GBM Lecture + Masterpreisverleihung

Dienstag, 18. Januar 2021, 13.00 Uhr
via Zoom (Meeting-ID: 684 0388 4817; Passwort: 880758)

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Molecular mechanisms of CRISPR-associated genome editor nucleases and transposons

RNA-guided effector nucleases associated with prokaryotic CRISPR-Cas genome defense systems have been repurposed as powerful tools for precision genome editing in eukaryotic cells and organisms. In previous studies, my laboratory revealed how the genome editor nucleases Cas9 and Cas12 use guide RNAs to recognize and cleave their DNA targets. Despite their intrinsically high specificity, these enzymes can nevertheless cleave mismatched off-target DNA sequences, which presents a concern for their therapeutic use. By determining multiple structures of Cas9 in complexes with off-target substrates, we now show that its off-target activity is primarily enabled by the formation of non-canonical base pairs and preservation of base stacking within the guide RNA–off-target heteroduplex. These findings provide a structural rationale for the off-target activity of Cas9 and facilitate engineering of ultraspecific guide RNA designs for clinical applications.
Although the canonical function of CRISPR-Cas systems is to provide adaptive immunity against mobile genetic elements, some CRISPR systems have been adopted by Tn7-like transposons to mediate RNA-guided DNA transposition. Our recent structural work focuses on the type V CRISPR-associated pseudonuclease Cas12k and its transposase partner TnsC, showing how these proteins recognize and remodel target DNA. These studies advance our mechanistic understanding of CRISPR-associated transposons and will guide their development of as programmable site-specific gene insertion tools.

Host: Junior GBM Regensburg
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