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• 中文摘要

Chronic myelogenous leukemia (CML)是髓性血球前驅細胞不斷增殖的一種疾病，這種細胞喪失分化的能力。Activin A 屬於 transforming growth factor (TGF)-β 家族的一員，可以誘導細胞分化成紅血球系細胞。我們先前的研究顯示，basic fibroblast growth factor (bFGF)藉由將 p38 MAP kinase (p38)去活化而拮抗 activin A 誘導 K562 細胞的生長抑制和血紅素生成(Biochemical and Biophysical Research Communications 320:1247 - 1252, 2004)。這些結果顯示 bFGF 和 activin A 這兩個細胞激素對於 p38 的調控扮演不同的角色，而分別使 K562 細胞不分化和分化。K562 細胞是表現 BCR／ABL 的 CML 細胞株。p38 pathway 決定細胞命運的角色可以做爲一個研究的模式去了解 CML 細胞的增殖和分化的分子機制。我們利用 PCR-selectcDNA subtraction analysis 篩選出影響 K562 細胞不分化的基因，我們發現一個基因，CD69，其表現受到 activin A 的負調控，而於 activin A 和 p38 抑制劑 SB203580 同時作用下其表現量會恢復。大量表現 p38 dominant negative mutants，p38αAF 或 p38βAF，於 K562 細胞中，activin A 抑制 CD69 表現的能力會被降低、且增加細胞增生和降低細胞分化能力。我們更進一步證明，activin A 會透過抑制 Erk1／2 活性來抑制 CD69 表現。我們利用 BCR／ABL 的抑制劑 STI571 處理 K562 細胞，會降低細胞的 CD69 mRNA 和蛋白的表現。除此之外，我們發現，BCR／ABL 會正調控 CD69 promoter 活性。這些研究結果顯示 CD69 爲 BCR／ABL 下游的蛋白，可做爲 CML 細胞未分化的標識。

• 英文摘要

Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder of stem cells that has lost their differentiation activity. Activin A is a pleiotropic cytokine belonging to the transforming growth factor (TGF)-beta superfamily. In a previous study, we showed that basic fibroblast growth factor (bFGF) antagonizes activin A-mediated growth inhibition and hemoglobin synthesis in K562 cells by deactivating p38 MAP kinase (p38) (Biochemical and Biophysical Research Communications 320:1247-1252, 2004). These results suggest that the two cytokines, bFGF and activin A, which maintained K562

cells in undifferentiated state and caused cell differentiation, respectively, have different roles in the regulation of p38 pathway. The K562 cells are CML cell lines that express the BCR／ABL protein. The cell fate determining role of the p38 pathway may be used as a tool to understand the molecular mechanisms of proliferation and differentiation in these CML cells. We have used the PCR-select cDNA subtraction analysis to screen for genes involved in maintaining the undifferentiated status of K562 cells. We found a gene, CD69, was down regulated by activin A; CD69 expression levels were restored by the combination of p38 inhibitor SB203580 with activin A. The Activin A-inhibited CD69 expression was reduced in K562-derived cells stably overexpressing the p38 dominant negative mutants, p38alphaAF or p38betaAF, which was associated with increased cell proliferation and decreased differentiation. We further demonstrated that Activin A inhibited CD69 expression by deactivating ERK1／2. The exposure of K562 cells to the Bcr／Abl tyrosine kinase inhibitor STI571 resulted in decreased expression of CD69 mRNA and protein. In addition, Bcr-Abl was found to up-regulate CD69 promoter activity. Taken together, these results suggest that CD69 is a downstream protein of Bcr／Abl and CD69 may be as an undifferentiated marker in CML cells.