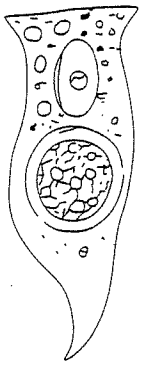
21 Sertoli Cell-peritubular Myoid Cell Interactions



Drawing (Fig. IIId) modified from Sertoli's original article (1865).

M. K. Skinner

University of California, San Franscisco

The peritubular myoid cell is the mesenchymal/stromal cell type that surrounds the seminiferous tubule and is in contact with the basal surface of the Sertoli cells [1-4]. Therefore, the Sertoli cells and peritubular cells interact to form the somatic element of the seminiferous tubule. Peritubular myoid cells have been shown to be an integral testicular component in all mammalian species investigated, including the rat [1, 2, 3, 5], rabbit [6], mouse [4, 7], hamster [8], reptiles [9], and humans [10]. Although differences in the thickness of the peritubular cell layers exist [1, 10], the widespread occurrence of this cell type suggests it is an important functional component of the mammalian testis. Several parameters of peritubular myoid cell biology are outlined in Table 1. Peritubular cells are derived from the mesenchyme in the fetal gonad and a mesenchymal stem cell population in the interstitial tissue of the postnatal testis [11]. Peritubular cells are localized surrounding the seminiferous tubule and can exist in multiple layers with the more differentiated myoid cells in direct contact with the basement membrane of the tubule. The peritubular cell is a fibroblastic/stromal cell with muscle characteristics. The peritubular cells appear to be involved in the movement of spermatozoa within the tubule lumen [9-13]. In addition, peritubular cells contributed to the structural integrity of the tubule. The cells contain androgen receptors and prepubertal peritubular cell differentiation appears to be under-androgen control [7, 14]. Peritubular cells secrete a number of substances including extracellular matrix components and growth factors.

Due to the integral association of Sertoli cells and peritubular myoid cells, it is not surprising that important cell-cell interactions have evolved to maintain testis and Sertoli cell function. The two major types of cell-cell interactions involved are environmental and regulatory cellular interactions [15, 16]. The environmental interactions are mediated primarily through the extracellular matrix that separates the basal surface of the Sertoli cell and the peritubular myoid cell. The regulatory interactions are mediated by the numerous secretory products produced by both cell types that can act as paracrine factors. Both these types of cellular interactions have been investigated and will be discussed [15, 16, 17].

Cell-cell Interactions

Interactions between peritubular cells and Sertoli cells provide an example of interactions between mesenchymal and epithelial cells. Mesenchymal cells have been shown to regulate the development of adjacent epithelial cells during embryogenesis for a number of different organs [18, 19]. Mesenchymal-epithelial interactions also may be required to maintain cellular differentiation at later stages of development including the adult [20, 21]. Observations to be discussed support the concept that the mesenchymally derived peritubular cells can influence and maintain the differentiation and phenotypes of the epithelial-like Sertoli cells. Prior to tubulogenesis in the fetal gonads, primordial germinal cells in the genital ridge of the male embryo associate with Sertoli cell precursors and become trapped in primary cords that are embedded in the interstitial mesenchyme [22-24]. Sertoli cells are thought to be derived from this embryonic mesenchyme but quickly lose mesenchymal characteristics and become epithelial-like cells [25, 26]. Peritubular cells also originate from the pluripotent urogenital mesenchyme and form a peritubular sheath around the cords early in development [11]. It is postulated that Sertoli cell migration during cord formation and tubulogenesis is dependent on the adjacent mesenchymally derived peritubular cells and the specific extracellular matrix components present [17, 27]. The role peritubular cells may have in the induction of Sertoli cell differentiation during fetal gonad development remains to be determined.

Peritubular cell-Sertoli cell interactions are also postulated to be an important mesenchymal-epithelial cell interaction in the adult to maintain Sertoli cell differentiation. As previously discussed, peritubular myoid cells provide structural integrity for the tubule and play a role in contraction of the tubule [1, 10] to promote movement of

Table 1
Parameters of Peritubular Myoid Cell Biology

cellular source	Pluripotent urogenital mesenchyme in the fetal gonad and interstitial mesenchymal stem cell population postnatally.
cellular localization	Surrounds the seminiferous tubule and separated from the basal surface of the Sertoli cell by a complex extracellular matrix (i.e., basement membrane).
cellular properties	A fibroblastic/stromal cell type that provides structural integrity for the tubule; cooperates in the formation of the tubule basement membrane; has contractile properties to allow movement of spermatozoa in the tubule lumen; and regulates Sertoli cell function, growth and differentiation.
hormonal regulation	Androgens promote prepubertal peritubular myoid cell differentiation in cooperation with FSH actions on Sertoli cells.
secretory products	Extracellular matrix components (e.g., fibronectin, collagen and proteoglycans); growth factors (e.g., TGFα, TGFß) and paracrine factors (e.g., PModS).

spermatozoa in the tubule lumen. This peritubular cell contractility is developmentally regulated [12] and associated with the stages of the seminiferous epithelium [13].

Environmental Interactions

One of the major cellular interactions between Sertoli cells and peritubular cells is an environmental interaction [16]. This cell-cell interaction is defined as being mediated by extracellular matrix components and cell adhesion molecules to influence the extracellular environment and morphology of a cell [15]. A complex extracellular matrix [i.e., basement membrane] is present between peritubular cells and the basal surface of Sertoli cells. This extracellular matrix contributes to the structural integrity of the tubule and acts as a partial permeability barrier or prefilter to help create the blood-testis barrier [28]. The basement-membrane of the seminiferous tubule is produced cooperatively by both peritubular cells and Sertoli cells [29, 30, 31]. Each of the cell types produce individual components of the extracellular matrix, Table 2. Sertoli cells produce laminin, collagen type I, collagen type IV [29] and proteoglycans which contain chondroitin and heparin [32]. Peritubular cells produce fibronectin [29, 33, 34], collagen type I [29] and proteoglycans that contain chondroitin [32]. In addition to the production of individual components of the basement membrane, both peritubular cells and Sertoli cells are required to be present to get a deposited extracellular matrix *in vitro* [29]. Coculture of peritubular cells and Sertoli cells was also found to increase Sertoli cell attachment and viability [35, 36]. Peritubular cell presence can influence the pattern and rate of Sertoli cell migration *in vitro* [27, 37, 38].

To confirm the importance of environmental interactions between peritubular cells and Sertoli cells, the effects of an extracellular matrix on Sertoli cell morphology and function were investigated *in vitro*. The presence of an extracellular matrix promoted a Sertoli cell histotype similar to that found *in vivo* with a columnar cell shape, nucleus near the basal surface of the cell and tight junctions between Sertoli cells [39, 41-43]. The extracellular matrix, however, was not found to have dramatic effects on Sertoli cell functions on a molecular level [43]. In addition to effects on cell morphology, extracellular matrix can also influence the polarized [basal versus adluminal] secretion of Sertoli cell products [44-47]. Peritubular cells were found to increase a Sertoli cell permeability barrier and alter polarized secretion of Sertoli cell products [48-52]. Further details of the effects of extracellular matrix on Sertoli cells are discussed in Chapters 5 and 6. Observations indicate that the environmental interactions between Sertoli cells and peritubular cells, mediated by the complex extracellular matrix between the cells, is essential for normal Sertoli cell physiology.

An aspect of this environmental interaction to consider is the degradation and turnover of the extracellular matrix between peritubular cells and Sertoli cells. The production of proteases and antiproteases can influence the composition and half-life of the extracellular matrix. As discussed more thoroughly in Chapter 9, Sertoli cells produce plasminogen activator [53] that can influence the degradation of the basement membrane of the tubule and junctional interactions between Sertoli cells. In contrast, peritubular cells produce an antiprotease that can inhibit plasminogen activator activity [54]. Therefore, Sertoli cells and peritubular cells can interact through the production of specific proteases and antiproteases to influence the turnover of the extracellular matrix between the cells and permeability barrier associated with the blood testis barrier [50].

Table 2
Extracellular Matrix Components Produced

Sertoli Cell	Peritubular Cell
Laminin	Fibronectin
Collagen I	Collagen I
Collagen IV	Chondroitin/Proteoglycans
Chondroitin Proteoglycan	Cell Chondroitin Proteoglycan
Hybrid Heparin/ Chondroitin Proteoglycan	
Cellular Heparin Proteoglycan	

Regulatory Interactions

This cell-cell interaction is defined as the ability of one cell type to produce a regulatory agent that can subsequently act on an adjacent cell type to influence cellular function and differentiation on a molecular level. As previously discussed, mesenchymal cells have been shown to regulate the differentiation of adjacent epithelial cells [19]. The ability of the mesenchymally derived peritubular myoid cell to regulate the epithelial-like Sertoli cell differentiation was initially investigated with the use of cocultures of the two cell types. The presence of peritubular cells was found to stimulate the production of ABP [35, 55] and transferrin by Sertoli cells [56]; alter the enzyme histochemistry of Sertoli cells [57]; and influence the vectorial secretion of proteins by Sertoli cells [48, 51, 58]. These observations implied that peritubular cells may produce regulatory agents to influence Sertoli cell function. Serum-free peritubular cell secreted proteins were found to stimulate the production of a number of proteins by Sertoli cells including ABP and transferrin [59-61]. Peritubular cells were shown to produce a non-mitogenic paracrine factor that modulates Sertoli cell function and has been termed PModS [59, 60]. PModS has been purified, characterized and found to have a more dramatic effect on Sertoli cell function *in vitro* than any individual regulatory agent previously identified, including FSH [62]. A combination of PModS and hormones [FSH, insulin and retinol] has an additive response with a ten-fold stimulation of Sertoli cell function. PModS stimulates transferrin and ABP gene expression with an

increase in messenger RNA levels [63]. The actions of PModS are in part mediated through the induction of early-event genes involving transcription factors. Subsequently these factors influence a set of genes associated with the differentiated state of the Sertoli cells such as transferrin gene expression [64]. PModS stimulates most functions associated with the differentiation of the cell, however, a cellular function that declines with differentiation, aromatase activity, is suppressed by PModS [65, 66]. Other functions independent of Sertoli cell differentiation, such as plasminogen activator production, are not influenced by PModS [60, 66]. PModS can influence Sertoli cell function at various stages of pubertal development and PModS is the only individual agent currently known to stimulate transferrin production by adult Sertoli cells in culture [67]. Observations imply that PModS may act as a mesenchymal inducer substance to promote Sertoli cell differentiation and maintain optimal cellular function in the adult. As previously discussed, peritubular cells contain the androgen receptor [68-70] at approximately the same level as Sertoli cells [70]. Peritubular myoid cell development appears to be dependent on androgens [7, 14] at the early stages of puberty [1, 3, 4, 71]. Peritubular cells respond to androgens *in vitro* [14, 59, 65, 72, 73] and PModS production by peritubular cells appears to be under androgen control [59, 73]. Therefore, PModS may provide an important mode of androgen action in the testis. Further analysis of the *in vivo* actions of PModS is required to determine the physiological importance of this testicular paracrine factor and its regulation of Sertoli cell function.

An additional category of paracrine factors that are produced by peritubular cells and can act on Sertoli cells are growth factors. Several growth factors are produced by peritubular cells including transforming growth factors alpha [TGFα] and beta [TGFß] and insulin-like growth factor type 1 [IGF1]. Peritubular cells express the epidermal growth factor [EGF]-like substance TGFα that binds to the EGF receptor and mimics the actions of EGF [74]. Although localization of the EGF receptor on Sertoli cells has been reported with immunocytochemistry [75], functional EGF receptors have not been detected [74]. EGF has been shown to influence several Sertoli cell functions [76, 77]; however, cellular functions such as transferrin production were not influenced by TGFα/EGF in highly purified preparations of Sertoli cells [74]. A peritubular cell contaminant in Sertoli cell preparations was found to indirectly mediate TGFα/EGF effects on Sertoli transferrin production [74]. Further examination of the actions of TGFα/EGF and localization of EGF receptor expression in the seminiferous tubule is required. Peritubular cells also produced TGFß [78] that can inhibit the actions of growth factors such as TGFα/EGF. TGFß was not found to affect several major Sertoli cell functions [78] but may influence selected functions such as lactate production [79]. Whether TGFß may act at specific stages of Sertoli cell development remains to be investigated. Peritubular cells also produce IGF-I [80, 81] that is known to influence a number of Sertoli cell functions. The somewhat ubiquitous presence of IGF-1 and high concentrations of IGF-1 in interstitial fluid question the importance of IGF-1 mediated interactions between peritubular cells and Sertoli cells. Therefore, although a number of growth factors are produced by peritubular cells, their role in the regulation of Sertoli cell growth and function remains to be elucidated.

The ability of Sertoli cells to regulate peritubular cell function and differentiation was first postulated from the observation that androgens alone could not promote peritubular cell differentiation. Gonadotropin action on Sertoli cells is also required to indirectly effect androgen induced peritubular cell differentiation [7]. This observation suggested that Sertoli cells may produce paracrine factor[s] that influence peritubular cell differentiation. Culture of peritubular cells on an extracellular matrix or in the presence of Sertoli cells promotes a peritubular cell morphology that is similar to that observed *in vivo* [82]. The only paracrine factors currently known to be produced by Sertoli cells that can influence peritubular cells are growth factors. Sertoli cells synthesize and secrete TGFα [74] that is postulated to be the EGF-like substance previously shown to be produced by Sertoli cells [83]. Peritubular cells have functional EGF/TGFα receptors and TGFα stimulates the growth of peritubular cells [74]. Sertoli cells also produce TGFß [78] that can inhibit the stimulatory actions of TGFα/EGF on peritubular cell growth. Therefore, the production of TGFα and TGFß by Sertoli cells may act as paracrine factors to regulate the growth of peritubular cells. TGFß can also influence peritubular cell differentiation and increase the production of specific proteins [78] such as the plasminogen activator inhibitor antiprotease [84]. TGFß may also promote peritubular cell chemotaxis to assist in the morphogenesis of the seminiferous tubule [34]. Further examination of secreted paracrine factors will likely reveal additional regulatory agents that can mediate Sertoli cell-peritubular cell interactions.

Summary

Interactions between Sertoli cells and peritubular cells are initiated at the early stages of gonadal development to assist in cord formation and tubulogenesis. This cell-cell interaction persists throughout development and the widespread occurrence of the peritubular myoid cell in mammalian species suggests that the peritubular cell is an integral testicular component involved in the control of Sertoli cell physiology. One of the main interactions between Sertoli cells and peritubular cells is the environmental interaction mediated by the basement membrane separating the two cell types. This environmental interaction is critical for the maintenance of the structural integrity of the seminiferous tubule; for the induction and maintenance of normal cell histotype and tubule morphol-

ogy; for the promotion of a polarized Sertoli cell structure and vectoral secretion; and for assistance in the creation of the blood-testis barrier. Both Sertoli cells and peritubular myoid cells cooperate in the production and formation of the seminiferous tubule basement membrane.

Another primary interaction between Sertoli cells and peritubular cells are regulatory interactions mediated by the production of specific paracrine factors (Fig. 1). Observations imply that the mesenchymally derived peritubular cells under androgen control produce a paracrine factor, termed PModS, that regulates the differentiation and functions of the adjacent epithelial-like Sertoli cells. This provides direct biochemical evidence for the previous hypothesis that steroids act on mesenchymal cells to promote the production of an inducer substance that regulates the differentiation of the adjacent epithelial cells [19]. This is postulated to be a general phenomenon present in most organs and the tissue specificity of PModS remains to be elucidated. PModS was found to have a more dramatic effect on Sertoli cell function *in vitro* than any previously identified regulatory agent, including FSH. Therefore, it is postulated that PModS mediated peritubular-Sertoli cell interactions will be important in the regulation of Sertoli cell differentiation and function as well as provide an important mode of androgen action in the testis. Future *in vivo* experiments involving PModS are required to determine the physiological importance of this cell-cell interaction. Additional paracrine factors that can mediate Sertoli cell-peritubular cell interactions are growth factors. Both Sertoli cells and peritubular cells produce TGFα, TGFß and IGF1. The peritubular cells, however, appeared to be the primary responsive cell type for TGFα and TGFß. Although several growth factors have been identified as potential paracrine factors, additional studies are now needed to understand the role these factors have in the regulation of cell growth and function.

In conclusion, the Sertoli cell and peritubular myoid cell have a intimate association throughout development that involves a number of critical cell-cell interactions. These cells form a functional unit that needs to be considered in understanding the maintenance and regulation of Sertoli cell biology. The Sertoli cell should not be considered an autonomous cell type, for the literature reviewed indicates that Sertoli cells are dependent on interactions with the adjacent peritubular myoid cell.

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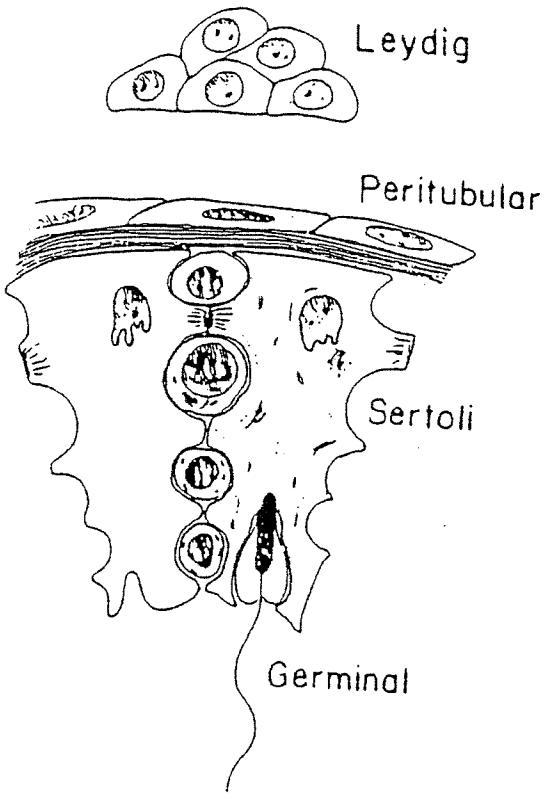

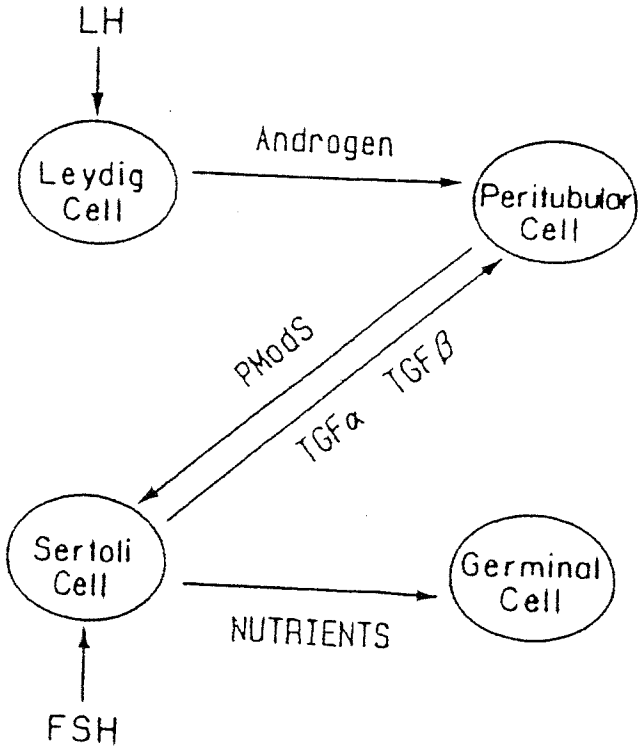

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Edited by

Lonnie D. Russell
Laboratory of Structural Biology
Department of Physiology
Southern Illinois University, School of Medicine
Carbondale, IL

Michael D. Griswold
Washington State University
Department of Biochemistry and Biophysics
Pullman, WA

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