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Control of spermatogenesis by transcriptional and post-transcriptional regulation of gene expression

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Spermatogenesis is a cell differentiation programme that allows a normally dividing diploid cell to become haploid and to acquire the morphological characteristics required to reach and to fertilize the female gamete. Many of the steps involved in this differentiation programme necessitate profound modifications of the genome, rendering it unable to play its template role for the synthesis of mRNAs. Therefore, de novo transcription is not a continuous process during germ cell differentiation and many mRNAs need to be synthesized and stored at specific times to be available during the transcriptionally inactive stages of spermatogenesis. Activation of signal transduction pathways orchestrate RNA metabolism at specific steps of spermatogenesis. In particular, translation of stored mRNAs accounts for protein synthesis during the transcriptionally inactive stages of spermatogenesis. A key step in mRNA translation is the assembly of the initiation complex EIF4F, which is regulated by the mTOR and MNK pathways. By performing in vivo labeling studies we have shown that pachytene spermatocytes display higher rates of protein synthesis, which are partially dependent on mTOR and MNK activity. By contrast, haploid spermatids are characterized by lower levels of protein synthesis, which are independent of the activity of these pathways. Notably, external cues differentially modulated the activity of these pathways in meiotic and haploid cells. Thus, our results have demonstrated that translational regulation is differentially dependent on signalling pathways during germ cell differentiation.

An additional layer of regulation is provided by the high levels of expression of RNA-binding proteins in germ cells. These proteins assist many post-transcriptional events in gene expression and the generation of mouse knockout models has highlighted the essential role played by these proteins for the correct progress of spermatogenesis and for the formation of a fertile male gamete. Our laboratory has contributed to the field by elucidating the role of Sam68 in the regulation of spermatogenesis. Sam68 is a KH-type RNA-binding protein involved in several steps of RNA metabolism with potential implications in cell differentiation and cancer. We have shown that Sam68 knockout male mice are infertile and display several defects in spermatogenesis, demonstrating an essential role for Sam68 in male fertility. Sam68 knockout mice produce few spermatozoa, which display dramatic motility defects and are unable to fertilize eggs. Expression of a subset of messenger mRNAs and of microRNAs is affected in the testis of knockout mice. Interestingly, Sam68 is associated with polyadenylated mRNAs in the cytoplasm during the meiotic divisions and in round spermatids, when it interacts with the translational machinery. We have described that Sam68 is required for polysomal recruitment of specific mRNAs and for accumulation of the corresponding proteins in germ cells and in a heterologous system. Thus, our observations have demonstrated a novel role for Sam68 in mRNA translation and have highlighted its essential requirement for the development of a functional male gamete.

In conclusion, these studies illustrate how a tight control of RNA metabolism insures the correct flow of gene expression in differentiating male germ cells, in spite of discontinuous rates of mRNA transcription due to the profound genomic modifications required for the production of a functional male gamete.