Dissecting the role of TE-mediated immune responses following epigenetic treatment in Acute Myeloid Leukemia (AML)

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Abstract

The human genome has been continuously subjected to genome invasions of transposable elements (TEs) throughout evolution, which has led to almost two-thirds of our genome being TE-derived. Regulation of these elements, some of which are still mobile, is critical for genomic integrity and normal cellular function of gene expression programs, most of which are under strict epigenetic control. However, epigenetic dysregulations stemming from genome-wide loss of DNA methylation, global changes in histone modification marks and dysregulation of RNA modifications are all hallmarks of cancer and are typically synonymous with TE reactivation. Indeed, various studies demonstrate transcriptional activation of TEs in several cancer cell types.
Our work aims to dissect the potential impacts of TEs on the host genome in a context which provides an epigenetically relaxed environment for their activation: acute myeloid leukaemia (AML). AML is a highly heterogeneous and aggressive haematological malignancy, characterised by relatively few genetic mutations compared to other cancers. Indeed, existing therapies are often accompanied by complications in drug toxicity, refraction and relapse, and so, there remains an unmet clinical need for the identification of new therapeutic targets and strategies for AML patients.

We aim to uncover how epigenetic therapies can be harnessed to help potentiate anti-tumour immune responses against endogenous TEs in AML. Specifically, we focus on DNA hypomethylating agents (5-AZA, Decitabine and DNMT1i) and those targeting histone modifications (HDACi and EZHi) to assess their combinatorial effects in promoting anti-tumour immune responses in patients of various genetic backgrounds. Our preliminary findings suggest that these agents result in differential TE and immune response activation in the presence and absence of DNMT3A mutations, the most commonly mutated epigenetic modifier in AML. Our next steps focus on uncovering the mechanism of 'viral mimicry' by interrogating the effects of TE-derived dsRNA and cDNAs on endogenous nucleic sensing pathways.

Keywords: Cancer, AML, TE, Epigenetics, Immunotherapy, Viral mimicry

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