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A novel murine lymphoma model identifies mutational synergy with CREBBP loss through forward insertional mutagenesis.

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Diffuse large B-cell lymphoma (DLBCL) is the most common form of lymphoma. Despite considerable improvements in the treatments, it remains incurable in ~40% of the cases. Genetic studies have identified several genes and pathways frequently mutated, among them, the gene coding for the acetyltransferase *CREBBP*. Although CREBBP loss-of-function mutations are often seen in patients, its precise role in driving the disease and its cooperation with additional mutations have not yet been fully elucidated. Additionally, the contribution of the initial cell population that sustains Crebbp loss in the course of disease and its phenotype still remains elusive.

To address these questions, we established two DLBCL mouse models which combine *Crebbp* loss with a transposon-based insertional mutagenesis system. Cre-mediated *Crebbp* excision could occur either in the HSPC compartment (early loss) or in the more committed B-cell progenitors (late loss), using an Mx1 or Cd19-promoter respectively. Both models synergize with dynamic insertions of the GrOnc transposon within the B-cell lineage to generate lymphoma.

Comparison with our *Crebbp*-replete cohort (lacking the Mx1Cre transgene) showed that early *Crebbp* loss facilitated B-cell lymphoma development of a shorter latency, which recapitulated features of the human disease, such as lymph node involvement. Although the absence of *Crebbp* at later stage during B-cell ontogeny also resulted in B-cell lymphoma, the latency was greatly increased. Detailed analyses of tissues from both models revealed the presence of an aberrant B220low B cell population expressing germinal centre markers. These malignant cells were transplantable and generated an identical aggressive disease. Sequencing analyses of this population demonstrates GrOnc insertions in several critical genes for B-cell development including *Pax5* and *Ebf1,* as well as in therapeutically targetable signalling pathways. Transcriptional studies reveal similarities between our murine tumours and their human counterparts and differences dependent upon Crebbp status. Future work will involve comparisons with further patient data, functional validation of candidate synergistic mutations and therapeutic studies.