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LYMPHOID NEOPLASIA

Comment on Bucher et al, page 121

A role for NFAT signaling in ABC-DLBCL

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In this issue of *Blood*, Bucher et al investigate the role of calcium-induced nuclear factor of activated T cells (NFAT) signaling in subtypes of diffuse large B-cell lymphoma (DLBCL) and identify a potential therapeutic vulnerability in a subtype of the disease.[1]

DLBCL, the most common form of non-Hodgkin lymphoma, can be subdivided into subtypes based on differences in gene expression.[2] The germinal center B-cell-like (GCB) subtype and activated B-cell-like (ABC) subtype are thought to be derived from different cells of origin and are reliant on different signaling pathways for their survival. ABC-DLBCL is the more clinically aggressive subtype of DLBCL, and thus there has been a significant effort to identify signaling pathways that can be targeted therapeutically in this specific subtype. Increased activity of NF-κB is a hallmark of ABC-DLBCL and can be the result of a variety of perturbations, including chronic active B-cell receptor (BCR) signaling or activating mutations in signaling molecules associated with BCR-induced NF-κB or in the toll-like receptor adapter protein MyD88.[3] Inhibition of Bruton tyrosine kinase (BTK) can suppress activation of NF-κB in many cell line models of ABC-DLBCL and has been leveraged as a single agent and in combination with other agents to treat ABC-DLBCL. Unfortunately, clinical responses to BTK inhibitors as single agents are often transient in ABC-DLBCL, and thus, the search is ongoing for other signaling pathways that might be therapeutically targeted in ABC-DLBCL.[4]

Bucher et al identify another signaling pathway that operates in cell line models of ABC-DLBCL to promote their survival by a mechanism that is distinct from dysregulated NF-κB signaling. They found that the transcription factor NFAT is active in ABC-DLBCL cell lines. NFAT is activated by the phosphatase calcineurin whose activity is controlled by intracellular calcium. When NFAT is dephosphorylated by calcineurin, it can enter the nucleus and control transcription. Inhibition of calcineurin led to reduced activity of NFAT and was selectively toxic to ABC-DLBCL cells. A previous study showed that BCR signaling can promote expression of 1 NFAT isoform.[5] Bucher et al have extended this finding by demonstrating that increased NFAT activity in ABC-DLBCL was largely independent of BCR signaling. The authors then went on to identify several gene targets of NFAT activity that mediate the pro-survival effect. Specifically, they found that NFAT promoted the expression of the transcription factor Jun and the cytokines interleukin-6 (IL-6) and IL-10. Jun is a member of the AP-1 family of transcription factors that are active in ABC-DLBCL.[6] In addition, production and autocrine activity of IL-6 and IL-10 has been implicated in promoting survival of ABC-DLBCL cell lines.[7]

The calcineurin inhibitors cyclosporin A and tacrolimus (also known as FK506) are widely available clinically and have been used for decades as immunosuppressive agents that inhibit T- cell activation. The results presented by Bucher et al suggest that blockade of calcineurin signaling should be explored further in preclinical studies of ABC-DLBCL. One caveat to this approach will be the potential of calcineurin-directed therapy to inhibit the immune response to lymphoma that may be an important part in clearing disease during conventional therapy or when patients receive immunotherapy. Additional study is needed to determine whether there are specific factors that control NFAT signaling in B cells (as opposed to T cells) that could be specifically targeted to avoid the immunosuppression of calcineurin inhibitors.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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