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. Gostissa *et al.* have used mouse models to show that the *Igh* 3′ regulatory region (*Igh*3′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 (iEμ) in V(D)J recombination and the *Igh*3′RR in class-switch recombination, and both of these sequences are oncogenic when fused to *Myc* in transgenic mouse models. However, iEμ is frequently deleted by *Igh–Myc* translocations, often leaving the translocated *Myc* gene more than 200 kb upstream of the *Igh*3′RR. In these instances, is *Igh*3′RR required for lymphomagenesis?

To address this question, the authors deleted the *Igh*3′RR from mouse models of B cell lymphoma. p53-deficient mice expressing *loxP*-flanked *Xrcc4* alleles develop mature B cell lymphomas 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 *Igh*3′RR prevented the development of mature B cell lymphomas. The *Igh–Myc* fusions identified in $p53^{-/-}$ $Xrcc4^{-/-}$ B cell lymphomas always involved the *Igh* locus with an intact *Igh*3′RR. In addition, inactivation of *Igh*3′RR in normal B cell progenitors did not affect the frequency of *Igh–Myc* translocations initiated by V(D)J recombination. Therefore, the authors conclude that *Igh*3′RR is required for mature B cell *Igh–Myc*-induced lymphomagenesis following class-switch recombination 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 iEμ is inactivated. Consequently, targeting the *Igh*3′RR is a potential treatment for certain types of B cell lymphoma.

Nicola McCarthy, Chief Editor,
Nature Reviews Cancer

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)