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Review

The immune privilege of testis and gravid uterus: Same difference?

Petra Arck [a,1], María Emilia Solano [a,1], Magdalena Walecki [b], Andreas Meinhardt [b,*]

[a] Laboratory for Experimental Feto-Maternal Medicine, Department of Obstetrics and Fetal Medicine, University Medical Center Hamburg, 20246 Hamburg, Germany
[b] Department of Anatomy and Cell Biology, Justus-Liebig-University of Giessen, 35385 Giessen, Germany

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ABSTRACT

The fetus in the gravid uterus and the developing spermatogenic cells in the adult testis both comprise special challenges for the host immune system. Protection of the neoantigens of the fetus and male germ cells from immune attack, defined as immune privilege, is fundamental for the propagation of species. Immune privilege is not simply the absence of leukocytes, but involves immune and non-immune cells acting synergistically together at multiple levels to create a unique tolerogenic environment. A number of the pathways are shared by the testis and gravid uterus. Amongst them steroid hormones, namely testosterone in the male and progesterone in the female, seem to function as key molecules that govern the local production of immunoregulatory factors which finally control the overall immune environment.

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1. Introduction

Founded by Medawar, Billingham and Owen over six decades ago (Billingham et al., 1953; Medawar, 1953; Owen, 1945), and fostered by technical improvements in the recent past, such as the availability of transgenic mouse models and the development of cell purification methods to perform *in vitro* studies using

* Corresponding author. Address: Department of Anatomy and Cell Biology, Justus-Liebig-University of Giessen, Aulweg 123, 35385 Giessen, Germany. Tel.: +49 641 9947024; fax: +49 641 9947029.
E-mail address: andreas.meinhardt@anatomie.med.uni-giessen.de (A. Meinhardt).
[1] Both authors contributed equally to this work.

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human tissue, the field of male and female reproductive immunology is thriving (Arck and Hecher, 2013; Meinhardt and Hedger, 2011; Tung and Teuscher, 1995). In both sexes and respective reproductive organs, key focus of research is given towards unraveling mechanisms involved in maintaining the 'immune privilege'. Such insights may then foster to understand the pathogenesis of diseases resulting from a disturbed immune privilege. In general, immune privilege manifests as tolerance for the otherwise highly immunogenic antigens of the fetus in the placenta and of developing germ cells in the testis.

In the female, research attention has been given to the maternal immune response, because the 'absence of rejection' of the 'fetal semi-allograft' during pregnancy has long been inexplicable from the perspective of the immunologist. We now know that the fetus cannot be directly compared to an allograft, as trophoblast cells in humans express a unique selection of class I human leukocyte antigen (HLA)-C and non-classical HLA-G and HLA-E antigens, whilst class I antigens HLA-A and HLA-B and class II antigens are absent (Apps et al., 2009; Kovats et al., 1990). Similarly, in mice, the distinct expression of the major histocompatibility complex (MHC) class I antigen in the absence of non-classical MHC antigens could be identified (Madeja et al., 2011). However, we have known for a long time that fetal antigens stimulate a cellular and humoral response of the maternal immune system (Van Rood et al., 1958). Direct contact between the maternal immune system and fetal antigens occurs at the feto-maternal interface, where maternal immune cells face trophoblast cells, or systemically upon shedding of placental debris into the maternal circulation. Moreover, fetal cells cross into the maternal system – a phenomenon called fetal microchimerism – and these cells can persist for decades (Seppanen et al., 2013).

In the testis, meiosis and subsequent cytodifferentiation events involved in spermiogenesis occur long after the establishment of systemic self-tolerance. Despite the expression of new auto-antigens unique to these cells, fertility is preserved because an immune response against these cells is not evoked (O'Rand and Romrell, 1977; Tung and Fritz, 1978). Testicular immune privilege was initially confirmed by the long periods of survival of foreign tissues transplanted into the testis. At the beginning of the 20th century, grafted ovarian tissue appeared not to degenerate after several months within rodent testes (Sand, 1919; Setchell, 1990). These findings were consolidated by hallmark studies in the 1970s, when a wide range of tissues that included the parathyroid gland, adrenal, skin, and pituitary survived for extended periods intratesticularly (Setchell, 1990). More recently supporting the concept, syngeneic and allogeneic transplantation of germs cells into recipient testis to restore fertility in impaired spermatogenesis did not result in immunorejection in various domestic species (Honaramooz and Yang, 2010). The exact mechanisms responsible are still under investigation, but the blood–testis barrier (BTB), the physical structure of the testis, immune cells with immunosuppressive characteristics in the interstitium, as well as the testicular somatic cells appear to cooperate in order to maintain and regulate testicular immune privilege. In this light it seems paradoxical that infection and inflammation are the second most important aetiology in male infertility, accounting for 13–14% of cases (Meinhardt and Hedger, 2011; Schuppe et al., 2008). It is now known that immune privilege in the testis and at the fetal-maternal interface is maintained as an active, regulated process where sex steroids, locally-produced immunoregulatory factors, structural component and a distinct phenotype of local leukocytes synergistically act together to create an environment that allows the successful generation of offspring and propagation of species.

2. Structural and cellular mechanism to preserve tolerance to developing germ cells in the testis

2.1. The role of the BTB

The principal functions of the testis are the synthesis and controlled release of androgens, with testosterone as the principal product (steroidogenesis), and the production of spermatozoa (spermatogenesis). Once liberated from the Sertoli cells into the lumen of the seminiferous epithelium, spermatozoa are passively transported in Sertoli cell secretions via the rete testis and efferent tubules to the epididymis. The epididymis, in turn, is responsible for the maturation, storage and concentration of spermatozoa. Testicular spermatozoa are unable to fertilize the egg in natural conception. This ability is acquired only after further maturation processes in the epididymis and finalized by biochemical modifications after ejaculation mediated by the seminal plasma and secretory products of the female reproductive tract. Advanced germ cells in the testis, as well as spermatozoa in the epididymis, are protected from immune cells by special barriers. The BTB and the blood–epididymis-barrier (BEB) create a unique microenvironment essential for spermatogenesis, maturation and storage inside these respective tissues. Both barriers limit the entry of leukocytes and antibodies into the luminal compartment and prevent contact of immunoglobulins and immune cells with auto-antigens and thereby protect germ cells and spermatozoa against immune attack (Cheng and Mruk, 2012; Cyr et al., 2007; Mital et al., 2011).

Between neighboring Sertoli cells, specialized tight junctions (TJ), basal ectoplasmic specialisations, gap junctions and desmosome-like junctions form the BTB, which separates the seminiferous epithelium into a basal and apical (adluminal) compartment and distinguishes this barrier from that of the brain, where junctions between endothelial cells constitute the blood–brain barrier (Cheng et al., 2011; Mruk and Cheng, 2012; Su et al., 2011). In the epididymal epithelium, TJ and adherens junctions connect principal cells in the apical region to form the BEB (Cyr et al., 2007; Gregory and Cyr, 2006; Hoffer and Hinton, 1984). The BTB is not an impermeable wall. Spermatogonia and preleptotene spermatocytes are located inside the basal compartment and pass through the BTB in a dynamic and highly regulated process involving a transient state where an additional barrier is formed underneath the migrating leptotene spermatocytes before the existing junctions above permit passage (Smith and Braun, 2012). Moreover, the basolateral and apical membranes of the Sertoli cells contain specific transporters that allow and control the entry and exit of specific molecules from the lumen of the seminiferous epithelium (Cheng et al., 2011; Cyr et al., 2007; Mruk and Cheng, 2012; Su et al., 2011). Immune cells, however, cannot penetrate the BTB and are found inside the seminiferous epithelium only in severely inflammatory condition when the barrier is dysfunctional. Vasectomy is a classic example where changes in immune tolerance can disrupt the integrity of the BTB and BEB. Vasectomized animals and humans show formation of autoreactive lymphocytes and antibodies against spermatozoa which could result in abnormal seminiferous tubules including penetration of immune cells through Sertoli cell tight junctions as well as epididymal granuloma formation (Haddad Kashani et al., 2013; Neaves, 1978; Qu et al., 2008; Samuel et al., 1975; Tung, 1975; Tung et al., 1981; Turner et al., 1979; Wheeler et al., 2011).

Originally assumed to be the principal mechanism for immune privilege in the testis, the passive protection provided by the BTB is now seen as only one of several, mostly active mechanism that all need to act together to establish this unique tolerogenic environment (Fig. 1). In support of this, a recent study using Sertoli