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"PERITUBULAR MYOID CELL-SERTOLI CELL INTERACTIONS"

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Introduction

The maintenance and regulation of cellular function, growth and differentiation is essential for the physiology of a specific organ or tissue. Although externally derived regulatory agents are important for the control of tissue function, local cell-cell interactions within a tissue also have a critical role in the modulation of cell function. A complex array of different types of cell-cell interactions are possible and have previously been classified into environmental, nutritional and regulatory type cellular interactions (1). To investigate more thoroughly cell-cell interactions on a molecular level, the testis was chosen as a model tissue. Observations to be presented provide information regarding the regulation of testis function as well as develop insight into general cell-cell interactons which occur in many different tissues.

The process of spermatogenesis occurs within the seminiferous tubule which is composed of peritubular myoid cells, Sertoli cells and germ cells, Figure 1. Sertoli cells form the tubule, provide the cytoarchitectural support for the developing germinal cells and create the microenvironment required for germ cell development. Peritubular (myoid) cells surround and form the exterior wall of the tubule. The interactions which occur between peritubular cells and Sertoli cells will be discussed, as well as the influence these cellular interactions may have on the process of spermatogenesis. In addition, the effect that the endocrine system and Leydig cells have on this cell-cell interaction will also be reviewed.

Cellular Function

Specific cellular functions provide biochemical markers for a cell and a mechanism to investigate the actions of regulatory agents and cell-cell interactions. Therefore, the functions of peritubular cells and Sertoli cells will be discussed to provide insight into the physiological significance of the cell-cell interactions identified.

Peritubular cells are a mesenchymal cell type which have primarily been investigated for participation in the production of extracellular matrix. Components such as fibronectin (2), collagen (3) and unique proteoglycans (4) are produced by peritubular cells. Alternative products and functions, distinct from the production of extracellular matix, remain to be examined.

Sertoli cells have a critical role in the maintenance of germ cell development and provide a target cell for the endocrine system. For these reasons, Sertoli cell functions have been more thoroughly investigated. The complex cytoarachitectural support that the Sertoli cells provide the developing germ cells has been examined morphologically by numerous laboratories (5). The maintenance of this specialized epithelial cell support is essential for the process of spermatogenesis. Sertoli cells also create the unique microenvironemnt within the tubule through the formation of the blood-testis barrier and the secretion of unique cell products. Sertoli cells produce components such as energy metabolites (6) and transport proteins (1) that provide the developing germ cells with essential substances. Examples of Sertoli cell secreted proteins include transferrin (7) for iron transport, ceruloplasmin (8) for copper transport and androgen bound protein (ABP) (9) for steroid transport. Although the specific functions of individual Sertoli products may not be completely understood, the unique environment created by Sertoli cells within the tubule is critical for the process of spermatogenesis. Therefore, regulatory agents and cell-cell interactions which influence Sertoli cell functions will indirectly effect germ cell development.

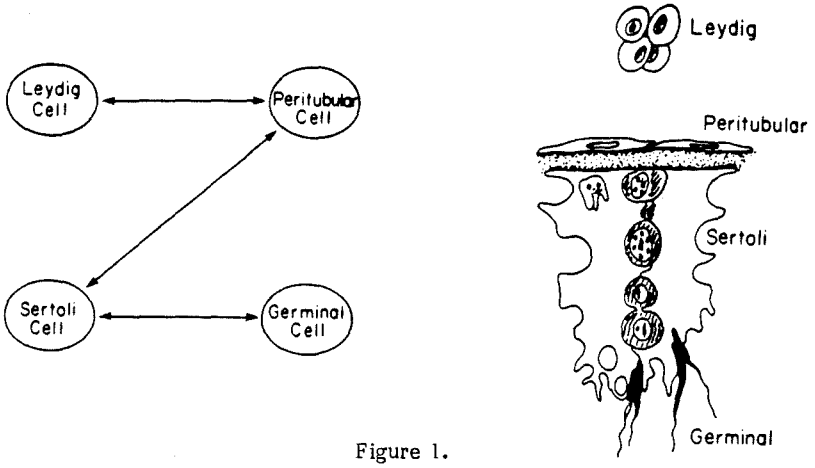

Figure 1.

Cell-Cell Interactions

The primary cell types involved in cell-cell interactions in the testis are illustrated in Figure 1. In addition to the consideration of specific interactions between peritubular cells and Sertoli cells, the ability of Leydig cells to influence this interaction and the effect of this cell-cell interaction on germ cell development will also be considered. The different interactions will be categorized into environmental, nutritional and regulatory type interactions as previously described (1). Environmental interactions are mediated by the surroundings of the cell with components such as an extracellular matrix. Nutritional interactions are mediated by the transport of essential metabolic substances

between different cell types. Regulatory interactions are mediated by paracrine factors which influence the cell on the molecular level via a receptor mediated signal transduction process.

Environmental interactions are primarily mediated via the complex extracellular matrix, basement membrane, formed between Sertoli cells and peritubular cells. This matrix helps maintain structural integrity of the seminiferous tubule (10) and the proper cytoarchitecture for the epithelium. Both peritubular cells and Sertoli cells cooperate in the production and formation of this basement membrane (3). Peritubular cells produce fibronectin and collagen type I, whereas Sertoli cells produce laminin, collagen type IV and collagen type I (3). Both cells produce unique secreted and cell surface-associated proteoglycans (4). The deposition of a complex matrix in vitro requires the presence of both cell types. Extracellular matrix has been shown to have profound effects on Sertoli cell morphology in vitro and may aid in maintaining the differentiated state of the cell (11). The environmental interaction mediated by the extracellular matrix between peritubular cells and Sertoli cells clearly has an important role in the maintenance of testicular function.

Nutritional interactions between peritubular cells and Sertoli cells are limited. Both cell types are in contact with the circulatory system which can provide the cells with essential metabolic components. The transfer of metabolic substances between the cells may not be necesary to maintain cellular function. Gap junctions between peritubular cells and Sertoli cells have also not been well documented. Therefore, nutritional interactions would not appear to be required, nor have any been identified.

Regulatory interactions between peritubular cells and Sertoli cells have been postulated and identified (1). Initial investigations used the co-culture of Sertoli cells and peritubular cells which resulted in a stimulation of ABP production by Sertoli cells (12, 13). The hypothesis was made that peritubular cells may produce a paracrine factor that could influence Sertoli cell function. Serum-free conditioned medium from peritubular cell cultures was found to stimulate transferrin production by Sertoli cells (14). This observation indicated that peritubular cells produce a paracrine factor that can modulate Sertoli cell function which was termed P-Mod-S (14). P-Mod-S was found to be a non-mitogenic protein on a number of different cell types examined and size exclusion chromatography implied a molecular weight between 50,000 and 60,000 (15). Purification of P-Mod-S to homogeneity revealed two forms of P-Mod-S, P-Mod-S (A) and P-Mod-S (B) (16). P-Mod-S (A) is a acid sensitive 55 kDa apparent glycoprotein. P-Mod-S (B) is a 59 kDa protein with an apparent blocked N-terminal amino acid. The biological activities of these two forms of P-Mod-S are the same (16) which implies a possible structural and functional relationship. P-Mod-S can stimulate a number of Sertoli cell functions including the production of transferrin, ABP and total protein (15, 16). P-Mod-S has a greater influence in stimulating Sertoli cell function than any individual regulatory agent previously identified, including FSH (16), Figure 2.

Observations indicate that P-Mod-S alone can stimulate transferrin production to the same extent as a combination of regualtory agents FSH, insulin, retinol and testosterone (FIRT). Previously FIRT was thought to be required for maximal stimulation of Sertoli cell function (17). A mixture of FIRT and P-Mod-S results in approximately a 8-fold stimulation in transferrin production, Figure 2. This degree of stimulation has not previously been achieved for Sertoli cells in culture and implies that different signal transduction systems may exist for P-Mod-S versus FIRT. The peritubular cell derived paracrine factor P-Mod-S may therefore have a crucial role in regulating Sertoli cell function and indirectly the process of spermatogenesis. This regulatory type cellular interaction between peritubular cells and Sertoli cells is postulated to be required for the maintenance of testis function.

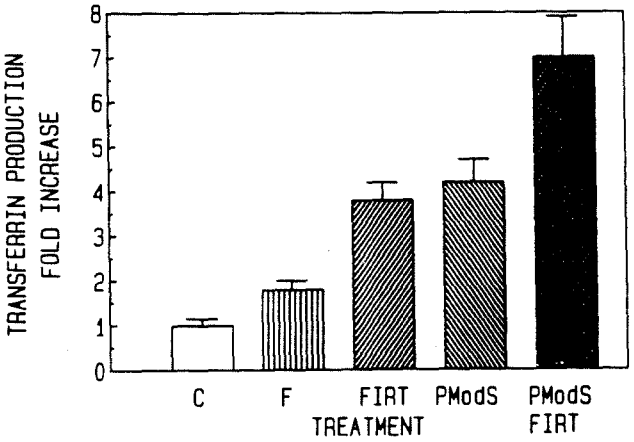

Figure 2. Effects of agents on transferrin production (Fold Increase) by Sertoli cells cultured in the absence (C) or presence of FSH (F); combination of FSH, insulin, retinol and testosterone (FIRT); P-Mod-S (P-Mod-S); and a combination of P-Mod-S and FIRT

The endocrine regulation of peritubular cell-Sertoli cell interactions can be mediated via gonadotropins or steroids. Leydig cell androgen production provides a potentially important regulator of this cellular interaction. Quantitation of androgen receptors in the seminiferous tubule demonstrates that peritubular cells contain a high percentage of the total androgen reception in the seminiferous tubule (18). This observation correlates with the effects of androgens on peritubular cell development previouly described (19). Primary cultures of peritubular cells were found to respond to androgens by increasing the apparent production of P-Mod-S (14). The presence of peritubular cells in co-culture with Sertoli cells were also found to significantly augment the actions of androgens on Sertoli cell function (20). Combined observations indicate that androgens can influence peritubular cell-Sertoli cell interactions by increasing the production of P-Mod-S by peritubular cells. Whether the actions of androgens on the seminiferous tubule are mediated directly through the Sertoli cell and/or indirectly through the peritubular cell remains to be investigated. Clearly, the indirect mode of androgen action mediated via the peritubular cells may be significant due to the potent

regulatory activity of P-Mod-S on Sertoli cell function. The inability of cultured Sertoli cells to respond well to androgens supports the concept that indirect actions may be involved. The endocrine regulation of peritubular cell-Sertoli cell interactions may therefore have an important role in the control of the process of spermatogenesis.

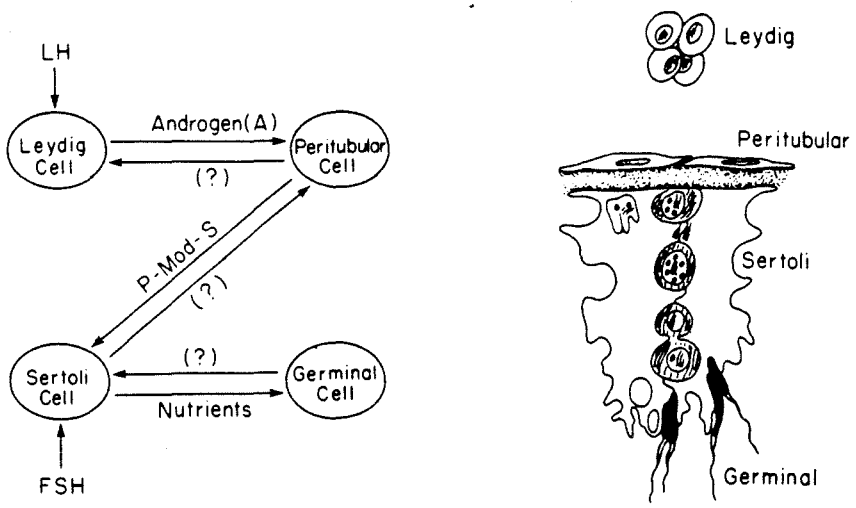

Figure 3. Summary of cell-cell interactions, (?) designates uncharacterized interaction.

Summary

Cellular interactions between peritubular cells and Sertoli cells will have an integral role in the maintenance and control of the process of spermatogenesis and testicular function. As discussed, agents which influence Sertoli cell function and differentiation will indirectly effect germ cell development. The primary types of interactions between peritubular cells and Sertoli cells which appear essential are the environmental interaction mediated via the basement membrane and regulatory interactions mediated via the paracrine factor, P-Mod-S. The cell-cell interaction is postulated in which androgens produced by leydig cells may act on peritubular cells to stimulate the production of the paracrine factors, P-Mod-S, that influences Sertoli cell functions involved in the process of spermatogenesis, Figure 3. Whether additional paracrine factor may be involved in peritubular cell-Sertoli cell interactions are under investigation. Further elucidation of the paracrine factor P-Mod-S and general peritubular cell-Sertoli cell interactions will provide a better understanding of the cell biology of the testis and the molecular control of cellular function and differentiation.

In addition to developing a better understanding of the cell biology of the testis, the observations made provide insight into general cell-cell interactions for many other tissues. The hypothesis has been made that mesenchymal cells associated with a tissue may produce inducer substances that direct the differentiation and development of the

adjacent epithelial cell type (review 21). Peritubular cell-Sertoli cell interactions provide a classic example of mesenchymal-epithelial cell interactions. P-Mod-S may be a good candidate for a mesenchymal-inducer substance in the seminiferous tubule. The possibility that a class of non-mitogenic paracrine factors may be involved in specific cell-cell interactions associated with a given cell type or tissue will be a potentially important area of research.

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