blood® commentary

LYMPHOID NEOPLASIA

Comment on Yao et al, page 2841

Starving multiple myeloma cells via CDK7 inhibition

Antonio Sacco and Aldo M. Roccaro | Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

In this issue of *Blood*, Yao et al[1] have elegantly proven that cyclin-dependent kinase-7 (CDK7) influences the oncogenic programming of multiple myeloma (MM) cells by modulation of MYC and E2F transcription factors. The authors show that CDK7 inhibition counteracts E2F activity, leading to a reduction of the CDKs-retinoblastoma (Rb) axis and inhibition of MYC-regulated metabolic signatures. Thus, CDK7 inhibition is an appealing therapeutic target for MM.

E2F deregulation is a hallmark of MM and is associated with aggressive forms of the disease.[2] CDK7 inhibition activates Rb, thereby impacting E2F activity. However, cellular models of Rb inactivation, as well as genome-wide CRISPR knockout studies, suggest that CDK7 inhibition also works in the context of Rb loss and may effectively circumvent compensatory mechanisms by other cell cycle–associated kinases, as observed for the clinically available CDK4/6 inhibitors. Thus, CDK7 inhibition may have several therapeutic advantages. Therapeutic use of CDK inhibitors, including those targeting cyclin D partners CDK4/6, has been thwarted by the lack of single agent efficacy, suggesting that targeting of cell cycle regulation alone is insufficient to produce a durable response in MM.[3] MM also relies on glycolysis for energy, and this increased dependence on glycolysis is due to MYC deregulation.[4,5] This elicits a unique vulnerability separable from the lineage/enhancer axis targeted by immunomodulatory drugs and bromodomain and extra terminal protein inhibitors, which can be targeted by CDK7 inhibition. The current studies provide evidence for demonstrating how CDK7 controls MYC cellular levels in MM cells and that both translational and post-translational regulatory mechanism may contribute to CDK7 regulation of MYC in MM cells.

Metabolic reprogramming is a hallmark of cancer.[6] Tumor cells rely on aerobic glycolysis to supply energy by converting a majority of the glucose-derived pyruvate to lactate. Moreover, malignant cells engage glutamine anaplerosis to replace tricarboxylic acid cycle intermediates (eg, α-ketoglutarate), thus sustaining their metabolic status. Therefore, many human cancers use glucose and glutamine to rewire metabolism and to generate energy and sustain their growth. In contrast, normal cells have lower nutrient demands. Metabolic reprogramming represents a specific tumor cell vulnerability that could be therapeutically exploited.

In MM, metabolic signatures correlate with prognosis in MM.[7] Lactate dehydrogenase (LDH) is one of the prognostic factors that predicts for adverse outcomes in MM patients. Hexokinase II and LDH A are found in newly diagnosed myeloma patients, and their expression has greater upregulation in relapsed MM cases, highlighting that the elevated glucose metabolism plays a more important role in relapsed compared with newly diagnosed MM.

The current study builds on recent literature suggesting that cell cycle progression is closely coupled to the cellular metabolism in tumor cells, with cell cycle regulators controlling glucose consumption and glycolysis. Does CDK7 have more global effects on metabolism beyond glycolysis? This question will have to be explored with further investigation.

Overall, the studies by Yao et al provide clear evidence that CDK7 inhibition is a promising therapeutic strategy for both newly diagnosed and relapsed MM disease, which should spare normal cells. Additional studies are needed to understand the impact of CDK7 inhibition on the immune microenvironment and how such inhibition will impact and interact with current immunotherapies in MM.

Conflict-of-interest disclosure: A.M.R. receives research funding from AstraZeneca, European Hematology Association, Transcan2ERANET, and Italian Association for Cancer Research (Fondazione AIRC) and honoraria from Amgen, Celgene, Janssen, and Takeda. A.S. declares no competing financial interests. ■

REFERENCES

1. Yao Y, Ng JF, Park WD, et al. CDK7 controls E2F- and MYC-driven proliferative and metabolic vulnerabilities in multiple myeloma. *Blood*. 2023;141(23):2841-2852.
2. Fulciniti M, Lin CY, Samur MK, et al. Non-overlapping control of transcriptome by promoter- and super-enhancer-associated dependencies in multiple myeloma. *Cell Rep*. 2018;25(13):3693-3705.e6.
3. Tiedemann RE, Mao X, Shi CX, et al. Identification of kinetin riboside as a repressor of CCND1 and CCND2 with preclinical antimyeloma activity. *J Clin Invest*. 2008;118(5):1750-1764.
4. Galbraith MD, Andrysik Z, Pandey A, et al. CDK8 kinase activity promotes glycolysis. *Cell Rep*. 2017;21(6):1495-1506.

5. Wang H, Nicolay BN, Chick JM, et al. The metabolic function of cyclin D3-CDK6 kinase in cancer cell survival. *Nature*. 2017;546(7658):426-430.

6. Ward PS, Thompson CB. Metabolic reprogramming: a cancer hallmark even Warburg did not anticipate. *Cancer Cell*. 2012;21(3):297-308.

7. Maiso P, Huynh D, Moschetta M, et al. Metabolic signature identifies novel targets for drug resistance in multiple myeloma. *Cancer Res*. 2015;75(10):2071-2082.

https://doi.org/10.1182/blood.2023020254

MYELOID NEOPLASIA

Comment on Hakkarainen et al, page 2853

ERCC6L2 syndrome: attack of the TP53 clones

Marcin W. Wlodarski | St. Jude Children's Research Hospital

In this issue of *Blood*, Hakkarainen and an international team of clinical investigators provide an in-depth analysis of 52 patients with excision repair cross-complementation group 6 like 2 (ERCC6L2) syndrome caused by germline biallelic *ERCC6L2* mutations.[1] Their findings offer new insights into the clinical phenotypes, genetics, clonal evolution, and outcomes in this syndrome, providing invaluable knowledge for understanding its natural history and devising surveillance strategies.

Since the first description of ERCC6L2 syndrome in 2014 in patients with bone marrow failure (BMF),[2] 20 unique cases have been reported in 6 studies. The affected patients were diagnosed as children or young adults with hypocellular BMF, with approximately half of them presenting with constitutional features, such as microcephaly and developmental delay (see the article by Hakkarainen et al for all previously reported cases). In 2019, Douglas et al described 5 individuals with germline ERCC6L2 mutations who presented with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) with erythroid predominance resembling AML M6.[3] For the first time, the authors also established a link between ERCC6L2-related MDS/AML and somatic *TP53* mutations. This study expanded the spectrum of this novel predisposition syndrome and revealed that AML can be an initial clinical presentation, leading to the important conclusion: "Our families have acknowledged for years that AML with a dismal prognosis runs among them. This study has finally discovered the culprit and has also supplied some family members with a relieving verdict."[3]

Despite the multiple studies, there was no comprehensive understanding of the clinical spectrum, natural history, and disease progression. The current study by Hakkarainen et al systematically addresses these outstanding questions and successfully integrates the numerous clinical and genetic puzzle pieces. This multicenter retrospective study is exceptional in several ways. First, it includes the largest cohort of patients with this syndrome ever reported (52 cases across 35 families in 9 countries; see figure), which will inform future clinical practice. Second, it provides prognostic estimates for patients at different stages of hematologic disease (BMF, MDS, and AML), aiding in better patient management. Third, it identifies a common Finnish founder mutation and expands the *ERCC6L2* mutation spectrum, valuable for genetic counseling and testing. Finally, the study provides insights into surveillance strategies, helpful for early detection and long-term management.

ERCC6L2, also known as RAD26L and helicase mutated in bone marrow failure (HEBO), is a SWI/SNF (SWItch/Sucrose Non-Fermentable)-like ATPase[2] and a bona fide nonhomologous end-joining (NHEJ) factor.[4] It is a centromeric protein with a role in DNA double-strand break repair via NHEJ pathway, DNA recombination, translocation, and chromatin unwinding.[2,5] Cells from patients with biallelic loss-of-function mutations in ERCC6L2 are sensitive to ionizing radiation and phleomycin (both DNA double-strand break-damaging agents) and only weakly sensitive to mitomycin C.[6] ERCC6L2 was also demonstrated to participate in RNA polymerase II–mediated transcription to resolve DNA-RNA hybrids (R loops), pointing to ERCC6L2 deficiency as a primary transcription deficiency rather than a stereotypical DNA repair syndrome.[7] In the current study, only 3 of 52 patients had microcephaly and developmental delay, which is a common feature of DNA repair disorders with disrupted NHEJ pathway. Likewise, other features common of DNA repair syndromes, such as immunodeficiency or high prevalence of lymphatic and solid tumors, were lacking. In this cohort, hypocellular BMF with cytopenia was the most common initial manifestation in nearly two-thirds of patients, followed by MDS/AML in 29% and asymptomatic state in 10%. The median age in patients presenting with BMF was 12 years, whereas patients with MDS/AML were older, with a median age of 29 years at initial presentation, and 37 years for all patients with MDS/AML, including patients who progressed (Hakkarainen et al, Table 1). Compared with BMF, the MDS/AML cohort was characterized by a higher number of patients carrying somatic loss-of-function *TP53* mutations and a higher *TP53* variant allelic frequency, pointing to a *TP53*-mediated clonal progression similar to what has been recently observed in Shwachman-Diamond syndrome[8] and xeroderma pigmentosum.[9]

In patients with inherited BMF syndromes, annual bone marrow surveillance is usually conducted to detect leukemic evolution, with complete blood counts (CBCs) performed in between; changes in CBC might suggest AML progression, prompting an earlier bone marrow examination. However, this strategy is not applicable in ERCC6L2 disease, as CBC abnormalities appear mild despite the presence of *TP53*-mediated clonal evolution or marrow dysplasia, which is analogous to Shwachman-Diamond syndrome. This study highlights the importance of incorporating bone marrow assessments and high-sensitivity TP53 mutation testing into the clinical follow-up of ERCC6L2-affected individuals.

The present study has implications for genetic diagnostics and counseling. One-third of the affected families were consanguineous, which was defined as parents