

Diverse functions of U7 snRNP during the cell cycle

During the evolution of eukaryotes, molecular mechanisms were established that ensure accurate DNA replication and appropriate assembly of chromatin. Therefore, in the S phase of the cell cycle DNA synthesis is coupled to histone protein synthesis. These two processes are finely balanced as disturbances can result in misregulation of gene expression, cell cycle arrest and chromosome instability. Any one of them can result in developmental failure. Thus, histone gene expression is strongly up-regulated in S phase reaching ~35-fold increment in histone mRNA level due to activated transcription, efficient 3' end processing and enhanced transcripts stability. Then, at the end of S phase their level drops again. Small nuclear ribonucleoprotein complex U7 snRNP is one of the crucial factors mediating correct 3' end processing of histone mRNAs. However, although its function is tightly restricted to S phase, all three unique components of U7 snRNP: U7 snRNA as well as Lsm10 and Lsm11 proteins are constitutively expressed and their level remain unchanged during the entire cell cycle. Therefore, the question arises what is the role of U7 snRNP out of the S phase of the cell cycle?

The main goal of the project is to investigate the additional function of U7 snRNP complex or its specific components that can be played besides the role in the 3' end processing of histone gene transcripts in S phase. One of our hypotheses assumes that U7 snRNP, in cooperation with two other factors, FUS and hnRNP UL1, acts as a repressor of replication-dependent histone gene expression out of S phase thereby preventing the potentially toxic effect of histone synthesis at other times in the cell cycle. We suppose, that two opposite functions of U7 snRNP, as an activator and repressor, are switched depending on the cell cycle phase by altered binding with mediating proteins. Further investigations of phosphorylation status, location and mutual interactions between U7 snRNP, FUS and hnRNP UL1 should provide insights into this dual role of U7 snRNP and the important mechanism of regulation of replication-dependent histone gene expression during the cell cycle.

Alternative hypotheses assume that U7 snRNP or its specific components that might exist outside of the complex, play additional function in the cell that is not related to replication-dependent histone gene expression. To answer this question we are planning to monitor the location of the complex within the cell in selected cell cycle phases or during the entire cell cycle in wild type cells or in cells with U7 snRNA depletion or Lsm10 and Lsm11 knockdown. Moreover, histone gene expression-unrelated proteins bound to U7 snRNP beyond of S phase will be identified. We will also try to describe the composition of aberrant U7 snRNP complex or other complex containing Lsm10/Lsm11 heterodimer. Finally, the gene expression profile will be analyzed in cells after U7 snRNA depletion since it was shown that U7 snRNA might negatively regulate expression of other genes by interacting with specific transcription factors.

Our three hypotheses are based on published reports and our preliminary, unpublished data. We are convinced that the experiments in the proposal "Diverse functions of U7 snRNP during the cell cycle" planned for detailed characterization of U7 snRNA, Lsm10, Lsm11 as well as the U7 snRNP complex during the cell cycle will help to unravel their additional role(s) and explain their constitutive expression in cells. We will be able to decipher a unique mechanism of snRNP-mediated transcriptional control that restricts histone synthesis to S phase, thereby preventing harmful effects of histone synthesis at other times in the cell cycle, such as genomic instability or cell cycle arrest. Otherwise, it will bring a significant contribution to describing additional molecular processes that require U7 snRNP or its components.