Myc-induced SUMOylation is a therapeutic vulnerability for B-cell lymphoma.

Abstract:

Myc oncogenic transcription factors (c-Myc, N-Myc, and L-Myc) coordinate the control of cell growth, division, and metabolism. In cancer, Myc overexpression is often associated with aggressive disease, which is in part due to the destruction of select targets by the ubiquitin-proteasome system (e.g., SCF(Skp2)-directed destruction of the Cdk inhibitor p27(Kip1)). We reasoned that Myc would also regulate SUMOylation, a related means of posttranslational modification of proteins, and that this circuit would play essential roles in Myc-dependent tumorigenesis. Here, we report marked increases in the expression of genes that encode regulators and components of the SUMOylation machinery in mouse and human Myc-driven lymphomas, resulting in hyper-SUMOylation in these tumors. Further, inhibition of SUMOylation by genetic means disables Myc-induced proliferation, triggering G2/M cell-cycle arrest, polyploidy, and apoptosis. Using genetically defined cell models and conditional expression systems, this response was shown to be Myc specific. Finally, in vivo loss-of-function and pharmacologic studies demonstrated that inhibition of SUMOylation provokes rapid regression of Myc-driven lymphoma. Thus, targeting SUMOylation
represents an attractive therapeutic option for lymphomas with MYC involvement.

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