Tubulin-interacting agents 之抗血管增生作用

Anti-angiogenic effects of tubulin-interacting agents

中文摘要

血管增生是從已經存在的血管中發展出新血管的過程，對於原發性的腫瘤生長、侵入以及轉移扮演著關鍵性的角色。血管增生需要持續提供腫瘤營養，所以對於腫瘤生長是重要的。Tubulin-interacting agents，例如 colchicine 和 the vinca alkaloids ，除了有抗有絲分裂的功能，還會破壞腫瘤的血管，也顯示具有 anti-vascular 或是 antiangiogenic 能力。本研究的主要目的是證實五種 tubulin-interacting agents, combretastatin A4 (CA4)、combretastatin A4 phosphate (CA4-P)、DBPR104、D-24851 和 DBPR204 是否具有 anti-angiogenic 作用。在體外實驗中，這些 compounds 在 concentration- 和 time-dependent 的實驗中，會抑制人類臍帶靜脈內皮細胞 (human umbilical vein endothelial cells, HUVECs)的增生及遷徙。CA4, CA4-P, DBPR104, DBPR204 和 D-24851 抑制細胞增生的 IC50s 濃度分別是 1.6、4.1、2.3、12.9 和 1.6 nM。在 ex vivo rat aorta tube formation 的實驗中，這些 compounds 都具有抑制動脈環的血管增生能力，所使用的方法是我們實驗室所建立的 MTS 的測定方法。CA4、CA4-P、DBPR104、D-24851 和 DBPR204 抑制血管增生的 IC50s 濃度分別是 23、70、20、43 和 17 nM。DBPR104 也對裸鼠皮下種殖之子宮頸癌腫瘤有 anti-angiogenic 作用。我們的實驗結果證實了這五種 tubulin-interacting agents 都具有 anti-angiogenic 的能力。而其詳細的機制則需更進一步的探討。

英文摘要

Angiogenesis, the formation of new vessels from existing vasculature, has a critical role in primary tumor growth, invasion, and metastasis. Angiogenesis is necessary for tumor growth that requires constant supply of the nutrients. Tubulin-interacting agents, such as colchicine and the vinca alkaloids could, in addition to their antimitotic effects, induce vascular shutdown in experimental tumor systems and also showed anti-vascular or antiangiogenic activity. The aim of this study was to examine the anti-angiogenic effects of five tubulin-interacting agents, combretastatin A4 (CA4), combretastatin A4 phosphate (CA4-P), DBPR104, D-24851, and DBPR204. The present study found that these compounds showed in vitro anti-angiogenic effects in the growth of human umbilical vein endothelial cells (HUVECs) in a concentration- and time-dependent manner. The IC50 of the compounds is 1.6, 4.1, 2.3, 12.9, 1.6 for CA4, CA4-P, DBPR104, DBPR204 and D-24851, respectively. In the ex vivo rat aorta tube formation model, all of these compounds inhibited angiogenesis shown by

a colorimetric MTS method established in our laboratories. The IC50s in inhibiting the angiogenesis were at 23, 70, 20, 43, and 17 nM for CA4, CA4-P, DBPR104, D-24851, and DBPR204, respectively. Furthermore, in vivo study using nude mice with subcutaneously implanted KB tumor also showed anti-angiogenic activity for DBPR104. Our results showed that the tested five tubulin-interacting agents exhibited an anti-angiogenic effect. However, the detailed molecular mechanism needs to be further investigated.