Host chromatin invasion by retroviral genomes

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Abstract

Cell chromatin constitutes the first non-return contact point between the genome of incoming infectious agents, as integrative viruses, and their Host. Retroviruses infect both human and animals by integrating their genome into the host chromatin, constituting therapeutic tools, as in gene transfer strategies, and are sources for potential new emerging diseases and zoonoses. The integration of retroviral genome requires the functional association between the viral integration complex (intasome) and the host chromatin involving multiple interfaces between the integrase, the target DNA and the histone components of the nucleosome. These associations are regulated by cellular factors or the structure of the chromatin surrounding the targeted nucleosome. Our project aims to identify these functional interfaces and to analyze the influence of factors regulating integration.
We first characterized the HIV-1 IN-chromatin interactions by biochemical approaches and in a model of chromosomes spreads highlighting IN intrinsic properties of binding to the chromatin and its regulation by its cellular LEDGF/p75 cofactor. We have also shown the importance of both histone tails and the carboxy-terminal CTD domain of IN in this process. Importantly, we demonstrated that the neighboring nucleosomes modulate the functional binding of the intasome to the substrate nucleosome. The use of selected drugs or mutations targeting these interfaces confirmed that they participate in the efficiency of integration but also in the insertion site selection both *in vitro* and in infected cells.

Altogether, these data suggest that retroviral IN CTDs act as sensors of the chromatin structure by scanning available histone and DNA interactions for the selection of functional interfaces for efficient genome invasion.

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*Speaker

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