LABORATORY OF

RNA BIOLOGY

RNA splicing, snRNPs, spliceosome, nuclear structure, retinitis pigmentosa

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Our DNA encodes information for synthesis of all our proteins. However, this information in DNA is fragmented and genes contain long sequences that need to be removed in a process called RNA splicing. Unused RNA sequences are removed by a large, sophisticated and dynamic molecular machine called the spliceosome, which is the most complex particle in our cells consisting of several non-coding RNAs and dozens of auxiliary proteins. Our long-term goal is to determine how the spliceosome assembles at the right time and place. We also investigate how the nuclear architecture contributes to correct formation of the spliceosome. Finally, we aim to determine why mutations in spliceosomal components cause retinitis pigmentosa, a human genetic disease characterized by photoreceptor cell degeneration.

Formation of spliceosomal complexes *in vivo*

Combing advanced microscopy techniques with molecular biology and biochemistry approaches, we explore where and when the spliceosome components assemble in the cell nucleus. We identified a conserved nuclear compartment, the Cajal body, as the site of assembly and recycling of spliceosomal particles. Recently, we provided evidence that the Cajal body acts as a quality controller that surveillances formation of spliceosomal components and sequesters defective particles, and we determined the molecular mechanism that discriminates between correctly and incorrectly assembled particles.

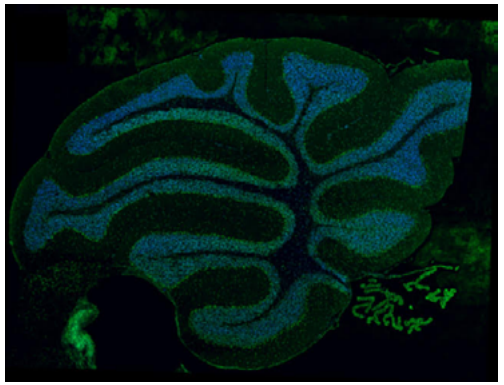

Figure 1. A section of mouse cerebellum immunostained for splicing factor Prpf8 (green). Nuclei counterstained by DAPI (blue).

Spliceosome and retina degeneration

The autosomal dominant disorder retinitis pigmentosa (RP) is characterized by progressive loss of peripheral and night vision, which eventually leads to total blindness. RP is caused by molecular defects in many different proteins, including those found in the spliceosome. Why mutations of ubiquitous spliceosomal components specifically affect retina cells, however, remains elusive. In our research, we combine model organisms, 3D organoids and cell cultures to identify the detrimental effects of RP mutations on RNA splicing in retina cells.

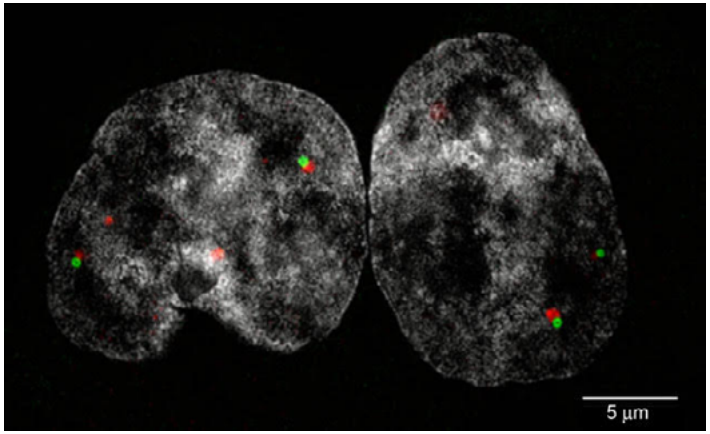

Figure 2. Human cells immunstained for coilin (red) and SMN protein (green). Coilin is a marker of nuclear structures called Cajal bodies, SMN is a marker of nuclear structures called gems. Nuclei counterstained by DAPI (white).

Selected publications:

1. Krchnáková Z, Thakur PK, Krausová M, Bieberstein N, Haberman N, Müller-McNicoll M, Stanek D* (2019) Splicing of long non-coding RNAs primarily depends on polypyrimidine tract and 5′ splice-site sequences due to weak interactions with SR proteins. ***Nucleic Acids Res,* 47**:911-928
2. Roithová A, Klimešová K, Pánek J, Will CL, Lührmann R, Stanek D*, Girard C* (**2018**) The Sm-core mediates the retention of partially-assembled spliceosomal snRNPs in Cajal bodies until their full maturation. ***Nucleic Acids Res,* 46**:3774-3790
3. Malinová A, Cvačková Z, Matějů D, Hořejší Z, Abéza C, Vandermoere F, Bertrand E*, Staněk D*, Verheggen C* (**2017**) Assembly of the U5 snRNP component PRPF8 is controlled by the HSP90/R2TP chaperones. ***J Cell Biol,* 216**:1579-1596
4. Staněk D, Fox A* (**2017**) Nuclear bodies: news insights into structure and function. ***Curr Opin Cell Biol,* 46**:94-101
5. Krausová M, Staněk D* (**2018**) snRNP proteins in health and disease. ***Semin Cell Dev Biol,* 79:92-102.** pii: S1084-9521(17): 30150-7

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