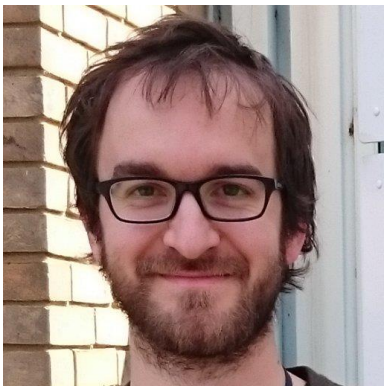
UniversitätsKlinikum Heidelberg

External Seminar Speaker



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Place: **Analysezentrum 3, 2. OG, Room 02.332**
Date: **Tuesday, July 16th**
Time: **12 am**

Functional dynamics of chromatin topology in human cardiogenesis and disease

Functional changes in spatial genome organization during human development or disease are poorly understood. We have investigated these dynamics in two models: (1) the differentiation of human pluripotent stem cells into cardiomyocytes (hPSC-CM); (2) hPSC-CM from patients with cardiac laminopathy, a genetic dilated cardiomyopathy with severe conduction disease due to mutations in *LMNA*, which encodes for the nuclear intermediate filament proteins Lamin A/C. We combined omics methods to probe nuclear structure (Hi-C), chromatin accessibility (ATAC-seq), and gene expression (RNA-seq), and genetic perturbations by CRISPR/Cas9. We found that as hPSC differentiate the heterochromatin compacts and large cardiac genes transition from a repressive (B) to an active (A) compartment. We identified a network of such gene loci that increase their association inter-chromosomally, and are targets of the muscle-specific splicing factor RBM20. Genome editing studies showed that *TTN* pre-mRNA, the main RBM20-regulated transcript in the heart, nucleates RBM20 foci that drive spatial proximity between the *TTN* locus and other RBM20 targets such as *CACNA1C* and *CAMK2D*. This mechanism promotes RBM20-dependent alternative splicing of the resulting transcripts, indicating the existence of a cardiac-specific *trans*-interacting chromatin domain (TID) functioning as a splicing factory. In the context of disease, we found that Lamin A/C haploinsufficient hPSC-CM have marked electrophysiological, contractile, and gene expression alterations. While large-scale changes in chromatin topology are evident, differences in chromatin compartmentalization are limited to a few hotspots. These regions normally transition from A to B during cardiogenesis, but remain in A in mutant hPSC-CM. Non-cardiac genes located within such aberrant domains are ectopically expressed, including the neuronal P/Q-type calcium

channel *CACNA1A.* Importantly, pharmacological inhibition of the resulting currents partially mitigates elongation of field potential duration during the contraction of mutant hPSC-CM. Altogether, this work demonstrates the dynamic nature of genome organization during human cardiogenesis and in disease, and shows how these spatial relationships can regulate lineage-specific gene expression.

Host: **Prof. Dr. med. Johannes Backs**
Director of the Department Molecular Cardiology and Epigenetics
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