CANCER GENOMICS

Translocation patterns revealed

Somatic genomic rearrangements are crucial for the immune functions of lymphocytes and involve re-ligating DNA ends from different double-stranded breaks (DSBs). This occurs during V(D)J recombination and activation-induced cytidine deaminase (AID)-induced immunoglobulin class-switch recombination. However, disruptions to these mechanisms can result in chromosomal translocations, including oncogene activation events. Two recent studies describe new methods for mapping translocations genome-wide, revealing that oncogenic patterns of translocations might be an intrinsic feature of the translocation process, even before long-term positive selection during oncogenesis.

To induce a DSB at a specific locus and thus recapitulate the initiation of translocation, Klein *et al.* and Chiarle *et al.* used mouse B lymphocytes (both wild-type and AID$^{-/-}$) with engineered *I-SceI* sites at either the immunoglobulin heavy chain (*IgH*) or *Myc* locus; these loci are common oncogenic translocation partners and hence important locations of physiological translocations. *I-SceI* sites were converted to DSBs by the action of the transduced yeast I-SceI endonuclease. Both teams carried out amplification and high-throughput sequencing of the induced rearrangements. This was possible because the sequence on one side of the engineered breakpoint is known. They identified hundreds of thousands of independent chromosomal translocation events in hundreds of millions of B lymphocytes.

Genome-wide analysis of translocation sites showed that most rearrangements occurred intrachromosomally, particularly within 350 kb of the induced breakpoint, suggesting that proximity of DSBs is a key determinant of translocation sites. Outside this proximal region, both teams found an enrichment of translocation events in genic regions. Intriguingly, this intrachromosomal and genic bias is also seen in the genomes of tumours.

Additionally, translocations were favoured in expressed versus silent genes, particularly at transcription start sites, an effect that was enhanced in the presence of AID. This is consistent with the known propensity of ssDNA strands that occur during stalled or productive transcription to suffer damage and to be AID-binding sites.

Both teams identified particular genes as being hotspots for translocations. The numbers of hotspot genes increased in the presence of AID, emphasizing an important role for AID in generating translocation-initiating breakpoints throughout the genome. These AID-dependent translocation hotspot genes included 19 genes that are found in oncogenic fusion events in B cell lymphomas, indicating that these translocations can be surprisingly frequent and early events during B lymphocyte activation. Owing to the short (~3 day) time course of the experiments and apparent lack of translocation orientation bias, these events are unlikely to have been subjected to considerable positive selection.

Because the translocation events in these studies were experimentally initiated by I-SceI, it will be interesting to determine whether oncogenic translocation events are intrinsic properties of rearrangements from physiological DSBs, including those that occur during V(D)J recombination or chemotherapy treatment.

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ORIGINAL RESEARCH PAPERS
Klein, I. A. *et al.* Translocation-capture sequencing reveals the extent and nature of chromosomal rearrangements in B lymphocytes. *Cell* **147**, 95–106 (2011) | Chiarle, R. *et al.* Genome-wide translocation sequencing reveals mechanisms of chromosome breaks and rearrangements in B cells. *Cell* **147**, 107–119 (2011)