complex. To this end, iDuo NK cells are clonally derived from a master human iPSC line. This allows product scalability and the possibility of homogenous cell-bank renewable manufacture for on-demand access without need for further engineering or enrichment. While the consistency of iPSC-NK cell manufacture is noteworthy, these cells have prior been shown to be relatively undifferentiated with high inhibitory receptor NKG2A expression and an immature phenotype.[9] Cichocki et al posit that iDuo NK cells are superior anti-cancer agents to peripheral blood-derived NK cells (PB-NKs). It is interesting that iDuo NK cells upregulate activating receptor expression,[1] potentially due to continued IL-15RF stimulation in cis and trans. However, it is worth noting that even without additional modification, ex vivo expanded PB-NKs have consistent and high expression of activating receptors, are functionally mature with robust cytotoxic capacity, and express high levels of KIRs that play an important role in NK cell education and licensing.[10] A direct comparison of cell killing between iDuo NK cells and similarly modified PB-NKs (with and without rituximab) is critical to truly ascertain superiority.

Ultimately, Cichocki et al present an exciting approach to targeted cell therapy that can mitigate treatment resistance due to antigen loss or tumor heterogeneity. NK cells are powerful tools with innate cytotoxic mechanisms that can complement the specific cell killing mediated by CARs. The genetic engineering of iDuo NK cells realizes this potential, with the iPSC-derived product having unique advantages for clinical translation. Given the preclinical data, iDuo NK cells are likely to have anti-tumor activity against B-cell malignancies when tested in clinical trial. The engineered iPSC platform is also well suited to parallel translation with CARs to alternate targets for malignancies similarly in need of visionary therapies. Discovery necessarily will continue such that the full potential of NK cells as fully effective anticancer immunotherapeutics can be realized.

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LYMPHOID NEOPLASIA

Comment on Vanden Bempt et al, page 2463

A N(ew) MYC joins T-cell lymphomagenesis

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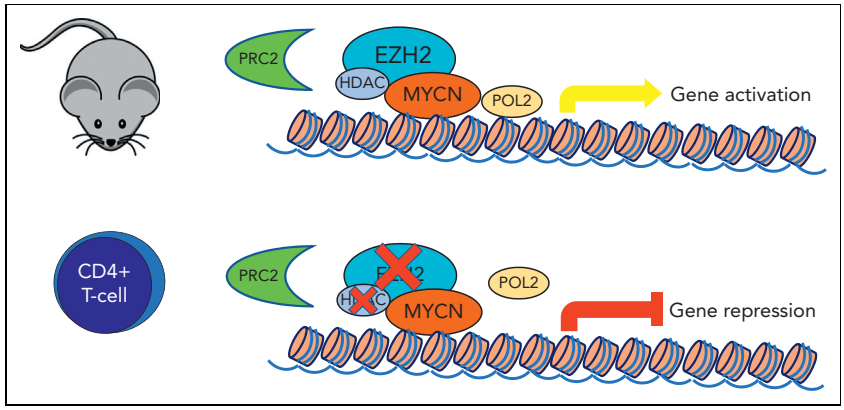
In this issue of *Blood*, Vanden Bempt et al,[1] using a well-designed mouse model, identify MYCN as a novel oncogenic driver in mature T-cell lymphoma. MYCN directly cooperates with enhancer of zeste homolog 2 (EZH2) and may represent a targetable mechanism implicated in the pathogenesis of T-cell lymphoma.

Human mature postthymic T-cell lymphomas are rare diseases (~10% of lymphomas) but show enormous heterogeneity with more than 30 entities established by the recently published International Consensus Classification of Mature Lymphoid Tumors and 5th edition of World Health Organization Classification of Lymphoid Neoplasms.[2,3] Many entities have well-characterized clinical, morphological, and genomic features, but ~30% of all mature T-cell lymphomas remain unclassified, and thus are lumped into a single group (and most common type) known as peripheral T-cell lymphoma (PTCL), not otherwise specified (NOS).[4]

The rarity and heterogeneity of these neoplasms, as well as the lack of experimental models, have, until recently, limited the discovery of significant driver abnormalities, thereby impeding development of new therapeutic approaches. Anthracycline-based chemotherapy protocols, with or without autologous hematopoietic transplantation, have been the standard therapeutic approach for decades. Despite the recent addition of new agents, both overall survival and progression-free survival of most patients with PTCL remain dismal with urgent need of improvement.[4]

This situation is now changing with improvements in genomic testing that have identified significant defects that impact essential signaling pathways and foster T-cell transformation.[5] Within the PTCL-NOS group, distinct subgroups have been identified, one of which is characterized by high expression of the transcription factor GATA3 and its target genes, as well as high *MYC* (and proliferation) gene



Induced MYCNexpression in CD4+ T-cell mouse model shows interaction with EZH2 through a noncanonical function independent of PRC2. MYCN activation is sensitive to selective EZH2 degradation, which was synergistic with histone deacetylase inhibitors.

expression signature that is associated with poor clinical outcome.[6,7]

The *MYC* family of oncogenes is deregulated in >50% of human cancers, frequently correlating with poor prognosis and unfavorable patient survival. The *MYC* family contains 3 members, *MYC*, *MYCN*, and *MYCL*, that encode MYC (also called MYCC), MYCN, and MYCL, respectively. MYC is a major regulator of the genome affecting 10% to 15% of all human genes. Many core cellular functions and pathways are under control of MYC, such as cell proliferation and growth, DNA replication, protein biosynthesis, and regulation of metabolism and energy. *MYC* is one of the most frequently disrupted genes in human lymphomas, as seen in the more common and well-described aggressive B-cell lymphomas.[8] The critical oncogenic role of MYC has stimulated the search for therapeutic strategies that may counteract its damaging functions. Yet, MYC protein itself has so far been considered "undruggable."[8]

In the current study, Vanden Bempt et al focused their experiments on MYCN, a MYC paralogue often associated with neuroblastoma pathogenesis and rarely implicated in lymphoid neoplasms. Up to this point, the sole lymphoid neoplasm reported to involve MYCN was Burkitt lymphoma.[9] The authors used a well-designed induced MYCN mouse model that promoted the development of $CD4^+$ T-cell lymphomas (and, interestingly, B-cell lymphomas). Using transcriptomic and epigenetic approaches, they dissected the gene expression program modulated by MYCN and identify EZH2 as an essential transcriptional cofactor required to sustain MYCN activation, independent of the polycomb repressive complex 2 (PRC2) and linked to CDK1-mediated phosphorylation. These findings are in keeping with previous reports on the role of MYCN (as well as MYCC) and EZH2 in neuroblastoma, solid cancers, and Burkitt lymphoma cell lines.[10]

In the current study, MYCN-induced mice T-cell lymphoma cells were only slightly affected by inhibition of the EZH2 enzymatic activity but were sensitive to selective EZH2 degradation or CDK1 inhibition, which displayed synergy with US Food and Drug Administration–approved histone deacetylase inhibitors (see figure).

The induced MYCN mouse model data were correlated with *MYC* and *MYCN* expression data of human PTCL samples. Using a cohort of 28 human PTCL samples (the majority PTCL, NOS), the authors showed *MYCN* to be overexpressed in 5 of their 28 cases (18%) and in 13 of the 152 cases (9%) of the combined current study and publicly available PTCL datasets. Yet, half of all PTCL cases showed a high *MYC* signature, which means that MYCN was a significant player in less than half of the MYC-associated PTCL cases. Moreover, 2 of the 7 cases (29%) with *MYCN* overexpression showed a low expression of *MYC* signature. This suggests (like the rare reports of *MYCN* role in B-cell lymphoma) that MYCN has an oncogenic role in a small but most likely significant number of PTCL cases.

Validation of the MYCN relevance in human PTCL is certainly needed using larger cohorts of well-characterized PTCL samples. However, given the urgent need for an improved understanding of these gloomy lymphomas, this study by Vanden Bempt et al provides a relevant model that could be used as the basis for further investigations exploring combinatorial therapies in a small but significant subset of PTCL.

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

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