

Global Approaches in Studying RNA-Binding Protein Interaction Networks

Ziel des Reviews

Der Review beschreibt die verschiedenen Interaktionsarten die RNAs und RBPs haben, beschreibt ein paar Aufgaben und nennt Methoden mit denen die Interaktionen charakterisiert werden können.

Was für unser Projekt interessant sein könnte

- Relevanz des Themas (s. importance of research)
- Verschiedene Arten der Interaktion

Zusammenfassung des Inhalts

Importance of research:

- RBPs regulate the function and control the fate of all RNAs through post-transcriptional regulation (mRNA and noncoding RNA)
- Highly conserved in eukaryotes
(darauf wird im Paper nicht eingegangen aber vlt kann man das für anderes nutzen)
- ➔ Misregulation of RBPs is often associated with disease
- ➔ By modulating RBP activity (-> more post-translational modifications) changes in gene expression are faster ➔ better than altering mRNA translation and stability

individual RBP function

- ➔ Binding and impact of individual Proteins on RNA landscape helps to understand their molecular mode of action

Methods:

Knockdown, knockout, overexpression, RNA-seq, microarray analysis, RT-qPCR (reverse transcription), deep sequencing, high-throughput capillary electrophoresis, splicing reporters & CRISPR/Cas9 screens

It's Important to understand how the RNA landscape affects RBP function and binding preferences and vice versa

What they try to find out

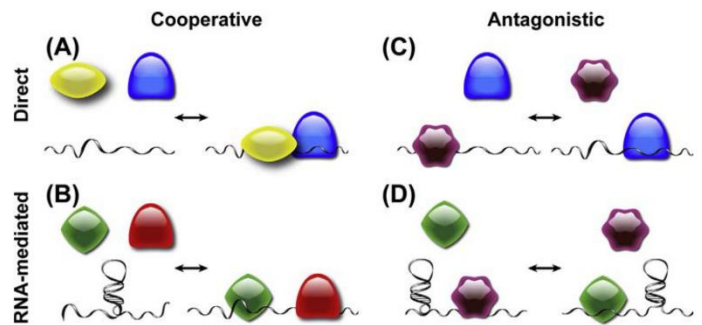
- What is the binding target, site, specificity, and preference of that RBP?
- What are changes in RBP targeting (in contrast to static binding pictures)?
-> changes in cellular environment and disease
- How is targeting different under specific conditions?
- ➔ Measurements of expression, cellular localization, changes in RNA landscape and binding partners, shifting RBP binding preferences are fundamental to understand the regulatory role of RBPs.

Higher order RBP-RBP interactions

➔ RBPs form large regulatory networks that act to coordinate complex cellular processes

Interaction Types

- direct corecruitment to their target RNA
- one RBP changes RNA secondary structure to promote second binding
- Direct competition, steric hindrance
- one RBP changes RNA secondary structure to prevent second binding



How can RBP-RBP interactions be beneficial?

- Increased flexibility in regulating the expression of a given mRNA, depending on cellular context.
- Safeguard to misregulation

Transcriptome-wide Integrative Approaches for Detection and Characterization of RBP-RBP interactions

- Combinations of computational and experimental data used to study the characteristics of RBP interactions (e.g., interaction types)

(e.g., interaction types)

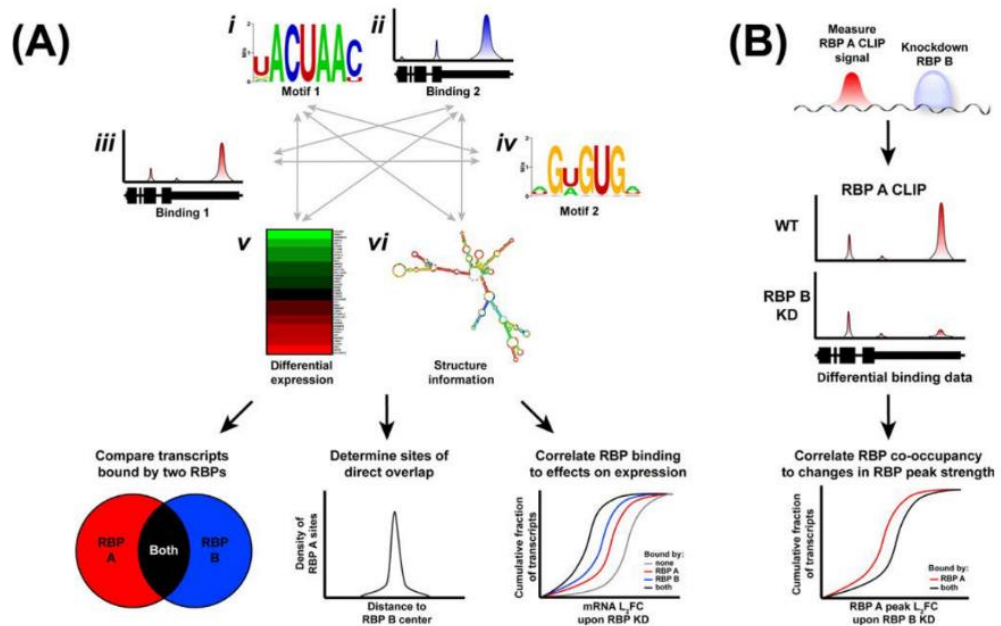
ii, iii: RNA binding data

v: differential expression data

i, iv: motif predictions

vi: RNA secondary structure information

- Determining how the binding of RBP A is influenced by the binding of RBP B



➔ Analyzing *in vivo* binding data provides further insights into RBP coregulatory effects on RNA expression-

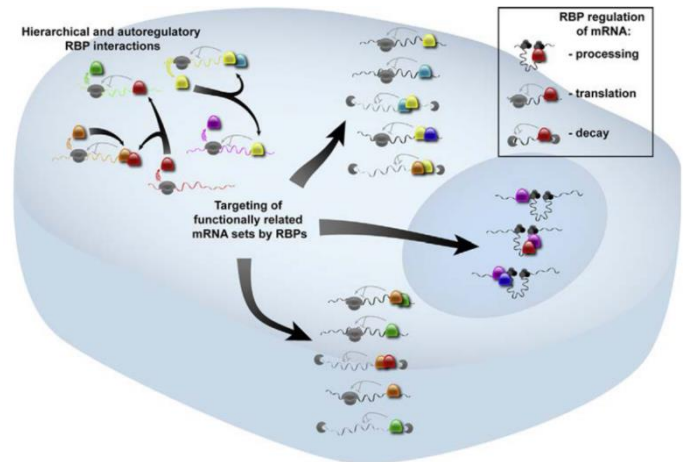
Higher order Interaction Networks

Used methods:

CLIP-seq (RBP binding), Immunofluorescence (RBP localization), RNA-seq data (transcript abundance), annotation of gene ontology (transcript function)

What they found out:

- High prevalence for autoregulation (RBPs typically control their own expression in a feedback loop)
- Regulatory networks often appear hierarchical
- The location of a RBP corresponds to the processes they are involved in
- RBPs influence RNA operons
 - > coordinated expression of many transcripts
 - > greater amount of fine-tuning



Phase-separated condensates:

RNAs and RBPs do not only participate in strong, binary interactions, but also in less specific, more dynamic and multivalent interactions. Through different interactions they can form membrane-less organelles that might have different functional roles. Because the interactions are unstable, they are highly dynamic and reversible. As a result they can easily change localization and concentration. In some neurodegenerative disorders these normally weak interactions become stable, thus forming solid aggregates or plaques that can cause problems.

Sternburg et al., Global Approaches in Studying RNA-Binding Protein Interaction Networks, 2020, Trends in Biochemical Sciences