Application of 3-dimensional Co-culture System on Reproductive Biology Therapy

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Cell differentiation is cooperatively regulated by signals through soluble factors, ECM proteins, hormones, and junctional cell-cell interactions. In existing experimental systems, cell-to-cell communications are studied in such ways that cells were 2-D cultured and regulatory factors were adjusted in situ.

The in vitro endometrial 3-D culture system described here differs from other systems in many respects. First, epithelial cells are well differentiated as secretory phase endometrium does in vivo. Second, we can manipulate culture conditions either in epithelial/stromal culture alone or in epithelial/stromal co-culture. Third, molecules involved in the paracrine interaction can be identified by simply adding or omitting them to the culture system. Thus, this 3-dimensional culture system enables us to study paracrine mechanisms for endometrial differentiation and cancer invasion.

The secretory phase of the endometrial cycle is a critical branch point in the development and differentiation of the endometrium. In this study, we showed that the 3-D cultured endometrial epithelial/stromal cells underwent morphological and biochemical changes under progesterone dominant condition. These changes are found identical to the secretory endometrium in vivo.

The interaction between the endometrial compartments is known to be an important factor for the endometrial differentiation. Therefore, we investigated cell-to-cell interactions in decidualization processes. Using the 3-D culture we found that the TGF-β was expressed from epithelial cells under the progesterone dominant condition, and that induced stromal decidualization through Smad phosphorylation in vitro. Thus, we concluded that TGF-β is a possible paracrine mediator of the stromal decidualization through Smad phosphorylation.

Invasion and metastasis of cancer cells are known to be initiated by interactions between cancer cells and host cells, and ECM plays a major role in recognition and migration of cancer cells. Our findings presented in this thesis demonstrated that the in vitro interaction between cultured endometrial carcinoma cells and cultured normal endometrial stromal cells (as a host) paracrinally regulates the expression of MMP-2 and MMP-9 in a similar way as the endometrial stromal cell and epithelial cell do in vivo.

So far, the paracrine mechanisms of differentiation are known to be complicated processes in living tissues. Many researchers used to challenge themselves to clarify these mechanisms, but often faced limitation because commonly used 2-D culture tectonics could not imitate the aspects of living tissues. As shown in this thesis, 3-D co-cultured system could overcome the defects of 2-D culture system and has been

successfully applied in investigation of paracrine communication between the cellular components in human endometrium in vitro.

Based on our results, it is suggested that the present endometrial 3-D culture system is a powerful tool for studying the human endometrial receptivity and pathogenesis in vitro.