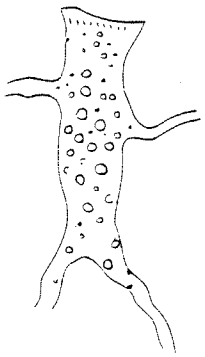
10 Secretion of Growth Factors and Other Regulatory Factors



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

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The Sertoli cell population forms a secretory epithelium that produce several categories of proteins. As previously discussed (see Ch. 7), these secretory products include transport and binding proteins; proteases and antiproteases; and extracellular matrix components (1, 2). These products have critical roles in maintaining the nutritional microenvironment and cytoarchitecture of the seminiferous tubule. Another category of secreted proteins are regulatory agents that are defined as substances that are secreted and subsequently bind to specific receptors to induce a signal transduction event to influence the function, growth or differentiation of a cell on a molecular level (2). These regulatory agents can act as autocrine factors in that they are produced by Sertoli cells and subsequently act on neighboring Sertoli cells. Alternatively, the regulatory agents can act as paracrine factors in that they are produced by Sertoli cells and act on adjacent cell types such as Leydig cells, peritubular myoid cells or developing germinal cells.

One of the major sub-categories of regulatory agents produced by Sertoli cells are growth factors. The properties of a number of the major growth factors identified in the testis are shown in Table 1. Observations regarding the production of the growth factors by Sertoli cells and subsequent actions are reviewed below. The major function for a growth factor is to regulate cell proliferation within a tissue. The ability of a growth factor to influence the differentiated function of a cell may be indirectly related to effects on cell proliferation. Previously growth and differentiation have been shown to be inversely related (3). Therefore, cells produce another sub-category of regulatory agents that are primarily involved in the control of cellular function and differentiation independent of cell growth. The production of a number of these hormone-like substances by Sertoli cells will also be discussed below. The production of these two types of regulatory agents provides a mechanism for Sertoli cells to maintain and control cell proliferation and differentiated function at various stages of development. The production of these factors by Sertoli cells can influence Sertoli cell growth and differentiation, as well as the other cell types within the testis.

Growth Factors

Precise growth regulation is necessary for the development of the testis and maintenance of spermatogenesis (4). During fetal development all testicular cell types proliferate. The Leydig, peritubular, and Sertoli cells also actively grow in the prepubertal testis. Sertoli cells terminally differentiate and cease to divide at an early stage in pubertal development (5). Peritubular cells continue to proliferate in the adult with a defined turnover rate (6). Leydig cells appear in late fetal development and continue to grow and differentiate before puberty (7) and have a slowed but continuous rate of growth in the adult (6, 8). Germinal cells exhibit a delayed growth pattern, but some development begins shortly after birth when gonadocytes mitotically divide forming spermatogonia. At the onset of puberty germinal cell mitosis and meiosis begins initiating "waves" of spermatogenic cell proliferation. The control of cell proliferation of these various cell types throughout testis development requires the local production and action of various growth factors. Some of these growth factors will likely be Sertoli cell products.

Table 1
Properties and Nomenclature of Several Common Growth Factors

Growth factor		Approx. size (kDa)	Examples of physiological action	Receptor(s)
Insulin-like Growth Factor-I	IGF-I	7.5	skeletal growth	IGF-I receptor
Insulin-like Growth Factor-II	IGF-II	7.5	fetal development	IGF-I and IGF-II
Epidermal Growth Factor	EGF	6	tissue growth	EGF receptor
Transforming Growth Factor Alpha	TGF-α	5	tissue growth	EGF receptor
Transforming Growth Factor Beta(s)	TGF-ß	25/dimer	growth inhibition/tissue repair	TGF-ß, type 1, 2, and 3 receptors
Fibroblast Growth Factor	FGF	17	angiogenesis/tissue growth	FGF receptor
Nerve Growth Factor	NGF	13	neuronal development	NGF receptor
Interleukin-1	IL-1	17	immune response/ inflammation	IL-1 receptor

Insulin-Like Growth Factors

The insulin-like growth factors (IGF) have structural similarity to insulin (9). IGF-I was previously termed somatomedin C and is considered an essential progression factor for cell growth and DNA synthesis. Production and secretion of IGF-I by the liver accounts for the high levels of IGF-I in serum and interstitial fluid (10). Another member of this family is IGF-II that may act as a growth factor during fetal development.

IGF-I mRNA was originally identified in whole testis (11). All testicular somatic cells have been shown to express and produce IGF-I (12-14) including Sertoli cells (15, 16). In addition, all testicular cell types appear to also respond to IGF. Both Sertoli and germinal cells contain receptors for IGF-I (17-19). IGF-I stimulates DNA synthesis (20) as well as increases transferrin and lactate production in immature Sertoli cells (19, 21). The presence of the blood-testis barrier prevents interstitial fluid-derived IGF-I from directly affecting sequestered germ cells. Thus, Sertoli cell production of IGF-I may allow for paracrine control of germinal cell proliferation. This is further suggested by the presence of IGF-I receptors and immunoreactivity in spermatocyctes and spermatids (22). Local production of IGF binding proteins may act as a mechanism to concentrate local levels of this factor (13). Although IGF-I may influence cell function, proposed cell-cell interactions involving IGF-I need to be questioned since all the somatic cell types are exposed to high levels of liver derived IGF-I present in interstitial fluid.

IGF-II has also been suggested to be involved in local interactions because both Sertoli and germinal cells contain IGF-II receptors (23). IGF-II, however, does not appear to be expressed locally (24). IGF-II appears to have the ability to stimulate Sertoli cell differentiation, perhaps by cross-reacting with IGF-I receptors (20). Neither IGF-I nor IGF-II have been demonstrated to act directly on germ cells and further study is necessary to understand the physiological importance of these factors.

Transforming Growth Factor-α/Epidermal Growth Factor

Transforming growth factor-alpha (TGF-α) is a structurally related member of the epidermal growth factor (EGF) family (25, 26). Due to similar protein structure, these factors act at the same receptor to stimulate cell growth (27). TGF-α is synthesized as a transmembrane precursor which may activate EGF receptors on neighboring cells or be proteolytically cleaved to release mature peptide. TGF-α is produced by non-transformed cells and appears to have an important role as a growth regulator in normal tissues.

EGF has been implicated to be involved in the maintenance of spermatogenesis (28). Removal of the salivary glands, a major site of EGF productions, from mice show 50% reduction of mature sperm and EGF replacement returns spermatogenesis to normal levels (29). Circulating concentrations of EGF, however, are considered too low to mediate endocrine effects (30). EGF does not appear to be expressed in the rodent testis (31). EGF actions may be mediated by a locally produced EGF-like factor that blocks EGF from binding to its receptor (32). TGF-α is an EGF-like factor that is expressed by both peritubular cells and Sertoli cells, but not germinal cells (31). TGF-α has also been immunohistochemically detected in Leydig cells (33). Scatchard analysis indicates that high-affinity EGF receptors are present on peritubular cells, but not Sertoli cells (31). TGF-α stimulates DNA synthesis and cell division in peritubular cells, but not Sertoli cells (31). Both peritubular and Sertoli cell production of TGF-α may contribute to peritubular cell growth. At present it is unclear whether Sertoli or germinal cells contain functional receptors for EGF. Scatchard analysis and histochemistry do not indicate the presence of receptors on differentiated Sertoli cells (31, 34). However, another report presents immunological evidence that Sertoli cells may contain EGF receptors (35). Sertoli cells and germinal cells were recently found to contain very low, but detectable, levels of EGF-receptor mRNA (36). Recent literature suggests EGF may alter Sertoli cell function, including stimulation of lactate and inhibin production (37, 38). However, some actions of TGF-α/EGF on Sertoli cells may be mediated indirectly by peritubular cell production of other factors (31). The role of TGF-α in Sertoli cell-germ cell interactions is not clear. Speculation that developing spermatogonia respond to TGF-α (39) might provide an appropriate mechanism for Sertoli cells to influence spermatogonial growth. Two models utilizing TGF-α in transgenic mice, which overexpress TGF-α in the testis, show no abnormal features in testis morphology or spermatogenesis (36, 40, 41).

Transforming Growth Factor-ß

Transforming growth factor-beta (TGF-ß) is a multifunctional regulatory molecule which can stimulate or inhibit aspects of cellular growth and differentiation (42). TGF-ß acts by inhibiting the actions of growth factors such as EGF/TGF-α. TGF-ß can also promote cellular differentiation, extracellular matrix production and chemotaxis. Different sub-types of TGF-ß (TGF-ß1, TGF-ß2, and TGF-ß3 in mammals) are produced as latent secreted precursors. Most cell types contain receptors for this ubiquitous factor.

TGF-ß may act as a growth inhibitor in the testis to prevent spermatogonial growth before puberty and to terminate growth of the maturing Sertoli cell. Studies suggest that TGF-ß is produced by Sertoli cells and may be modulated by gonadotrophins (39, 43, 44). Interestingly, the testis appears to be one of the few tissues where TGF-$ß_3$ is expressed (45). Sertoli cells express all three forms of TGF-ß (46). Sertoli cell TGF-ß1 expression is high in prepubertal animals and declines during puberty to low levels in the adult. TGF-ß2 expression is also high in prepubertal animals and at the onset of puberty in response to FSH is reduced to very low levels (46). TGF-ß3 interest-

ingly is primarily expressed by the Sertoli cells for a short period during development at the onset of puberty until spermatogenesis is inhibited, days 10-15 of rat testis development (46). This pattern of TGF-ß expression by Sertoli cells during development suggests a potential Sertoli-germinal cell interactions. Sertoli cell TGF-ß2 expression may be needed to prevent prepubertal germinal cell mitosis. Sertoli cell TGFß-3 expression may be needed to induce spermatogonial development and/or Sertoli cell differentiation at the onset of the spermatogenesis. Although germinal cells contain TGF-ß receptors (47), the specific functions of the Sertoli cell TGF-ß expression on germinal cells remains to be elucidated.

TGF-ß does not appear to dramatically affect immature Sertoli cell growth or cellular differentiation (43). However, TGF-ß may be important in regulating environmental interactions necessary for spermatogenesis. TGF-ß increases Sertoli cell plasminogen activator production that may be involved in tissue remodeling for germ cell development (48). Due to the antagonistic growth regulation of TGF-α by TGF-ß, the local production of TGF-ß may act to limit TGF-α actions in the tubule.

Peritubular cells also express and produce TGF-ß (43). TGF-ß acts as a growth inhibitor for peritubular cells and blocks TGF-induced peritubular proliferation (46). A number of observations suggest that TGF-ß is important in peritubular cell differentiation. TGF-ß may regulate the production of extracellular matrix components by peritubular cells (43) and increase production of plasminogen activator inhibitor type 1 (PAI-1) by peritubular cells. TGF-ß induces peritubular cell contractility that is potentially required for sperm transport in the tubule (49) and for migration and colony formation of peritubular cells in culture (43). TGF-ß-stimulated chemotaxis may be a mechanism to recruit non-differentiated fibroblasts to the exterior of the tubule in development. Therefore, TGF-ß may influence morphogenesis and structural formation of the seminiferous tubule. The possibility that Sertoli cell-derived TGF-ß may act as a paracrine factor for peritubular cells remains to be determined.

TGF-ß also may regulate Leydig cell growth and differentiation. Similar to TGF-α, TGF-ß inhibits LH-induced steroidogenesis, possibly by decreasing LH receptor binding (50, 51). During development, the growth of maturing Leydig cells slows and may require a growth inhibitor like TGF-ß. TGF-ß decreases DNA synthesis in a transformed Leydig cell line; however, TGF-ß has little affect on Leydig growth in primary culture (44, 52). The local production of TGF-ß in the interstitium needs to be determined to elucidate the importance of Sertoli cell derived TGF-ß for Sertoli-Leydig cell interactions.

Fibroblast Growth Factor

Fibroblast growth factor (FGF) can influence aspects of both cellular growth and differentiation (53). Aside from growth stimulation, recent studies indicate that FGF may play a critical role in angiogenesis and tissue repair. FGF has many cellular targets and widespread tissue distribution and is important in many organ systems, including the testis (54).

Basic FGF (bFGF) has been isolated from bovine and human testis (55-56). Sertoli cells appear to produce an FGF-like substance (57). Recently, Sertoli cells have been shown to express the FGF gene and secrete basic FGF in response to FSH (58). The angiogenic properties of FGF suggest that this factor may be involved in vascularization of this tissue during development. FGF is mitogenic for immature Sertoli cells (57, 59). The ability of FSH to stimulate Sertoli cell growth may be mediated indirectly by the ability of FSH to stimulate FGF production (58). Basic FGF may also be important in tissue remodeling for spermatogenesis in its ability to stimulate Sertoli cell plasminogen activator activity (59). FGF action on germ cells has not been demonstrated; however, immunolocalization of bFGF in germ cells has been demonstrated (60). Further molecular studies are necessary to localize cellular expression of FGF and its receptor to determine the potential function of Sertoli derived FGF.

Nerve Growth Factor

Nerve growth factor (NGF) is another mitogen which may mediate intercellular interactions involving growth (61). NGF is important for the development and maintenance of sympathetic neurons in the peripheral nervous system and cholinergic neurons in the central nervous system. NGF expression typically correlates with the amount of sympathetic innervation. Surprisingly, NGF is expressed at higher levels than expected in testosterone-dependent organs, including the testis.

NGF mRNA is present in spermatocytes and early spermatids of the adult mouse (62, 63), while Sertoli cells express NGF receptor (64). Hypophysectomy increases NGF receptor mRNA in whole testis, while luteinizing hormone (LH), but not FSH replacement returns expression to basal levels. This observation suggests that testosterone down-regulates the receptor and may be an example of a gene that is negatively regulated by androgens. Interestingly, levels of NGF receptor may also correlate with stage VI-VIII of the seminiferous cycle, perhaps stimulating the Sertoli cell for later steps in germ cell maturation. The function of NGF in the testis is not known and requires further study.

Interleukin-1

The interleukins (ILs) are a family of cytokines produced by activated lymphocytes and macrophages. One of these factors, IL-1, may play an important role in mediating cellular activation during inflammation and infection (65). The ß form of IL-1 is typically secreted by lymphocytes; however, IL-1α is produced by non-immune tissues. The mitogenic properties of these factors suggest that IL-1 may mediate growth regulation.

IL-1α-like activity was isolated from cultures of

mature Sertoli cells, while not found in cultures of other testicular cell types (66, 67). IL-1 activity in conditioned media increases at puberty, coinciding with the onset of spermatogenesis (68). IL-1 is mitogenic for a variety of cell types, thus the Sertoli cell might directly stimulate germ cell development through production of IL-1. One study indicates that intratesticular injection of IL-1 into hypophysectomized rats stimulates [^{3}H]thymidine incorporation in spermatogonia (69). Presently, it is not known which cells contain IL-1 receptors; however, IL-1 can inhibit Leydig steroidogenesis (70). Another potential role for this cytokine is to mediate immune suppression.

Additional Testicular Growth Factors

Other mitogenic factors found in the testis include seminiferous growth factor (SGF) and Sertoli cell-secreted growth factor (SCSGF). SGF was the first mitogenic factor identified in the tubule (71). This 16 kDa mitogen was isolated from Sertoli cells based on its affinity for heparin and appears immunologically distinct from FGF (72, 73). SGF stimulates growth in transformed TM4 Sertoli, TM3 Leydig cells, and 6 day-old mouse Sertoli cells (74). SGF activity has been detected in many species and is predominant during prepubertal development (71). Another Sertoli cell secreted growth factor SCSGF has also been partially purified and appears mitogenic for a number of cell lines (75). SCSGF has some similarities to TGF-α, including its apparent molecular weight of 8 kDa and its ability to displace radiolabelled EGF from binding its receptor (75). Both SGF and SCSGF have not been fully characterized, and whether these factors are previously identified growth factors remains to be thoroughly investigated.

A number of additional growth factors have been shown to act on specific cell types or to be localized in interstitial fluid. The site of production and specific functions of these agents remains to be investigated. Factors such as activin have been shown to influence germ cell proliferation *in vivo* (76). Whether the actions of such agents are direct or indirectly mediated through alterations in the production of more classic growth factors previously discussed remains to be elucidated.

Additional Regulatory Agents

The regulation of cellular function and differentiation is required at various stages of testis development. Sertoli cell and germinal cell differentiation is induced at the onset of puberty and maintained at optimal levels in the adult. Peritubular myoid cells also differentiate at the early stages of pubertal development. Leydig cells undergo an initial stage of differentiation prenatally and then progressively develop throughout pubertal development. The ability of Sertoli derived regulatory agents to control aspects of this process is not understood; however, a number of unique regulatory agents have been shown to be produced by Sertoli cells.

Inhibin/Activin

The Sertoli cells have been known for several decades to produce a regulatory agent termed inhibin (77) that inhibits FSH production by the pituitary (78, 79). Two precursor subunit gene products of inhibin exist, α and ß, which upon formation of a mature αß dimer forms inhibin to inhibit gonadotrophin production, while a ß dimer forms a molecule termed activin that can stimulate FSH production (80-82). Inhibin and activin are now known to have a wide variety of biological functions and are produced by a number of different tissues. Sertoli cells under the control of FSH or agents that alter cAMP levels produce inhibin (83-88). Although a major function for inhibin is to act on the pituitary to regulate FSH production, potential local actions of inhibin have been postulated. Inhibin and activin both can influence Leydig cell steroidogenesis (89-90). Leydig cells have been postulated to be involved in the regulation of Sertoli cell inhibin production (91-92). Therefore, inhibin may mediate a regulatory interaction between Sertoli cells and Leydig cells. Leydig cells, however, have also been shown to produce both inhibin and activin (93-96). The ability of both Sertoli cells and Leydig cells to produce inhibin and related peptides questions the relevance of inhibin mediated interactions between the cells. The observation that other cell types, such as the germinal cells (97), may provide additional sites of action for inhibin or activin suggest that understanding the role of inhibin/activin in the testis will require further investigation of sites of action and production. Therefore, the function for Sertoli cell produced inhibin remains to be fully elucidated, but will likely be both an endocrine agent for the pituitary and a paracrine factor within the testis.

Müllerian Inhibiting Substance

Müllerian inhibiting substance (MIS) is a 140 kDa factor that causes regression of the Müllerian ducts during development and has also been referred to as anti-Müllerian hormone (98, 99). MIS was first identified in fetal and neonatal testes (100) and was subsequently found to be produced by Sertoli cells of the neonatal testes (101-102). MIS has been cloned (103) and shown to be a member of the TGF-ß superfamily due to sequence similarity. FSH appears to be an important modulator of MIS production by apparently inhibiting MIS production as the Sertoli cell differentiates in response to FSH (104). MIS is primarily produced in the fetal testis with minimal levels in the adult (105). Therefore, a major function for MIS production by neonatal Sertoli cells will be to assist in sexual development and fetal testis differentiation. Whether MIS has additional paracrine roles to modulate germinal cell development or effect cellular functions at later stages of development remains to be elucidated.

Sertoli/Leydig Factors

The ability of Sertoli cells to affect Leydig cell function was first proposed from observations that Leydig cell

morphology was altered by seminiferous tubules with abnormal function and spermatogenesis (106-107). Damage of the seminiferous tubule with cytotoxic agents, cryptorchidism or pathological conditions causes an altered Leydig cell function and morphology (108-120). Leydig cell morphology also changes with the stage at the seminiferous tubule cycle (121-123). Therefore, the ability of Sertoli cells to produce regulatory agents that influence Leydig cell function has been examined. A number of different laboratories have used conditioned medium from cultures of Sertoli cells or seminiferous tubules. Investigators have found that Sertoli cell conditioned media contains factor(s) that can increase basal and hormone stimulated Leydig cell function (124-136), as well as decrease Leydig cell function (68, 137-143). The specific regulatory agents present in Sertoli cell conditioned media that influence Leydig cell function remain to be purified and characterized. It is likely that several of the growth factors produced by Sertoli cells previously discussed may contribute to the ability of Sertoli cell conditioned media to influence Leydig cell function.

One factor postulated to be produced by Sertoli cells and which can modulate Leydig cell function is an LHRH-like substance (144-149). Leydig cells from some species contain receptors for LHRH (150-153) and LHRH has long term inhibitory effects on Leydig cell steroidogenesis (154, 155). The production of an LHRH-like substance by Sertoli cells, however, has been questioned (156) and appears somewhat species specific. Further analysis of species specificity, sites of production, sites of action and biochemical characterization is required.

Although the production of factors by Sertoli cells to influence Leydig cell function may be needed during development of the testis, the function of such agents in the adult needs further consideration. The concentration of androgen present in the adult testis is significantly higher than the concentrations needed to maintain Sertoli cell or germinal cell function (157-160). Reduction of androgen levels by 80-90% may not have major effects on testis function. Therefore the physiological need to regulate Leydig cell steroidogenesis needs to be carefully considered; however, alternate Leydig cell functions may require a more active regulation by Sertoli cells.

Summary

The literature reviewed indicates that Sertoli cells produce a number of regulatory agents that can have both paracrine and autocrine roles in the regulation of testis cell growth and differentiation. The majority of the regulatory agents shown to be produced by Sertoli cells are growth factors. The integrated actions of various factors such as TGF-α and TGF-ß could provide an efficient mechanism to regulate cell proliferation during gonadal development. The potential role that Sertoli cell derived growth factors may have in the regulation of various cell types is shown in Figure 1. Observations obtained imply that growth factors will likely be critical regulatory agents

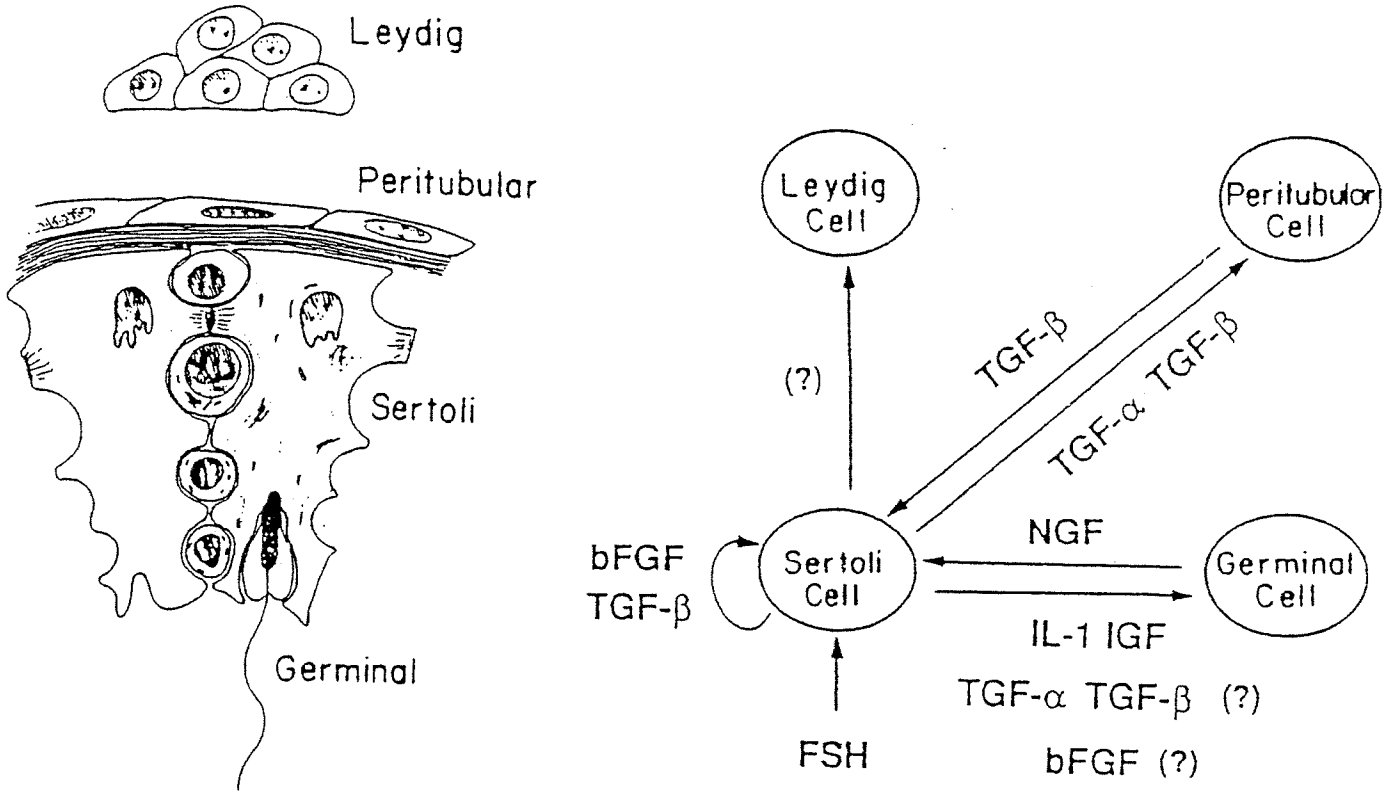

Table 2
Regulatory Agents Produced by Sertoli Cells

Secretory Product	Proposed Site Action	Potential Function
Growth Factors		
IGF-1	Sertoli/germinal/peritubular/Leydig	metabolism/growth
TGF-α	peritubular/?germinal/?Sertoli	growth stimulation
TGF-ß	peritubular/?germinal/?Sertoli	growth inhibition/cellular differentiation
IL-1	?germinal	growth regulation
FGF	Sertoli/?germinal	growth stimulation
Other Regulatory Agents		
Inhibin	Leydig/pituitary	alter steroidogenesis/regulate FSH
MIS	fetal gonad	promote gonadal development
LHRH-like factor	Leydig	decrease steroidogenesis

(?) denotes speculated site of action.

involved in gonadal cell-cell interactions. The endocrine regulation of testis growth may be influenced by indirect effects on growth factor production. An example of this is the ability of FSH to increase FGF production and suppress TGF-ß2 production. Besides growth factors, Sertoli cells also produce a number of regulatory agents that influence cellular function and differentiation. A partial list of the regulatory agents produced by Sertoli cells is shown in Table 2. Although numerous factors have been shown to be produced by Sertoli cells, their physiological roles in regulation of testis growth and differentiation remains to be elucidated. Further analysis of the regulatory agents produced by Sertoli cells will provide insight into the importance Sertoli cells have in the control and maintenance of testis function on a molecular level.

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The Sertoli Cell

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