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LYMPHOID NEOPLASIA

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Agent myeloma has a new weapon from (ch1)Q

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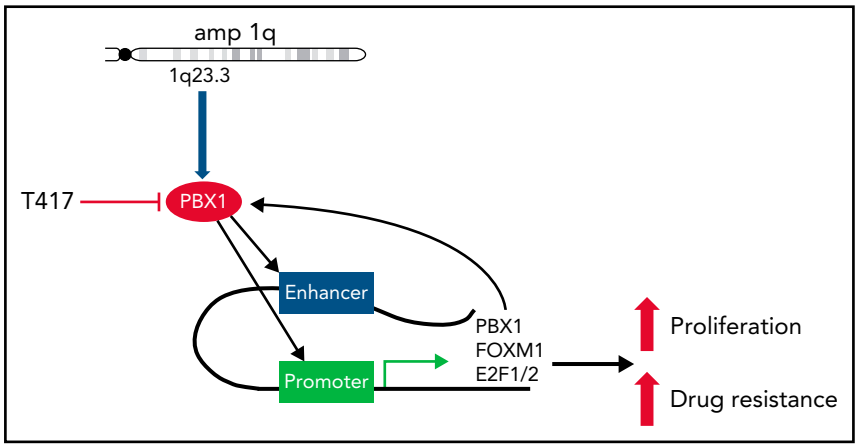
In this issue of *Blood*, Trasanidis et al[1] use a multiomics analysis to define a novel transcriptional network that is important in driving the poor outcomes associated with amplification of chromosome 1q in multiple myeloma.

In the Ian Fleming books and the movies based on these books, Agent 007 is equipped with amazing gadgets designed by the Q Branch to help him fight enemies or to make improbable escapes from their clutches (the Lotus Esprit submarine from *The Spy Who Loved Me* is a favorite!). Like James Bond, multiple myeloma uses weapons such as dysregulation of oncogenes, cell survival pathways, and hijacking the bone marrow microenvironment to initiate tumor growth, as well as escape the initial immune responses to disease and survive the stresses of therapy. Dysregulation of these pathways is driven by genomic alterations, including translocations, point mutations, and copy number variations.[2] Of these, one of the most common changes is gain of the long arm of chromosome 1 (+1q) which is observed in ~40% of patients with newly diagnosed multiple myeloma and has been associated with poor outcomes, particularly when amplification (amp) of 1q occurs, designating the presence of 4 or more total copies of 1q.[3] Because of the size of the region and the number of genes encoded on 1q (>2200) and because many of these genes have known roles in myeloma pathogenesis (eg, IL6R, MCL1), growth control (eg, CKS1B), and altered gene expression (eg, ADAR1), the identification of a specific driver of poor outcomes in multiple myeloma has remained a challenge. Moreover, much of the focus has been on 1q21, despite amplification of the whole chromosome arm. Thus, the goal of the current study was to take a multiomics approach to identifying genes on 1q that are potential drivers in +1q multiple myeloma.



PBX1 is upregulated by amp1q and activates a transcriptional network that results in increased proliferation and drug resistance in multiple myeloma.

To achieve this goal, Trasanidis et al analyzed copy number data from the MMRF CoMMpass trial (registered on www.clinicaltrials.gov, as #NCT01454297) to determine areas that were co-amplified and then applied a computational method used for defining topologically associated domains (TADs), they identified 4 regions of genomic co-amplification, which they refer to as topologically co-amplified domains (TCDs). When comparing the TCDs to the TADs that were previously identified in human myeloma cell lines,[4] they found borders of the regions to be similar; however, they differed from the TADs identified in normal B cells, suggesting that amplification resulted in a reorganization of the genomic architecture of the region. They then applied genomic, transcriptomic, and epigenomic data as well as outcome data to identify which of the >2200 genes on 1q could be drivers of poor outcomes and determined that 103 genes met their criteria of expression and outcome and were found in the 4 TCDs (primarily B1 and B4). Of these genes, many have been identified and are found on 1q21 (eg, MCL1, CKS1B, ILF2, and ARNT); however, when corrected for gene density, 1q23.3 had the highest association with outcome. Therefore, they focused on the gene with the highest activation signal (H3K27ac) in this region, the transcription factor PBX1.

PBX1 is a homeobox domain transcription factor that was first identified as a component of t(1;19) found in pre–B-cell acute lymphocytic leukemia and results in an E2A-PBX1 fusion product. Subsequent studies demonstrated that PBX1 plays an important role in driving developmental programs including self-renewal.[5] Through functional characterization, Trasanidis et al

showed that PBX1 was both necessary and sufficient to drive myeloma proliferation, and analyses of transcriptomics and chromatin binding demonstrated a network of genes that are regulated by PBX1 binding to promoters and enhancers. This network includes the additional transcription factors FOXM1 and E2F1/2, which regulate the cell cycle, as well as its own transcription (see figure). These data are consistent with the findings that proliferation is a significant contributor to poor outcomes in myeloma.[6] FOXM1 is also a transcriptional regulator of NEK2, a gene that has been associated with drug resistance and poor outcomes,[7] and it is also downregulated upon silencing of FOXM1 or PBX1.

Although identifying a network of genes that drive myeloma proliferation is important from a prognostic standpoint, developing therapies to target these networks could have a significant impact on patient outcomes. In fact, therapeutic targeting of the dysregulated cell proliferation pathways is a major unmet need in multiple myeloma, for which the most effective therapies target normal plasma cell biology rather than the genomic aberrations that drive progression.[8] Targeting of such pathways will become a critical area of therapeutic development in myeloma, particularly for patients with biologically aggressive disease that is less sensitive to standard therapies, including those with amp1q. Trasanidis et al use an inhibitor of FOXM1 and a novel PBX1 inhibitor that they recently developed[9] and demonstrate that pharmacological inhibition of this pathway can inhibit myeloma growth/survival both in vitro and in vivo. Importantly, the activity of the PBX1 inhibitor appears to be dependent on the presence of +1q. Moreover, this compound's activity is not limited to myeloma, as cells from several solid tumors that harbor 1q gains are also sensitive. This fact suggests that the transcriptional remodeling associated with +1q that occurs in myeloma very likely occurs in other tumors with this copy number alteration. Although the PBX1 inhibitor is in early stages of development, it offers a promising opportunity to neutralize and target a key regulator of proliferation in +1q myeloma and other cancers, as well as to sensitize tumors to other therapies. One is left to wonder whether this could also include newer immunotherapeutic approaches, as the genes that are repressed by PBX1 are associated with interferon responses. It is also important to investigate whether the context of 1q copy number (gain vs amp) and/or co-occurring cytogenetic abnormalities such as t(4;14), which are known to influence outcomes among patients with +1q,[10] affect myeloma cells' susceptibility to inhibition of this pathway. PBX1 appears to be one of the most active genomic "gadgets" yet to be discovered in the (ch1)Q branch, and perhaps a double agent has left the door open for targeted therapy in +1q myeloma.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

REFERENCES

1. Trasanidis N, Katsarou A, Ponnusamy K, et al. Systems medicine dissection of chr1q-amp reveals a novel PBX1-FOXM1 axis for targeted therapy in multiple myeloma. *Blood*. 2022;139(13):1939-1953.
2. Barwick BG, Gupta VA, Vertino PM, Boise LH. Cell of origin and genetic alterations in the pathogenesis of multiple myeloma. *Front Immunol*. 2019;10:1121.
3. Schmidt TM, Fonseca R, Usmani SZ. Chromosome 1q21 abnormalities in multiple myeloma. *Blood Cancer J*. 2021;11(4):83.
4. Wu P, Li T, Li R, et al. 3D genome of multiple myeloma reveals spatial genome disorganization associated with copy number variations. *Nat Commun*. 2017;8(1):1937.
5. Veiga RN, de Oliveira JC, Gradia DF. PBX1: a key character of the hallmarks of cancer. *J Mol Med (Berl)*. 2021;99(12):1667-1680.
6. Greipp PR, Lust JA, O'Fallon WM, Katzmann JA, Witzig TE, Kyle RA. Plasma cell labeling index and beta 2-microglobulin predict survival independent of thymidine kinase and C-reactive protein in multiple myeloma. *Blood*. 1993;81(12):3382-3387.
7. Zhou W, Yang Y, Xia J, et al. NEK2 induces drug resistance mainly through activation of efflux drug pumps and is associated with poor prognosis in myeloma and other cancers. *Cancer Cell*. 2013;23(1):48-62.
8. Boise LH, Kaufman JL, Bahlis NJ, Lonial S, Lee KP. The Tao of myeloma. *Blood*. 2014;124(12):1873-1879.
9. Shen YA, Jung J, Shimberg GD, et al. Development of small molecule inhibitors targeting PBX1 transcription signaling as a novel cancer therapeutic strategy. *iScience*. 2021;24(11):103297.
10. Schmidt TM, Barwick BG, Joseph N, et al. Gain of chromosome 1q is associated with early progression in multiple myeloma patients treated with lenalidomide, bortezomib, and dexamethasone. *Blood Cancer J*. 2019;9(12):94.

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Ward et al, page 1999

Always be prepared for success

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In this issue of *Blood*, Ward et al[1] report the promising efficacy and manageable toxicity profile from an investigator-initiated phase 1 trial combining brentuximab vedotin and lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who had received or were ineligible for autologous stem cell transplantation (ASCT).

For patients with relapsed or refractory DLBCL, second-line treatment algorithms have historically categorized patients based on their fitness for potential high-dose chemotherapy and ASCT, or, to state this more succinctly, either curative or palliative intent. Patients who were ineligible for or relapsed after ASCT potentially benefit from additional therapy; however, results were often transient and toxic. Thankfully, this paradigm is shifting.

Brentuximab vedotin, an antibody drug conjugate targeting CD30, and lenalidomide, an immunomodulatory drug targeting cereblon, are both Food and Drug Administration approved for various hematologic malignancies. As single-agent therapy for patients with relapsed DLBCL, both drugs have resulted in modest efficacy, with brentuximab vedotin achieving an overall response rate (ORR) of 44% and complete response