

The production of male reproductive cells, i.e. sperm, occurs in the seminiferous epithelium of the mammalian testis. Testis is considered an immune privileged organ, meaning it is less likely to provoke an immune response than most other organs in the mammalian body. Despite many years of research, knowledge about the mechanism of cooperation between the immune system and seminiferous epithelium cells in the process of developing and maintaining the immune privilege of the testis is still incomplete. At the same time, it should be noted that local infections and inflammations, by activating the immune system, have a negative effect on both the production of sex hormones and the differentiation of male reproductive cells, which can lead to reduced fertility. Previous studies have shown that infections and inflammations of the male reproductive organs are the cause of about 6–15% of all cases of fertility disorders. Therefore, it is particularly important to understand the mechanisms involved in the interactions between the immune system and testicular cells. In the testis, the cells responsible for immune privilege are mainly Sertoli and Leydig cells, which can induce the process of lymphocyte death (preventing inflammation in the testis) by producing a number of anti-inflammatory molecules.

It is well established that the proper functioning of numerous intracellular receptors is necessary for the maintenance of male fertility. Some of these receptors were initially referred to as "orphan receptors" because their specific activating molecules (ligands) were unknown. Orphan receptors whose ligands have been identified in recent years have been termed "adopted orphan receptors" and include, among others, liver X receptors (LXR), farnesoid X receptor (FXR), and pregnane X receptor (PXR). The role of adopted orphan receptors in the regulation of Sertoli and Leydig cell function has already been well studied. Several studies indicate their involvement in the maintenance of fertility. However, until now, the relationship between these receptors and immune privilege in the testis has not been explained.

The research hypothesis assumes that signaling via LXR, FXR and PXR receptors regulates the immune function of Sertoli and Leydig cells, and the activity of these receptors plays an important role in maintaining the testis immune privilege. The main goals of the project are to identify the components of the LXR, FXR, and PXR pathways in the inflammatory environment in the rodent testes, to determine the role of these pathways in the induction and progression of testicular inflammation, and to explain the role of LXR, FXR, and PXR in the control of T lymphocyte physiology.

Experiments will be carried out using animal models (mice) and cell cultures. The first part of the project will allow to explain whether inflammation disrupts the activity of the LXR, FXR and PXR signaling pathways, as well as to determine the participation of these receptors in the induction and development of testicular inflammation. For this purpose, a mouse model of experimental autoimmune testicular inflammation will be used, as well as cultures of mouse Sertoli cells and Leydig cells, in which the activity of LXR, FXR or PXR receptors will be blocked. The next step will allow to examine the role of LXR, FXR and PXR in the control of the immune functions of testicular cells. For this purpose, cultures of mouse Sertoli and Leydig cells and lymphocytes will be used, as well as transplantation of Sertoli cells with activated/inhibited receptors under the kidney capsule of adult mice.

The obtained results will expand the knowledge on molecular mechanisms involved in the control of a key process involved in maintaining male fertility, which is the testis immune privilege. Considering that inflammation is one of the main causes of reduced male fertility, and the activation of LXR, FXR and PXR has shown immunosuppressive effects in other tissues and autoimmune diseases, the results of the proposed studies may in the long term have clinical significance in diagnostics and facilitate the identification of the causes of some cases of male infertility.