights into patient stratification strategies for NFκB-pathway targeted agents.