A KJELDGAARD LECTURE

Thursday 17 May 2018 at 13:15
1593-012, iNANO Aud.
Same location for the PhD session

Martin Jinek
University of Zurich, Switzerland

CRISPR-Cas systems: from biology to genome editing

In bacteria, the CRISPR-Cas system functions as an adaptive system to provide resistance against molecular parasites such as viruses and other mobile genetic elements. RNA-guided effector nucleases associated with CRISPR-Cas system have been repurposed as powerful tools for precision genome editing in eukaryotic cells and organisms. My prior work demonstrated that the CRISPR-associated protein Cas9 functions as a programmable DNA-cutting enzyme whose sequence specificity is determined by a short guide RNA molecule and subsequently demonstrated that the enzyme can be programmed to induce double-strand DNA breaks in cultured human cells, paving the way for CRISPR-based genetic engineering. In my research group at the University of Zurich, our current work focuses on studying the molecular mechanisms of Cas9 and other CRISPR-associated nucleases using a combination of structural, biochemical and biophysical approaches. To this end, we previously determined the three-dimensional structures of Cas9 in complex to a guide RNA and target DNA, revealing the atomic interactions underpinning the recognition of a short motif in the substrate DNA (the protospacer adjacent motif, PAM), which is necessary to facilitate strand separation in the DNA and guide RNA hybridization. These studies have provided a structural framework for engineering novel Cas9 variants with altered PAM specificities. More recently, we have studied Cas12a (Cpf1), another RNA-guided nuclease enzyme that has emerged as a complementary genome editing tool to Cas9. The crystal structure of Cas12a bound to a guide RNA shows that, like Cas9, Cas12a structurally preorganizes the seed sequence of the guide RNA to facilitate target DNA recognition. In turn, the structure of Cas12a bound to a guide RNA and a double-stranded DNA target captures the Cas12a in a pre-cleavage state, revealing the mechanism of R-loop formation. Together with supporting biochemical experiments, the structure also reveals that Cas12a contains a single nuclease active site that sequentially cleaves both strands of the target DNA. Collectively, our studies provide a mechanistic foundation for understanding the molecular function of CRISPR-based genome editor nucleases and for the on-going development of CRISPR-Cas genetic engineering for biotechnological and therapeutic applications.

Host: Esben Lorentzen, Structural Biology
Department of Molecular Biology and Genetics, Aarhus University

The lecture will be followed by a chalk-board session for PhD students

The Kjeldgaard Lecture Series is organised by
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