

Steroidogenic enzymes, their related transcription factors and nuclear receptors in human sebaceous glands under normal and pathological conditions

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学 位 論 文 要 約

博士論文題目 Steroidogenic enzymes, their related transcription factors and nuclear receptors in human sebaceous glands under normal and pathological conditions (正常および病的ヒト脂腺での各種ステロイド合 合成酵素、転写因子、核内受容体の発現解析)

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Abstract

Several types of sebaceous lesions have been known to arise from sebocytes of the skin. Skin diseases involving sebaceous glands include acne and others also well known to be influenced by sex steroids. In situ or local sex steroid hormone synthesis has been known in human skin and those locally produced sex steroids could also exert their effects upon the functions of human sebaceous glands and their diseases but the details have not been yet clarified. Therefore, in this study I performed immunohistochemical analysis of steroidogenic enzymes, nuclear receptors and transcription factors in a total of 59 human skin specimens retrieved from pathology files including 22 normal human sebaceous glands, 12 sebaceous nevus, 12 sebaceous gland hyperplasia, 3 sebaceoma and 10 sebaceous carcinoma. In addition, I used immortalized human SZ95 sebocytes cell lines treated with forskolin or vehicle for 3 h, 6 h, 12 h or 24 h for in vitro analysis in order to further understand the roles of sex steroids in sebaceous glands and their disorders. In this cell model, the mRNA levels of steroidogenic enzymes and transcription factors were evaluated at each time point using quantitative RT-PCR (qPCR). Results of immunohistochemical analysis demonstrated that immunoreactivity of 3 β -HSD1, CYP11A1, StAR, 17 β -HSD5, CYP17A1, 5 α -red1, PRB, AR, and NGFI-B was detected in normal human sebaceous gland, with relatively lower levels of all those above in pathological sebaceous glands. To the best of my knowledge, my present study is indeed the first one to directly evacuate the specific 3 β -HSD subtypes in human skin and also to demonstrate the presence of 3 β -HSD1 and the absence of 3 β -HSD2 in human sebaceous glands under both normal and pathological conditions. This differentiation is considered very important, as type one and type two distinctively differ in the human sebaceous gland, suggesting that different transcription factors could possibly regulate the transcription of each isoform, and this regulation could be also associated with a tissue/cell-specific pattern. The in vitro study also revealed that the

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levels of 3β -HSD1, CYP11A1, StAR, 5α -red1, 17β -HSD5 and NGFI-B mRNAs were significantly increased in FSK-treated cells compared to untreated cells, and this increase occurred in a different time-dependent fashion indicated that active adenylate cyclase in sebaceous gland and suggesting its dependence on cAMP. These results all indicated that 3β -HSD1 and other steroidogenic enzymes expressed in sebaceous glands result in biologically relevant in situ androgen and progesterone synthesis and these locally produced sex steroids influence the functions of normal as well as pathological sebaceous glands of human skin.