An epigenetic Achilles' heel in extranodal NK/T-cell lymphoma?

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In this issue of *Haematologica*, de Ramon Ortiz and colleagues report a heavily pretreated patient with extranodal natural killer/T-cell lymphoma (ENKTCL) who achieved a complete metabolic response to azacytidine, enabling subsequent allogeneic stem cell transplantation.[1] This striking observation points to a potential therapeutic vulnerability in ENKTCL and suggests that hypomethylating agents may warrant further investigation in this disease.

The case illustrates the therapeutic impasse frequently encountered in ENKTCL. The patient developed treatment refractory disease despite multiple prior lines of therapy, including asparaginase- and platinum-based chemotherapy, immune checkpoint inhibition, radiotherapy, and high-dose cytarabine and methotrexate. In the setting of pathogenic TET2 and BCOR variants, azacytidine was initiated. Remarkably, treatment was followed by clearance of circulating Epstein Barr virus (EBV) DNA, resolution of neurological symptoms with cerebrospinal fluid (CSF) clearance, and a rapid complete metabolic remission after just one cycle. This depth of response permitted potentially curative allogeneic stem cell transplantation, although disease relapse subsequently occurred a few months later.

The importance of this case lies not simply in its clinical novelty, but in what it may reveal about ENKTCL biology. Genomic studies have consistently demonstrated that ENKTCL is enriched for alterations affecting epigenetic regulators, with mutations in chromatin modifying and DNA methylation-associated genes present in a substantial proportion of cases.[2] *TET2*, mutated in approximately 10% of ENKTCL, encodes a key enzyme involved in DNA demethylation, whereas loss of function alterations in *BCOR*, which are enriched in ENKTCL when compared with other lymphoid malignancies,[3] lead to derepression of Polycomb Repressive Complex 1 (PRC1.1)-regulated gene programs. The convergence of these lesions could create a profoundly dysregulated epigenetic landscape, providing a biologically plausible explanation for the marked sensitivity to azacytidine observed in this case.

However, the relationship between genetic alterations in epigenetic modifiers and hypomethylating agent sensitivity is unlikely to be straightforward. As de Ramon Ortiz and colleagues note,[1] TET2 mutation status alone appears insufficient as a predictive biomarker of response,[4] arguing against overly simplistic genotype response models. What may distinguish this case is the co-occurrence of lesions involving different facets of epigenetic regulation, namely DNA methylation and Polycomb-mediated transcriptional repression. TET2/BCOR co-mutation is rare in other peripheral T-cell lymphoma subtypes. The distinct BCOR alteration identified at relapse in this patient is intriguing, as it is consistent with convergent evolution and supports the hypothesis that BCOR loss of function may confer a selective advantage in this disease. Added to this is the known interplay between EBV, a defining feature of ENKTCL, and epigenetic dysregulation.[5] Taken together, these observations support a model in which ENKTCL is epigenetically constrained, highlighting a potentially distinct therapeutic vulnerability.

Beyond tumor-intrinsic mechanisms, immune modulation may also have contributed to the observed response. Recent data in ENKTCL suggest that hypomethylating agents can induce viral mimicry through activation of endogenous retroviral elements, restoring interferon signaling and antigen presentation, and thereby resensitizing tumors to checkpoint inhibition.[6] Prior exposure to pembrolizumab may, therefore, be relevant in this case, raising the possibility that azacytidine acted not only through tumor-intrinsic epigenetic effects, but also through immune priming. The clearance of CSF disease is particularly notable, given the limited central nervous system penetration of azacytidine, and further supports a tumor-extrinsic mechanism rather than direct cytotoxicity alone.

So where does this case leave us? First, it illustrates how, in rare diseases such as ENKTCL, exceptional responses can serve as hypothesis-generating observations that refine our understanding of therapeutic vulnerabilities. Second, it

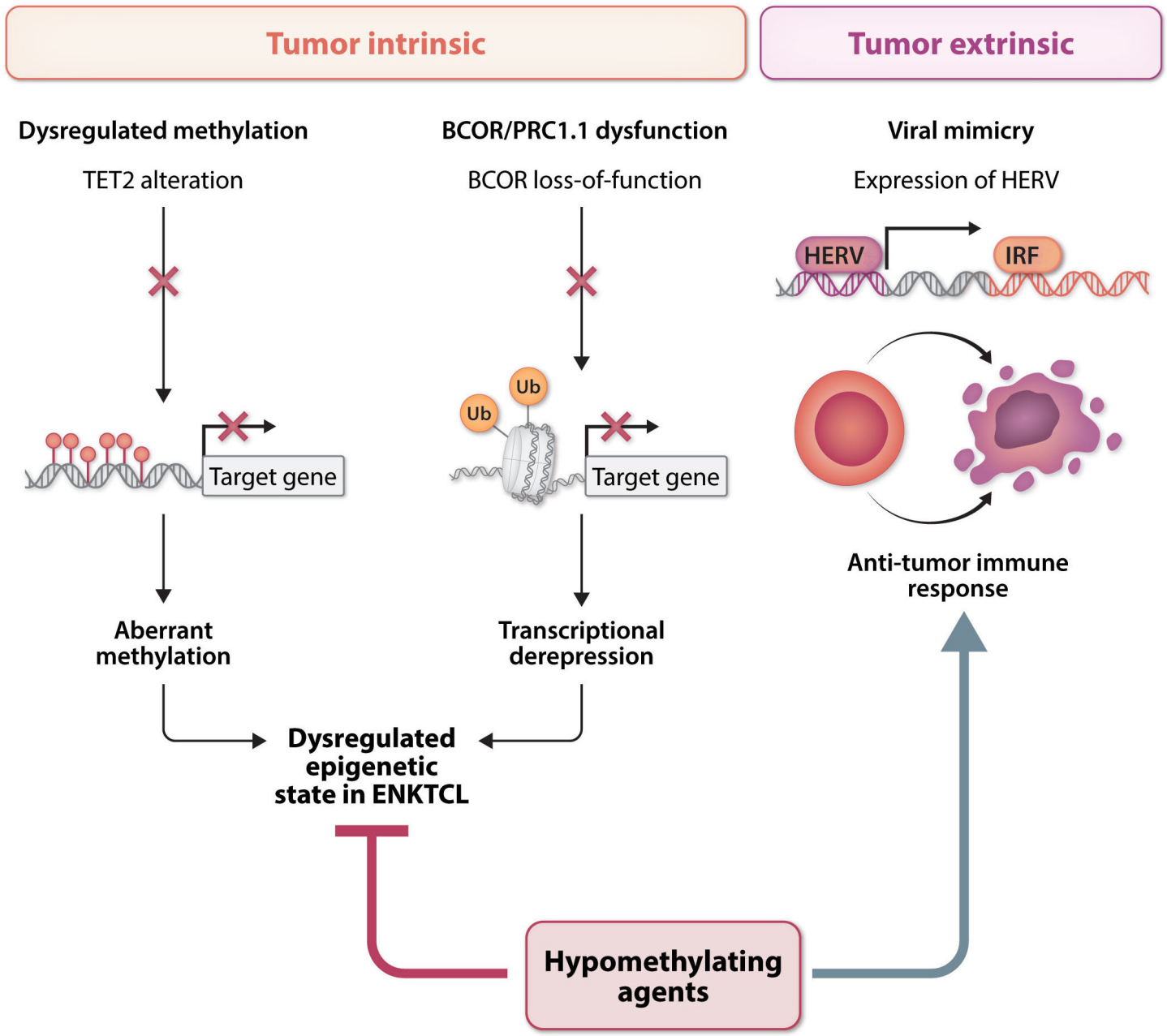


Figure 1. Proposed mechanisms of hypomethylating agent sensitivity in extranodal natural killer / T-cell lymphoma. Hypomethylating agents may act through both tumor-intrinsic and tumor-extrinsic mechanisms. Intrinsic effects may reflect disruption of complementary epigenetic programs, whereas tumor extrinsic effects may involve viral mimicry, triggering interferon signaling and enhanced antitumor immunity. ENKTCL: extranodal NK/T-cell lymphoma; PRC1.1: Polycomb repressive complex 1.1; HERV: human endogeneous retroviral elements.

underscores the need to integrate genomic data with transcriptional, methylation, and chromatin profiling in order to build a truly holistic view of ENKTCL biology. Although this is an ambitious goal, particularly given the rarity of the disease, it is one that can be met through co-ordinated international collaboration. Initiatives such as the PETAL consortium (https://www.petalconsortium.org/), set up to collect primary material from patients with mature T- and NK-cell neoplasms for multimodal profiling, represent an important step towards this goal. Third, in the light of recent retrospective data suggesting that hypomethylating agents can restore sensitivity to checkpoint inhibition in ENKTCL, there is an urgent need to define which patients benefit from this strategy, to clarify the mechanisms driving response, and to determine how best to deploy this approach in the clinic.

These findings raise the question of whether hypomethylating agents should now be prospectively evaluated in ENKTCL, both as single-agent therapy and as immune-priming agents used sequentially with, or in combination with, checkpoint inhibitors. Ultimately, the successful incorporation of hypomethylating agents, and of epigenetic therapies more broadly, will depend on our ability to define the epigenetic and immunologic contexts that confer vulnerability in ENKTCL. This case extends emerging evidence that such contexts do exist and that defining them should now be a priority.

Disclosures

No conflicts of interest to disclose.

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