（生体制御学専攻解剖細胞生物学講座）　　（別記様式第５号）
（課程・論文博士共通）

論　文　内　容　要　旨

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論文題目	Cell biology of fallopian tube epithelium with special references to the mechanism of differentiation and ciliogenesis （卵管上皮の分化機構と繊毛形成に関する細胞生物学的研究）		

論文内容要旨

Background:

The fallopian tube (FT) lumen is lined with a simple columnar epithelium consisting of ciliated, secretory and basal cells. The fallopian tube epithelium (FTE) can produce tubular fluid that nourishes the early embryo, and ciliated cells can facilitate transport of gametes, which is important for human reproduction. Meanwhile, the FTE has been implicated as a potential site of origin of high-grade serous ovarian cancer following genetic mutation.

Establishing a high-fidelity model of culturing fallopian tube epithelial cells (FTECs) and keep the highly polarized property is a valuable tool for functional studies and uncovering the mechanism of FTECs differentiation. Although there are some attempts in establishing FTECs in vitro, we still faced some problems. It is necessary to establish a stable culture model of FTECs, including optimizing the culture medium and the number of cell passages, determining the condition of storing the FTECs, and optimizing the condition for inducing the differentiation.

The mechanism of FTE differentiation and the way to respond to various hormonal and neuronal stimuli is incompletely understood. The lineage decision between secretory and ciliated cells is tightly regulated during development, homeostasis, and regeneration. The presence of stem-like basal cells in fallopian tube has been proved, and these cells serve for the precursor that can differentiate into secretory or multi-ciliated cells (MCCs) in the FT. Estrogen (E2) is one of the most important hormones in female and E2 is suggested to promote the ciliogenesis in FTECs, but we still need more direct evidence to verify that the differentiation of MCCs is regulated by estrogen pathway in FTECs.

From another standpoint, notch is one of the major highly conserved signaling pathways that have profound and ubiquitous roles in the determination of cell fates and cell-cell communication during development. Several studies have shown that Notch signaling controls the equilibrium of ciliated and secretory cells. In the developing airway, Notch activation is sufficient to drive secretory cell formation at the expense of ciliated cells. On the other hand, epidermal growth factor (EGF) plays a central role in proliferation and differentiation of the cell, as well as the pathogenesis of various tumors. Notch signaling activates the EGFR pathway leading to MUC5AC expression in tracheal epithelium, which is a molecular marker of secretory cells. EGF stimulates the synthesis of Notch1 as well as production of Notch intracellular domain (NICD). Until now, the interaction among estrogen, EGF, and Notch pathway is unclear. In this study, I focused on elucidating the interrelationship among E2, EGF, and Notch pathways, in term of differentiation of MCCs, by utilizing primary culture system of porcine FTECs.

備　考

１　※印の欄には記入しないこと。

２　論文題目が外国語の場合は，カッコを付し和訳を付記すること。

３　論文題目が日本語の場合は，カッコを付し英訳を付記すること。

４　論文内容要旨は，（研究の目的），（方法），（結果），（考察），（結論）の順に日本語（２，０００字程度）もしくは英語（半角５，０００字程度）でまとめ，タイプ等で印字すること。　（文字数を記載してください。）

論文内容要旨（続紙）	（ふりがな） 氏名（自署）	印

Objective:

1. To establish a high-fidelity culture system of FTECs in terms of expansion and differentiation in vitro, which is useful for studying the differentiation mechanism of fallopian epithelium, and cell communication. Moreover, this study partly addresses the issue that transformation of FTECs leads to HGSC.
2. To elucidate the interrelationship among E2, EGFR, and Notch pathways in regulation of ciliogenesis and homeostasis of FTECs.

Methods:

FTECs were recovered from the porcine FT after digestion with collagenase type IV and DNase I. Primary FTECs were expanded in defined expansion medium. Differentiation of FTEC in defined differentiation medium was induced by placing them into air-liquid interface (ALI) culture condition.

Results:

1. Established a systematic long-term culture model of FTECs both in expansion and differentiation stage.
2. E2 promotes ciliogenesis through ERβ.
3. EGFR-MEK-ERK pathway regulates cell fate during ciliogenesis through modulating Notch signaling.
4. Estrogen pathway regulates MCCs differentiation by modulating the intercellular communication through Notch signaling.
5. Estrogen pathway facilitates amplification of centrioles through deuterosome-dependent pathway in FTECs.

Conclusion:

1. I have established an ideal model for expansion and differentiation of FTECs. This model can meet the requirements for fresh tissue samples. Moreover, long-term self-renewal of FTEC population at lower cost. Meanwhile, this model also allows us to assess the physiological responses of specific cell subpopulations and enables us to better understand the mechanism of tumor initiation and progression from FTECs.
2. Base on this model, I have shown the direct evidence that E2 promoted the differentiation of MCCs through ERβ. During FTECs differentiation, EGF coordinated with Notch signaling in cell fate determination. Moreover, I also found that estrogen pathway facilitated centrioles amplification in the deuterosome-dependent manner. This is mediated by the cell to cell communication via DLL1 pathway. Taken together, the differentiation of MCCs in FT depends on the balance of EGF and Notch signaling in the early stage. In addition, the centrioles amplification induced by E2 in the late stage.

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