RETROVIRUSES

Integration hotspots for disease?

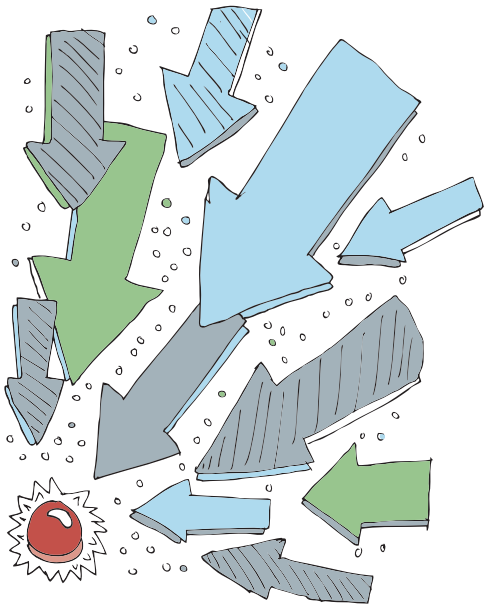
A team led by Charles Bangham has compared the integration preferences of human T-lymphotropic virus-1 (HTLV-1) *in vitro* and *in vivo*. In a recently published *PloS Pathogens* paper, Kiran Meekings, Charles Bangham and colleagues report that there is a clear relationship between HTLV-1 integration and disease.

Retroviruses persist in a dormant state in host cells by integrating copies of their genome (provirus) into host chromosomes. The integration process is not random, as there is a specific consensus integration sequence for each retrovirus and the pattern of integration sites varies: HIV favours integration into active genes, whereas murine leukaemia virus favours integration into the 5′ end of genes. In this report, Meekings *et al.* compared the integration of HTLV-1 *in vitro*, in the absence of immune selection, and *in vivo*, where the host immune response exerts a selective pressure on viral replication.

Sites of HTLV-1 integration were pinpointed using linker-mediated PCR and sequencing. The distribution of integration sites was compared with the distribution of random control sites. Statistical analyses were used to interrogate datasets and deduce the favoured integration sites under different conditions. Comparison of integration sites in cultured human lymphocytes and peripheral blood mononuclear cells (PBMCs) isolated from infected individuals showed that HTLV-1 integrates at the same sequence-specific target sites in host chromosomes *in vitro* and *in vivo*. The *in vitro* integration data generated by Meekings *et al.* confirmed the conclusions of a recent study by Derse and colleagues — HTLV-1 preferentially integrates into transcriptionally active regions of chromosomes *in vitro*, including genes and CpG islands. But the picture during infection was markedly different: HTLV-1 integrated into transcriptionally active regions of the chromosomes far more often in PBMCs from infected individuals compared with cultured cells, although proviruses in PBMCs were far less likely to be found in genes than were proviruses in cultured cells.

Infection with HTLV-1 can result in leukaemia or a chronic inflammatory disease of the central nervous system (HTLV-1-associated myelopathy/tropical spastic paraparesis; HAM/TSP). A high level of expression of the viral protein Tax is correlated with the risk of HAM/TSP. Meekings *et al.* found that HTLV-1 integration into transcriptionally active regions was associated with a higher level of expression of Tax and, consistent with this, integration in such sites was significantly more frequent in individuals with HAM/TSP than in those who had no symptoms.

The authors propose that the distribution of HTLV-1 integration sites *in vivo* results from opposing selection forces, by which integration into transcriptionally active regions of the genome favours the expression and persistence of the provirus and increases the risk of inflammatory disease. Two forces oppose this pattern of integration: the immune response to HTLV-1 and disruption of cellular functions by integration into genes.



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ORIGINAL RESEARCH PAPER Meekings, K. N., Leipzig, J., Bushman, F. D., Taylor, G. P. & Bangham C. R. M. HTLV-1 integration into transcriptionally active genomic regions is associated with proviral expression and with HAM/TSP. *PLoS Pathog.* **4**, e1000027 (2008)
FURTHER READING Derse, D. *et al.* Human T-cell leukemia virus type 1 integration target sites in the human genome: comparison with those of other retroviruses. *J. Virol.* **81**, 6731–6741 (2007) | Bushman, F. *et al.* Genome-wide analysis of retroviral DNA integration. *Nature Rev. Microbiol.* **3**, 848–858 (2005)