ID de Contribution: **42** Type: **Non spécifié**

CTCF binding controls the expression of imprinted Dlk1-Dio3 and Igf2-H19 loci by structuring allele-specific sub-domains

Mammalian genome are organized into structural units known as Topological Associating Domains (TADs), with CTCF protein being enriched at their borders. Mammalian genomic imprinting provides a unique paradigm to explore intra-cellular differences in chromatin 3D-structuration.
In this presentation, I will focus on the two conserved paternally-imprinted domains in mammals, the Igf2-H19 and Dlk1-Dio3 domains. Both contain allele-specific CTCF binding sites at or near differentially methylated regions (DMRs) essential for correct imprinting.
Although Igf2-H19 and Dlk1-Dio3 domains are embedded into TADs with similar borders on the two parental chromosomes, the internal sub-TAD organization is pronouncedly different between the parental chromosomes. On both loci, the allele-specific binding of CTCF can hijack existing sub-TAD organization to constrain regulatory elements. Importantly, on the Dlk1-Dio3 locus, the formation of allelic distinct 3D-organization is functionally important to prevent the activation of the paternally-expressed Dlk1 gene from the maternal chromosome. Our results thus highlight the importance of allele-specific 3D-orgnization to ensure correct mono-allelic expression at paternally imprinted domains.

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