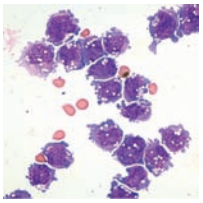
Lymphoma

Major Finding: A *Tbl1xr1* loss-of-function mutation promoted memory B-cell fate and an aggressive lymphoma subtype.

Concept: The corresponding disease-associated mutation in humans is associated with a similar phenotype.

Impact: This pinpoints *TBL1XR1*'s role in diffuse large B-cell lymphoma and suggests a memory B-cell origin.

TBL1XR1 MUTATIONS BIAS TOWARD MEMORY B-CELL FATE TO PROMOTE LYMPHOMA



An aggressive subtype of activated B-cell diffuse large B-cell lymphomas (ABC-DLBCL) with an unusual extranodal distribution is characterized by mutations in the poorly understood gene *TBL1XR1*. Venturutti and colleagues discovered that a missense mutation in *Tbl1xr1* found in these lymphomas and some developmental disorders diminished the germinal center reaction in mice. Further investigation revealed that this missense mutation mimicked complete *Tbl1xr1* loss of function. Proliferation in germinal centers was impaired by *Tbl1xr1* mutation, explaining the lower levels of germinal center B cells in *Tbl1xr1*-mutant and *Tbl1xr1*-knockout mice. *Tbl1xr1*-mutant mice exhibited elevated levels of precursor memory B cells, leading to bias toward the generation of memory B cells and away from the generation of plasma cells. Mechanistically, TBL1XR1 is a key part of the SMRT–NCOR1 transcriptional corepressor complex, and *TBL1XR1*-mutant human cells exhibited increased association of this complex with the memory B cell–associated transcription factor BACH2 over the germinal center–associated transcription factor BCL6, explaining why loss of TBL1XR1 function shifts the balance between memory B cells and plasma cells toward the former cell type. Upon antigen recall, *Tbl1xr1*-mutant memory B cells, rather than differentiating into plasma cells, exhibited a bias toward reentering the germinal center reaction, becoming germinal center B cells. Importantly, this demonstrates that lymphoma-associated mutations can direct B cells toward undergoing repeated cycles of mutagenesis, supporting the idea of cyclic immune stimulation as a driver of lymphomagenesis. Notably, *Tbl1xr1*-knockout mice developed lymphomas with marked similarities to human *TBL1XR1*-mutant ABC-DLBCLs. Consistent with the cyclic reentry notion, these lymphomas harbored abundant AID-associated somatic mutation, a genetic hallmark of extranodal ABC-DLBCLs. Finally, immunohistochemical analysis and mass cytometry supported the notion that human *TBL1XR1*-mutant ABC-DLBCLs also arise from memory B cells. In summary, this work uncovers a mechanism by which disease-associated mutations in the little-understood gene *TBL1XR1* promote the development of aggressive lymphomas with extranodal distribution and points to memory B cells as the cell type of origin for this disease subtype. ■

Venturutti L, Teater M, Zhai A, Chadburn A, Babiker L, Kim D, et al. TBL1XR1 mutations drive extranodal lymphoma by inducing a pro-tumorigenic memory fate. Cell 2020;182:297–316.e27.

Drug Development

Major Finding: An antibody blocking GRFAL–RET binding blunted GDF15-induced cachexia, preventing weight loss.

Concept: GDF15 altered metabolism and led to aberrant sympathetic nervous system activity to cause cachexia.

Impact: This work debuts a therapeutic antibody of interest in treating cachexia and reveals its mechanism.

A THERAPEUTIC GFRAL ANTIBODY BLOCKS CANCER-LINKED CACHEXIA IN MICE

Elevated levels of the cytokine growth differentiation factor 15 (GDF15) have been linked to cachexia and poorer survival in patients with cancer. Recent evidence indicates that GDF15 binding to the cell-surface receptor GDNF family receptor α–like (GFRAL), which triggers oligomerization with the receptor tyrosine kinase RET and consequent RET signaling, underlies the connection between GDF15 and cachexia. Based on these findings, Suriben, Chen, Higbee, and colleagues developed the GFRAL-targeting monoclonal antibody 3P10. *In vitro*, treatment with this high-affinity antibody did not disrupt GDF15–GFRAL binding, but instead blocked GFRAL–RET binding to inhibit GDF15-induced RET signaling. *In vivo*, 3P10 administration prevented weight loss induced by recombinant GDF15 and in mouse cancer models with highly GDF15-secreting tumors. This effect was not simply due to prevention of anorexia, as tumor-bearing mice on calorie-restricted diets also exhibited a reduction in body-weight loss. Alternatively, 3P10 treatment increased glucose oxidation and reduced lipid oxidation in tumor-bearing mice, bringing lipid- and glucose-oxidation levels closer to those of tumor-free mice. Notably, recombinant GDF15 induced expression of *Pnpla2*, encoding adipose triglyceride lipase (ATGL), and *Pnpla2* knockout prevented GDF15-induced weight loss without blunting anorexia and blocked the pathologic decrease in glucose oxidation and increase in lipid oxidation observed in GDF15-treated *Pnpla2*–wild-type mice. Additionally, chemical ablation of adrenergic neurons in the peripheral sympathetic nervous system did not prevent GDF15-induced reduction in food intake, but still substantially reduced weight loss, indicating a role for the sympathetic nervous system in GDF15-mediated cachexia. In summary, this work describes a novel therapeutic antibody that is worth investigating further—and is currently in clinical trials—for the treatment of cachexia and elucidates previously unknown mechanisms by which GDF15 causes food intake–independent weight loss. ■

Suriben R, Chen M, Higbee J, Oeffinger J, Ventura R, Li B, et al. Antibody-mediated inhibition of GDF15–GFRAL activity reverses cancer cachexia in mice. Nat Med 2020;26:1264–70.