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Poster: Targeting the 3D genomic and epigenetic changes in Mantle Cell Lymphoma

Recurrent chromosomal translocations found in most lymphomas frequently lead to overexpression of a certain oncogene, but in many cases, the expression of the oncogene alone does not suffice to produce a malignant phenotype. This is the case in mantle cell lymphoma (MCL), an aggressive B-cell non-Hodgkin lymphoma associated with the t(11;14)(q13;q32) translocation that results in the overexpression of cyclin D1 (CCND1), a potent cell-cycle regulator. Nevertheless, not all MCLs overexpress CCND1, and the CCND1 overexpression alone does not lead to malignancies in animal models. Thus, the development of MCL should be triggered by additional factors, which may guide the development of new therapies once discovered.
A chromosomal translocation can trigger large-scale changes in the 3D genome organization, as well as the transcriptional and epigenetic changes in the translocated loci. Here we demonstrated that the regions in the vicinity of the translocation breakpoint on derivative chromosomes 11 and 14 are relocated closer to the nuclear center in MCL cells. This was accompanied by the upregulation of gene expression in these regions, as well as the perturbation of the enhancer landscape of MCL cells. Several novel enhancers and superenhancers predicted to regulate the genes overexpressed in MCL were discovered, suggesting the potential utility of the enhancer-modifying substances for MCL treatment. We tested two substances with such properties, Abemaciclib and Minnelide, in MCL cell lines and the B cells from the venous blood of MCL patients. Both substances effectively reduced the viability of the malignant cells. These results provide valuable preclinical data and novel insights into the MCL pathogenesis.

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