# Dipyridamole經由抑制Akt活化來導致腎絲球環間膜細胞計劃性死亡

# Dipyridamole induces apoptosis by inhibiting Akt activation in rat mesangial cells

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摘要

Dipyridamole (Persantin)是一種常用來治療腎臟疾病的藥物。有抑制腎絲球環間膜細胞增生的功能。但是其機制尚未很明確，這種藥物的作用分成二個方向，其一是透過抑制非特異性 phosphodiesterase，來累積細胞內的 cAMP 及 cGMP；另一方面則是 uncleoside transport inhibitor。在我們的實驗中，利用 MTT Assay 可以觀察到 dipyridamole 對培養的環間膜細胞生長有抑制的作用，藉著[(上標 3)H]thymideine incoporation 的實驗，可發現經過 dipyridamole 處理的細胞其 DNA 合成量減少；但並未改變細胞釋出之 LDH，因此 dipyridamole 所造成細胞數目減少並非 necrosis 之故；同時，經由流式細胞儀發現細胞週期停滯，且 Sub-G1 期細胞有增加的趨勢。在經過 dipyridamole 處理 48 小時之後，可以發現細胞有計劃性死亡(apoptosis)的特徵，例如 DNA 階梯化(laddering)、sub G1 期的細胞增多及 Bc1-2 和 Apaf-1 的減少等。除此之外，我們發現 dipyridamole 處理過之環間膜細胞的 Akt/PKB 的磷酸化有減少的現象，所以由此結果推論，dipyridamole 可能是經由透過抑制 Akt/PKB 的磷酸化來降低存活訊息而導致環間膜細胞的計劃性死亡。

**Abstract**

Dipyridamole (persantin) is a nucleoside transport inhibitor and a non-specific phosphodiesterase inhibitor that increases intracellular levels of cAMP and cGMP through phosphodiesterase inhibition. Dipyridamole has been demonstrated to have an antiproliferative effect in glomerular mesangial cells. In the present study, we have confirmed that exposure of the mesangial cells to dipyridamole decreases the number of viable cells, as demonstrated by MTT assay. Dipyridamole suppressed [(superscript 3)H] thymidine incorporation into DNA and the reduction of viable cells are not due to toxicity because the LDH release from mesangial cells does not increase. Treatment of mesangial cells with dipyridamole arrests cell-cycle progression and increases the cell population at the sub G1 phase. Furthermore, incubation of mesangial cells with dipyridamole for 48 h induces characteristic features of apoptosis. The induction of mesangial cell apoptosis is correlated with Akt/PKB dephosphorylation and Bcl-2 down regulation. These data suggest that

dipyridamole may block Akt/PKB phosphorylation and play a crucial role in the induction of apoptosis in rat mesangial cells

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