RNA binding proteins as modulators of coding and non-coding RNA pathways

Gunter Meister

University of Regensburg, Regensburg, Germany

In animals, microRNAs (miRNAs) are transcribed as capped and polyadenylated primary transcripts. Mature miRNAs are processed from these transcripts by the subsequent action of the two RNase III enzymes Drosha and Dicer. In the cytoplasm, miRNAs directly bind to a member of the Argonaute (Ago) protein family and guide it to partially complementary target sites on mRNAs leading to inhibition of gene expression. Various studies have found that miRNA levels can be regulated post-transcriptionally at almost all steps of maturation and very often RNA binding proteins (RBP) are involved in such regulatory events. To find novel RBPs with functions in miRNA biogenesis, we have performed a proteomics screen and identify more than 100 RNA binding proteins, which specifically interact with miRNA precursors. We find that many of them positively or negatively regulate miRNA processing. It is becoming more and more apparent that a large number of RNA binding proteins form an additional layer of complexity in miRNA biogenesis and function. Based on our findings, we can also assign RNA-binding activity to proteins that have previously not been involved in RNA binding. We find that the NHL domain of TRIM-NHL proteins is a novel RNA binding domain. We have identified the binding motif of the TRIM-NHL domain protein Brain Tumor (BRAT) from Drosophila and crystallized it in complex with RNA. Brat has a specific function in self-renewal and differentiation processes in neuronal stem cells. Our work assigns a novel regulatory function to this important stem cell factor in Drosophila.