

RESEARCH WATCH

Lymphoma

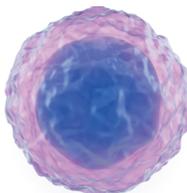
Major finding: BCL-W prevents lymphocyte apoptosis and is negatively regulated by MYC-induced miR-15 family members.

Clinical relevance: BCL-W is highly expressed in patients with Burkitt lymphoma and DLBCL and linked to poor survival.

Impact: BCL-W may be a potential therapeutic target to induce apoptosis in patients with B-cell lymphoma.

BCL-W PROMOTES B-CELL SURVIVAL AND CONTRIBUTES TO B-CELL LYMPHOMA

The antiapoptotic BCL2 proteins, including BCL2 and BCL-XL, are often overexpressed in cancer and promote cell survival. The antiapoptotic BCL2 protein BCL-W has a crucial role in spermatogenesis, but its role in tumorigenesis is not clear, prompting Adams and colleagues to investigate its role in lymphoma. BCL-W was expressed in lymphocytes, and loss of expression promoted apoptosis in response to cytokine deprivation or MYC activation, indicating an essential role for BCL-W in lymphocyte survival. *In vivo*, BCL-W loss delayed lymphoma growth and extended survival in a mouse model of MYC-driven B-cell lymphoma. BCL-W expression was negatively regulated by MYC, which induced transcription of miR-15 family members that bound directly to *BCL-W* to reduce its expression and thereby promote apoptosis. Consistent with these findings, depletion of BCL-W, via BCL-W shRNA or overexpression of miR-15a, induced apoptosis in Burkitt lymphoma cell lines, suggesting the possibility for therapeutic targeting of BCL-W in Burkitt lymphoma. In addition, pharmacologic inhi-



tion of BCL-W with the BH3 mimetic compounds ABT-737 and ABT-263 induced apoptosis in Burkitt lymphoma cells, which could be prevented by overexpression of BCL-W. Moreover, BCL-W was overexpressed in patients with Burkitt lymphoma, whereas miR-15a was expressed at low levels, further indicating that BCL-W may contribute to Burkitt lymphoma pathogenesis. BCL-W was also overexpressed in diffuse large B-cell lymphoma (DLBCL) cell lines and patient samples, and its overexpression was correlated with a poorer survival in patients, suggesting that BCL-W may also contribute to DLBCL. Taken together, these findings indicate that BCL-W enhances cell survival to promote B-cell lymphoma, and suggest that BCL-W may be useful as a prognostic biomarker or therapeutic target in patients with B-cell lymphoma. ■

Adams CM, Kim AS, Mitra R, Choi JK, Gong JZ, Eischen CM. BCL-W has a fundamental role in B cell survival and lymphomagenesis. *J Clin Invest* 2017;127:635–50.

Tumorigenesis

Major finding: eIF2A promotes translation from upstream initiation sites during tumor initiation.

Concept: Depleting conventional eIF2 complexes negatively affects normal growth but not oncogenic growth.

Impact: Targeting eIF2A-mediated translation may potentially suppress translation of cancer-related mRNAs.

TRANSLATION FROM ALTERNATE START SITES ENRICHES ONCOGENIC PROTEINS

Translational regulation is essential for determining protein abundance, and oncogenic drivers can alter the activity of eukaryotic initiation factors (eIF) and ribosomal proteins. To test the hypothesis that oncogenes modify protein synthesis programs to promote tumor initiation and progression, Sendoel and colleagues used a mouse model of premalignant induction of the transcription factor SOX2, a driver of squamous cell carcinoma (SCC), in the embryonic epidermis. Parallel RNA sequencing and ribosome profiling allowed a genome-wide comparison of transcription and translation, and 573 genes were identified that exhibited translational, but not transcriptional, differences in response to SOX2 expression. SOX2⁺ cells had a reduced translational efficiency compared with wild-type cells, which was generally associated with reduced protein synthesis. However, a small subset of mRNAs, many of which were associated with cancer, was efficiently translated in SOX2⁺ cells, suggesting that cancer-related genes may escape translational suppression. SOX2 expression increased ribosome occupancy at 5' untranslated regions and the use of upstream open reading frames (uORF), many of

which contained alternative CUG codons instead of the conventional AUG initiation site, suggesting that translation from uORFs increases the translation efficiency of cancer-related mRNAs. Depletion of translational regulators in an *in vivo* RNAi screen revealed that normal cells, but not cancer cells, depended on the conventional eIF2 α (encoded by *EIF2S1*) for translation and cell growth. In contrast, the alternative initiation factor eIF2A was required for SCC tumor initiation and translation from CUG uORF start codons. Further, data from The Cancer Genome Atlas showed that the *EIF2A* locus is frequently amplified in patients with SCC, and increased *EIF2A* mRNA expression is associated with reduced overall survival. In addition to suggesting a mechanism by which cancer-related mRNAs may be translated from uORFs during global translational repression, these findings suggest the potential for therapeutic targeting of eIF2A-mediated translation. ■

Sendoel A, Dunn JG, Rodriguez EH, Naik S, Gomez NC, Hurwitz B, et al. Translation from unconventional 5' start sites drives tumour initiation. *Nature* 2017;541:494–9.

CANCER DISCOVERY

Translation from Alternate Start Sites Enriches Oncogenic Proteins

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