Non-coding RNAs in the control of imprinted chromosomal domains

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Résumé

Dear Organisers,
Thanks a lot for putting together this exciting meeting. I would like to come along to listen to and support our junior scientists. You should give the slots for talks to them!

There is no need for me to present, but if you could please include the below abstract into the programme that would be nice.

Best wishes,
Robert

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Genomic imprinting is an essential epigenetic phenomenon in mammals that induces patern-of-origin dependent gene expression during development. Imprinted genes are clustered in large, evolutionarily conserved chromosomal domains. These domains all express one or more long non-coding RNAs (lncRNAs), whose precise cis/trans functions in chromatin and gene regulation remain unclear.

Our team is interested in the Dlk1-Dio3 domain on mouse chromosome 12. This disease-associated domain comprises the developmental Dlk1 and Rtl1 genes, which are silenced on the maternal chromosome. The domain’s ‘Imprinting Control Region’ (ICR) brings about allele-specific chromatin organization and asynchronous DNA replication. Furthermore, on the maternal chromosome, this ICR is an enhancer that activates in cis a polycistron that
produces the lncRNA Meg3 and many miRNAs (Mirg) and C/D-box snoRNAs (Rian). Although Meg3 lncRNA is strictly nuclear and associates with the maternal chromosome, it is unknown whether it controls gene repression in cis.

We created hybrid mouse embryonic stem cells (mESCs) with specific deletions, or with an inserted ectopic poly(A) signal that reduced expression along the polycistron. Rian-/- mESCs were generated as well. Upon differentiation of the different recombinant mESC lines, our combined studies show that the Meg3 lncRNA represses Dlk1 and Rtl1 on the maternal chromosome. Induction of biallelic Meg3 expression and focal lncRNA accumulation upon CRISPR-TET1-mediated demethylation of the paternal Meg3 promoter led to biallelic Dlk1 and Rtl1 repression in differentiated cells. Importantly, Meg3 expression directly correlated with maintained hypo-methylation and CTCF binding. Using an allele-specific Capture Hi-C (cHi-C) approach, we find that this creates a Topologically Associating Domain (TAD) organization that brings the Meg3 gene in close proximity to Dlk1 on the maternal chromosome. The requirement of Meg3 expression for gene repression and TAD structure explains why in humans, aberrant MEG3 expression associates with different imprinting disorders.


Mots-Clés: epigenetics, development, genomic imprinting, chromatin architecture, lncRNA