Peritubular Cell-Sertoli Cell Interactions: Role of P-Mod-S and Transforming Growth Factors

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INTRODUCTION

Cell-cell interactions have become increasingly important to our understanding of the maintenance and control of tissue physiology. The specific interactions that have evolved regulate cellular function, growth and differentiation. Therefore, it is not surprising to find that the endocrine regulation of tissue function may be mediated indirectly through alterations in local cell-cell interactions. The cell types in the testis that interact include the Leydig cell, peritubular myoid cell, Sertoli cell and the developing germinal cells. The cell-cell interactions between these cells (reviews, 1, 2, 3) can occur through environmental, nutritional and regulatory type interactions (1). The current manuscript will be confined to a discussion of several specific cell-cell interactions that occur between peritubular myoid cells and Sertoli cells.

PERITUBULAR CELL-SERTOLI CELL INTERACTIONS

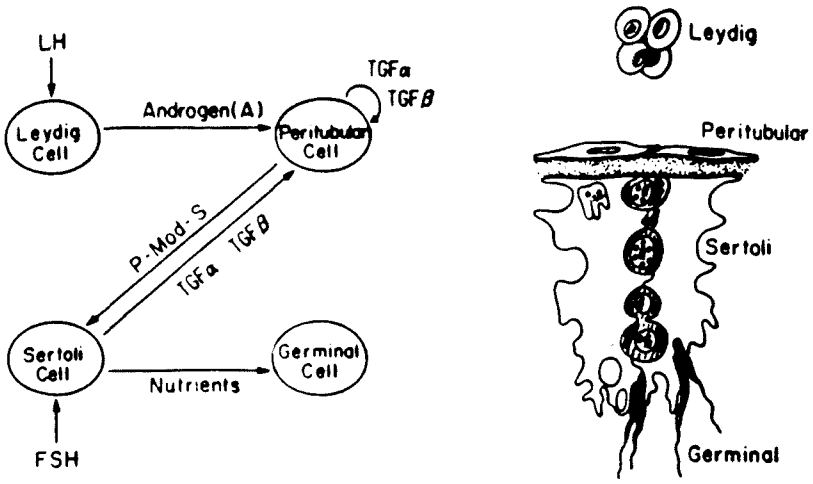
In contact with the basal surface of the Sertoli cells, that form the seminiferous tubule and support the developing germinal cells, are the peritubular myoid cells which surround the tubule. Between the peritubular cells and Sertoli cells is a complex extracellular matrix (ie basement membrane) (4) that is produced cooperatively by the two cell types (5). The environmental interaction mediated by this extracellular matrix is essential for the integrity of the seminiferous tubule and the structural differentiation of the Sertoli cell (6). Although this extracellular matrix between peritubular cells and Sertoli cells is an important environmental interaction in the testis, this extracellular matrix does not appear to provide a regulatory type interaction between the cells to influence Sertoli cell functions on a molecular level (7). Peritubular cells and Sertoli cells do not appear to interact through nutritional type interactions because few gap junctions are present and

both cell types are in contact with the circulatory system. The control of cellular function on a molecular level through regulatory type interactions has been identified between peritubular cells and Sertoli cells with the isolation of specific paracrine factors. These regulatory cell-cell interactions will be discussed in more detail.

Peritubular cells in co-culture with Sertoli cells were found to stimulate Sertoli cell function (8, 9). Subsequently, peritubular cells were found to produce a non-mitogenic paracrine factor that modulates Sertoli cell function termed PModS (10). PModS has been purified and shown to have a more dramatic effect on Sertoli cell function than any individual regulatory agent previously identified, including FSH (11). The dramatic effects of PModS on Sertoli cell function is thought to be due in part to its apparent unique signal transduction system involving cGMP (12). PModS stimulates the production of a number of Sertoli cell products including transferrin, androgen binding protein (11) and inhibin (13). Due to the dramatic effects of PModS on Sertoli cell differentiation, this paracrine factor is postulated to have an important role in the maintenance and control of testis function (1).

The endocrine regulation of testis function relies on the actions of FSH on Sertoli cells and LH on Leydig cells. LH stimulates the production of androgens by Leydig cells which subsequently act on the seminiferous tubule to maintain testis function and the process of spermatogenesis. Approximately equivalent amounts of androgen receptor are present in peritubular cells and Sertoli cells (14), however, purified populations of Sertoli cells generally have a negligible response to androgens in vitro. The presence of a peritubular cell contaminant in Sertoli cell cultures augments the actions of androgens on Sertoli cell functions (15). This mode of androgen action is postulated to be due to the ability of androgens to stimulate the apparent production of PModS (10). The cell-cell interaction is proposed that LH acts on Leydig cells to stimulate the production of androgens that then act on peritubular cells to stimulate the production of PModS that influences Sertoli cell functions involved in the maintenance of germinal cell development (Figure 1). This regulatory interaction between peritubular cells and Sertoli cells mediated via PModS is postulated to provide a major mode of androgen action in the testis.

Figure 1, Peritubular Cell-Sertoli Cell Interactions



Another factor that has been postulated to be involved in the regulation of testis cell growth for a number of years is epidermal growth factor (EGF) (16). The EGF-like substance transforming growth factor-α (TGFα) has recently been shown to be produced locally in the testis (17). The TGFα gene is expressed in both Sertoli cells and peritubular myoid cells. EGF gene expression was not detected. Cultured Sertoli cells and peritubular cells also synthesize and secrete TGFα (17). The EGF/TGFα receptor was detected on peritubular cells isolated from prepubertal, mid-pubertal and adult animals. In contrast, the EGF/TGFα receptor was not expressed on Sertoli cells at any of these stages of development. The primary site of action of the locally produced TGFα in the seminiferous tubule appears to be the peritubular myoid cell (17). Although Sertoli cells are a terminally differentiated non-growing cell population in the adult animal, peritubular myoid cells require a continuous rate of cell proliferation (18). TGFα stimulates peritubular cell growth (17) from both prepubertal and adult animals. Therefore, TGFα produced by peritubular cells may act as an autocrine factor while TGFα production by Sertoli cells can act as a paracrine factor to stimulate and maintain peritubular cell proliferation (Figure 1).

The growth inhibitor and differentiation factor transforming growth factor-β (TGFβ) was also found to be produced by both peritubular cells and Sertoli cells. The TGFβ genes are expressed in both cell types (19) and TGFβ secretion has been determined for peritubular cells (19) and Sertoli cells (19, 20). TGFβ does not appear to influence the production of several major secreted proteins by Sertoli cells (19), but has been implicated to stimulate other Sertoli cell functions (20). TGFβ has dramatic effects on peritubular cell migration and colony formation in

vitro, therefore, may act as a chemotactic agent for peritubular cells (19). TGF_β also appears to stimulate the differentiation of peritubular myoid cells. In addition to the ability of TGF_β to act as a potential chemotactic agent and differentiation factor for peritubular cells, TGF_β also inhibits the ability of EGF/TGF_α to stimulate peritubular cell growth. Therefore, TGF_β may act as both an autocrine and paracrine factor in the seminiferous tubule (Figure 1) to minimally influence peritubular cell growth and differentiation.

SUMMARY

Investigation of the cellular interactions in the testis has developed a better understanding of the factors involved in the maintenance and control of testis physiology. This research has also provided insight into cell-cell interaction that may occur in many different tissues. One of the most common cell-cell interaction present is between mesenchymal cells and epithelial cells. In essentially every organ the functioning epithelial cell is in contact with a stromal/mesenchymal cell type. Mesenchymal-epithelial cell interactions have been postulated to be critical during embryonic development (21) and will likely be important in the adult tissue. Peritubular cells are a stromal/mesenchymal cell type while Sertoli cells are an epithelial cell type. Analysis of peritubular cell-Sertoli cell interactions, therefore, provides insight into mesenchymal-epithelial cell interactions. The interactions between peritubular cells and Sertoli cells mediated via PModS provides the first biochemical evidence for the hypothesis that a mesenchymally derived inducer substance regulates the differentiation of the adjacent epithelial cell. In addition, the indirect mode of androgen action in the testis, mediated via PModS, provides insight into the potential role of mesenchymal-epithelial cell interactions in regulating the actions of the endocrine system on tissue function. Although PModS has been identified and studied primarily as a testicular paracrine factor, the role PModS might play in mediating androgen actions in other responsive tissues remains to be investigated. Therefore, PModS is postulated to play an integral role in the maintenance and control of testis function, as well as potentially being a mesenchymally derived differentiation factor for other tissues. The role of transforming growth factors in mesenchymal-epithelial cell interactions has also been indicated through an analysis of peritubular cell-Sertoli cell interactions. The inverse actions of TGF_α and TGF_β provide an efficient mechanism to control the growth of a cell or tissue. The ability of mesenchymal-epithelial cell interactions mediated via TGF_α and TGF_β to regulate tissue growth and differentiation has previously been demonstrated in the ovary (22). The peritubular cell-Sertoli cell interactions mediated via transforming growth factors also is postulated to be important in the regulation of testis growth and differentiation. This cell-cell interaction may be present in

many different tissues and provides an efficient mechanism for stromal/mesenchymal cells to interact with epithelial cells to regulate tissue physiology. The investigation of peritubular cell-Sertoli cell interactions has provided a better understanding of the cell biology of the testis on a molecular level and given insight into cell-cell interactions that may be present in many different tissues and organs.

REFERENCES

1. Skinner, M.K. (1987): Ann. N.Y. Acad. Sci., 513:158.
2. Sharpe, R.M. (1984): Biol. Reprod., 30:29.
3. Fritz, I.B., Skinner, M.K. and Tung, P.S. (1986): In: Development and Function of the Reproductive Organs, eds A. Eshkol, B. Eckstein, N. Dekel, H. Peterson and A. Tsafriri, pp. 185. Christengraft Publ., Rome, Ares-Serono.
4. Dym, M. and Fawcett, D.W. (1970): Biol. Reprod., 3:308.
5. Skinner, M.K., Tung, P.S. and Fritz, I.B. (1985): J. Cell. Biol. 100:1941.
6. Haldey, M.A., Byers, S.W., Suarez-Quian, C.A., Kleinman, H.K. and Dym, M. (1985): J. Cell Biol., 101:1511.
7. Anthony, C.T. and Skinner, M.K. (1989): Biol. Reprod., 40:691.
8. Tung, P.S. and Fritz, I.B. (1980): Biol. Reprod., 23:207.
9. Hutson, J.C. and Stocco, D.M. (1981): Endocrinology, 108:1326.
10. Skinner, M.K. and Fritz, I.B. (1985): Proc. Natl. Acad. Sci., 82:114.
11. Skinner, M.K., Fetterolf, P. and Anthony, C.T. (1988): J. Biol. Chem., 263:2884.
12. Norton, J.N. and Skinner, M.K. (1989): Endocrinology, 124:2711.
13. Skinner, M.K., McLachlan, R.I. and Bremner, W.J. (1989): Molec. Cell. Endocrinol., 66:239.
14. Anthony, C.T., Kovacs, W.J. and Skinner, M.K. (1989): Endocrinology, 125:2628.
15. Skinner, M.K. and Fritz, I.B. (1985): Mol. Cell. Endocrinol., 40:115.
16. Stastny, M. and Cohen, S. (1972): Biochim. Biophys. Acta, 261:177.
17. Skinner, M.K., Takacs, K. and Coffey, R.J. (1989): Endocrinology, 124:845.
18. Clermont Y. and Perey, B. (1957): Am. J. Anat., 100:241.
19. Skinner, M.K. and Moses, H.L. (1989): Molec. Endocrinol., 3:625.
20. Benahmed, M., Cochet, C., Keramidas, M., Chauvin, M.A. and Morera, A.M. (1988): Bioch. Biophys. Res. Comm., 154:1222.
21. Cunha, G.R., Chung, L.W.K., Shannon, J.M., Taguichi, O. and Fujii, H. (1983): Res. Prog. Horm. Res., 39:559.
22. Skinner, M.K. (1989): In: Growth Factors and the Ovary, ed A. Hirshfield pp. 141, Plenum Publ.

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