The role of myosin VI in mammalian spermiogenesis

Every sixth couple at the reproductive age in the world has reproductive issues, and every third of them needs specialist medical care. For that reason World Health Organization recognized infertility as one of the civilisation diseases which is now a widespread problem. Male infertility contributes to at least 30% of all infertility cases and it has many causes. One of them is abnormal production and/or function of sperm, which are essential for fertilization of the female egg. Disturbed production and function of male gametes can result from easy to diagnose causes, including anatomical changes, inflammation, varicose veins within genitourinary tract, bacterial infections, and others. Unfortunately, part of male infertility cases has idiopathic nature that means their basis is not defined. Because the process of mature sperm development is remarkably complex, it seems that disruptions in their structure and/or function may be caused by difficult to diagnose or not yet defined molecular factors crucial for spermatogenesis. Therefore, studies in the field of fundamental cellular processes at every stage of spermatogenesis are needed.

Spermatogenesis takes place in seminiferous tubules of male testes. During its final stage – spermiogenesis – initial cells called spermatids transform into sperm of characteristic shape. At the beginning, every spermatid is the round cell and needs morphological and biochemical changes. As a result of spermiogenesis, with the use of numerous proteins, the spermatid nucleus is condensed and lengthened, the excess cellular content is removed, and the tail is formed – the element of every sperm essential for its movement within the female birth canal. During this process, the acrosome is also formed – specific structure localized at the top of the sperm head, which enables the penetration of egg by sperm. Dynamic cellular structure called actin cytoskeleton plays an important role during every phase of spermiogenesis. It is involved in the cellular shaping, the cytoplasm organization, and it is responsible for the cellular movement. Numerous proteins participate in the regulation of cytoskeleton organization and dynamics. One of them is myosin VI (MYO6), motor protein involved in *cargo* transport along actin filaments and/or *cargo* (*eg*. other proteins) anchoring in the target sites within the cell. To date MYO6 was showed to play a role in many cellular processes (including endo- and exocytosis), and to be crucial for proper functioning of the Corti organ in the inner ear of mouse. Moreover, in fruit fly the lack of MYO6 leads to male infertility, which might indicates that it is the crucial protein for spermatogenesis. Unfortunately, it is not known whether this protein is involved in the process of sperm development in mammals.

Snell's walzter mice (*sv/sv* mice) that do not have MYO6 are the ideal model for research on the possible role of this protein in spermiogenesis of mammals. Microscopic studies have revealed structural and functional disruptions of actin cytoskeleton in *sv/sv* mice, which causes the great number of dysfunctions. Although *sv/sv* males have reduced fertility, no studies have been published that address the possible role of MYO6 in spermatogenesis of this organism. Results of my pioneering studies in that field show the presence of MYO6 in spermatids of wild type mice. Analysis using both light and electron microscopy have revealed that MYO6 is associated with organelles and specialised actin structures, which play an important role in the transformation of round spermatids into mature sperm. Additionally, during spermiogenesis in *Snell's waltzer* mice, I have noticed ultrastructural changes in these organelles and structures, what can be a reason for their reduced fertility. However, to determine the molecular basis of these disruptions, further comparative and functional studies using *sv/sv* mutants and control mice are needed.

During the realization of proposed project I will reveal sites at which MYO6 is produced in mice testes, identify with which proteins and how MYO6 interacts during spermatogenesis, and determine potential effects of MYO6 lack in *sv/sv* males. Obtained results should allow us to define the biological role of this protein in spermiogenesis of mammals, which has not been determined so far. The proposed project has also wider meaning. Its results will broaden our knowledge in the area of fundamental mechanisms controlling spermiogenesis, which are similar in evolutionally distinct animal species. Perhaps I will also identify unknown facts about spermatids maturation. Therefore, there is a chance that obtained results will have also applicative value in the future – in the correct diagnosis of male infertility having the molecular basis.