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Chapter 342

Cell–Cell Signaling in the Testis and Ovary

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Introduction

The evolution of multicellular organisms was facilitated by the ability of different cells to communicate and interact. This cell–cell signaling generates a higher order functional state than that possible with individual cell types. Cell–cell interactions have become an essential requirement for the physiology of any organ or tissue and are critical in the regulation of any cell's biology. For this reason, elaborate networks of cell–cell interactions have evolved to control the development and maintenance of tissue functions. The focus of the current chapter is on the regulatory signals that mediate cell–cell interactions in the testis and ovary.

Several previous reviews have discussed the cell–cell interactions in the testis [1, 2] and ovary [3, 4]. These include a focus on secretory products of the various cell types and actions of individual regulatory molecules. The current chapters briefly discusses the advances in cell–cell signaling in these organs.

Many different types of cell–cell interactions are required for the control of tissue physiology and cellular functions. These have been previously categorized into regulatory, nutritional, and environmental classifications [1]. Regulatory interactions are generally mediated by extracellular factors that through receptor-mediated events cause a signaling event to modulate cell functions. Nutritional interactions generally involve the transport of nutritional substances, energy metabolites, or metabolic substrates between cells. Environmental interactions involve extracellular environmental factors that affect cell contacts and cytoarchitecture. The focus of this chapter is primarily on regulatory-type interactions that involve a receptor-mediated signaling event. It is this type of cellular signaling that regulates a cell's function on a molecular level. The factors involved are generally paracrine and autocrine agents such as growth factors and cytokines.

Both the testis and ovary are endocrine organs. Endocrine hormones from the pituitary [i.e., gonadotropins, follicle-stimulating hormone (FSH), and luteinizing hormone (LH)] act on various cell types to influence cellular functions and cell–cell interactions. The influence these endocrine hormones have on cell–cell signaling events is briefly reviewed. The testis and ovary are also sites for the production of hormones. These gonadal hormones have an endocrine role in regulating a wide variety of tissues in the body, but can also act in a paracrine manner within the gonads to influence cell–cell signaling and cellular functions. Again the role these gonadal steroids and peptide hormones play in the regulation of cell–cell signaling within the gonad are discussed in this chapter.

Cell–Cell Signaling in the Testis

Testis Cell Biology

The adult testis is a complex organ that is composed of seminiferous tubules that are enclosed by a surrounding interstitium. The seminiferous tubules are the site of spermatogenesis where germ cells develop into spermatozoa in close interaction with Sertoli cells (Fig. 1). The Sertoli cell is an important testicular somatic cell that controls the germ cell environment by the secretion and transport of nutrients and regulatory factors. The Sertoli cells [5] form the basal and apical surface of the seminiferous tubule and provide the cytoarchitectural arrangements for the developing germ cells [6]. Tight junctional complexes between the Sertoli cells contribute to the maintenance of a blood–testis barrier [7] and create a unique environment within the tubule [8]. The structure of the Sertoli cell has

been reviewed by several investigators (for a review, see [6]), and a three-dimensional reconstruction has increased appreciation for the complexity of the structural relationships between cells within the seminiferous tubule [9]. The biochemical analysis of the Sertoli cell has primarily focused on an examination of the components synthesized and secreted by the cell. The list of products includes steroids such as estradiol [10], metabolites such as lactate [11], and various proteins such as plasminogen activator [12], testicular transferrin [13], testicular ceruloplasmin [14], inhibin, and others (for a review, see [2]). The majority of the secretory products are hormonally regulated and provide useful markers of Sertoli cell differentiation.

Surrounding the basal surface of the Sertoli cells is a layer of peritubular myoid cells (Fig. 1) that function in contraction of the tubule. The peritubular cells surround and form the exterior wall of the seminiferous tubule. Peritubular cells are mesenchymally derived cells that secrete fibronectin [15] and several extracellular matrix components [16]. Both the peritubular and the Sertoli cells form the basement membrane surrounding the seminiferous tubule and their interactions are important in germ cell development.

The interstitial space around the seminiferous tubules contains another somatic cell type, the Leydig cell (Fig. 1), which is responsible for testosterone production. Leydig cells have a major influence on spermatogenesis through the actions of testosterone on both the seminiferous tubule and the pituitary. Although the Leydig cell has numerous secretory products [1], testosterone is the most significant secretory product of the cells. Thus, interaction of all three somatic cells—Sertoli, peritubular, and Leydig—are important for regulation of normal spermatogenic function in the testis (for a review, see [1]).

Testis Development

The process of fetal testis formation occurs late in embryonic development (embryonic day 13 where plug date = E0 (E13) in the rat) and is initiated by migration of primordial germ cells, first from the yolk sac to the hindgut and then from the hindgut to the genital ridge. The first phase of migration is proposed to occur through a mechanism in which transient interactions between fibronectin molecules on the extracellular matrix and corresponding receptors on the primordial germ cells cause movement of the germ cells. The second migration is thought to occur by the release of chemoattractant factors from the genital ridge. Kit ligand and its receptor c-kit appear to be involved first in the migration to the genital ridge and later in the proliferation of germ cells after colonization of the genital ridge. Expression of kit ligand has been localized to cells along the migratory pathway, and c-kit is expressed by primordial germ cells at this time in development (for a review, see [17]). After migration, germ cell differentiation in the gonad is dependent on locally produced factors such as prostaglandins [18] and the induction of specific transcription factors [19]. It is a complex network of cellular interactions that control testis and germ cell development.

The gonad is bipotential after germ cell migration and can be distinguished morphologically from the adjoining mesonephros (E12 in rat), but cannot be identified as an ovary or a testis. A variety of genes such as SRY, SOX-9, SF1, and DMRT1 are involved in the transcriptional induction of sex determination and testis development [20-27]. Two morphological events occur early on E13 to alter the bipotential gonad. First, Sertoli cells, which are proposed to be the first cell in the testis to differentiate, aggregate around primordial germ cells [28, 29]. Secondly, migration of mesenchymal cells occurs from the adjoining mesonephros into the developing gonad to surround the Sertoli cell–germinal cell aggregates. The migrating population of cells has been speculated to be preperitubular cells [30, 31, 32]. The mechanism for this migration is unknown, but a signal from the testis is proposed to occur and cause cell migration. This is postulated due to the observation that ovarian mesonephros can also be stimulated to initiate cell migration after close interaction with a developing testis [33]. In addition, using an organ culture system in which mesonephros and embryonic testis were separated by an embryonic ovary, mesonephros cells migrated through the ovary to the testis [30]. Therefore, during early testis development Sertoli–peritubular cell interactions may allow for cord formation to occur. The cords develop neonatally into seminiferous cords and at the onset of puberty develop into the seminiferous tubules. Sertoli cells have been postulated to originate from stem cells in the coelomic epithelium at an early stage in gonadal development. Other cells that may potentially originate from the coelomic epithelium are interstitial or Leydig cells [34].

Seminiferous cords, precursors of adult seminiferous tubules, form as the Sertoli cell–primordial germ cell aggregates become more organized and are fully surrounded by mesenchymal cells. The formation of the seminiferous cords (E14 in rat) is a critical event in the morphogenesis of the testis since this is the first indication of male sex differentiation [26]. During the process of cord formation, Sertoli cells undergo a number of morphological changes including a change in expression of mesenchymal to epithelial cell markers (vimentin to cytokeratin; [35]), a change in expression of cytokeratin 19 to cytokeratin 18 (cytokeratin 21 expressed in ovary; [36]), and expression of Müllerian inhibiting substance (MIS), which inhibits the development of the Mullerian duct, the precursor of the female uterus, cervix, fallopian tubes, and upper vagina [37, 38, 39].

Outside of the seminiferous cords, the peritubular layer of cells becomes identifiable from the interstitium or Leydig cells at E15 [38] and 3 β HSD production is detected after E15 [39]. Leydig cells have been hypothesized to differentiate after cord formation and Sertoli cell differentiation is completed [40, 41]. This is important because the production of testosterone and androgens by the Leydig cells has been demonstrated to stabilize the Wolffian duct derivatives, hence allowing normal male duct development [42, 43]. Therefore, appropriate differentiation of somatic cell types in the testis around the time of cord formation is crucial not only to the normal development of the testis, but also for the continued presence of the Wolffian duct and normal male reproductive tract development.

Testis Cell–Cell Interactions

Table I outlines a number of the factors produced locally in the testis that mediate cell–cell signaling events in the control of spermatogenesis and testis function. Several reviews address the topic of cell–cell interactions in the testis and the control of spermatogenesis [1, 2, 44, 45]. Recent observations are cited next.

Transforming growth factor α (TGF-α) is an epidermal growth factor (EGF) superfamily member and is produced by Sertoli, peritubular, and Leydig cells. TGF-α can act as a growth stimulator on all major cell types in the testis [46, 47, 48]. As with TGF-α, transforming growth factor β (TGF-β) is also produced by Sertoli, peritubular, and Leydig cells and can act on all the major cells in the testis [49, 50, 51, 52, 53]. In contrast, TGF-β primarily acts as a growth inhibitor and can stimulate a variety of differentiated functions. Another example of a factor that is produced by all of the somatic cells and acts on all major cell types in the testis is insulin-like growth factor 1 (IGF-1) [54, 55, 56]. IGF-1 plays a general role in regulation of the growth cycle and homeostasis of the testis. A related family member, IGF-2, mediates paracrine interactions between Sertoli cells and germ cells [57]. These are examples of regulatory factors that mediate cell–cell signaling events between the majority of the cell types in the testis.

Several interleukins (IL-1 α, IL-1 β, IL-6) are produced in the testis by Sertoli cells and Leydig cells. These interleukins can regulate Sertoli, Leydig, and germ cell growth and differentiated functions [58-65]. Although further analysis is needed, interleukins appear to mediate primarily Sertoli–germ cell and Leydig–Sertoli cell interactions, as well as autocrine roles for these factors.

Several hormonal factors produced in the testis also act locally within the testis as paracrine factors. An example is inhibin and its related peptide activin [66, 67, 68]. Inhibin is primarily produced by Sertoli cells and can act on germ cells and Leydig cells. Further investigation of the actions of inhibin and related compounds within the testis is needed. Another major endocrine factor produced in the testis is testosterone by Leydig cells that can in turn act on Sertoli, peritubular, and Leydig cells [69]. Androgens have a major role in the maintenance of testis function by inducing cellular differentiated functions.

Fibroblast growth factor (FGF) family members have been shown to be expressed in the testis and regulate the growth and differentiation of a variety of cells [70-75]. FGF receptors are predominant in germ cells and Leydig cells, but are also present in the other cell types [71]. FGF-14 has recently been shown to be expressed in spermatocytes and may influence adjacent Sertoli or peritubular cells. FGF-9 null mutants also suggest a role in early testis development, but remain to be investigated in the adult [74]. Basic FGF is produced by Sertoli cells and can also act on the other cells [75]. The variety of FGF ligands and receptors role in testis function remains to be elucidated.

Platelet-derived growth factor (PDGF) has been shown to be produced by Sertoli cells and influence peritubular cells and Leydig cells [76, 77, 78, 79]. Although PDGF in the adult may also be produced by the Leydig cell [76], it appears to be a factor produced within the seminiferous tubules that acts on adjacent peritubular cells and Leydig cells. Another factor that is only produced by Sertoli cells is stem cell factor (SCF)/kit ligand (KL), which has a direct role in regulating spermatogonial cell proliferation [80, 81, 82, 83]. Mutations in SCF/KL block the process of spermatogenesis. This is one of the better examples of a somatic–germ cell interaction.

Leukemia inhibitory factor (LIF) is a pleiotropic cytokine that influences stem cell growth and survival. LIF is predominantly produced by peritubular cells, but also by Sertoli cells and Leydig cells [84]. Although LIF has been shown to influence germ cell growth and survival [85], other functions remain to be elucidated.

Tumor necrosis factors (TNF-α) and related ligands (TRAIL) are produced in the testis by germ cells and Leydig cells. Both TNF and TRAIL have a role in regulating germ cells and Sertoli cells [86, 87, 88]. The function of these regulatory factors for the germ cells may be more for apoptosis regulation, unlike for Sertoli cells, which may be

more for cellular differentiated functions.

Hepatocyte growth factor (HGF) is generally a mesenchymal-derived factor that acts on adjacent epithelial cells. HGF was found to be expressed by the mesenchymal-derived peritubular cells, and its receptor (c-met) was found on both Sertoli cells and Leydig cells [89, 90, 91]. Interestingly, c-met was also found in the peritubular cells. HGF may also have a role in seminiferous tubule formation [91].

Several neurotropins have been shown to be expressed in the testis. Nerve growth factor (NGF) is produced by the germ cells in the adult and appears to act on the Sertoli cells [1]. In embryonic development neurotropin-3 is expressed by Sertoli cells and acts on the migrating mesonephros cells to promote seminiferous cord formation [92]. Further investigations are needed to elucidate the roles of these and other neurotropins in the testis.

Additional factors are anticipated to be identified and have critical roles in testis development. Recently identified factors such as erythropoietin expression in Sertoli cells and peritubular cells [93], or interferon-gamma actions on Sertoli cells [94], or relaxin-like factor (RLF) expression by Leydig cells [95] are all likely to have roles in cell–cell signaling in the testis. These and other factors such as PModS [96] need to be further investigated to determine their roles in testis cell biology. Clearly, a complex network of cell–cell signaling events and factors regulates testis function and spermatogenesis.

Cell–Cell Signaling in the Ovary

Ovarian Cell Biology

The ability of somatic cells in the gonad to control and maintain the process of gametogenesis is an essential requirement for reproduction. The basic functional unit in the ovary is the ovarian follicle, which is composed of somatic cells and the developing oocyte (Fig. 2). The two primary somatic cell types in the ovarian follicle are the theca cells and granulosa cells. These two somatic cell types are the site of action and synthesis of a number of hormones that promote complex regulation of follicular development. The proliferation of these two cell types is in part responsible for the growth of the ovarian follicle. The elucidation of factors that control ovarian somatic cell growth and development is critical to an understanding of ovarian physiology.

Granulosa cells are the primary cell type in the ovary that provides the physical support and microenvironment required for the developing oocyte (Fig. 2). Granulosa cells are an actively differentiating cell with several distinct populations. Alteration in cellular differentiation is required during folliculogenesis from a primordial stage of development through ovulation to a luteal stage of development. Regulation of granulosa cell cytodifferentiation requires the actions of a number of hormones and growth factors. Specific receptors have been demonstrated on granulosa cells for the gonadotropins FSH [97] and LH [98]. In addition, receptors have been found for factors such as EGF [99, 100], insulin-like growth factor [101], and anti-Mullerian hormone [102]. The actions of these hormones and growth factors on granulosa cells vary with the functional marker being examined and the stage of differentiation. The biosynthesis of two important ovarian steroids, estradiol and progesterone, is a primary function of the granulosa cells in species such as the bovine, human, and rodent. Estrogen biosynthesis is controlled by the enzyme aromatase, which requires androgen as a substrate. Progesterone is synthesized from cholesterol by a series of steroidogenic enzymes. As the follicle develops, granulosa cells differentiate and estrogen biosynthesis increases. FSH promotes this follicular development via the actions of cAMP. As the follicle reaches stages before ovulation, the granulosa cells develop an increased capacity to synthesize and secrete progestins under the control of LH. In contrast, the early follicle stage (e.g., primordial) granulosa appear hormone independent and are nonsteroidogenic.

Another important cell type in the ovary is the ovarian theca cell (Fig. 2). These are differentiated stromal cells that surround the follicle and have also been termed theca interstitial cells [103]. The inner layer of cells, the theca interna, has a basement membrane separating it from the outermost layer of mural granulosa cells. One of the major functions of theca cells in species such as the bovine, human, and rodent is the secretion of androgens [104]. Theca cells respond to LH by increasing the production of androgens from cholesterol [105] (Fig. 2). Theca cells also produce progestins under gonadotropin control [106, 107, 108, 109]. Other secretory products of theca cells have not been thoroughly investigated. At the primordial stage no theca cells are present; however, during transition to the primary stage, theca cells (i.e., precursor cells) are recruited to the follicle [3].

Follicle Growth and Differentiation (Folliculogenesis)

The control of ovarian follicle development is complex and involves multiple waves of growth [110]. In both the human and bovine ovary, two or three waves of follicles are initiated to develop in a single ovarian cycle [111, 112]. For both of these species, follicles expand from several millimeters to up to 2 cm during this process. A combination of granulosa cell growth, theca cell growth, and antrum formation results in the expansion of the ovarian follicle. Although rapid stimulation of cell growth is required for the ovulatory follicle to develop, the vast majority of follicles undergo atresia in which cell growth is arrested at various stages of follicle development. Hormones such as estrogen and FSH have been shown to promote follicle cell growth *in vivo*, however, these hormones alone do not stimulate growth of ovarian cells *in vitro* [113]. The possibility that these hormones may act indirectly through the local production of growth factors is proposed for later stages of development. Therefore, the regulation of ovarian cell growth is a complex process that requires an array of externally and locally derived regulatory agents. Interactions between theca cells, granulosa cells, and oocytes are required for follicular maturation [114]. The individual processes such as dominant follicle selection [115] and follicle cell apoptosis/ atresia [116, 117] also require integrated cell–cell interactions. A variety of specific growth factors produced in the follicle appear to mediate many of these cellular interactions in later stages of follicle development.

Ovarian Cell–Cell Interactions

Table II outlines a number of the factors produced locally in the ovary that mediate cell–cell signaling events in the control of follicle development and ovarian function. Several reviews address the topic of cell–cell interactions in the ovary and the control of follicle development [3, 4, 118, 119]. Recent observations are cited next.

TGF-α has been shown to be produced by theca cells [120, 121, 122, 123] and to influence the growth of both theca and granulosa cells [120, 124]. Several *in vivo* experiments have shown that TGF-α can influence follicle development [125, 126]. TGF-α appears to be important for follicle development and involves theca cell–granulosa cell interactions. TGF-α has also been localized to isolated granulosa cells but appears predominantly in theca cells [127]. The primary function of TGF-α is growth stimulation. TGF-β is also predominately produced by theca cells [128], but is produced by isolated granulosa cells in selected follicle stages [129]. TGF-α and TGF-β differentially regulate granulosa and theca cell differentiated functions and growth [130, 131, 132]. Although TGF-β inhibits TGF-α growth stimulation, TGF-β also can influence cell functions.

HGF is produced by theca cells and acts on granulosa cells to promote cell proliferation and function [133, 134]. This is an excellent example of the role HGF plays in mediating mesenchymal–epithelial interactions in tissues. Interestingly, SCF/KL produced by the granulosa cells can feed back on the theca to regulate HGF production [135, 136]. In a similar manner, keratinocyte growth factor (KGF) is produced by theca cells and acts on granulosa cells to regulate cell growth [137, 138]. KGF is also expressed in the corpus luteum [139]. SCF/ KL was found to also stimulate KGF expression by theca [135]. These factors reflect the importance of the theca cell in the regulation of follicle growth.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) was found to primarily be expressed by theca cells and most cells in the ovary [140, 141]. The GM-CSF can influence granulosa cell growth and function. Null mice had abnormal follicle development that suggested effects on the local cell–cell interactions [141].

Apoptosis is an essential aspect of follicle development and ovarian function. The vast majority of follicles undergo atresia and apoptosis. TNF has been shown to be produced by most cell types in the ovary associated with apoptosis [142, 143, 144, 145]. TNF can act on all cell types and induce apoptosis and growth regulation. Another death ligand that binds death receptors to induce apoptosis is Fas ligand. Fas is also produced by all the cells associated with apoptosis and acts to promote apoptosis in the atretic follicles [146, 147, 148, 149]. These signaling molecules are essential for ovarian function in the promotion of follicle atresia during folliculogenesis.

Nerve growth factor (NGF) was found to be expressed by theca cells and act on theca and granulosa cells [150]. The localization and actions of NGF suggest a potentially important role at the time of ovulation [150]. Other neurotropins (e.g., NT-4) are also expressed at various stages of ovary development [151] and require further investigation.

Basic fibroblast growth factor (bFGF) has been shown to be expressed by granulosa cells and to a lesser extent by theca cells [152]. Basic FGF can regulate both granulosa cell and theca cell growth and differentiated functions [153, 154]. During follicle development the expression of bFGF changes, being initially in the oocyte at the primordial stage and then in the granulosa in the primary stage [3]. The role of other FGF family members has not been rigorously addressed.

Growth differentiation factor 9 (GDF-9) is a member of the TGF-β superfamily and is specifically localized to the oocyte. GDF-9 can act on both granulosa cells and theca cells to regulate steroidogenesis and differentiated functions [155, 156, 157, 158, 159]. The actions of GDF-9 are follicle stage specific and it appears to be expressed in a variety of species. GDF-9 may regulate the expression of other paracrine factors such as SCF/KL in the developing follicle [159]. This is one of the few oocyte-specific products identified to be involved in cell–cell signaling in the ovary.

Another factor specifically expressed in the oocyte that appears to regulate granulosa cell function is bone morphogenic protein 15 (BMP-15) [160, 161]. BMP-15 and GDF-9 may act synergistically during follicle development. Other BMP family members include BMP-4 and -7, which are primarily localized in the theca cells and appear to act on the granulosa cells [162]; BMP-2, which acts on granulosa cells [163]; and BMP-6, which is also expressed in the oocyte and acts on the granulosa cells [164]. The BMP family of growth factors are TGF-β superfamily members and appear to be critical to follicle development [165, 166].

SCF/KL is produced by the granulosa cell and acts on the oocyte and theca cells [167, 168, 169, 170, 171]. The null mutant suggests a critical role in oocyte viability and recruitment of primordial follicles. In addition to the role in granulosa–oocyte interactions, granulosa KL also influences theca cell function and development [170]. Oocytes appear to have a regulatory role in influencing the expression of KL by granulosa cells [171]. As found in the testis, this is a critical somatic–germ cell interaction. Another factor found to be expressed by granulosa cells that regulates oocytes is LIF [172, 173]. LIF is also produced by stromal cells in the ovary. This action of LIF in mediating granulosa–oocyte interactions is supported by levels of LIF that increase in follicular fluid as the follicle develops [172, 173].

Vascular endothelial growth factor (VEGF) has a critical role in angiogenesis. This process is important for developing follicles past the primary stage of development. VEGF is primarily expressed in theca cells and to a reduced level by granulosa cells [174, 175, 176, 177, 178]. VEGF has a major role in acting on endothelial cells to promote angiogenesis, but also can influence granulosa cell functions [175]. This cell–cell signaling event controlled by VEGF is critical for follicle development.

Cytokines as seen with the testis also influence ovary function. Interleukins 1, 6, and 8 have all been shown to regulate follicle development. IL-1 is expressed by the granulosa and affects granulosa function [179, 180]. IL-8 is primarily expressed by the theca and to a lesser extent by granulosa and influences cellular function [181]. IL-6 is also expressed by granulosa cells an acts on various cells, including granulosa [182]. Further investigation of the specific roles of these and other member of the interleukin family is needed.

IGF-1 also has a role in the ovarian follicle [183]. IGF-1 is expressed by granulosa and theca cells and acts on the oocyte, granulosa, and theca cells [183, 184, 185]. Mice with null mutations in IGF-1 have impaired follicle development [184]. Other members of the family IGF-2 and the IGF-binding proteins also have a critical role in follicle development [185].

Inhibin also has a paracrine role in the developing follicle. Inhibin is primarily produced by the granulosa cells and acts on the oocyte, theca, and granulosa cells [186, 187]. Related family members such as the activins are also anticipated to have similar roles. This is distinct from the roles these factors have in the endocrine system.

Additional signaling factors are anticipated to be essential for ovarian function and follicle development. One example is anti-Müllerian hormone (AMH), which is expressed by the granulosa cells, but specific biological function remains to be determined [188]. AMH may have a role as a negative regulator of oocyte viability or of primordial follicle development. Local steroid production is also expected to influence the network of local cell–cell signaling events. This includes both androgen and estrogen production.

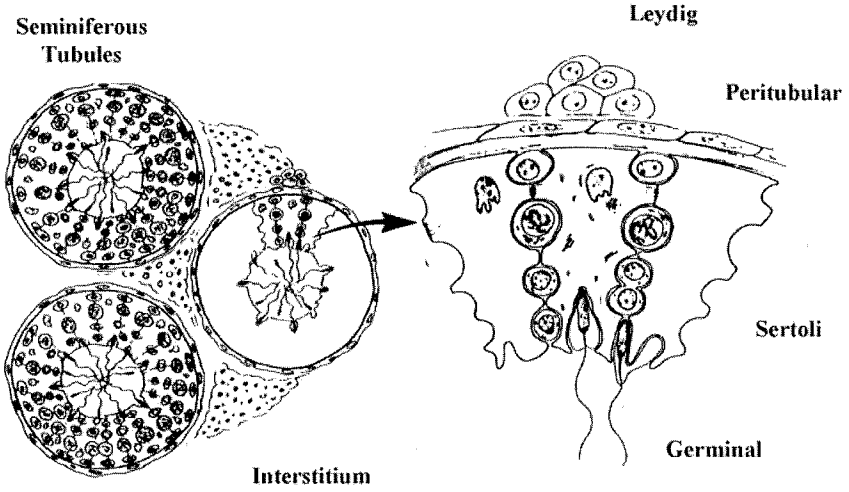
Conclusions

The preceding descriptive discussion of cell–cell signaling in the testis and ovary demonstrate a growing complexity in the networks of cellular interactions and factors. It is anticipated that some of these factors will have compensatory roles to ensure growth and differentiation of the tissues. The list of factors provided is likely to be only partially complete and more will be added as investigation of cell–cell interactions in the gonads expands. Currently, we are primarily in the identification of the site of production and action research phase. The functions of some individual factors are also being analyzed. However, the next research phase of cell–cell signaling will involve a more systems biology type of approach that should tie together all potential interactions and provide more insight into the regulation of testis and ovary function.

The specific cell–cell signaling events identified are shown in most cases to change during development. The requirements and physiology of the embryonic testis and ovary are very different from the adult. Another research area to expand is the elucidation of cell–cell signaling at these different stages of development.

A comparison of the cell–cell signaling events between the testis and ovary is very useful. Some signaling events are the same, for example, the role SCF has in mediating direct somatic–germ cell interaction or the role HGF and KGF play in mesenchymal–epithelial cell interactions. A direct correlation among the cell–cell interactions of the testis and ovary will be invaluable in elucidating the system biology approach to understand gonadal function.

Elucidation of cell–cell signaling events is required for the future development of therapeutic agents to control fertility and treat reproductive diseases. By understanding the signaling events involved in testis and ovarian function, basic information is provided to design more effective therapeutics. Significant advances are anticipated to be in the area of contraceptive and fertility agent development and treatment of diseases such as polycystic ovarian disease or premature ovarian failure. Although an understanding of the intracellular signaling events is essential for understanding how a factor acts, the elucidation of the network of extracellular signaling molecules that regulates a cells function is essential to our understanding of how a tissue or organism functions.



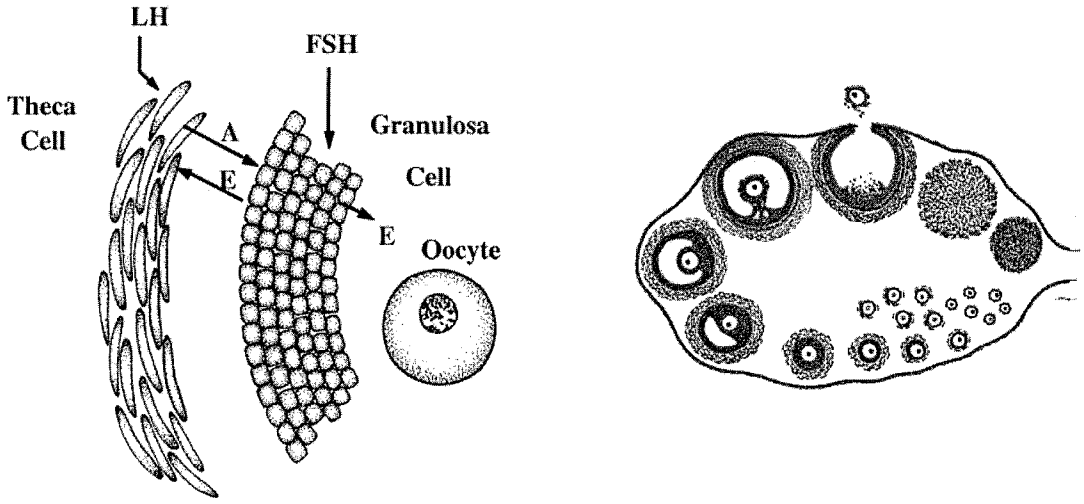


Table I Cell–Cell Signaling Factors in the Testis

Signaling factor	Site production	Site action	Functions	Ref
Transforming growth factor α (TGFα)	Sertoli Peritubular Leydig	Sertoli Peritubular Leydig Germ	Growth stimulation	46–48
Transforming growth factor β (TGFβ)	Sertoli Peritubular Leydig	Sertoli Peritubular Leydig Germ	Growth inhibition Differentiation stimulation	49–53
Insulin-like growth factor (IGF1)	Sertoli Peritubular Leydig	Sertoli Peritubular Leydig Germ	Homeostasis and DNA synthesis	54–56
Interleukin-s	Sertoli Leydig	Sertoli Leydig Germ	Growth regulation Cellular differentiation	58–65
Inhibin	Sertoli	Germ Leydig	Cellular differentiation	66–68
Androgen	Leydig	Sertoli Peributular Leydig	Cellular differentiation	69
Fibroblast growth factors	Sertoli Germ Leydig	Germ Peritubular Sertoli Leydig	Growth stimulation	70–75
Platelet derived growth factor (PDGF)	Sertoli	Peritubular Leydig	Growth stimulation Cellular differentiation	76–79
Stem cell factor/Kit ligand (SCF/KL)	Sertoli	Germ	Growth stimulation	80–83
Leukemia inhibitory factor (LIF)	Peritubular Sertoli Leydig	Germ	Growth stimulation Cell survival	84–85
Tumor necrosis factors	Germ Leydig	Sertoli Germ	Cellular apoptosis Cellular differentiation	86–88
Hepatocyte growth factor (HGF)	Peritubular	Leydig Peritubular Sertoli	Growth stimulation Tubule formation	89–91
Neurotropins	Germ Sertoli	Sertoli Peritubular	Growth stimulation Cell migration Cellular differentiation	1,92

Table II Cell–Cell Signaling Factors in the Ovary

Signaling factor	Site production	Site action	Functions	Ref
Transforming growth factor α (TGFα)	Theca	Granulosa Theca	Growth stimulation	120–127
Transforming growth factor β (TGFβ)	Theca Granulosa	Granulosa Theca	Growth inhibition Cellular differentiation	128–132
Hepatocyte growth factor (HGF)	Theca	Granulosa	Growth stimulation	133–136
Keratocyte growth factor (KGF)	Theca	Granulosa	Growth stimulation	137–139
Colony stimulating factor (CSF)	Theca	Granulosa Theca	Growth regulation	140–141
Tumor necrosis factor (TNF)	Granulosa Theca Oocyte	Oocyte Granulosa Theca	Apoptosis Growth regulation	142–145
Fas ligand	Granulosa Theca Oocyte	Oocyte Granulosa Theca	Apoptosis	146–149
Nerve growth factor (NGF)	Theca	Granulosa Theca	Growth stimulation Ovulation	150
Fibroblast growth factor (bFGF)	Granulosa Theca Oocyte	Granulosa Theca	Growth stimulation	152–154
Growth differentiation factor -9 (GDF-9)	Oocyte	Granulosa Theca	Cellular differentiation	155–159
Bone morphogenic poteins (BMP)	Oocyte Theca	Granulosa Theca	Cellular differentiation	160–166
Kit Ligand/Stem cell factor (KL)	Granulosa	Oocyte Theca	Growth stimulation	167–171
Leukemia inhbitory factor (LIF)	Granulosa	Oocyte Theca	Growth stimulation Cellular differentiation	172–173
Vascular endothelial factor (VEGF)	Theca Granulosa	Edothelium Granulosa	Angiogenesis	174–178
Interleukins	Granulosa Theca	Granulosa Theca	Cellular differentiation	179–182
Insulin-Like growth factor (IGF-1)	Granulosa Theca	Oocyte Granulosa Theca	Growth stimulation Cellular differentiation	183–185
Inhibin	Granulosa	Oocyte Theca Granulosa	Cellular differentiation	186–187