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 patent-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

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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.

Farhadova S. et al (2024). Meg3 lncRNA mediates imprinted gene expression during stem cell differentiation. *Nucleic Acids Res.*, April, https://doi.org/10.1093/nar/gkae247

Moindrot B., Imaizumi Y, Feil R (2024). Differential 3D genome architecture and imprinted gene expression: cause or consequence? *Biochem Society Transactions,* https://doi.org/10.1042/BST20230143
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Mots-Clés: epigenetics, development, genomic imprinting, chromatin architecture, lncRNA