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Translocations involving the immunoglobulin heavy chain (*Igh*) locus and *Myc* are oncogenic, but the elements that are involved in activating the transcription of these fusion genes have not been resolved. Fred Alt, Monica Gostissa and colleagues have used mouse models to show that the *Igh* 3′ regulatory region (*Igh3′ RR*) can function over long distances to activate the transcription of translocated *Myc*.

B cells expand their receptor repertoire by rearrangements at the *Igh* locus using two mechanisms: V(D)J recombination in developing B cells and class switch recombination in mature B cells. These rearrangements are promoted by two elements, the intronic enhancer (*iE*μ) in V(D)J recombination and the *Igh3′ RR* in class switch recombination, and both of these sequences are oncogenic when fused to *Myc* in transgenic mouse models. However, *iE*μ is frequently deleted by *Igh–Myc* translocations, often leaving the translocated *Myc* gene more than 200 kb upstream of the *Igh3′ RR*. In these instances, is *Igh3′ RR* required for lymphomagenesis?

To address this question, Gostissa and colleagues deleted the *Igh3′ RR* from mouse models of B cell lymphoma. p53-deficient mice expressing loxP-flanked *Xrcc4* alleles develop peripheral B cell lymphoma when *Xrcc4* is inactivated using a Cre recombinase. The *Igh–Myc* translocations in these mice are initiated by class switch recombination, and the authors showed that inactivation of *Igh3′ RR* prevented the development of peripheral B cell lymphomas. The *Igh–Myc* fusions identified in these B cell lymphomas always involved the *Igh* locus with an intact *Igh3′ RR*. In addition, inactivation of *Igh3′ RR* in normal B cell progenitors did not affect the frequency of *Igh–Myc* translocations. Therefore, the authors conclude that *Igh3′ RR* is required for peripheral B cell *Igh–Myc*-induced lymphomagenesis owing to its capacity to activate translocated *Myc* genes over long distances. They also suggest that this regulatory element could be involved in pro-B cell tumours in which *iE*μ is inactivated. Consequently, targeting the *Igh3′ RR* is a potential treatment for certain types of B cell lymphoma.

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ORIGINAL RESEARCH PAPER Gostissa, M. *et al.* Long-range oncogenic activation of *Igh–c-myc* translocations by the *Igh* 3′ regulatory region. *Nature* **462**, 803–807 (2009)