CHAPTER

18

Sertoli Cell–Somatic Cell Interactions

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I. INTRODUCTION

This chapter will review the current understanding of Sertoli cell–somatic cell interactions in the testis. Several other chapters are dedicated to Sertoli cell–germ cell interactions, so this topic will not be emphasized here. The literature during the past decade will also be emphasized with earlier literature being primarily cited in the form of previous reviews.

A. Cell Biology

The testis is composed of a number of somatic cell types that create the morphological characteristics and endocrinology of the organ. The primary function of the testis is to support and control the process of germ cell development (i.e., spermatogenesis). The Sertoli cell is the primary somatic cell that forms the seminiferous tubule and provides the cytoarchitectural support for the developing spermatogenic cells (Fig. 18.1). The peritubular myoid cell is the mesenchymal-derived cell that surrounds the tubule and is separated from the Sertoli cell by a basement membrane. Within the interstitial space are the Leydig cells that are responsible for testosterone production (Fig. 18.1). Other somatic cells in the interstitium are the testicular macrophages and vascular endothelial cells.

The germ cell populations within the seminiferous tubule are spermatogonia, spermatocytes, spermatides, and the mature spermatozoa (Fig. 18.1). The process of germ cell development (i.e., spermatogenesis) is in large part supported by the Sertoli cells on both a nutritional and structural basis. Therefore, the regulation of Sertoli cell function is one of the most critical elements influencing spermatogenesis, testis function, and male reproduction. The critical regulatory steps within the testis that influence Sertoli cells and the process of spermatogenesis are cell–cell interactions between the various testicular cell types.

B. Cell–Cell Interactions

The evolution of multicellular organisms was prompted by the ability of different cell types to interact and develop higher order integrated functions. For this reason no cells in a multicellular organism or tissue are autonomous. Therefore, the different cell types within an organ (e.g., testis) form a functional unit with a network of cellular interactions essential for tissue function and the regulation of individual cell types. The testis provides an excellent example of how a network of cell–cell interactions controls cellular functions [1]. A large number of reviews have addressed different aspects of cell–cell interactions in the testis [1–12]. The majority have focused on Sertoli cell–germ cell interactions due to the critical function of the testis

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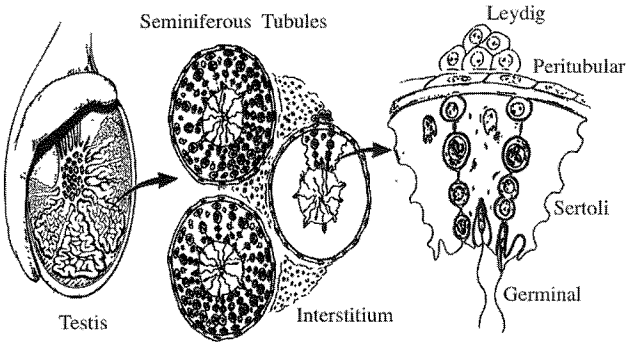

FIGURE 18.1 Cell biology of testis.

being linked to spermatogenesis [2]. Others have focused on somatic cell interactions [4, 6, 10] and specific cell types or factors [9, 12]. The primary cellular interactions in the testis to consider are between the somatic cells and germ cells (Fig. 18.2).

Somatic cell–germ cell interactions are primarily mediated by the Sertoli cell. The only somatic cell type in direct contact with the spermatogenic cells is the Sertoli cell. In addition, the blood–testis barrier created by tight junctional contacts between Sertoli cells results in a serum-free microenvironment within the tubule that other cell secretory components cannot penetrate [13–15]. Therefore, Sertoli cells are the primary cell supporting the spermatogenic process and interacting with germ cells (Fig. 18.2). Sertoli cell–spermatogenic cell interactions involve structural and environmental elements to support the complex cytoarchitecture between the cells [16–18]. Nutritional and regulatory substances are also required to provide nutrient support and regulatory control of the spermatogenic cells [1–3]. Several other chapters in this book review the details of Sertoli cell–germ cell interactions (Chapters 17 and 23) so the current chapter will focus on somatic cell interactions with the Sertoli cell. The majority of cellular interactions identified have the primary function of directly or indirectly influencing spermatogenesis through the Sertoli cell.

Somatic cell interactions with Sertoli cells primarily involve the Leydig cells and peritubular myoid cells (Fig. 18.2). The interactions between both of these cell types and Sertoli cells will be reviewed. Other cell types also exist in the testis that have not been extensively investigated but are likely to have critical cellular interactions. Therefore, a network of cell–cell interactions is essential for the maintenance and control of testis function [1–12]. To help clarify the variety of cellular interactions, several categories have been developed to classify different types of cell–cell interactions (Table 18.1) [1]. This categorization separates into three classes the functionally distinct types of cell–cell interactions. The first is termed *environmental* interactions. These types of interactions are mediated through the extracellular environment of the cell to influence the cytoarchitecture of the cell. An environmental cell–cell interaction is influenced by an extracellular matrix or cell adhesion molecules. The primary functional effect is an influence on cell shape, contact, and tissue organization. The second type of cell–cell interaction is a *nutritional* interaction. These interactions involve the delivery of essential nutrients between cells via energy metabolites and vitamins. The functional effect is to support cell viability and metabolism. The final category is termed a *regulatory* interaction (Table 18.1). This involves the

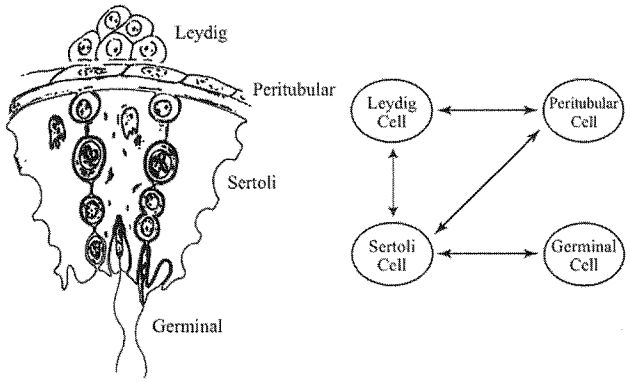

FIGURE 18.2 Cell–cell interactions in the testis.

TABLE 18.1 Categorization of Cell–Cell Interactions

Classification	Definition	Examples/mediators
Environmental	Interactions that influence the extracellular environment of the cell to affect cell contacts and cytoarchitecture	Extracellular matrix; cell adhesion molecules
Nutritional	Interactions involved in the delivery of essential nutrients between cells	Transfer of energy metabolites, metals, or vitamins
Regulatory	Agents provided by a cell that, through a signal transduction event, regulate another cell's function on a molecular level	Paracrine/autocrine factors; growth factors; differentiation factors; cytokines

production of a regulatory substance that is secreted and then, through a receptor-mediated signal transduction event, influences cellular functions on a molecular level. Examples of these regulatory substances are growth factors and cytokines [1]. This categorization of cell–cell interactions helps classify the different cellular interactions to be discussed as environmental, nutritional, or regulatory interactions (Table 18.1).

II. SERTOLI CELL–LEYDIG CELL INTERACTIONS

The Leydig cell [19] located in the interstitium of the testis was one of the first somatic cells identified as critical for Sertoli cell functions [1].

Environmental cell–cell interactions do not exist between Leydig cells and Sertoli cells. These cells are not in direct contact with each other nor do they have an extracellular matrix in common. The inability of these cells to physically interact indicates that direct environmental interactions between Sertoli cells and Leydig cells are not possible *in vivo*.

Nutritional cell–cell interactions also are negligible between Leydig cells and Sertoli cells. The blood–testis barrier prevents Leydig cell products from entering the seminiferous tubule. Both Sertoli cells and Leydig cells are in contact with the nutrient supply from vasculature in the interstitial space. Therefore, neither cell type is dependent on each other for nutrient supply or transport. Junctional contacts are not present between the cells to transfer metabolites either. Due to the separation and distinct cellular localization of Leydig cells and Sertoli cells (Figs. 18.1 and 18.2), only regulatory interactions occur between the cells.

Regulatory cell–cell interactions are critical between Leydig cells and Sertoli cells. The identification of androgen (i.e., testosterone) production by Leydig cells [20–26] and the ability of androgens to maintain the process of spermatogenesis [26–29] have led to observations that an essential regulatory interaction between Leydig cells and Sertoli cells is mediated by androgens. The gonadotropin leuteinizing hormone (LH) acts on Leydig cells to increase testosterone production and then acts on Sertoli cells to influence spermatogenesis [1]. This is a well-established regulatory cell–cell interaction between Leydig cells and Sertoli cells that is known to be essential for testis function. Although the androgen receptor is present in Sertoli cells, *in vitro* analysis has demonstrated minimal genes directly regulated by androgen. The specific mechanism of how androgen regulates Sertoli cell function remains to be elucidated. As discussed later, peritubular myoid cells also contain the androgen receptor and may help mediate androgen actions on the Sertoli cell [1]. Therefore, the regulatory interaction between Leydig cells and Sertoli cells mediated by androgens is well established, but the specific mechanism of how androgens act on Sertoli cells remains to be elucidated.

In addition to the steroidal substances produced by Leydig cells, a number of protein factors also are produced and can regulate Sertoli cell function *in vitro* [1]. Factors shown to be produced by Leydig cells that can potentially influence Sertoli cells include renin [30, 31], prodymorphin [32], oxytocin [33], pro-opiomelanocortin (POMC) peptides (β endorphin, αMSH, ACTH) [34–37], and growth hormone releasing hormone (GHRH) [38] (Table 18.2). The majority of these peptide factors have been shown to be produced by Leydig cells and have negligible effects on Sertoli cells in comparison to

TABLE 18.2 Sertoli Cell–Leydig Cell Regulatory Interactions

Potential paracrine factor	Site production	Site action	Actions/proposed function
Androgen	Leydig	Sertoli	Regulate/maintain function and differentiation
POMC peptides β endorphin, MSH, ACTH	Leydig	Sertoli	Decrease FSH actions; increase FSH actions
GNRH-like factor	Sertoli	Leydig	Decrease steroidogenesis
Estrogen	Sertoli	Leydig	Decrease steroidogenesis
IGF-1	Sertoli	Leydig	Increase steroidogenesis
TGFα	Sertoli	Leydig	Decrease steroidogenesis; increase growth
TGFβ	Sertoli	Leydig	Increase steroidogenesis
IL-1	Sertoli	Leydig	Decrease steroidogenesis
Inhibin	Sertoli	Leydig	Increase steroidogenesis
MIS	Sertoli	Leydig	Cell proliferation
SCF	Sertoli	Leydig	Cell proliferation
Dhh	Sertoli	Leydig	Cell proliferation

follicle-stimulating-hormone (FSH) actions. The *in vivo* function for these factors remains to be elucidated.

A number of studies have demonstrated that Sertoli cells appear to directly regulate Leydig cell function [1]. One approach that has been used is to selectively destroy Leydig cells and determine how Sertoli cells may influence their regeneration [39]. More direct studies have shown that Sertoli cell–secreted products can regulate Leydig cell steroidogenesis and function [40–42]. Recently, using patients with acquired hypogonadotropic hypogonadism and recombinant LH and FSH, observations support a role for local Sertoli cell–derived paracrine factors to influence Leydig cells [43]. Another recent *in vivo* experiment used the FSH receptor knockout mouse model and demonstrated that Leydig cell hormone responsiveness and function are impaired in the absence of normal Sertoli cells [44]. These two *in vivo* experiments provide further support that Sertoli cell products directly feed back and regulate Leydig cell function. The factors that mediate this response remain to be fully elucidated.

A number of regulatory factors have been shown to be produced by Sertoli cells that can act on Leydig cells and influence cellular function (Table 18.2) [1]. Estrogen produced by Sertoli cells has been shown to suppress androgen production by Leydig cells *in vivo* [45, 46], but the physiological relevance of this needs to be determined. In addition, mature adult animals have negligible estrogen production by Sertoli cells. Protein regulatory factors include gonadotropin releasing hormone (GnRH) [47–49], which has been shown to be expressed by and can act on Leydig cells *in vitro*. Insulin growth factor-1 (IGF-1) is produced by both cell types and can influence the functions of both cell types [50], but the high circulating levels of IGF-1 lead us to question the role of local production. Transforming growth factors alpha (TGFα) and beta (TGFβ) are also produced by Sertoli cells and can influence Leydig cells [1, 9, 51]. However, Leydig cell production of TGFβ isoforms and other cells in the interstitium questions the specificity of Sertoli cell–Leydig cell TGFα or TGFβ mediated interactions.

The interleukins have also been suggested as paracrine factors, but the specifics of cellular localization and action again question the specificity of such an interaction. Inhibin production by Sertoli cells has also been shown to influence Leydig cell function as a paracrine factor [1, 52–54]. Several recently identified protein factors shown to be produced by Sertoli cells that potentially affect Leydig cells have expanded the list in Table 18.2. Stem cell factor/kit ligand has been shown to be produced by Sertoli cells *in vitro* and can influence Leydig cell function [55]. Müllerian-inhibiting substance (MIS) is also produced by Sertoli cells, and observations in MIS knockout animals demonstrate that MIS can influence Leydig cell proliferation [56]. In contrast, MIS-overexpressing animals have Leydig cell hyperplasia, supporting a role for MIS mediated Sertoli cell–Leydig cell interactions. This is one of the few Sertoli cell factors shown *in vivo* to influence Leydig cells. Another interesting factor is desert hedgehog (Dhh), which has been shown to be expressed by Sertoli cells and acts on Leydig cells [57]. Whether this is only an early embryonic development phenotype or also an adult cell–cell interaction remains to be assessed. Additional protein factors have been postulated to mediate Sertoli cell–Leydig cell interactions, but require further investigation [58–60]. The majority of these factors have been shown to be expressed and act on Leydig cells *in vitro*, however, the physiological significance of the factors *in vivo* remains to be elucidated.

III. SERTOLI CELL–PERITUBULAR CELL INTERACTIONS

The peritubular myoid cell is the mesenchymal/stromal cell population that surrounds the seminiferous tubules and is adjacent to the basal surface of the Sertoli cell (Fig. 18.1) [1, 12, 61–64]. The peritubular cells and Sertoli cells are separated by a basement membrane and the two cell types make up the somatic elements of the seminiferous tubule. Peritubular cells have been shown to exist in all mammalian species examined [1, 12], with some differences in the number of layers of peritubular cells. Early in embryonic development at the time of testis determination, the peritubular cells are derived from mesenchymal cells within the mesonephros adjacent to the developing gonad. Mesonephros cells migrate into the gonad and promote cord formation, with Sertoli and primordial germ cell aggregates, to become the outer layer of cells and precursor peritubular cells. The developing peritubular cells appear to provide structural integrity to the developing testis cords and have a regulatory role in testis development. At the onset of puberty, androgen promotes the formation of peritubular myoid cells to develop smooth muscle characteristics [65, 66].

In the adult the peritubular cells have smooth muscle characteristics and are involved in contracting the seminiferous tubules and promoting movement of spermatozoa within the lumen of the tubules into the rat testis [1, 12, 66–68]. The contractility of the peritubular cells has been observed and postulated to be involved in spermatogenic cell movement within the tubule. The contractility of the peritubular cells appears to be developmentally regulated and stage specific [68].

Regulatory factors described later appear to influence this process. The integral association of Sertoli cells and peritubular myoid cells has promoted the evolution of critical cell–cell interactions between the cell populations. This is the classic example of a mesenchymal cell–epithelial cell interaction found to be important for the development of all tissues examined [69, 70]. The cellular interactions between peritubular cells and Sertoli cells are mediated by a variety of secretory products including extracellular matrix components and growth factors [1, 12].

Environmental cell–cell interactions are critical between peritubular cells and Sertoli cells [1, 12]. This environmental interaction is mediated by the extracellular matrix (i.e., basement membrane) separating the two cell populations. This basement membrane contributes to the structural integrity of the tubule and acts as a partial component (i.e., prefilter) to help develop the blood–testis barrier [71]. The extracellular matrix is produced cooperatively by both peritubular cells and Sertoli cells [1, 12, 72]. Each cell population produces different components of the extracellular matrix (Table 18.3). Sertoli cells have been shown to produce laminin, collagen I, collagen IV, and chondroitin proteoglycans [1, 12]. Peritubular cells produced fibronectin, collagen I, and chondroitin proteoglycans [1, 12]. The coculture of peritubular cells and Sertoli cells has been shown to influence the expression of these extracellular matrix components by the other cell type, suggesting a regulatory interaction between the cells in the control of extracellular matrix production [73–75].

The regulation of extracellular matrix degradation is also critical in the dynamic interactions between peritubular cells and Sertoli cells via the basement membrane. The expression of collagenases and glycosidases by the two cell populations [76, 77] suggests that interactions between the cell types is required [1, 12]. Abnormal expression and/or degradation of the extracellular matrix may be a factor in some forms of human male infertility [78]. In addition to the classic extracellular matrix components, other extracellular factors such as cell adhesion molecules (e.g., cadherins) also are likely involved in environmental peritubular and Sertoli cell interactions [79].

TABLE 18.3 Extracellular Matrix Components Produced

Sertoli cell	Peritubular cell
Laminin	Fibronectin
Collagen I	Collagen I
Collagen IV	Chondroitin proteoglycans
Chondroitin proteoglycan	Cell chondroitin proteoglycan
Heparin/chondroitin proteoglycan	
Cellular heparin proteoglycan	

Regulatory cell–cell interactions between peritubular cells and Sertoli cells are critical in the regulation of Sertoli cell function [1, 12]. Initial observations utilized cocultures of peritubular cells and Sertoli cells to demonstrate the ability of peritubular cells to influence Sertoli cell functions [80–83]. This influence has been confirmed more recently by demonstrating that the presence of peritubular cells in cocultures influences Sertoli glycosaminoglycan synthesis [84] and androgen binding protein (ABP) production [85]. Cocultures of the cells also influence cell proliferation and hormone responsiveness of the cells [86]. These observations have been extended by using peritubular cell conditioned medium to influence Sertoli cell functions *in vitro* [1, 12]. Serum-free conditioned medium from peritubular cells was found to stimulate the expression of a number of Sertoli cell gene products [87–89]. Subsequently a peritubular cell line was generated that produced conditioned medium with similar activity [90] and the same investigators found that stromal cell lines from several tissues also produced conditioned medium that can stimulate Sertoli cells [91].

The bioactive component within the peritubular cell conditioned medium was isolated and termed PModS [92, 93]. The PModS activity was found to influence a number of Sertoli cell functions [92–97] and utilized signal transduction pathways distinct from other hormones (e.g., FSH) known to influence Sertoli cells [98, 99]. The PModS activity has been isolated [93] but has not been fully characterized. Rigorous biochemical separation of individual peptides alters bioactivity, suggesting that a complex of multiple proteins is required for full bioactivity and this has complicated purification and cloning procedures. Verhoeven *et al.* [100] have shown that the PModS bioactivity cannot be attributed to other paracrine factors such as IGF-1, bFGF, EGF, TGFβ, NGF, PDGF heregulins, or neu differentiation factors [91, 100, 101]. PModS appears to be unique and remains to be characterized on a molecular level. The bioactivity associated with PModS suggests that it is a major regulatory factor stimulating Sertoli cell differentiation and mediating peritubular cell–Sertoli cell interactions.

Peritubular cells contain high levels of androgen receptor [102–104] and their development is dependent on androgen [65, 66]. Peritubular cells respond to androgens *in vitro* and can modulate Sertoli cell functions [87, 105–107]. The production of PModS appears to be stimulated by androgens and in part mediates

androgen effects on Sertoli cells via the peritubular cells [1, 12, 108]. Further analysis of androgen mediated peritubular cell–Sertoli cell interactions is needed to understand how androgens control Sertoli cell function and spermatogenesis.

A number of other potential paracrine factors have been shown to be produced by peritubular cells that can influence Sertoli cell function [1, 12]. Peritubular cells express the epidermal growth factor (EGF) family member TGFα [109, 110] and Sertoli cells do have low levels of the EGF receptor [110, 111]. TGFα does not have major effects on Sertoli cell functions [109, 110], but does influence specific functions such as lactate production [112]. Sertoli cells also produce TGFα [110] and the peritubular cells are stimulated to proliferate in response to TGFα/EGF. Therefore, the importance and specificity of TGFα mediated peritubular cell–Sertoli cell interactions remains to be determined. Peritubular cells also produce TGFβ [113–116], which can inhibit the actions of growth factors such as TGFα. Sertoli cells also produce TGFβ isoforms [115–117] such that the specificity of the cell–cell interaction is difficult to assess. Sertoli cells do not respond to TGFβ with any major functional changes measured, but peritubular cell proliferation is inhibited by TGFβ. Another growth factor produced by both cell types that can act on both cell types is IGF-1 [118, 119]. The degree to which IGF-1 acts as a paracrine factor between the cells is unclear.

Recently, peritubular cells have been shown to express activin, which can act on Sertoli cells to influence prepubertal cell proliferation [120]. This is a novel site for the expression of activin and it was found that Sertoli cells produced negligible levels. Therefore, activin may be a paracrine factor mediating peritubular cell–Sertoli cell interactions. Peritubular cells also produce heregulins or neu differentiation factors (NDF), NDFα, and NDFβ, which can act through receptors on Sertoli cells [101]. Specific actions on Sertoli cells involve slight stimulation in the expression of gene products such as transferrin, but not as dramatic as FSH or PModS [101]. Peritubular cells recently have been shown to produce leukemia inhibitory factor (LIF) that can act on early-stage spermatogenic cells (e.g., spermatogonia) and potentially on Sertoli cells [121]. Specific actions on Sertoli cells remain to be examined [121]. All of the factors just described are summarized in Table 18.4. They have the potential to be produced by peritubular cells and to modulate Sertoli cell functions. However, many do not have major effects on Sertoli cells, but yet to be identified specific functions may be the primary targets of action. The physiological significance of these factors *in vivo* remains to be determined.

TABLE 18.4 Major Sertoli Cell and Peritubular Cell Paracrine Regulatory Products

Potential paracrine factor	Site production	Site action	Action / proposed function
PModS	Peritubular	Sertoli	Paracrine regulatory agent
TGFα	Peritubular	Sertoli	Growth stimulation/ EGF-like
TGFβ	Both	Both	Growth inhibition
IGF-I	Both	Both	Maintenance cell growth/ differentiation
NDFα/NDFβ	Peritubular	Sertoli	Increase differentiation
LIF	Peritubular	Gonia/ Sertoli	Growth stimulation
Activin	Peritubular	Sertoli	Growth stimulation
NT3	Sertoli	Peritubular	Embryonic chemotactic factor
bFGF	Sertoli	Peritubular	Growth stimulation

The ability of Sertoli cells to regulate peritubular cells was postulated from the observation that androgens alone could not promote peritubular cell differentiation, but gonadotropins acting indirectly through Sertoli cells were also required [67]. Several paracrine factors discussed are produced by both Sertoli cells and peritubular cells, which can act on peritubular cells including TGFα, TGFβ, and IGF-1 [110, 115–120]. The degree to which these factors act as paracrine mediators of Sertoli cell–peritubular cell interactions versus autocrine actions on each other remains to be determined. During early embryonic development, upon male sex determination, the Sertoli cells produce neurotrophin 3 (NT-3), which can act as a chemotactic factor and promote migration of the precursor peritubular cells into the testis and promote cord formation for testis sex differentiation [122]. This is perhaps the first Sertoli cell–peritubular cell interaction during development [122], but this NT-3 paracrine interaction does not appear to be critical in the adult testis. Other factors produced by Sertoli cells that have the capacity to influence peritubular cells include basic fibroblast growth factor (bFGF), which is produced by Sertoli cells in response to FSH and can promote the proliferation of peritubular cells [123]. As shown in Table 18.4, several factors may act as potential paracrine factors to mediate Sertoli cell–peritubular cell interactions that require further investigation to assess the importance of these cell–cell interactions.

Upon differentiation at the onset of puberty by androgens and gonadotropin actions on Sertoli cells, peritubular cells develop smooth muscle characteristics to become peritubular myoid cells [66, 67]. These cells have the ability to contract and move spermatozoa through the seminiferous tubules to the rete [67, 68]. Factors that may be involved in the contraction of peritubular cells have been identified. The peritubular cells have receptors and can respond to endothelins (ET) [124–126], vasopressin [127] and platelet-derived growth factor beta (PDGFβ) [128] to induce contractility of the seminiferous tubules. These factors are likely important for testis function, but the site of production of these factors remains to be elucidated. Sertoli cells have not been shown to be the site for production of these factors. As discussed later, other testicular cells in the interstitium may be involved (e.g., endothelial cells), but this remains to be investigated.

IV. OTHER SOMATIC CELL–SERTOLI CELL INTERACTIONS

Other testicular somatic cells that may interact with Sertoli cells are primarily located within the interstitium. A cell population that makes up approximately 20% of the interstitial cell population is the testicular macrophage [129]. These testicular macrophages appear to be unique and have been shown to interact with Leydig cells to influence steroidogenesis and Leydig cell function [129–132]. Factors mediating the macrophage–Leydig cell interaction include steroids [132] and tumor necrosis factor (TNF) [129, 131]. No major factors produced by macrophages have been shown to influence Sertoli cell functions. However, macrophage migration inhibitory factor (MIF) was found to influence peritubular cell calcium mobilization [133]. The ability of MIF to act on peritubular cells and indirectly affect Sertoli cells is a possibility that needs to be examined.

Another cell type in the interstitium is lymphocytes, which may have a role in the immunology of the testis [134], but factors that specifically influence Sertoli cell function have not been identified. Vascular and lymphatic endothelial cells are also relatively abundant in the interstitium of the testis [135]. As previously reviewed [1], the vasculature associates with the outer wall of the seminiferous tubules associated with peritubular cells and the lymphatic endothelial cells can envelop Leydig cells. Specific products of these endothelin cell populations that affect Sertoli cells have not been identified. However, it is anticipated that endothelial cell products such as endothelials may influence peritubular cells. Sertoli cell products that could influence endothelial cells such as bFGF [123] remain to be investigated. It is likely these other testicular cell populations have a role in testis cell–cell interactions, but such a role remains to be elucidated.

V. SUMMARY

In considering the categories of cell–cell interactions, the only major environmental somatic cell–Sertoli cell interactions are between peritubular cells and Sertoli cells. This environmental interaction is mediated by a basement membrane between the cells that is produced cooperatively by both cell types. This environmental interaction is critical for maintaining the structural integrity of the seminiferous tubules and polarized epithelial morphology of the Sertoli cells. Other somatic cells in the testis (e.g., Leydig cell) are not in direct contact with Sertoli cells and, hence, there are no environmental interactions between the cells. Because the blood–testis barrier encompasses the developing spermatogenic cells and Sertoli cells, no major nutritional interactions are required between the somatic cells. Nutritional interactions are essential between Sertoli cells and germ cells, but because the basal surface of the Sertoli cells and the other testicular somatic cells are in contact with serum derived nutrients, no major somatic cell–Sertoli cell nutritional interactions are required.

Regulatory cell–cell interactions between somatic cells and Sertoli cells are prevalent and required for normal testis function. These regulatory interactions are generally mediated by secreted factors that, through receptor mediated events, influence cellular function on a molecular level. The number of regulatory agents identified to potentially mediate somatic cell–Sertoli cell interactions has increased during the past decade [1, 12] and are summarized in Tables 18.2 and 18.4. The focus of the current review was on peritubular cell–Sertoli cell interactions and Leydig cell–Sertoli cell interactions. The majority of research has been on these somatic cell interactions. Although other somatic cells (e.g., macrophages and endothelial cells) are present in the interstitium, specific interactions with Sertoli cells have not been rigorously investigated. Further characterization of the network of regulatory cell–cell interactions is required to understand the development and control of testis function.

The list of potential paracrine regulatory factors has increased as shown in Tables 18.2 and 18.4. All of these factors have been shown to be produced by a specific testicular cell type, to have receptors, and to act potentially on another cell type. Some of the factors do have

major actions on the target cell to influence cell growth or differentiation. Others have negligible effects on the target cell considering the specific functions investigated. The importance of these specific regulatory factors remains to be determined and needs to be the primary focus of further analysis of the factor or cell–cell interaction. Relatively few factors have been shown to be critical on a physiological level. Examples are the production of MIS and inhibin by Sertoli cells and actions on adult Leydig cells. Through transgenic and knockout mouse models, the importance of these specific cell–cell interactions and paracrine factors has been established. Future analysis of specific regulatory factors needs to be extended to assess the physiological role of the cell–cell interaction of interest.

The classic endocrine concept and the control of tissue function need to be extended to effects on local cell–cell interactions. We now know that the ability of an endocrine agent to act on a specific cell type promotes a cascade of local cell–cell interactions. Understanding the local network of cell–cell interactions and the ability of endocrine agents to modulate them is essential to elucidate the endocrinology of a tissue. The two primary endocrine agents to influence testis function are the gonadotropins LH and FSH (Fig. 18.3). LH acts on Leydig cells to promote the production of androgen, which then acts on Sertoli cells and peritubular cells. The degree to which direct versus peritubular cell–mediated androgen actions have on Sertoli cell function is currently unclear. Very few genes have been shown to be directly responsive to androgens in Sertoli cells, such that direct molecular actions of androgens in Sertoli cells are uncertain at this time. Peritubular cell secreting products (e.g., PModS) are androgen responsive and have dramatic effects on the Sertoli cell, but the molecular characteristics of this factor remain to be elucidated. Therefore, the actions of androgens in the testis likely involve both Leydig cell–Sertoli cell and peritubular cell–Sertoli cell interactions, but the specific action of androgens requires further investigations. FSH acts on Sertoli cells and also likely promotes cell–cell interactions with other cells in the testis such as Leydig cells (Fig. 18.3). Although the ability of Sertoli cells to respond to FSH and influence Leydig cell function (e.g., steroidogenesis) is well established, the specific factors that modulate this interaction require further investigation. Elucidation of the cell–cell interactions in the testis and the ability of the endocrine system (e.g., gonadotropins) to regulate these interactions will provide the next phase of our understanding of male reproductive endocrinology and the regulation of testis biology.

As previously discussed the majority of research on cell–cell interactions in the testis has been focused on Sertoli cell–germ cell interactions. Due to the complex architectural support and unique microenvironment within the seminiferous tubule, the spermatogenic cells are dependent on normal and optimal Sertoli cell function. In the mammalian testis, the existence of the blood–testis barrier and germ cell syncytium indicates the complexity and integrated dependence the germ cells have on the Sertoli cell. Any factor that regulates or influences Sertoli cell function indirectly controls spermatogenesis and male fertility. Therefore, local somatic cell interactions within the testis have a critical role in the regulation of testis function and male reproduction. Both Leydig cell and peritubular cell interactions with Sertoli cells are now known to be essential for Sertoli cell development and function. The complex network of testis cell–cell interactions is starting to be elucidated, but significant future research is needed to identify and characterize the specific paracrine factors and the actions of these factors on the various cell types. This will be a fruitful area of research for the future and assist in the identification of pharmaceutical agents to treat testis pathophysiologies such as male infertility and develop male contraceptive agents.

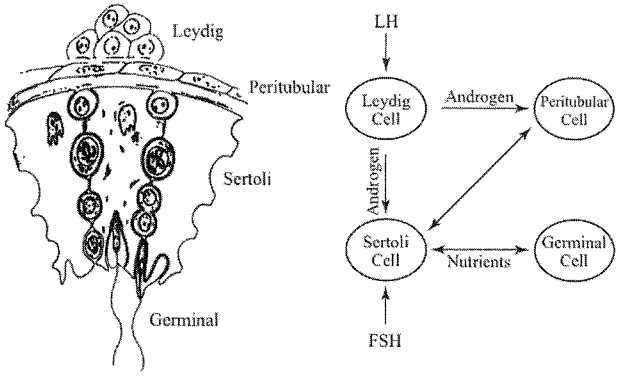

FIGURE 18.3 Endocrine cellular interactions.

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