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• 研究人員	李宏謨 Lee, Horng-Mo		
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• 中文摘要

人類原生性顱內腫瘤多數爲膠質母細胞癌。由於膠質癌細胞生長快速且具高度侵襲性，侵襲大腦週邊組織而造成臨床治療的問題。在成年人膠質母細胞瘤中而最惡性的爲多型性膠質母細胞瘤(Glioblastoma multiforme ，簡稱 GBM)。GBM 的治療與術後普遍不佳。膠質母細胞癌的高侵襲性和過度表現間質金屬蛋白胰(MMPs)有關。因此抑制腦瘤間質金屬蛋白胰的活性可望降低其侵襲性並有效的控制膠質細胞癌轉移能力。MMPs 的基因表現已知可循 p38 MAPK; ERK 等訊息傳遞路徑。因此若能降低 MAPK 的酵素活性，可以有效降低腦瘤間質金屬蛋白胰的活性。MKP-1 (MAPkinase phosphatase 1) 屬於 dual specificity MAPK phosphatases (DS-MKPs)其中一員，其功能可以抑制 MAPK (MAP kinase)的活性。目前我們發現，糖尿病用藥 peroxisome proliferator activated receptor-gamma(PPAR-gamma 的活化物 rosiglitazone 與抗發炎藥物 dexamethasone 可以活化 MKP-1 蛋白的產生且有效抑制腦瘤間質金屬蛋白胰的活性。因此我們認爲常用來抗發炎藥物 dexamethasone 或糖尿病用藥 Rosiglitazone 也許可用來做爲膠質母細胞癌的治療或術後的輔助療法(adjuvant therapy)。此外，iNOS 普遍表現於惡性度較高的腦瘤細胞中，在本實驗中，利用 NO 合成胰抑制劑(l-NAME)與 NO donor(SNP)證實 NO 的存在可促進 MMP-2 蛋白活化過程。Dexamethasone 與 rosiglitazone 透過 MKP-1 可以有效抑制 iNOS 的表現，降低 NO 的產生，影響 MMP-2 活性。綜合上述結果，可知增加 MKP-1 蛋白生成可以抑制 MAPK 的活性，減低 MMP-2 蛋白的產生與活化達到抑制腫瘤侵襲性的效果。

• 英文摘要

The majority of primary intracranial tumors in human are gliomas. Tumor cell hyperproliferation and invasiveness are key features of glioma. Glioblastoma multiforme (GM) is the most common form of astrocytomas in adults. Despite radical surgery, radiation therapy

and conventional chemotherapy prognosis remains poor and is associated with low survival rate. Matrix metalloproteinases (MMPs) have been implicated as important factors in the control of the invasive capability of glioma cells. Induction of MMPs is known to mediate through many signaling pathways including MAPK (MAP kinase) dependent pathways. MKP-1 (MAP kinase phosphatase 1), which is a member of the dual specificity MAPK phosphatases (DS-MKPs), inactive MAPK activity. We found that Dexamethasone, an anti-inflammatory agent and Rosilitazone, an agonist of peroxisome proliferator activated receptor-gamma(PPAR-gamma have been shown to inhibit MMP-2 activity via induction of MAPK phosphatase -1 (MKP-1). Thus, we propose to explore the possibility of whether dexamethasone and Rosiglitazones can be used as a therapeutic agent to treat malignant glioma invasiveness and cell growth. In addition, iNOS only expressed in high grade of malignant glioma cells. Treatment of glioma cells with l-NAME (NOS inhibitor) or Sodium nitroprusside (Nitric Oxide donor), We found that Nitric Oxide regulate MMP-2 activity. By using siRNA to knockdown MKP-1 also reversed Dexamethasone- and Rosiglitazones-reduced MMP-2 activity. These data suggesting NO is the positive regulator of MMP-2 in malignant glioma cells and dexamethasone and Rosiglitazone-induced MKP-1 which regulates MMP-2 activity and invasiveness in human malignant glioma cells via iNOS.