BJ-601 對於人類血管內皮細胞的生長抑制作用

The anti-proliferation effect of BJ-601 in human vascular endothelial cells

中文摘要

藉由抑制血管的增生（angiogenesis）進一步抑制腫瘤的生長，爲近年來相當熱門的研究課題。血管增生主要是內皮細胞的增生及遷移現象。本篇論文主要爲探討藥物 BJ-601 對人類臍帶靜脈內皮細胞(human umbilical vein endothelial cell，HUVEC)及人類包皮微血管內皮細胞(human dermal micro-vascular endothelial cell，HDMVEC)生長的抑制，並且探討可能的作用機制。

本研究顯示，BJ-601 能使 HUVEC 及 HDMVEC 的生長產生抑制作用，其抑制效果與 BJ-601 的劑量呈正相關性(dose-dependent)。以 3H-thymidine incorporation 的研究觀察，在加藥 24 小時後，BJ-601 明顯的抑制內皮細胞 DNA 的合成，並且將細胞週期停滯在 G0/G1 期。利用 Western blotting 方法我們偵測到，內皮細胞以 BJ-601 處理後，可以觀察到和細胞週期停滯（cell cycle arrest）有關的蛋白 p21、 p27 及 p53 比對照組有明顯的增加。我們分別利用 anti-cdk2 antibody 及 anti-cdk4 antibody 進行免疫沉澱法（immuno-precipitation）發現加藥組和 cdk2-cyclin complex 結合的 p27 以及和 cdk4-cyclin complex 上結合的 p21 的確比對照組有增加的現象。利用 kinase assay 發現，p21 及 p27 的增加會抑制 cdk2 的活性，進而造成細胞週期停滯在 G0/G1 時期。

本研究提出，BJ-601 對 HUVEC 及 HDMVEC 兩種內皮細胞的生長週期停滯的可能作用機制，期能藉由 BJ-601 對血管增生的抑制，而進一步達成治療癌症的功效。

英文摘要

Recently, anti-angiogenesis has become an attractive, potential strategy for cancer therapy. In this thesis, we investigated the anti-proliferation effect of BJ-601 on human umbilical vein endothelial cell (HUVEC) and human dermal micro-vascular endothelial cell (HDMVEC), and its underlying molecular mechanism.

In this study, we demonstrated that BJ-601 induced a dose-dependent inhibition on HUVEC and HDMVEC. After treatment of the cells with BJ-601 for 24 hours, the DNA synthesis was reduced, and the cell cycle was arrested in G0/G1 phase evidenced by H3-thymidine incorporation studies. Using western blotting analysis, we demonstrated that BJ-601 changed the level of the cell cycle related proteins; the level of cyclin-dependent protein kinase inhibitors, p21, p27, and p53, were significantly increased, while the level of cyclin-dependent protein kinase-2 (cdk-2) protein was decreased. Furthermore, immuno-precipitation study show that the cdk4-cyclin-linked

p21 as well as the cdk2-cyclin-linked p27 proteins were significantly increased after BJ-601 treatment. Using kinase assay method to measure the kinase activity, we further demonstrated that the cdk-2 activity was decreased in the BJ-601 treated HDMVEC.

In this study, we delineated the possible mechanisms of the BJ-601 inhibitory effects on the cell cycle of HUVEC and HDMVEC. The findings from the present study suggest that BJ-601 might have the potential to inhibit the occurrence of angiogenesis.