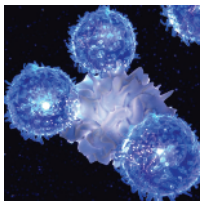
Immunology

Major finding: WDFY4 is required for classic dendritic cell–mediated cross-presentation of tumor and viral antigens.

Mechanism: WDFY4 interacts with endosomal membrane proteins to promote endosomal-to-cytosol antigen trafficking.

Impact: Therapeutic activation of WDFY4-mediated cross-presentation may enhance immunotherapy efficacy.

ANTIVIRAL- AND ANTITUMOR-SPECIFIC T-CELL IMMUNITY IS WDFY4-DEPENDENT



The ability of lymphocytes to recognize microbial and tumor-associated antigens is mainly dependent upon the binding affinity of surface MHC-I for peptides. The MHC-I antigen–presenting classical dendritic cells (cDC) are comprised of BATF3-dependent cDC1s, which mediate cross-presentation of tumor and viral MHC-I antigens, and cDC2s, which mediate cross-presentation of pathogen MHC-I antigens. To further elucidate the mechanisms underlying cDC1–mediated cross-presentation, Thiesen, Davidson, and colleagues established a functional CRISPR/Cas9 screen to identify regulators of cross-presentation in cDC1s. The *in vitro* CRISPR/Cas9 screen demonstrated that loss of WDFY4, a transmembrane protein that is a member of the BEACH domain–containing protein family of scaffolding proteins, resulted in impaired mouse cDC1–mediated cross-presentation. While cDC1s developed normally in *Wdfy4*$^{-/-}$ but not *Batf3*$^{-/-}$ mice, the cDC1-mediated cytotoxic CD8^{+} T-cell response to the presence of cell-associated or bacterial antigens was ablated *in vitro* in *Wdfy4*$^{-/-}$ mice. Affinity purification mass spectrometry identified interactions between WDFY4 and proteins involved in assembling protein complexes and subcellular vesicular trafficking, particularly the formation and trafficking of endocytic vesicles. In particular, WDFY4 was selectively associated with HSP90AB1, which is involved in the processing of antigens during cross-presentation and shown to be co-localized with early endosomes and the ER near the plasma membrane. A highly immunogenic murine fibrosarcoma was rejected by control, *Wdfy4*$^{+/-}$ mice, and mice transplanted with mixtures of control and *Batf3*$^{-/-}$ bone marrow; conversely, the same murine fibrosarcoma grew in *Batf3*$^{-/-}$, *Wdfy4*$^{-/-}$ mice, and mice transplanted with mixtures of *Wdfy4*$^{-/-}$ and *Batf3*$^{-/-}$ mice, suggesting that the failure to reject tumors was due to the loss of *Wdfy4* in cDC1s. Similarly, tumors in *Wdfy4*$^{-/-}$ mice exhibited cDC1 infiltration and decreased CD8^{+} T-cell infiltration. These results identify WDFY4 as a critical regulator of cDC1-mediated cross-presentation of viral and tumor antigens and suggest potential avenues of preclinical investigation. ■

Theisen DJ, Davidson JT IV, Briseño CG, Gargaro M, Lauron EJ, Wang Q, et al. WDFY4 is required for cross-presentation in response to viral and tumor antigens. Science 2018;362:694–9.

Oncogenes

Major finding: A protein interaction screen reveals 336 MYC-binding proteins that bind to distinct MYC homology boxes (MB).

Mechanism: Two MBs cooperate to promote tumorigenesis, MB0 by binding to TFIIF and MBII by binding to TRRAP-HAT.

Impact: Only a subset of MYC interactors promote tumorigenesis, an insight that may aid therapeutic targeting of MYC.

TWO MYC HOMOLOGY BOXES DRIVE TUMORIGENESIS

The MYC family proteins MYC, MYCL1, and MYCN are frequently deregulated in cancer. These proteins harbor six highly conserved regions termed MYC homology boxes (MB), but the mechanisms by which MYC promotes tumorigenesis and the contribution of the individual MBs are not well understood. To delineate the function of the MBs, Kalkat and colleagues conducted proteomic profiling to identify the binding partners of wild-type MYC and six deletion mutants each with one of the MBs deleted. A total of 336 MYC-interacting proteins were identified, and each MB deletion resulted in loss of a subset of interactors. Deletion of MB0 resulted in loss of 94 interacting partners, and deletion of MBII resulted in loss of 43 interacting partners including a previously identified histone acetyltransferase (HAT) complex component TRRAP. Only two of the MB domains, MB0 and MBII, were required for tumorigenesis. Deletion of MB0 or MBII suppressed cell proliferation *in vitro* and suppressed the growth of MYC-dependent breast cancer xenografts *in vivo*. MB0 and MBII had distinct functions in promoting transcription and tumorigenesis. RNA sequencing showed minimal overlap between the genes upregulated by each MB, indicating that each regulates a distinct set of genes. MBII interacted with TRRAP–HAT complexes to promote tumor initiation, and deletion of MBII suppressed MYC-mediated histone acetylation. In contrast, MB0 interacted directly with the TFIIF transcription elongation complex to regulate transcription and accelerate tumor growth. Coexpressing both the mutant lacking MB0 and the mutant lacking MBII was sufficient to rescue tumor growth, further indicating that MB0 and MBII have independent but complementary effects in tumor promotion. Collectively, these findings reveal two MYC domains that cooperate to drive tumorigenesis, insights that may have implications for the development of MYC-targeted therapies. ■

Kalkat M, Resetca D, Lourenco C, Chan PK, Wei Y, Shiah YJ, et al. MYC protein interactome profiling reveals functionally distinct regions that cooperate to drive tumorigenesis. Mol Cell 2018;72:836–48.