Talk title: “RNA-binding proteomes and translation cycle dynamics”

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Talk abstract:

Eukaryotic mRNAs form dynamic and complexes with RNA-binding proteins (RBPs), frequently through regulatory motifs situated in their untranslated regions (UTRs). Such combinatorial mRNP formation acutely regulates mRNA function and represents a key aspect of gene expression control.

We have incomplete knowledge of RBPs that are active in a given cellular context. Addressing this, we employed two in vivo proteomic methods, mRNA interactome capture and RBDmap, to identify 1148 proteins as the RBP repertoire of beating cardiomyocytic HL-1 cells. Included were many proteins with known roles in RNA biology but those with roles in cardiovascular physiology or disease, mitochondrial function and intermediary metabolism were also highly represented. Notably, we identified 73 metabolic enzymes as RBPs. RNA-enzyme contacts frequently involve Rossmann fold domains with examples for mutual exclusivity of, or compatibility between, RNA-binding and enzymatic function. The findings suggest previously hidden RNA-mediated regulatory interactions between cardiomyocyte gene expression, physiology and metabolism.

Regulation by RBPs and mRNA UTR elements often target the initiation phase of translation, during which the 40S ribosomal small subunit (SSU) binds near the mRNA 5' cap, ‘scans’ in 3' direction until it detects the start codon and is joined by the 60S ribosomal large subunit (LSU) to form the 80S ribosome and commence polypeptide synthesis. Scanning and other dynamic aspects of the initiation model remained conjecture as methods to trap early intermediates were lacking. To address this we developed translation complex profile sequencing (TCP-Seq) and use it to detect SSU footprints along 5' UTRs as well as at start and stop codons in the yeast transcriptome. This provided evidence for a ‘cap-severed’ and ‘eIF-pushed’ model of scanning, documented changes at the SSU entry channel following AUG recognition and indicated a staged ribosome disassembly during termination. Overall, our results underpin mechanistic models of translation initiation with direct genome-wide in vivo evidence. TCP-seq captures ribosomal complexes at all phases of translation and will aid in studying translation dynamics in diverse cellular contexts.

Biographical Information

Thomas Preiss is Professor of RNA Biology at The Australian National University (ANU) https://researchers.anu.edu.au/researchers/preiss-t. From 1986-91 he studied Chemistry at the Philipps-Universität, Marburg (Germany) and the University of Bristol (UK). With his PhD research (1992-95) at the University of Newcastle upon Tyne (UK) he joined the field of RNA research. He spent the next seven years (1995-2002) as a postdoctoral scientist with Matthias Hentze at the European Molecular Biology Laboratories (EMBL), Heidelberg (Germany). In 2002 he relocated to Australia and started his own group at the Victor Chang Cardiac Research Institute (VCCRI) in Sydney. In 2011 he moved to ANU in the national capital Canberra. He further holds honorary appointments at VCCRI and EMBL Australia. His lab focuses on determining the mechanisms and transcriptome-wide patterns of eukaryotic mRNA utilisation and its regulation by RNA-binding proteins, RNA modifications and non-coding RNAs. Some of the work is best described as discovery science but he also studies these phenomena in the medically relevant contexts of cardiac and neurodegenerative disease, stem cell biology and cancer. Thomas has by now mentored ~40 postdocs and PhD/Masters level students and he is very active in peer review at various journals and funding agencies.