MMP-3 於卵巢癌細胞株 SKOV-3 之表現以及對於侵襲與增殖的影響

MMP-3 Expression and its Effect on the Invasion and Proliferation in Ovarian Cancer Cell Line SKOV-3

中文摘要

上皮性卵巢癌是女性的重要癌症之一，主要造成腹腔內的癌病瀰漫。腹腔內的腫瘤擴散，與腫瘤細胞、腹膜、細胞外基質之間的交互作用有關。因此，基質治療或許是將來可以考慮的卵巢癌治療策略之一。

MMP (Matrix Metalloproteinase) 在細胞外基質之作用反應方面，扮演重要角色。動物實驗顯示，多種 MMP 會促進癌細胞的侵襲和轉移，MMP 因而被認爲是一種治療癌症的標的。然而，在絕大多數的關於抑制 MMP 的癌症臨床試驗之中，患者的存活並沒有改善，有些試驗甚至還因爲存活率更差或是副作用過大而提早終止。這些失敗，是由於人類對於 MMP 的複雜作用與多重角色了解不夠。欲發展出有效足以抑制癌症的基質治療，應該要先了解不同的 MMP 在不同種類或不同階段的癌症當中的角色。

MMP-3 在上皮性卵巢癌鮮少有相關研究，角色不明。本研究探討 MMP-3 在人類卵巢癌 SKOV-3 細胞株的表現，以及對於 SKOV-3 細胞侵襲與增殖的影響。

本實驗結果顯示，單獨培養時，卵巢癌 SKOV-3 細胞少量地表現 MMP-3，但是其 MMP-3 無法被明確偵測到有釋放到培養皿上清液當中。單獨培養時，纖維母細胞 WS-1 本身則可測得有釋放少量的 MMP-3。在兩種細胞共同培養時，卵巢癌 SKOV-3 細胞可以促進周圍的纖維母細胞 WS-1 釋放出更大量的 MMP-3。活化狀態的 MMP-3 存在於細胞外，且其數量與釋放到細胞外的總 MMP-3 濃度大致有正相關的趨勢。在裸鼠腫瘤模式當中，較晚期的腫瘤，其細胞核的 MMP-3 染色程度較顯著，但是其細胞核外則較無 MMP-3 之呈色。纖維母細胞 WS-1 和卵巢癌 SKOV-3 細胞共同培養，會增加 SKOV-3 細胞的侵襲程度。在單獨培養卵巢癌 SKOV-3 細胞時，不論加入 recombinant human pro-MMP-3、MMP-3 inhibitor-1、recombinant human TIMP-3 (tissue inhibitor of matrix proteinase-3)，其細胞侵襲穿透的程度，以及細胞增殖的數量都會增加。然而，當共同培養卵巢癌 SKOV-3 細胞與纖維母細胞 WS-1 時，微量的 MMP-3 inhibitor-1、TIMP-3 以及過量的 pro-MMP-3，則各別會抑制細胞侵襲穿透的程度。

基於本研究可以推知，癌細胞周遭的基質細胞, 對於癌細胞的增殖與侵襲等行爲有著顯著的影響。這些影響，部份是經由 MMP/TIMP 系統來作用。然而，此系統的作用複雜且難以預測。想藉由操縱 MMP/TIMP 系統來進行上皮性卵巢癌的基質治療，其可行性恐怕還要三思。

英文摘要

Epithelial ovarian cancer (EOC) is one of the major cancers in the female. The most

common and most suffering condition in terminal stage is intra-abdominal carcinomatosis. Intraperitoneal tumor spreading involves the interaction between the tumor cells, peritoneum, and the extracellular matrix (ECM) around them. Therefore, stromal therapy might be an option of future strategy for the treatment of EOC. Matrix metalloproteinase (MMP) play important roles in these ECM reactions. Animal models had shown that many kinds of MMP facilitate cancer invasion and metastasis, and several kinds of MMP are regarded as treatment targets in cancer. However, most of the MMP-inhibition clinical trials failed to demonstrate survival benefit in cancer patients and some of the clinical trials were terminated early because of excessive side effect or even worse survival. The failure of MMP-inhibition clinical trials is due to the inadequate understanding of the complicated functions and multiple roles of MMP. To develop an effective stromal therapy to inhibit tumor progression, it is important to understand the role of various MMP in various kinds of cancer in various stages.

MMP-3 (stromelysin-1) is rarely studied in EOC, and its role on EOC is not clear. The current study investigated the expression of MMP-3 in human ovarian carcinoma cell line SKOV-3, and its influence on the invasion and proliferation of SKOV-3 cells. The results of the current study revealed that while cultured alone, ovarian cancer SKOV-3 cells itself express small amount of MMP-3, but MMP-3 couldn't be definitely detected in the supernatant in the culture dish. While cultured alone, fibroblast WS-1 cells released small amount of MMP-3. When the two kinds of cells were co-cultured together, ovarian cancer SKOV-3 cells promoted their surrounding fibroblast WS-1 to release much more MMP-3 than when cultured alone individually. The activated form of MMP-3 was located extracellularly, and its quantity had a grossly positive correlation with the quantity of total MMP-3 released extracellularly. In the SKOV-3 tumor model in nude mice, the tumor of more advanced stage had more prominent MMP-3 stain in the nucleus but less extra-nuclear MMP-3 stain. Co-culturing with fibroblast WS-1 cells significantly enhanced the invasive potential of the ovarian cancer SKOV-3 cells. For the ovarian cancer SKOV-3 cells cultured alone, the addition of either recombinant human pro-MMP-3, MMP-3 inhibitor-1, or recombinant human TIMP-3 (tissue inhibitor of matrix proteinase-3) enhanced the invasive potential and cell proliferation. When the ovarian cancer SKOV-3 cells were co-cultured with fibroblast WS-1, the addition of either trace MMP-3 inhibitor-1, trace TIMP-3 or excessive pro-MMP-3 inhibited the invasive potential of the SKOV-3 cells.

Based on the current study, it implies that the stromal cells surrounding the cancer cells exert significant influence on the proliferation and invasion of the cancer cells. Such influence partly functions via the MMP/TIMP system. However, the function of

the MMP/TIMP system is complicated and difficult to predict. The feasibility of a stromal therapy strategy requires thorough deliberation if the strategy is to be exerted via manipulating the MMP/TIMP system.