尼古丁乙醯膽素受體於台灣婦女乳癌組織之表現

Nicotinic Acetylcholine Receptors Expression in Breast Cancer Tissues of Taiwanese Female Patients

中文摘要

目前流行病學的研究，仍無法確定吸煙是否會促進乳癌的發生。但研究顯示 serine/threonine kinase Akt (protein kinase B) 的活化在癌症發生扮演一重要角色，Akt pathway 的活化於肺部上皮細胞受到尼古丁(nicotine)及煙草特異致癌物 4-(methylnitrosamino) -1-(3-pyridyl)-1- butanone (NNK) 誘導，於乳房細胞則受雌性激素（estradiol）所誘導。 這些研究提供了一個假設，即 nicotine 及 NNK 的暴露同樣能活化乳房細胞的 Akt，進而導致乳房細胞增生(proliferation)。本研究的目的即在台灣乳癌婦女的乳房組織上，評估其尼古丁乙醯膽素受體(nicotinic acetylcholine receptors, nAchRs) 的表現，進而分析這些受體表現與臨床病理的關係。我們收集了十八位侵犯性管道癌(invasive ductal carcinoma)及兩位原位癌(ductal cancinoma in situ)之乳房組織，以反轉錄聚合酶連鎖反應（Reverse Transcription-Polymerase Chain Reaction, RT-PCR）偵測乳癌組織、癌病變旁之正常組織以及人類乳癌細胞株（human breast cell lines）的 nAchRs 之 cDNA 表現。實驗顯示於二十例乳癌組織中，十九例顯示出有 α9 nAchRs 表現，十一例顯示有 α10 nAchRs 表現；於二十例正常之乳房組織中，十八例及九例顯示出含有 α9 及 α10 之 nAchRs 表現，其他 nAchR 次單元的表現則較不明顯。進一步比較 nAchR 在乳癌及正常乳房組織的表現強度，則 α9 與 α10 次單元於乳癌組織上的表現大部份均較正常組織上的表現強。且當 α9 與 α10 次單元同時表現於乳癌及正常組織時，該乳房病變的體積越大 (P=0.009)。以多變項直線模型進一步分析顯示，相較於其他次單元，乳癌細胞有 α10 之 nAchRs 表現爲影響腫瘤大小的最主要因子。而乳癌細胞株 MCF-7，則發現含有 α1、α3、α5、α7、α9、α10 和 β4 nAchRs 之表現，而 MDA-MB-231 細胞株則只有 α5 及 α9 次單元表現。以上結果，對 nicotine 及 NNK 促使人類乳房細胞癌化及成長此一假說，提供了立足點，惟仍需進一步之細胞及動物實驗加以證明。

英文摘要

Epidermiological reports on the role of smoking in breast carcinogenesis are controversial. However, evidences indicate that rapid serine/threonine kinase Akt (Protein kinase B) activation play an important role of carcinogenesis, such pathway were induced by nicotine and the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-
1-butanone (NNK) in lung epithelial cell and also by estradiol in breast cell. It

provides the idea that nicotine and NNK exposure may activates Akt , resulting of cell proliferation in breast cell. Our objective of study is to evaluate the nicotinic acetylcholine receptors (nAchRs) expression in breast cancer tissues of Taiwanese female patients, and the relation of clinicopathologic features between such receptors expression is analyzed. We obtained human breast specimens from 18 patients with invasive ductal carcinoma and 2 patients with ductal carcinoma in situ. cDNA of nAchRs were studied by Reverse Transcription- Polymerase Chain Reaction (RT-PCR) in breast cancer specimens, normal breast tissue adjacent to the cancer and human breast cancer cell lines. α9-containing andα10-containing nAchRs were expressed in 19 and 11 of 20 breast cancer samples; they were also expressed in 18 and 9 of 20 normal breast samples adjacent to the cancer, respectively. Expression of other subunits of nAchR are not frequent. Compare with the intensity of nAchR band, most specimens showed significant expression of α9 and α10 subunits in breast cancer tissue relative to the corresponding normal tissue. Besides, there was a significant association between α9- containing andα10-containing nAchRs synchronous expression in both cancer and normal tissues with local tumor extent (P=0.009). Multivariate general linear model showed thatα10-containing nAchR expression in breast tumor cells is the most importart factor of tumor size among the other subunits. In breast cancer cell line MCF-7, α1, α3, α5, α7, α9, α10 andβ4-containing nAchRs were expressed, whereas onlyα5 andα9 subunits expression in MDA-MB-231 cell. Our data support the hypothesis that nicotine and NNK may contribute to the initiation and progression of human breast cancer, further in vitro and in vivo studies to confirm such hypothesis is required.
Key words: nAchRs, nicotine, NNK, tobacco-related carcinogen, estradiol, Akt, MCF-7, MDA-MB-231, invasive ductal carcinoma, ductal carcinoma in situ