asthma patients suffer from chronic rhinosinusitis with nasal polyposis and peripheral blood eosinophilia, one wonders if dexpramipexole might be of benefit to patients with eosinophilic asthma. Patients with myeloproliferative (primary, neoplastic) HES were excluded from the Panch et al study, but one also wonders if certain patients in whom a kinase target has not been identified would be helped.

The mechanism of dexpramipexole's eosinophil-reductive activity is unknown. Bone marrow analyses in the HES patients showed mainly eosinophil precursors (promyelocytes), indicating the possibility of interference in an early step of eosinophil maturation. Presently, there is no in vitro assay to investigate dexpramipexole's activity, and such a tool would be useful for studies to determine its mechanism of action and to probe related compounds that could be identified in a chemical library. Additionally, recognizing that a discouraging aspect of the reported study is that a robust response was observed only in 3 of the 10 HES patients; a test that identifies responders to the eosinophil-reductive effects would be valuable to determine which patients would benefit from the therapy and/or give clues as to how to make the therapy effective in more patients.

The take-home message is that dexpramipexole, a drug abandoned for lack of efficacy in its initial pharmacological application, shows promise as a well-tolerated orally administered therapy based on the serendipitous discovery of its ability to reduce eosinophils. In the 2 reports on HES and on chronic rhinosinusitis and nasal polyps, blood and tissue eosinophils were significantly diminished. These findings set the stage for phase 3 clinical trials in patients with common eosinophil-related diseases. Since the early 1950s, long-term glucocorticoid therapy, with its attendant adverse effects on most of the metabolic systems in the body, has been the mainstay of treatment of most eosinophil-related diseases. These early results encourage belief that this drug could herald a welcome change. As a final note, the patients responding to dexpramipexole appear devoid of eosinophils, raising consideration of whether this is a health hazard. However, review of patients (and mice) without eosinophils suggests that there are no obvious clinical consequences,[7] at least in the absence of helminth infections.

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REFERENCES

1. Panch SR, Bozik ME, Brown T, et al. Dexpramipexole as an oral steroid-sparing agent in hypereosinophilic syndromes. *Blood*. 2018;132(5):501-509.
2. Alavian KN, Dworetzky SI, Bonanni L, et al. Effects of dexpramipexole on brain mitochondrial conductances and cellular bioenergetic efficiency. *Brain Res*. 2012;1446:1-11.
3. Danzeisen R, Schwalenstoecker B, Gillardon F, et al. Targeted antioxidative and neuroprotective properties of the dopamine agonist pramipexole and its nondopaminergic enantiomer SND919CL2x [(+)2-amino-4,5,6,7-tetrahydro-6-Lpropylamino-benzathiazole dihydrochloride]. *J Pharmacol Exp Ther*. 2006;316(1):189-199.
4. Cudkowicz ME, van den Berg LH, Shefner JM, et al; EMPOWER investigators. Dexpramipexole versus placebo for patients with amyotrophic lateral sclerosis (EMPOWER): a randomised, double-blind, phase 3 trial [published correction appears in *Lancet Neurol*. 2013;12(11):1042]. *Lancet Neurol*. 2013;12(11):1059-1067.
5. Cudkowicz M, Bozik ME, Ingersoll EW, et al. The effects of dexpramipexole (KNS-760704) in individuals with amyotrophic lateral sclerosis. *Nat Med*. 2011;17(12):1652-1656.
6. Prussin C, laidlaw T, Panettieri R, et al. Dexpramipexole effectively lowers blood and tissue eosinophils in subjects with chronic rhinosinusitis with nasal polyps [abstract]. *J Allergy Clin Immunol*. 2017;139. Abstract 64.
7. Gleich GJ, Klion AD, Lee JJ, Weller PF. The consequences of not having eosinophils. *Allergy*. 2013;68(7):829-835.

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LYMPHOID NEOPLASIA

Comment on Boudesco et al, page 510

HSP110 and MYD88: blame the chaperone

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In this issue of *Blood*, Boudesco et al show that heat shock protein HSP110 (HSPH1) stabilizes wild-type and mutant MYD88, facilitating NF-κB activation in diffuse large B-cell lymphoma (DLBCL).[1]

Molecular analysis can classify DLBCL into a usefully small number of subtypes with distinctive biological features, potentially guiding the assignment of targeted therapy. Recent studies of mutations suggest that there are about 5 DLBCL subtypes,[2,3] but the older classification of 2 subtypes still has merit. In "activated B cell" (ABC) DLBCL, cell lines and primary tumors show constitutive and essential activation of the canonical NF-κB pathway.

Therapeutic inhibition of NF-κB in ABC-DLBCL requires targeting its upstream activating pathways. One of these is signaling by the B-cell receptor (BCR), which in ABC-DLBCL resembles BCR signaling acutely triggered in normal B cells by cognate antigen encounter and is similarly dependent on Bruton tyrosine kinase (BTK) activity and activation of the CARD11/BCL10/MALT1 (CBM) complex.[4] Another pathway is MYD88-dependent signaling, normally activated by most Toll-like receptors (TLRs) and certain cytokine receptors upon ligand binding. MYD88 promotes signaling by nucleating multiprotein complexes ("MyDDosomes") that include the kinase IRAK4 and its target IRAK1. The Toll/interleukin-1 receptor (TIR) domain of MYD88 mediates interactions with activating receptors as well as with TIR domains of other proteins including MYD88 itself.

Both of these pathways are abnormally activated in ABC-DLBCL. "Chronic active" BCR signaling in ABC-DLBCL is continuous and driven by self-antigen, implying evasion of normal tolerance mechanisms, and associated with recurrent Y196 mutation of CD79B, one of the BCR signal transduction units.[4] Less common activating mutations in CARD11 can replicate or enhance the effects of BCR signaling in ABC-DLBCL. Recurrent mutations in the MYD88 TIR domain, predominantly L265P (also found in

mucosa-associated lymphoid tissue lymphomas and virtually all cases of Waldenstrom macroglobulinemia), spontaneously activate NF-κB, JAK-STAT3, and type I interferon signaling in ABC-DLBCL.[5] The L265P MYD88 mutation promotes oligomerization and spontaneous MyDDosome formation, including with wild-type MYD88 (although homodimerization of mutant TIRs is energetically preferred), helping to explain its usual heterozygous occurrence.

BCR signaling and MYD88 work together in ABC-DLBCL, as evidenced by coincidence of mutations, clinical responses to BTK inhibition, and the just-published finding of signaling by a supercomplex formed by IgM, TLR9, and MYD88 in ABC-DLBCL lines.[6] In mice, combined mutations homologous to CD79B Y196 and MYD88 L265P enable B cells with BCR self-reactivity to break tolerance, that is, to escape peripheral deletion and differentiate into autoantibody-secreting plasmablasts.[7] This is consistent with long-standing evidence that self-antigens that activate signaling by both the BCR and nucleic acid–sensing TLRs (TLR7 and TLR9) are associated with autoantibody production.

Boudesco et al found that knockdown of HSPH1 reduced viable cell number and triggered apoptosis in BTK-dependent ABC-DLBCL cell lines, specifically by reducing NF-κB activity. Proximity ligation assays (PLAs) and immunoprecipitation showed that HSPH1 binds to MYD88 in ABC-DLBCL cell lines and primary tumors. Independently consistent with new findings,[6] proximity of immunoglobulin M (IgM) to phosphorylated IκB (generated in canonical NF-κB activation) was shown to depend on HSPH1 in cell lines. Levels of both IgM and phospho-IκB also correlated with HSPH1 in primary ABC-DLBCL tumors. HSPH1 enhanced the stability of both wild-type and L265P-mutant MYD88 (by interfering with its proteasomal degradation), promoted MYD88-associated signaling events (IRAK1 phosphorylation and K63 ubiquitination of TRAF6), and synergized highly with L265P-mutant MYD88 in spontaneously activating NF-κB.

HSPH1 has multiple tumor-promoting effects in many cancers, including facilitation of Wnt/β-catenin signaling. HSPH1 interacts with the chaperone GRP78, essential for immunoglobulin folding and BCR assembly, but whether BCR surface levels were affected by HSPH1 knockdown was not shown. Boudesco and colleagues have shown elsewhere that in addition to intrinsic effects on tumor cells, HSPH1 secreted by tumor cells promotes immunosuppressive macrophage polarization. HSPH1 may also affect the tumor microenvironment through tumor cell–derived extracellular vesicles that deliver L265P-mutant MYD88 to inflammatory cells and activate MyDDosome signaling.

The mechanism by which HSPH1 stabilizes MYD88 protein in ABC-DLBCL, and whether it is the same for HSPH1 stabilization of oncoproteins MYC and BCL6 in other types of lymphoma cell lines,[8] is unclear. This is relevant to the development of HSPH1 inhibitors, which are currently unknown. Boudesco et al cite processes promoting MYD88 degradation, including ubiquitination, but whether HSPH1 interferes with these is unknown. As one of the HSP family of molecular "chaperones," HSPH1 has a "holdase" substrate-binding domain and may promote proper folding of MYD88. However, the ability of HSPH1 to promote stress responses and protein refolding may be indirect, by serving as a guanine nucleotide exchange factor for other HSPs, particularly HSP70. Data from Boudesco et al suggest that HSPH1 interacts more with MYD88 in ABC-DLBCL lines than with HSP70, but the technique used (PLA) does not establish that HSP70 does not participate in protection of MYD88 by HSPH1. Their data also suggest that HSPH1 may have a greater effect on L265P-mutant than wild-type MYD88, perhaps resembling the ability of HSP90 to promote cancer by "buffering" mutant forms of oncogenes.[9]

The findings of Boudesco et al suggest that targeting HSPH1 could inhibit both NF-κB–activating pathways in ABC-DLBCL. Targeting the transcription factor HSF1, which is essential for the expression of HSPH1 and other HSPs, may be an indirect approach for targeting HSPH1; HSF1 inhibitors have shown preclinical promise as anticancer agents.[10] However, multiple factors could affect the success of targeting HSPH1 as therapy for ABC-DLBCL or other cancers. Some of these are mentioned by Boudesco et al, including ways in which HSPH1 may promote antitumor responses. However, targeting L265P-mutant MYD88 could be antagonistic with lenalidomide in ABC-DLBCL, whose efficacy depends on unopposed interferon signaling. HSPH1 also has an important role in cellular disposal of protein aggregates, loss of which could have profound consequences. A better prediction of the effects of targeting HSPH1 could come from genetic manipulation; limited studies show that mice tolerate germ-line *hsph1* loss and become less susceptible to ischemic injury, but genetic inactivation of *hsph1* has not been used in studies of cancer or immunology.

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REFERENCES

1. Boudesco C, Verhoeyen E, Martin L, et al. HSP110 sustains chronic NF-κB signaling in activated B cell diffuse large B cell lymphoma through MyD88 stabilization. *Blood*. 2018; 132(5):510-520.
2. Schmitz R, Wright GW, Huang DW, et al. Genetics and pathogenesis of diffuse large B-cell lymphoma. *N Engl J Med*. 2018;378(15):1396-1407.
3. Chapuy B, Stewart C, Dunford AJ, et al. Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. *Nat Med*. 2018;24(5):679-690.
4. Davis RE, Ngo VN, Lenz G, et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. *Nature*. 2010; 463(7277):88-92.
5. Ngo VN, Young RM, Schmitz R, et al. Oncogenically active MYD88 mutations in human lymphoma. *Nature*. 2011;470(7332):115-119.
6. Phelan JD, Young RM, Webster DE, et al. A multiprotein supercomplex controlling oncogenic signalling in lymphoma [published online ahead of print 20 June 2018]. *Nature*. doi: 10.1038/s41586-018-0290-0.
7. Wang JQ, Jeelall YS, Humburg P, et al. Synergistic cooperation and crosstalk between MYD88L265P and mutations that dysregulate CD79B and surface IgM. *J Exp Med*. 2017; 214(9):2759-2776.
8. Zappasodi R, Ruggiero G, Guarnotta C, et al. HSPH1 inhibition downregulates Bcl-6 and c-Myc and hampers the growth of human aggressive B-cell non-Hodgkin lymphoma. *Blood*. 2015;125(11):1768-1771.
9. Karras GI, Yi S, Sahni N, et al. HSP90 shapes the consequences of human genetic variation. *Cell*. 2017;168(5):856-866.
10. Fok JHL, Hedayat S, Zhang L, et al. HSF1 is essential for myeloma cell survival and a promising therapeutic target. *Clin Cancer Res*. 2018;24(10):2395-2407.

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