RNA Horizons 2024
Therapeutics Symposium
Unlocking the RNA's Potential in Medicine

September 25-27, 2024
Alfandega Congress Centre, Porto, Portugal

Expanding Therapeutic Horizons: The Power of RNAylation to Shape Cellular Processes

Katharina Höfer

Max Planck Institute for Terrestrial Microbiology, Marburg, Germany

The mechanisms by which viruses hijack their host's genetic machinery are of enormous current interest. One mechanism is adenosine diphosphate (ADP) ribosylation, where ADP-ribosyltransferases (ARTs) transfer an ADP-ribose fragment from the ubiquitous coenzyme nicotinamide adenine dinucleotide (NAD) to acceptor proteins. In our study, we discovered that a bacteriophage T4 ADP-ribosyltransferase ModB not only accepts NAD but also NAD-capped-RNA as a substrate. This results in the covalent linkage of entire RNA chains to acceptor proteins, a process we term "RNAylation." ModB specifically RNAylates its host protein targets, such as ribosomal proteins rS1 and rL2, at arginine residues.
T4 phages expressing an inactive ModB mutant exhibit a slowed lysis and reduced burst size of E. coli during T4 infection. This underscores the biological importance of this post-translational protein modification in T4 phage infection. The attachment of specific RNAs to ribosomal proteins may serve as a strategy for the phage to influence the host's translation machinery.
Our findings challenge established views on phage infection and highlight the blurring boundaries between different classes of biopolymers. This work establishes the first direct link between RNA modification and post-translational protein modification. We propose that RNAylation by ARTs could play previously undetected roles in the interaction between phages and bacteria, or even in higher organisms. As ARTs have roles extending beyond viral infections, RNAylation may have broad implications in the cellular context. Additionally, the discovery of RNAylation could serve as a starting point for developing RNAylated-proteins as next-generation RNA therapeutics.