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• 中文摘要

Dexamethasone 是 glucocorticoids 的一種，目前已知具有抑制腫瘤侵襲的功能。然而其作用機制尚未闡明。在本實驗中，我們發現 dexamethasone 調控人類惡性膠質母細胞瘤侵襲能力的機制。我們證實 dexamethasone 減低 MMP-2 在人類惡性膠質母細胞瘤的活性。目前我們發現抗發炎藥物 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胨的活性。因此我們認爲常用來抗發炎藥物 dexamethasone 也許可用來做爲膠質母細胞癌的治療或術後的輔助療法(adjuvanttherapy)。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 合成胨抑制劑(l-NAME)與 NOdonor(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

Dexamethasone is one of glucocorticoids has been shown to inhibit tumor invasiveness. However, the underneath mechanisms have not been elucidated. In the present study, we investigated the mechanism by which dexamethasone regulated the invasiveness in human malignant glioma cells. We demonstrated that dexamethasone decreased MMP-2 activity in malignant glioma cells. Incubation of glioma cells with dexamethasone increased a dose- and time-dependent induction of MAPK phosphatase-1 (MKP-1). Pretreatment of cells with RU486 (glucocorticoid receptor antagonist), actinomycin D or cyclohexamide before addition of dexamethasone decreased MKP-1 protein level, suggesting dexamethasone-induced MKP-1 expression required de novo protein

synthesis through glucocorticoid receptor. Treatment of cells with RU486 reversed the inhibition of MMP-2 activity and cell invasiveness by dexamethasone. Similarly, knockdown of MKP-1 by small interfering RNA or expression of dominant negative MKP-1 reversed the inhibition of MMP-2 activity by dexamethasone. These data suggest that dexamethasone-inhibited MMP-2 activity and cell invasiveness via MKP-1. On the other hand, we found that iNOS was constitutiely expressed in human malignant glioma cells. We found that NO- regulate MMP-2 expression in U87MG cells. Over-expression of wild type MKP-1 decreased iNOS expression but not in MKP-1 dominant negative. Taken together, our data revealed that dexamethasone might inhibit MMP-2 activity by suppressing iNOS induction through a MKP-1-dependent pathway. These results suggest that dexamethasone can be used as a potential therapeutic agent for treatment of metastasis of human gliomas.