

Despite huge advances in assisted reproductive techniques (ART) approximately 15 % of couples face a problem at time to conceive and after one year of unsuccessfully intercourse are qualified as infertile. In half of such couples the dysfunction of the male reproductive system is responsible for unwanted childlessness. Worldwide infertility afflicts more than 40 million men and this number is growing continuously. There are several reasons for male infertility ranging from anatomic defects, spermatogenesis dysfunction, endocrinopathies and immunologic problems to erection, ejaculatory failure and exposures to stress factors. In 10-15% of men with fertility problems the genetic factor as chromosomal aberrations and gene mutations are the underlying cause. Thus the understanding of genetic control of male germ cells development is very important. But studying male fertility is not an easy task. There is no cell line resembling spermatogenesis process therefore, male fertility cannot be evaluated in a test tube. Only the in vivo studies can provide with meaningful information that can explain molecular mechanism regulating sperm quality. Thus, the generation and use of mouse models is critical to study genes controlling spermatogenesis. Mice are commonly used in reproductive biology because of their relative short reproduction cycle, large litter size, cheap housing conditions and genetic similarities to humans. To date more than 400 mouse models have been generated in order to study reproduction. Gene knockout technology is well acknowledged and recognized as a powerful tool to turn off a particular gene of interest. The analysis of male fertility in a specific knockout mice leads to the discovery of the ablated gene's function. The functions of many spermatogenesis relevant genes were discovered using this technique

For the proper male gametes production two opposite processes have to act in a balanced manner. On the one hand germ cells proliferation is required to provide adequate number of sperm and, on the other hand the elimination of damaged germ cells, usually by apoptosis, guaranties the quality of produced sperm. The elucidation of molecular mechanism controlling balance between pro-apoptotic factors activity and the action of anti-apoptotic molecules is important to understand reproductive health related issues.

Programmed cell death (apoptosis) is an active, highly regulated biological process that enables maintenance of tissue homeostasis by elimination of aged, overproduced, or dysfunctional cells. Apoptotic loss of germ cells during testicular development is very common in both normal and pathological conditions and it is critical to maintain the proper germ cells and somatic Sertoli cells ratio and to prevent generation of defect sperm. Despite increasing number of reports about pro-apoptotic factors acting during spermatogenesis the mechanisms underlying this important event in the male gonad still remain poorly understood.

We have identified a male germ cell specific gene encoding for pro-apoptotic protein. Enhance expression of this gene results in massive germ cells death in transgenic mice. We have also identified anti-apoptotic protein, that binds the pro-apoptotic factor and thus, protects germ cells from apoptosis. Analysis of mutant mouse with disruption of the anti-apoptotic protein encoding gene revealed also enhance germ cells death as in this mouse model a pro-apoptotic protein cannot be bind and inactivated by the ablated anti-apoptotic factor. Therefore we stress the hypothesis that balanced interaction of both proteins is crucial for spermatogenesis. To test this hypothesis we have developed a mouse model with simultaneous disruption of both pro- and anti-apoptotic genes. In this project we aim to utilize this mouse model to better understand the interplay of both proteins in spermatogenesis control and to determine the function of pro-apoptotic protein in testis. We suppose that this protein might be involved in elimination of defective gametes and as such might responsible to preserve high quality of produced sperm. This hypothesis will be also tested in our project.