Peritubular Myoid Cell-Sertoli Cell Interactions which Regulate Testis Function and Growth

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INTRODUCTION

The interactions between different cell types within a specific organ have an important role in the maintenance and control of tissue function and growth. Numerous types of cell-cell interactions are possible and have previously been classified into environmental, nutritional and regulatory type cellular interactions (1). The testis provides a convenient model tissue to more thoroughly investigate cell-cell interactions on a molecular level. Observations provide insight into general cell-cell interactions which occur in many different tissues as well as develop a better understanding of the regulation of testis function.

The maintenance of the process of spermatogenesis within the seminiferous tubules requires interactions between Leydig cells, peritubular myoid cells, Sertoli cells and germinal cells, Figure 1. Sertoli cells form the tubule and provide the cytoarchitectural support and microenvironment required for the developing germinal cells. Peritubular cells surround and form the exterior wall of the tubule. Leydig cells in the interstitium produce androgens which subsequently act on the seminiferous tubule. The interactions between peritubular myoid cells and Sertoli cells will be the primary focus of the current review. In addition, the effect of this cellular interaction on germinal cell development and the influence Leydig cells have on this interaction will also be addressed.

CELLULAR FUNCTION AND GROWTH

The specific functions of a cell provide biochemical markers which can be utilized to investigate the actions of regulatory agents on the cell. In addition, the functions of a cell provide insight into the physiological significance of the cell type. For these reasons the functions of Sertoli cells and peritubular cells will be discussed to understand the cell biology of interactions between the two cell types.

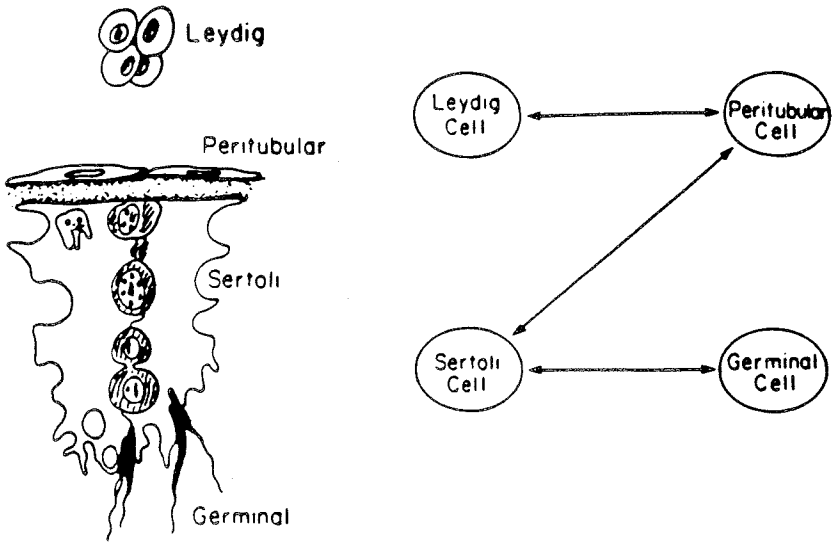
Sertoli cells control and maintain the process of spermatogenesis and provide a target cell for numerous endocrine agents. Sertoli cells have one of the most complex cellular morphologies identified due to their involvement in the support of developing germinal cells. Tight junctions formed between Sertoli cells create the blood-testis barrier which prevents the passage of most components from the circulatory system. For this reason Sertoli cells produce a number of components such as energy metabolites (2) and transport proteins (1) that provide the developing germ cells with essential substances. Examples of Sertoli cell secreted proteins include transferrin (3) involved in iron transport, ceruloplasmin (4) involved in copper transport and androgen binding protein (ABP) (5) involved in steroid transport. One of the major functions of Sertoli cells is to create a unique microenvironment in the tubule through the transport and synthesis of essential components for the germ cells. Regulatory agents which influence Sertoli cell function and differentiation, therefore, will indirectly influence germ cell development.

Peritubular myoid cells are a mesenchymal/stromal cell type which forms the exterior wall of the seminiferous tubule. Peritubular cells are separated from the basal surface of the Sertoli cell by a complex extracellular matrix. One of the primary functions of the peritubular cell is the maintenance of the structural integrity of the tubule. The role peritubular cells may play in the regulation of testis function will be discussed.

Growth of the testis involves the proliferation of a number of cell types. Germinal cell growth is initiated at the onset of puberty. Germinal cells expand to become the most abundant cell population in the testis and maintains the highest level of cell growth throughout adult life. Somatic cell growth is also required to both support the process of spermatogenesis and maintain testis function. Sertoli cell growth is needed in the prepubertal testis to expand and form the seminiferous tubules, but then is arrested at an early stage of puberty (6). Sertoli cells then become a terminally differentiated non-growing cell population. Therefore, regulation of Sertoli cell proliferation is only necessary in the prepubertal testis. Peritubular cell growth is maintained throughout adult life and does require continued growth regulation. Interstitial cell proliferation, including the Leydig cell, also is required to be maintained throughout adult life. The regulation of germ cell growth is not understood nor will be reviewed in deta...

Regulation of peritubular cell and prepubertal Sertoli cell growth will be addressed.

Figure 1



CELL-CELL INTERACTIONS

The different types of interaction will be categorized into environmental, nutritional and regulatory type interactions as previously described (1). Environmental interactions are mediated by the adjacent cell type through components such as extracellular matrix and cell adhesion molecules. Nutritional interactions are mediated by the transport of essential metabolites between different cell types. Regulatory interactions are mediated by a paracrine factor which is produced by one cell type and acts on an adjacent cell type via a receptor mediated signal transduction on a molecular level.

Environmental interactions between peritubular cells and Sertoli cells are mediated via a complex extracellular matrix, basement membrane. This extracellular matrix helps maintain the proper cytoarchitecture of the seminiferous epithelium. Both Sertoli cells and peritubular cell cooperate in the production and deposition of the basement membrane (7). Sertoli cells produce laminin, collagen IV, collagen I (7) and unique proteoglycans (8). Peritubular cells produce fibronectin (9), collagen I (7) and unique proteoglycans (8). The formation of a complex extracellular matrix in vitro requires the presence of both cell types (7). Extracellular matrix has also been shown to maintain the structural differentiation of Sertoli cells in vitro (10). The environmental interaction between peritubular cells and Sertoli cell mediated via this extracellular matrix clearly will have a critical role in the maintenance of testis function.

Nutritional interactions between Sertoli cells and peritubular cells have not been identified. Both cell types are in contact with the circulatory system and essential metabolic components. Therefore, the transfer of metabolites between the cells may not be required. For these reasons, the postulate is made that nutritional interactions between peritubular cells and Sertoli cells will not have an important role in the maintenance of testis function.

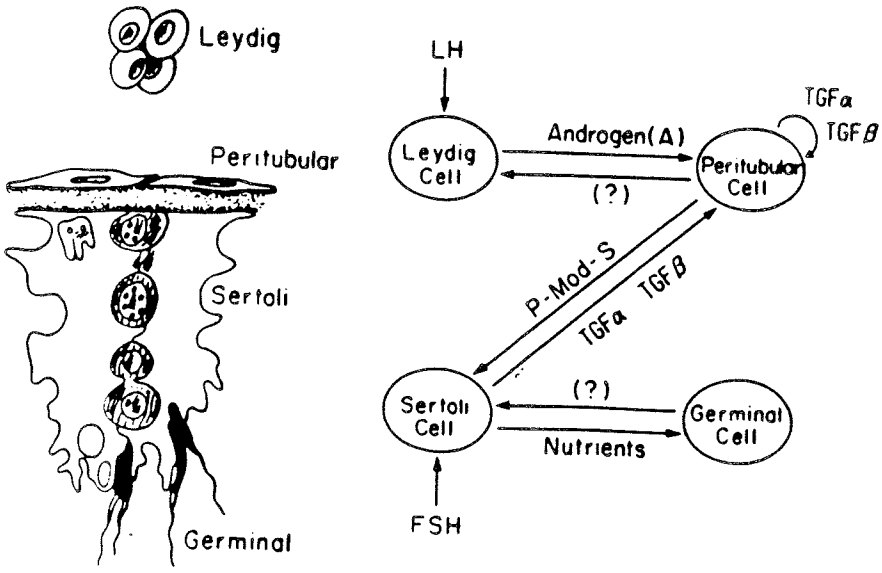
Regulatory interactions between peritubular cells and Sertoli cells were first postulated from the observation that ABP production by Sertoli cells was elevated in co-cultures of the two cell types (11, 12). Subsequently a paracrine factor was found to be produced by peritubular cells which could modulate Sertoli cell function and was termed PModS (13). A crude preparation of PModS was found to be non-mitogenic and could stimulate a large number of Sertoli cell functions (14). PModS was purified and fractionated into two forms termed PModS (A) and PModS (B) (15). PModS (A) was the less hydrophobic protein with a molecular weight of 56,000. PModS (B) was found to have a molecular weight of 59,000 and a blocked N-terminal amino acid residue. The biological activities of these two forms of PModS are essentially the same (15) which implies that they are functionally related and potentially derived from the same parent molecule. PModS can stimulate a large number of Sertoli cell functions including the production of transferrin, ABP, inhibin and aromatase. A number of unknown Sertoli cell functions also appear to be stimulated by PModS treatment (14). PModS has been found to have a more profound effect on Sertoli cell function than any regulatory agent previously described, including FSH (15). PModS stimulates most cellular functions to the same degree as a combination of regulatory agents thought to cause a minimal stimulation of Sertoli cells; FSH, insulin, retinol and testosterone (FIRT) (16). Interestingly, a combination of PModS and FIRT results in an additive response which can stimulate Sertoli cell functions 10-fold. PModS was found to have a unique signal transduction system which is in part the result of receptor mediated effects on cGMP levels. PModS has no initial effect on cAMP. PModS can also promote the gene expression of transferrin and ABP on a molecular level. The ability of PModS to have profound effects on Sertoli cell function is thought to be due to its unique signal transduction process. The regulatory interactions between peritubular cells and Sertoli cells mediated via PModS is postulated to be required for the maintenance of testis function.

The endocrine regulation of Sertoli cell-peritubular cell interactions may be mediated via gonadotropins or steroids. Under the control of leutinizing hormone Leydig cells produce androgens which subsequently act on the seminiferous tubule. Both Sertoli cells and peritubular cell contain androgen receptors (17) and provide sites of action for testosterone. Sertoli cells generally have negligable effects to androgens in vitro, therefore, peritubular cell mediated androgen effects were postulated. Primary cultures of peritubular cells were

found to respond to androgens by increasing the apparent production of PModS (13). In addition, the presence of peritubular cells in co-culture with Sertoli cells significantly augments the actions of androgens on Sertoli cells (18). Observations imply that androgens can influence peritubular cell-Sertoli cell interactions by increasing the production of PModS. This indirect mode of androgen action may be significant due to the potent actions of PModS on Sertoli cell function and differentiation. The endocrine control of testis function and the process of spermatogenesis may therefore involve the ability of androgens to influence peritubular cell-Sertoli cell interactions.

The potential production of growth factors by peritubular cells and Sertoli cells was investigated to determine whether interaction between these two cell types may regulate testis cell proliferation. Previously Sertoli cells were found to produce an epidermal growth factor (EGF)-like substance (19). This EGF-like material has recently been identified as transforming growth factor-α (TGFα) (20). TGFα is a unique gene product that shares a common receptor with EGF and mimics the biological activities of EGF (21). TGFα production was also identified by peritubular cells (20). Both Sertoli cells and peritubular cells express the TGFα gene and secrete the protein. Peritubular cells were found to contain the EGF receptor and TGFα stimulated peritubular cell growth (20). Adult and midpubertal Sertoli cells did not appear to contain the EGF receptor nor respond to EGF for growth stimulation. Whether prepubertal Sertoli cells respond to TGFα remains to be investigated. Combined observations indicate that both peritubular cells and Sertoli cells produce TGFα, which can act as an EGF-like substance to stimulate peritubular cell growth and potentially prepubertal Sertoli cells. Whether germinal cells are influenced by TGFα/EGF remains to be investigated. The postulate is made that TGFα may have an important role in regulating testis cell growth and provide an additional peritubular cell - Sertoli cell interaction. In addition to the production of a growth stimulator, the presence of a growth inhibitor was also identified. Transforming growth factor-β (TGFβ) is a family of unique gene products that inhibit cell growth, particularly EGF/TGFα responsive cells, and promotes cell differentiation (22). TGFβ was found to be produced by both peritubular cells and Sertoli cells through the identification of gene expression and protein secretion (23). TGFβ had no major effects on Sertoli cell function or growth. In contrast, TGFβ inhibited the ability of TGFα/EGF to promote peritubular cell growth. Therefore, TGFβ may have a role in inhibiting peritubular cell growth in response to TGFα. TGFβ also promoted peritubular cells to form colonies in cell culture and increased the production of extracellular matrix components (23). Therefore, TGFβ is speculated to have a potential role as a chemotactic agent for peritubular cells and influence seminiferous tubule morphogenesis. Combined observations indicate that Sertoli cells and peritubular cells produce TGFβ which appears to minimally have an important role in the differentiation and growth regulation of peritubular cells. Potential effects on prepubertal Sertoli cells and germinal cells remains to be investigated.

Figure 2



SUMMARY

Peritubular myoid cell-Sertoli cell interactions will have a critical role in the maintenance and control of testicular function and the process of spermatogenesis. This is primarily due to the fact that regulatory agents which effect Sertoli cell function will indirectly influence germinal cell development. The major interactions which appear essential are the environmental interaction mediated by the basement membrane between peritubular cells and Sertoli cells and the regulatory interaction mediated via the paracrine factor PModS. Due to the profound effects of PModS on Sertoli cell function the postulate is made that PModS will be an important regulator of Sertoli cell function and differentiation. The ability of androgens to stimulate PModS production implies that androgen actions on peritubular cells via PModS may be an important mode of androgen action in the testis. Further investigation of the paracrine factor PmodS will provide a better understanding of the cell biology of the testis and the molecular control of cellular function and differentiation.

The identification of local growth factors in the testis implies that peritubular cell-Sertoli cell interactions may also be important for testis cell growth regulation. Transforming growth factor-α (TGFα) production by Sertoli cells and peritubular cells may act as an important paracrine/autocrine growth stimulator for peritubular cells and potentially prepubertal Sertoli cells. Potential actions on leydig cells and germinal cells also need to be considered. Transforming growth factor-β (TGFβ) production by Sertoli cells and peritubular cells may act as an important paracrine/autocrine growth inhibitor and

differentiation factor for peritubular cells and potentially prepubertal Sertoli cells, Leydig cells and germinal cells. The inverse actions of TGFα and TGFβ provide an efficient mechanism for local growth regulation within the testis. Further investigation of transforming growth factor production in the testis will provide insight into the mechanism by which local cell-cell interaction may regulate testis cell growth.

The observations presented develop a better understanding of general cell-cell interactions in many different tissues. The cell-cell interactions in the testis provide biochemical evidence for the hypothesis that mesenchymal cells produce inducer substances that direct the differentiation and development of the adjacent epithelial cell type. Since peritubular cell-Sertoli cell interactions provide an example of a mesenchymal-epithelial cell interaction, PModS may be a good candidate for a non-mitogenic mesenchymal-inducer substance in the seminiferous tubule. Evidence for the participation of TGFα and TGFβ in mesenchymal-epithelial cell interactions was also presented. Further investigation of cell-cell interactions in the testis will undoubtedly provide insight into the cellular interactions which occur in many different tissues.

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