We hereby invite you to the upcoming

ATLAS and Functional Genomics and Metabolism

Joint Distinguished Seminar

Monday, December 17 from 13-14
in U20

Using bidirectional transcription to understand transcription regulation, disease and disease genetics

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Prof. Sandelin is invited by Prof. Susanne Mandrup, ATLAS and FGM

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Abstract

I will give a brief review on what we currently know about bidirectional transcription at promoters and enhancers, and then give an example on how bidirectional transcription can be used to find enhancers in a disease setting.

A new model for how transcription is initiated is emerging, where i) gene transcription start sites (TSSs) are located in nucleosome-free regions next to the nucleosome edge and ii) these gene TSS are accompanied by a secondary TSS placed at the opposite edge of the nucleosome-free region, firing in the opposite direction. This secondary TSS typically produces short, rapidly degraded RNAs, referred to as 'PROMPTs', which are often hard to detect without analyzing nascent RNA or by removing RNA degradation enzymes. The rapid degradation of PROMPTs is driven by DNA sequence motifs downstream of the TSS.

The same TSS constellations also occur at active enhancers, with the difference that the enhancer RNAs produced are more similar to PROMPTs than mRNAs, including their degradation patterns. This suggests a model where a generic transcription initiation block supports bidirectional transcription initiation, whose TSSs can produce any combination of enhancer RNA/PROMPTs or mRNA/lncRNAs, depending on the sequence content downstream of each TSS.

We recently profiled enhancers and promoters in gut samples from almost 100 inflammatory bowel disease (IBD) patients with the goal of understanding its pathology and genetics. We found that IBD-upregulated promoters and enhancers were highly enriched for IBD-associated SNPs and were bound by the same transcription factors. IBD-specific TSSs were associated to genes with roles in both inflammatory cascades and gut epithelia: TSSs distinguishing the two main classes of IBD - uterus polite and Crohns disease - were associated to gut epithelia functions. Using a combination of CAGE, nanofluidics qPCR and machine learning, we identified that 35 TSSs could distinguish uterus polite, Crohns disease and controls with 85% accuracy in an independent cohort.

The talk is based on the following papers:

· Boyd et al, Characterization of the enhancer and promoter landscape of inflammatory bowel disease from human colon biopsies. Nat Commun. 2018 Apr 25;9(1):1661

· Chen et al, Principles for RNA metabolism and alternative transcription initiation within closely spaced promoters. Nat Genet. 2016 Sep;48(9):984-94

· Anderson et al: Nuclear stability and transcriptional directionality separate functionally distinct RNA species. Nat Commun. 2014 Nov 12;5:5336.

· Anderson et al: An atlas of active enhancers across human cell types and tissues. Nature. 2014 Mar 27;507(7493):455-461

Read more about the Sandelin Group at http://albinsandelin.wixsite.com/sandelinlab