Dexamethasone 透過 MKP-1 訊息傳遞路徑抑制人類惡性神經膠質瘤細胞的侵襲性

Dexamethasone Inhibits Cell Invasion of Human Malignant Glioma Cells via MKP-1

中文摘要

Dexamethasone 已經知道可以抑制癌細胞的侵襲性，但是其中的機制還不清楚。本研究探討人類惡性神經膠質瘤細胞中 dexamethasone 抑制細胞侵襲性的機制。人類惡性神經膠質瘤細胞具有內生性 MMP-2 的活性，且其活性與細胞的惡性度有關。p38 MAPK 的抑制劑 SB203580 與 p42/44 ERK 的抑制劑 PD98059 都可以降低人類惡性神經膠質瘤細胞 U87MG 中 MMP-2 的活性。Dexamethasone 可以誘發 U87MG 細胞中 MKP-1 的表現，所誘發的 MKP-1 隨著 dexamethasone 濃度的增加而增加，並隨著時間的增加而持續性表現。轉錄作用的抑制劑 actinomycin D 與轉譯作用的抑制劑 cyclohexamide 都可以阻斷 U87MG 細胞中 dexamethasone 所誘發 MKP-1 的表現，顯示 dexamethasone 所誘發 MKP-1 的表現是經由新蛋白的合成。RU486 (糖皮質激素受體拮抗劑)與 triptolide (MKP-1 阻斷劑)都可以降低 U87MG 細胞中 dexamethasone 所誘發的 MKP-1，RU486 可以逆轉 dexamethasone 所抑制的細胞侵襲性。NO donor sodium nitroprusside (SNP)可以逆轉 U87MG 細胞中 dexamethasone 所抑制 MMP-2 的活性。Triptolide 可以逆轉 U87MG 細胞 dexamethasone 所抑制 iNOS 的活性。綜合以上結果可以得知，在 U87MG 細胞中，dexamethasone 透過誘發 MKP-1 而抑制 iNOS 的表現及 NO 的釋出，進而抑制 MMP-2 的活性與細胞侵襲性。

英文摘要

Dexamethasone has been shown to inhibit tumor invasion, however, the underneath mechanisms have not been elucidated. In the present study, we investigated the mechanism of which dexamethasone regulated the invasion in human malignant glioma cells. We found that human malignant glioma cells constitutively expressed MMP-2, which is well correlated with their malignancies. Treatment of glioma cells with SB203580 (a p38 MAPK inhibitor) or PD98059 (a p42/44 ERK inhibitor) reduced MMP-2 activity. Incubation of human malignant glioma cells with dexamethasone resulted in a dose- and time-dependent induction of a dual specific MAPK phosphatase, MAPK phosphatase-1(MKP-1). Treatment of glioma cells with actinomycin D (a transcription inhibitor) or cyclohexamide (a translation inhibitor) before the addition of dexamethasone decreased MKP-1 protein level, suggesting dexamethasone-induced MKP-1 expression required de novo protein synthesis.

Pretreatment of cells with RU486 (a glucocorticoid receptor antagonist) or triptolide (a pharmacological MKP-1 blocker) reversed the inhibition of MMP-2 activity and cell invasion by dexamethasone. Treatment of glioma cells with NO donor, sodium nitroprusside (SNP), reversed the inhibition of MMP-2 activity by dexamethasone. In addition, pretreatment of triptolide reversed dexamethasone-reduced inducible nitric oxide synthase (iNOS) expression. Taken together, our data suggest that dexamethasone may inhibit tumor cell invasion and MMP-2 activity through MKP-1 induction, and that NO is the positive regulator of MMP-2 in human malignant glioma cells.