Modern Concepts of the Structural Bases for the Reparative Regeneration of the Mammalian and Human Testis

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Modern concepts of the structural bases of the reparative regeneration of the mammalian and human testis are discussed in this article, based on published data and our own findings. The significance of the rete testis as a regeneration zone is discussed as well as the use of its potentials in clinical andrology.

Key Words: *mammalian and human testis; rete testis*

The dissertation of A. A. Maksimov was one of the first studies of regeneration of the testis [9]. Although some premises underlying this work proved to be controversial, this excellent investigation was the basis for many studies carried out by S. S. Raitsina. In 1985, summing up the studies of many years, this scientist, focusing on spermatogenesis as a biological phenomenon, introduced the concept of "reproductive strategy of spermatogenesis," which she interpreted as a set of adaptations or mechanisms providing for the greatest reproductive success under certain environmental conditions [16]. The totality of mechanisms underlying the protection of the genome in developing sex cells was first considered as one of the forms of reproductive strategy.

Cytoplasmic determinants of primary sex cells (PSC), their early individuation and subsequent migration to the germinal gonads, symbiotic relationships with somatic cells of the gonad, the blood-testis barrier (BTB), autoantigens of male sex cells and autoimmune processes resulting in the destruction of the seminiferous tubules, as well as their successive regeneration due to the rete testis epithelium and to the PSC preserved in it from the period of embryogeny form the structural basis of the adaptive reactions guaranteeing the participation of cells with an unchanged and completely sound genome in fertilization. Is the destruction of the seminiferous tubules the regular reaction of the testis affected by damaging factors? The destruction of the seminiferous tubules was described for the first time by Maksimov [9] after traumatic damage of the testis, namely after puncture with a hot needle or a small wedge-shaped resection of the tissue in rabbits. He found that the destructive processes were not restricted to the damaged region, but "rapidly occupied without any visible cause the entire organ," eventually resulting in atrophy of the testis. The damage to the seminiferous tubules and concomitant loss of the specific structure of the testis were accompanied by a drop in the weight of the organ. These observations were further confirmed by the studies of numerous authorities [2-4,12,13,36].

The autoimmune nature of the posttraumatic destruction of the seminiferous tubules is now considered as proven [4,15,48,49].

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The pathogenesis of autoimmune posttraumatic orchitis is thought to be a nonspecific rise of the BTB permeability due to impaired integrity of its structural components, which opens up access to autoantigen cells and is accompanied by an increase in the number of lymphocytes sensitized to testicular antigens. This may explain the rapid spread of destructive processes in the testis as well as their transference to the contralateral organ.

Does the effect of damaging factors that are different from trauma result in autoimmune destructive processes? There are now believed to be many factors besides BTB which prevent the development of autoimmune reactions in the testis, the interrelation of which is viewed as an immunological phenomenon of the testis [30]. Among them are the immunosuppressive factors regulating immune processes [41] as well as hormonal factors which may be mediators of the immune response [19]. In addition, morphological changes induced in the testis by various damaging agents are of the same type and appear approximately in the same sequence: the formation of interstitial lymphoid infiltrates, death of sex cells, pathological alterations of structural components of the seminiferous tubules with successive destruction of them and the formation of a resorption focus in the organ. It may be assumed that the autoimmune destruction of the seminiferous tubules occurs in experimental venous congestion in the testis, experimental cryptorchism, disorders of the hormonal regime, seasonal involution of the organ in animals with seasonal spermatogenesis, and local irradiation of the testis [3,4,6,8,10,17]. For example, the direct effect of local x-irradiation (1000 R) of the testis of mature rats causes the death of radiosensitive sex cells, changes of the hormonal regime, and an increased blood vessel permeability that results in the development of interstitial inflammatory infiltrates. The altered hormonal regime and the death of sex cells in turn increase BTB permeability. All this ultimately results in the development of a destructive process in the seminiferous tubules on the 24th-30th day after irradiation [7,8,40].

Thus, destruction of the seminiferous tubules is the regular reaction of the testis to seasonal and damaging factors. That is why there has to be a such a reliable, perfected method of restoration of structural units of the testis, namely of the seminiferous tubules and of spermatogenesis [16], in order to preserve the reproductive power of animals. It should be stressed that the regeneration of structural components of the testis (in particular, of the seminiferous tubules) is made possible only by a new formation of immature seminiferous tubules from the regeneration zone. Ingrowth of the preserved differentiated seminiferous tubules and the replacement of destroyed tubules are impossible, because by the onset of puberty the myoid cells of the tunica propria of the seminiferous tubules as well as Sertoli's cells irreversibly lose their capacity for mitotic division and therefore for elongation of the tubules [39]. In fact, in the regeneration period after any damage or seasonal involution the testis of pubertal animals acquires properties characteristic of mature animals, namely the ability to develop compensatory hypertrophy in response to the removal of the paired organ [7,10,26] and Sertoli's cells incorporate the radioactive thymidine isotope [7]. Variations of the number of Sertoli's cells are found both after various damaging influences such as experimental cryptorchism [23], administration of FSH to hypophysectomized animals [33], administration of bisulfane [44], and local irradiation of the testes [34], as well as during the yearly cycle in animals with seasonal spermatogenesis namely in sheep [26], and rodents [27,43]. These facts cease to be unexplainable or artifacts in light of the concept of the testis of pubertal animals as an unstable dynamic structure [7,8]. Many authorities have described characteristic morphological changes of the rete testis (the transformation of its epithelium from squamous to columnar or cuboidal, the onset of mitoses in its cells and the formation near the rete testis of the seminiferous tubules structurally corresponding to immature seminiferous tubules) which accompany the development of destructive processes in the tubules after various damaging factors [9,18,29,35]. However, only Raitsina considered the rete testis as a regeneration zone of the testis and thereby explained the existence of reactive changes of the rete testis after trauma and seasonal factors [16].

The capacity for and degree of reparative regeneration of the testis depend on the nature of the action and the degree of development of destructive processes [11,14,16]. When the regeneration zone of the testis is damaged, reparative regeneration is hindered. The rete testis is a system of mutually connected tubules and cavities which joins the seminiferous tubules with the seminal ducts and transports spermatozoa from the testis to the epididymis. THe anatomy, histology, and development of the rete testis have been described in detail in numerous publications [20,24,28,37,38,46]. Axial and surface types of rete testis are recognized depending on the position in the testis. The axial rete testis runs its entire length. It is found in the

rabbit, cat, dog, bull, sheep, pig, and guinea pig. The surface type, situated immediately under the tunica alba of the epididymal margin of the testis, is found in the rat, mouse, hamster, and man [24]. In the majority of mammals the rete testis is divided into three parts: intertesticular, intertunic, or intermediate extratesticular [37]. Electron microscopic study disclosed that epithelial cells of different parts of the rete testis are structurally similar, refuting their different origin [31]. The epithelial cells of the rete testis lie on a homogeneous electron-dense basement membrane. Cell nuclei are of polygonal or elongated shape. A large number of oval-shaped mitochondria and granular endoplasmic reticulum are situated in their cytoplasm. A characteristic feature of rete testis cells of all parts is the existence of dark electron-dense particles. Two types of cells, dark and light, are recognized in the epithelium of the human rete testis. The light cells contain less glycogen and lipids than the dark cells [20]. The rete testis is a secretory structure [45]. The fact that it secretes a substance inducing meiosis (in contrast to embryonic testicular cells, which inhibit meiosis) is of great interest. The meiosis-stimulating agent is not species-specific. During the growth and differentiation of the testicular cells the production of the meiosis-inhibiting substance stops and cells of the rete testis produce a factor which induces the prophase of meiosis of sex cells [25].

Considering the rete testis as a regeneration zone of structural units of the testis, it may be assumed that epithelial cells of the rete testis are the precursors of Sertoli's cells, and therefore they must have a common origin.

However, published data on the origin of Sertoli's cells and epithelial cells of the rete testis are controversial. There are several points of view on the origin of Sertoli's cells. According to the first concept, the precursors of Sertoli's cells develop from the coelomic epithelium covering the genital tori and growing into them [1,5]; another concept states that the genital cords are formed from disintegrated cords of the primary kidney [21,22,50]; a third theory considers a dualistic origin of Sertoli's cells [46]. It is known that there are two populations of Sertoli's cells, namely dark and light. It is assumed [46] that the dark Sertoli's cells are the meiosis-inducing cells and are of mesonephric origin, while the light cells are meiosis-inhibiting and are of coelomic origin. The existence of electron-dense particles and of glycogen in the cytoplasm of the dark cells makes them resemble rete testis cells. Roosen-Runge [37] concluded that the intertunic and extratesticular parts of the rete testis develop from the cells of the mesonephros while the intertesticular part differentiates from the blastema of the gonads. There is an opinion that the epithelium of the primary kidney does not participate in the development of the rete testis [1]. The intertesticular part of the human rete testis is formed from the central part of the growing genital cords [38]. However, most authorities note that in the early stages of embryogeny the tubules of the rete testis comprise cords consisting of cells structurally corresponding to immature Sertoli's cells and contain PSC, i.e., they are typical genital cords.

The fact that epithelial cells of the rete testis characteristically express cytokeratin, the protein of intermediate microfilaments, is also of interest. Usually cytokeratin is expressed by cells of the mesonephros. Sertoli's cells, stromal cells, as well as Leydig's cells express vimentin. Immature Sertoli's cells in atrophic tubules express cytokeratin as well [32].

The co-expression of vimentin and cytokeratin occurs in the cells of an indifferent gonad [47]. This may confirm the common origin of Sertoli's cells and epithelial cells of the rete testis. Hence, it would be important to compare the testis cytoskeleton in the period of reparative regeneration and in the embryonic period to decide whether epithelial cells of the rete testis participate in the reparative regeneration of the testis in pubertal mammals.

Are PSC preserved in the epithelium of the rete testis from the embryonic period to the period of puberty and can they be a source of restoration of spermatogenesis? It has been found that PSC may be ectopically situated during their migration from the yolk-sac to the genital tori. It is known that in mice PSC occupy the developing gonads toward the 13th day of embryogeny, and on the 12th-12.5th day the sex cells were found in the adrenals of the fetus [42]. The authors described in detail the behavior and fate of ectopic sex cells in the adrenals. On the 15th day of fetal life the number of sex cells in the adrenals is not great, only 3-4 cells in each adrenal, and they already have the morphological features of primordial sex cells. On the 17th day they enter into meiosis, regardless of sex. At the same time sex cells of the developing ovaries start meiotic division. Despite their extragonadal localization, the sex cells not only survive but differentiate; however, they completely degenerate toward the 12th day of postnatal life. It is evident from the findings that the differentiation of sex cells occurs autonomically. PSC enter into meiosis according to their program of development, which is completed unimpeded both in the gonadal and in the ectopic location in the female organism. In the male or-

ganism the only sex cells situated outside of the gonad may enter into meiosis in the embryonic period, because during the whole fetal and neonatal period somatic cells of the testis produce meiosis-inhibiting factor and the behavior of sex cells depends on the predominance of meiosis-inducing or meiosis-inhibiting substance. Therefore, it seems likely that PSC are preserved in the rete testis epithelium, through which they migrate, and serve as a source of the regeneration of spermatogenesis.

Contemporary data on the mammalian testis as an unstable dynamic structure are not only of general biological but also of medical importance. Equilibrium in the processes of destruction and regeneration of the seminiferous tubules is the guarantee of reproductive success of the individuum, while a breakdown of this equilibrium leads to infertility.

The study of the regeneration potentials of the testis and, in particular, of the regeneration zone, the rete testis, seems to be promising. The secretory function of the rete testis and of its meiosis-inducing factors in particular are of interest for clinical andrology.

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