Helmholtz Munich Distinguished Seminar

March 6th 2025, 14:30-16:00, building 3620 (HDC), room 033

HELMHOLTZ MUNICH

Prof. Michael Sattler hosts two world-leading researchers on the mechanism and regulation of alternative splicing: Prof. Juan Valcárcel and Prof. Reinhard Lührmann. Be sure not to miss this great event and the following get-together with drinks and snacks.

Reinhard Lührmann

Max Planck Institute for Multidisciplinary Sciences, Göttingen

Structural insights into the cascade of snRNP remodeling steps leading to the formation of a catalytically activated spliceosome

The spliceosome forms anew on each pre-mRNA intron through a pathway involving multiple, successive assembly intermediates. Early spliceosome formation involves the binding of the U1 and U2 snRNPs to the 5' and 3' ends of an intron, respectively, yielding the A complex. Recruitment of the U4/U5.U6 tri-snRNP leads to the formation of the pre-B complex, which is remodeled into the B complex. The pre-B to B transition, and the transformation of the pre-catalytic B complex into an activated (B^{act}) spliceosome, involves extensive protein exchanges and RNA rearrangements that lead to the formation of a catalytically active U2/U6 structure. Our cryo-EM structures of pre-B, B and several distinct pre-B^{act} assembly intermediates reveal an intricate cascade of highly coordinated structural changes during the activation phase of the human spliceosome. They also reveal unprecedented, large-scale translocations of proteins and entire RNP domains, with RNA helicases and kinases acting as driving forces. In addition, our studies reveal the molecular mechanism whereby formation of a catalytically active U2/U6 RNA network is facilitated by spliceosomal proteins, with a conformational change in the scaffold protein PRP8 playing a key role in facilitating its final 3D folding.

Juan Valcárcel

Center for Genomic Regulation (CRG), Barcelona

Functional networks of alternative splicing regulation in cancer

Most human genes undergo alternative pre-mRNA splicing, which is often regulated during cell differentiation and development. The process is deregulated in cancer, contributing to virtually every hallmark of tumor progression. By systematically knocking down 300 genes encoding splicing factors and regulators, and examining the corresponding transcriptomes, we have reconstructed functional splicing networks that reveal the remarkable regulatory architecture of the spliceosome. I will discuss how these functional maps can be used to identify mechanisms of splicing perturbations in cancer and hopefully pave the way to novel therapeutic approaches.