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Cell-Cell Interactions in the Testis Which Regulate Gonadal Function

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The interactions between different cell types became essential for survival with the evolution of multicellular organisms. The cell-cell interactions that have evolved are important for embryogenesis, organogenesis, and the maintenance of cellular function, growth, and differentiation. A large number of different types of cell-cell interactions have evolved and been previously categorized into environmental, nutritional, and regulatory interactions (1). Environmental interactions are mediated via extracellular matrix and cell adhesion components and are important for the structural differentiation of a cell and tissue. Nutritional interactions are those involving the transport of essential components and metabolites between cells needed for cell survival. Regulatory interactions are mediated by paracrine/autocrine factors via a signal transduction event to influence cellular function on a molecular level. Although the molecular mechanisms and functions of these three categories of interaction are distinct, all three types of interaction are essential. The testis provides an efficient model system to investigate cell-cell interactions. Observations can lead to an understanding of male reproduction and testis function, as well as provide insight into general cell-cell interactions which can occur in many different organs. This chapter will summarize several cell-cell interactions that influence testis function and that relate to the neuroendocrine regulation of male reproduction.

CELL-CELL INTERACTIONS

The primary cell types in the testis are the Leydig cells, peritubular myoid cells, Sertoli cells, and the germinal cells. The Sertoli cells form the seminiferous tubule and provide the micro-environment and cytoarchitectural support for the developing germinal cells. The peritubular myoid cells surround and form the exterior wall of the tubule. The Leydig cells are in the interstitium and are the site for the production of androgens. Neuroendocrine regulation of the pituitary indirectly regulates testis function through alterations in gonadotropin levels. Luteinizing

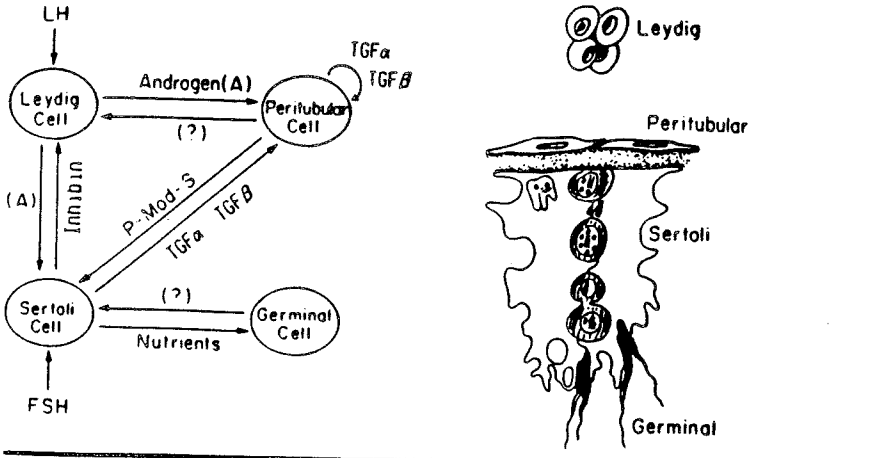

Fig. 1. An illustration of the major cell-cell interactions in the testis. This will likely be the first of many important cell-cell interactions yet to be identified. See the text for discussion.

hormone (LH) acts on the Leydig cells to stimulate androgen production which maintains the process of spermatogenesis. Androgens also feed back on the pituitary to alter gonadotropin production. Follicle stimulating hormone (FSH) acts directly on the Sertoli cell to promote and maintain cellular differentiation. This endocrine regulation of testis function is critical for the maintenance of male reproduction; however, local cell-cell interactions have also been found to have an important role in testis physiology.

Environmental interactions occur primarily between Sertoli cells and germinal cells as well as Sertoli cells and peritubular cells. The complex morphology and structural support that the Sertoli cells provide the developing germinal cells comprise a classic example of an environmental interaction. This elegant cytoarchitecture is essential to maintain the proper morphology of the germ cells. This environmental interaction between Sertoli cells and germ cells is critical for the process of spermatogenesis. To help maintain the structural integrity of the seminiferous tubule, a complex extracellular matrix is formed between Sertoli cells and peritubular cells. Both cell types cooperate in the production of individual components of this basement membrane (2), and this matrix has been shown to be important for the structural differentiation of Sertoli cells (3). Although this environmental interaction between peritubular cells and Sertoli cells is important for maintaining the structural differentiation and integrity of the tubule, this extracellular matrix does not appear to regulate Sertoli cell function on a molecular level (4).

Nutritional interactions occur primarily between Sertoli cells and germinal cells, due to the formation of the blood-testis barrier by Sertoli cells. Essential components from the circulatory system can be obtained by Leydig cells, peritubular cells, and Sertoli cells, but they cannot traverse the blood-testis barrier for the developing germinal cells. Therefore, these essential components and metabolites

must be transported through or synthesized by the Sertoli cell. A number of transport proteins are synthesized by Sertoli cells which carry metals, vitamins, and lipids to the developing germ cells (1). Sertoli cells also produce and secrete several energy metabolities, such as lactate and pyruvate, which are utilized by the developing germ cells. Therefore, the micro-environment created within the seminiferous tubule is essential for the process of spermatogenesis.

Regulatory interactions are possible between all the different cell types in the testis and can be mediated by a wide variety of paracrine and autocrine factors. The ability of the seminiferous tubule to influence Leydig cell androgen production has been shown with a number of in vitro experiments; however, the specific factors involved remain to be investigated. In addition, the level of androgen production by Leydig cells is nearly an order of magnitude higher than required for the maintenance of spermatogenesis in the adult. Therefore, small alterations in androgen production would not appear to be important for the maintenance of testis function. The apparent paradox may be resolved with the future identification of alternate potentially important secretory products of Leydig cells. Regulatory interactions between Sertoli cells and germinal cells have also been postulated; however, the factors involved remain to be identified and characterized. Whether the Sertoli cell–germ cell interactions required to maintain the process of spermatogenesis utilize a passive process involving primarily nutritional interactions or an active process involving a complex network of regulatory interactions remains to be elucidated.

Interactions between peritubular cells and Sertoli cells have been demonstrated with the identification of a nonmitogenic paracrine factor that is produced by peritubular cells, modulates Sertoli cell function, and is termed P-Mod-S (5). P-Mod-S has been purified and shown to have a more dramatic effect on Sertoli cell function than an individual regulatory agent previously identified, including FSH (6). The ability of P-Mod-S to have such a dramatic effect on Sertoli cell function is in part due to its unique signal transduction system involving cGMP (7). This paracrine factor is postulated to have an important role in the maintenance and control of testis function. The production of P-Mod-S by peritubular cells is regulated by androgens (5). Therefore, peritubular cell–Sertoli cell interactions mediated via P-Mod-S provide a potentially important mode of androgen action in the testis. Sertoli cells generally have negligible response to androgens in vitro, but the presence of peritubular cells augments the apparent actions of androgens on Sertoli cells (8). Due to the dramatic effects of P-Mod-S on Sertoli cell differentiation, this regulatory interaction between peritubular cells and Sertoli cells is postulated to provide a major mode of androgen action in the testis. P-Mod-S generally stimulates most Sertoli cell functions (6). Recently, P-Mod-S has also been found to stimulate inhibin production by Sertoli cells (9). Androgens have previously been shown to have negligible effects on inhibin production by Sertoli cells in vitro; therefore, the ability of P-Mod-S to regulate inhibin production provides a mechanism for androgens to regulate inhibin levels in vivo. This indirect effect of the endocrine system on inhibin production can in turn feed back to and regulate the endocrine system.

Other factors involved in peritubular cell–Sertoli cell interactions include transforming growth factor-α (TGF-α) and transforming growth factor-β

(TGF-β). Both peritubular cells and Sertoli cells produce the epidermal growth factor (EGF)-like peptide TGF-α and the growth inhibitor TGF-β (10, 11). The TGF-α and TGF-β produced by Sertoli cells can act as paracrine factors to influence peritubular cell growth (10) and differentiation (11), respectively. Sertoli cells do not appear to contain the EGF receptor, so they may not be a site of TGF-α action. TGF-β, however, may influence Sertoli cell functions. Therefore, the peritubular cell–Sertoli cell interaction mediated via TGF-α and TGF-β may be an important regulatory interaction in the testis to regulate testis growth and differentiation.

SUMMARY

Analysis of cell-cell interactions in the testis has developed a better understanding of the factors involved in the maintenance of testis physiology, as well as providing insight into the general cellular interactions present in essentially all tissues. As an example, the information regarding peritubular cell–Sertoli cell interactions mediated via P-Mod-S provides the first biochemical evidence for the hypothesis that mesenchymal cells influence epithelial cell function through the production of mesenchymally derived inducer substances. The environmental, nutritional, and regulatory interactions identified will all be important for the regulation of gonadal function. The ability of the endocrine system to influence these cell-cell interactions provides an efficient mechanism for a local control of testis function. This observation indicates how important an understanding of local cell-cell interactions is to the complete understanding of the actions of the endocrine system. The regulation of male reproductive biology by the neuroendocrine system appears to result in the initiation of a cascade of events that result in an influence on cell-cell interaction in the testis. Subsequently, these cell-cell interactions in the testis can feed back on the endocrine system through agents such as inhibin. Therefore, elucidation of the neuroendocrine regulation of reproduction will require further investigation of the local regulation of gonadal function.

REFERENCES

1. Skinner MK. Ann NY Acad Sci 1987;513:158.
2. Skinner MK, Tung PS, Fritz IB. J Cell Biol 1985;100:1941.
3. Hadley MA, Byers SW, Suarez-Quian CA, Kleinman HK, Dym M. J Cell Biol 1985;101:1511.
4. Anthony CT, Skinner MK. Biol Reprod 1989;40:691.
5. Skinner MK, Fritz IB. Proc Natl Acad Sci 1985;82:114.
6. Skinner MK, Fetterolf P, Anthony CT. J Biol Chem 1988;263:2884.
7. Norton JN, Skinner MK. Endocrinology 1989;124:2711.
8. Skinner MK, Fritz IB. Mol Cell Endocrinol 1985;40:115.
9. Skinner MK, McLachlan RI, Bremner WJ. Endocrinology 1989;63.
10. Skinner MK, Takacs K, Coffey RJ. Endocrinology 1989;124:845.
11. Skinner MK, Moses HL. Mol Endocrinol 1989;3:625.

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