ABSTRACT

Although germ cell development is divergent in different animal species, intriguingly, it demonstrates a remarkable evolutionary conservation regarding especially RNA-binding proteins (RBPs) that are involved, as for example NANOS proteins. The molecular mechanism of how these RBPs function is well known however, mRNA targets of NANOS1 and NANOS3 and biological consequences of NANOS-mediated mRNA regulation in human germ cells are largely unknown.

To address this, in this dissertation mRNA targets of both NANOS1 and NANOS3 RBPs were characterized using RNA-Sequencing (RNA-Seq) following *NANOS1* and *NANOS3* overexpression in TCam-2 cell line representing human post-migratory primordial germ cells (PGCs). RNA-Seq identified several pro-apoptotic genes, involved in p53 mediated apoptosis pathway downregulated upon *NANOS1* overexpression. Interestingly, overexpression of the mutant *NANOS1*, carrying mutations identified in infertile male patients is unable to repress these pro-apoptotic genes, suggesting that NANOS1 potentially safeguards PGCs from apoptosis by downregulated the identified pro-apoptotic mRNAs (Article #1). Furthermore, RNA-Seq showed that overexpression of *NANOS1* and *NANOS3* results in downregulation of hundreds of cell cycle related mRNAs. These cell cycle mRNAs are different for NANOS1 and NANOS3 suggesting that these RPBs are involved in regulation of different stages of the cell cycle. Namely, NANOS1 is involved in the G1/S phase and NANOS3 in the G2/M phase. Many of these cell cycle genes regulated by both NANOS1 and NANOS3 are known to be involved in infertility, and genes that demonstrate enriched expression in germ cells as well as overexpressed in cancer cells. Moreover, NANOS3 potentially regulates G2/M phase of cell cycle together with another RBP, PUM1, through regulating *FOXM1* mRNA encoding a transcription factor crucial for driving the expression of G2/M phase genes. (Article #2). Finally, since NANOS1 and NANOS3 are involved in processes such as apoptosis and cell cycle as well as regulate genes that are disrupted in cancer, we investigated their potential role in human cancers. By analyzing RNA-Seq datasets from publicly available databases, we showed that *NANOS1* and *NANOS3* are overexpressed in different types cancers, respectively (Article #3). Taken together, this dissertation contributes to our understanding of how NANOS RBPs function by providing the first global characterization of mRNAs regulated by these proteins and biological consequences of this regulation for germ development and disease.