ASK1 在氧化態低密度脂蛋白誘導腦內皮細胞死亡所扮演的角色

The Role of ASK1 in Ox-LDL-induced Cerebral Endothelial Cell Death

中文摘要

近四十年來缺血性中風始終是造成人類殘障甚至死亡的主因，而粥狀動脈硬化被認為是導致心肌梗塞以及中風的主要元凶。有研究指出中風病人其血中的膽固醇、三酸甘油脂及低密度脂蛋白有濃度較高的現象。另一方面，腦部內皮細胞與星狀細胞為構成血腦障蔽 (blood brain barrier) 的主要組成，可以調控血液與腦部間水份及其他營養物質的交換，並防止一些循環系統中的毒素或其他傷害性物質進入腦部，且維持中樞神經系統的恆定。因此我們推測氧化態低密度脂蛋白若能誘導腦部內皮細胞死亡便會使得血腦障壁損傷進而導致中風。然而，氧化態低密度脂蛋白是否誘導腦部內皮細胞死亡及其分子機轉至今仍待釐清。在本論文中我們探討 apoptosis signal-regulating kinase 1 (ASK1) 在氧化態低密度脂蛋白誘導腦部內皮細胞死亡作用中所扮演的角色。氧化態低密度脂蛋白可時間相關性的誘導 ASK1 去磷酸化，ASK1 去磷酸化後會導致 ASK1 與抑制性蛋白 14-3-3 分離，游離的 ASK1 活性增加並活化其下游的 c-Jun NH2-terminal kinase (JNK)/activating protein-1 (AP-1) 訊息傳遞路徑，進而誘導具有促進細胞凋亡功能的 Bim 表現增加。細胞轉染 ASK1 dominant-negative mutant (DN)、JNK1 DN 或 JNK2 DN 可抑制氧化態低密度脂蛋白所誘導的腦部內皮細胞死亡。此外，我們也利用流式細胞儀與 DNA 斷片分析證明氧化態低密度脂蛋白誘導的腦部內皮細胞死亡是經由細胞凋亡的方式進行。綜合以上結果推測，氧化態低密度脂蛋白可經由活化 ASK1/JNK/AP-1 訊息傳遞路徑誘導 Bim 表現增加，最後使得腦部內皮細胞凋亡。

英文摘要

Ischemic stroke is the main leading cause of human inability and mortality in these forty years. Atherosclerosis is believed to play an important role in the pathogenesis of myocardiac infarction and stroke. Several clinical studies demonstrated that plasma level of cholesterol, triglyceride, and low density lipoprotein are significantly higher in patients with stoke. Cerebral endothelial cell (CECs) and astrocytes constitute the blood brain barrier (BBB) to shield the brain from damage by harmful circulating toxins or deleterious cellular elements. As a result, CEC death appears to be a contributing factor in oxidized low density lipoprotein (ox-LDL)-induced BBB breakdown and stroke. However, the molecular mechanism of ox-LDL-induced CEC death has not been delineated. In the present study, We explore the role of apoptosis signal-regulating kinase 1 (ASK1) in ox-LDL-induced death in CECs. ox-LDL

time-dependently induced ASK1 dephosphorylation. ASK1 dephosphorylation resulted in its dissociation from 14-3-3. ASK1, released from 14-3-3 inhibition, activated JNK/AP-1 signaling cascade, which in turn transactivated the expression of Bim, a pro-apoptotic protein. Transfection with various dominant negative mutants (DNs) including ASK1 DN, JNK1 DN and JNK2 DN suppressed ox-LDL-induced CEC death. In addition, we also demonstrated that ox-LDL-induced CEC death is due to apoptosis using flowcytometry and DNA laddering assay. Taken together, these results suggest that ox-LDL activates the ASK1/JNK/AP-1 cascade to cause Bim expression and subsequent apoptosis in CECs.