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# Mutational synergy with CREBBP loss in lymphomagenesis identified through forward insertional mutagenesis in a new DLBCL mouse model

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## Résumé

Diffuse large B-cell lymphoma (DLBCL) is the most common form of lymphoma, that, despite considerable improvements in the treatments, 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, the functional significance of it in transformation and disease progression, most likely through cooperation with secondary genetic hits, has not yet been fully unravelled. Similarly, the contribution of the initial cell population sustaining CREBBP loss in the course of disease remains elusive.

To address these questions, we developed a new DLBCL mouse model integrating *Crebbp* loss at various stages of B cell development with a transposon-based insertional mutagenesis system.

We demonstrated that *Crebbp* loss from the HSPC compartment resulted in an aggressive DLBCL-like disease, recapitulating well-characterised histological and molecular features of the human disease. Although the absence of *Crebbp* at later stage during B cell ontogeny also resulted in DLBCL-like lymphoma, the latency was greatly increased. Detailed analyses of tissues from both models revealed the presence of an aberrant B220<sup>low</sup> B cell population expressing germinal centre markers. These neoplastic cells were transplantable and generated an identical aggressive disease. More importantly, from sequencing data, we identified candidate genes functionally equivalent to patient mutated genes. Those genes, mainly related to B cell development and cellular signalling, may represent novel therapeutic targets. Overall, this new model provides a powerful resource in which to conduct future mechanistic and therapeutic studies.

**Mots-Clés:** CREBBP, Lymphoma, DLBCL, Transposition

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