KOLLOQUIUM
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GOETHE UNIVERSITÄT FRANKFURT AM MAIN

Science in progress

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Friederike Biermann and Karthikeyan Dhamotharan

Friederike Biermann

Machine learning-based exploration, expansion and definition of the atropopeptide family of ribosomally synthesized and posttranslationally modified peptides

Ribosomally synthesized and posttranslationally modified peptides (RiPPs) constitute a diverse class of natural products. Atropopeptides are a recent addition to the fast-growing number of RiPP families. Characterized members of the peptide family feature a particular intricate three-dimensional shape. Here we developed AtrooFinder, a machine learning-based algorithm to chart the biosynthetic landscape of the atropopeptides. AtropoFinder identified more than 650 atropopeptide biosynthetic gene clusters (BGCs). Through bioinformatics and modeling analyses, we pinpointed crucial motifs and residues in leader and core peptide sequences, prompting a refined definition of the atropopeptide RiPP family. Our study revealed that a substantial subset of atropopeptide BGCs harbors multiple tailoring genes, thus suggesting a broader structural diversity than previously anticipated. To verify AtropoFinder, we heterologously expressed four atropopeptide BGCs, which resulted in the identification of novel atropopeptides with varying peptide lengths, number and type of modifications. Most notably, our study resulted in the characterization of an atropopeptide that is more extensively modified than previously identified members, resulting in an even more rigid 3-dimensional shape. Moreover, one characterized atropopeptide BGC encoding a single P450 is involved in the biosynthesis of two peptides with the same sequence but distinct and non-overlapping modification patterns. This work expands the atropopeptide chemical space, advances our understanding of atropopeptide biosynthesis and underscores the potential of machine learning in uncovering the uncharted biosynthetic diversity encoded in RiPP biosynthetic blueprints.

More Information: https://tinygu.de/kolloqmbw

Karthikeyan Dhamotharan

Structural basis for target RNA discrimination by SARS-CoV-2 nucleocapsid NTD domain variants

The nucleocapsid (N) protein of the SARS-CoV-2 plays a vital role in processing and packaging its viral genome. The multi- faceted role of N on its RNA is made possible by its the N- and C-terminal structured domains (NTD, CTD) connected to three intrinsically disordered regions (IDRs). The NTD plays a major role in the recognition of functional RNA elements, specific for replication, transcription, and packaging. The specificity is to date not derivable from high resolution complex structures, while our recent work has found an NMR-observable pattern for preferably formed NTD-RNA complexes. We have shown that the domain's flexible regions read the intrinsic signature of preferred RNA elements for selective complex formation within the large pool of available motifs (Korn et al. 2023). However, how exactly the single domain manages the precise identification of the correct motifs remains unanswered. Moreover, the evolution of the virus over the course of the pandemic since 2019 has introduced certain lineage defining mutations in several flexible regions of NTD. As the functions of the N protein are tightly coupled to RNA-interaction, the consequences of these mutations in its RNA-binding domain NTD needs to be addressed. Here, we have systematically characterized single point mutations in NTD from different SARS-CoV-2 lineages. With high-resolution crystal structures, we report the presence of a highly conserved contact network within the NTD RNA-binding interface, specifically evolved in Betacoronaviruses. We present the first NTD crystal structures obtained from variants of concern and show that the network is robust to mutations regarding RNA interactions. Based on individual structures of selectively network-mutated NTD versions and supported by NMR-spectroscopic patterns and quantitative RNA-binding data we identify key contacts locating around the NTD RNA binding interface that steer the general RNA-binding competence as well as selective interactions with RNA motifs. We propose the conserved network is crucial for NTD in providing the necessary intrinsic plasticity of flexible loop-regions involved in RNA-recognition and for the discrimination of target RNA.

Science in progress represents talks of institute members. Either post docs or advanced PhD students present and discuss their recent data.

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