↪ VIRAL INFECTION

Tracking down HIV's hiding place

> ❝ the HIV-1 genome integrates into the genome of its host cell in a nonrandom manner, with a preference for NPC-proximal regions at the nuclear periphery ❞

Integration of viral cDNA into the genome of host cells is an essential step in the life cycle of retroviruses, such as HIV-1. Rather than random insertions, HIV-1 cDNA is preferentially integrated into a subset of transcriptionally active genes, but the molecular basis of this preference is poorly understood. A new study by Marini *et al.* now shows that integration is strongly linked to the three-dimensional (3D) architecture of chromatin, such that transcriptionally active regions of chromatin that are proximal to the nuclear pores are favoured.

A meta-analysis of published sequence data sets revealed that the genes that are most susceptible to HIV-1 integration cluster into 'hotspots'. The authors used 3D immuno-DNA fluorescence *in situ* hybridization probes to determine the spatial arrangement of these hotspots in primary CD4+ T cells (the main cell type targeted by the virus) from both healthy donors and patients infected with the virus.

The vast majority of HIV-1 integration sites mapped to the nuclear periphery, within 1 μm of the nuclear membrane, whereas only a small minority of integration sites were in the innermost part of the nucleus. Additional experiments confirmed that preferential targeting of a gene by HIV-1 was dependent on its distance from the nuclear membrane.

However, as the peripheral region of the nucleus has a complex topography, higher resolution analysis using protein markers was required to establish the integration patterns with greater specificity. Chromatin in this region consists of two distinct classes: transcriptionally inactive regions (known as lamin-associated domains (LADs)) that are enriched with the repressive histone marks characteristic of heterochromatin; and nuclear pore complex (NPC)-proximal regions, which border LADs but are transcriptionally active. To determine which of these chromatin classes was favoured for integration, the authors assessed chromatin immunoprecipitation followed by sequencing (ChIP–seq) data for histone proteins and for NPC components. Consistent with a preference for NPC-proximal regions, HIV-1 cDNA insertion sites were associated with transcriptionally active histone marks and with NPCs, but not with the repressive histone marks present in LADs.

Collectively, these data show that the HIV-1 genome integrates into the genome of its host cell in a nonrandom manner, with a preference for NPC-proximal regions at the nuclear periphery. The authors propose that this spatial preference is due to the short life of the viral integrase and the presence of transcriptionally active open chromatin, which is permissive for cDNA integration. According to this model, after entering the nucleus through a nuclear pore, integrase targets the first open chromatin region it encounters, thereby excluding the closed heterochromatin of LADs and the distant chromatin of the nuclear interior. In support of this model, the authors found that a mutant virus with impaired integrase function produced a dispersed integration pattern in the nucleus.

Finally, the authors observed that this preference for NPC-proximal regions may also have a role in productive HIV-1 gene expression, as proteins within the NPC were found to be involved in transcriptional regulation of the viral genome.

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ORIGINAL RESEARCH PAPER Marini, B. *et al.* Nuclear architecture dictates HIV-1 integration site selection. *Nature* http://dx.doi.org/10.1038/nature14226 (2015)

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