RNA structures and interactions with Gag protein that specify Ty1 RNA functions during retrotransposon replication

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RNAs adopt specific structures to perform their activities in cells and during viral replication. RNA structure is influenced by primary sequence, cellular environment, the vectorial nature of transcription and translation, trans-acting factors and ion homeostasis. Specific proteins might interact with RNA *in vivo* that stabilize or protect its native structure. Understanding how RNA folding occurs *in vivo* is limited and reconstituting biologically active RNA structure *in vitro* often fails.
The major objective of our project is to study *in vivo* RNA structural elements and transitions on both 2D and 3D structure levels that specify Ty1 retrotransposon genomic RNA (gRNA) function at different stages of Ty1 replication in *S. cerevisiae*. Ty1 is the founding member of an evolutionarily important group of mobile genetic elements that contribute to genome function and disease. Ty1 replication cycle is similar to retroviruses but Ty1 never leaves the cell and is not infectious. The Ty1 RNA molecule serves as mRNA for protein translation, as well as the genomic RNA for reverse transcription. Resulting DNA integrates with the cell genome and serves as the template for Ty1 genomic RNA transcription.

Studying Ty1 retrotransposition in *Saccharomyces* is a powerful system to explore RNA structure/function relationships. We would like to understand the structural transitions that Ty1 gRNA undergoes during nuclear export, in the cytoplasm, retrosomes, and during assembly of the virus-like particles (VLP). Retrosomes are the specific cytoplasmic sites, where gRNA and Ty1 Gag proteins colocalize and the VLP assembly starts. A central idea in our proposal is that there may be different interactions between Gag and Ty1 gRNA that alter RNA structure and regulate retrotransposition. We aim to explore gRNA interactions with Ty1 Gag protein and nucleic acid chaperone activity of Ty1 Gag. Proteins with nucleic acid chaperone activity may facilitate folding and interactions of RNA molecules. An important aspect of this project is the use of genetics, molecular and cell biology in combination with a detailed analysis of RNA secondary and tertiary structure based on experimental approaches, modelling and structural bioinformatics.

Despite of intensive studies we are only beginning to understand transposons influence on genome function and evolution. The transposon's ability to insert into many genomic locations has been used to develop important tools in genetics, molecular and synthetic biology, and gene therapy. The proposed studies should significantly extend our knowledge of regulatory functions of retrotransposon RNA structures and help to understand the role of transposable elements in disease development and genome evolution. Focused on RNA secondary and tertiary structure transitions our project should have profound influence on the structure-function relationship studies in all fields of RNA research. Recent advances in recognizing the ways RNAs control viral pathogenesis and eukaryotic cell functions make it certain that RNA structures will become increasingly important targets for therapeutic intervention. Since Ty1 retrotransposon shares several important structural and functional characteristics with retroviruses, we foresee that our studies will extend research not only on retrotransposons in diverse organisms, but will be applicable to retroviral replication.