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• 中文關鍵字	阿茲海默式症; 樣澱粉 beta 胜太;腦血管樣澱粉病變; 腦內皮細胞; 細胞凋亡;
• 英文關鍵字	Alzheimer's disease (AD); Amyloid beta peptide (Abeta); Cerebral amyloid angiopathy (CAA); Cerebral endothelial cells (CECs); apoptosis; Apoptosis ; Signal-Regulating kinase1(ASK1)。
• 中文摘要	樣澱粉 beta 胜太(amyloid beta peptide)與阿？海默症的神經及血管退化具有相當的關連性。樣澱粉沈積在腦部血管稱爲腦血管樣澱粉病變 (cerebral amyloid angiopathy, CAA)，而無論是否爲阿？海默症的病患，腦血管樣澱粉病變皆是老年人出血性中風及缺血性中風的重要原因之一。最近的研究發現，樣澱粉 beta 會誘導腦血管內皮細胞產生細胞凋亡，然而其作用機制則尚未研究清楚。因此我們將探討樣澱粉引發腦內皮細胞凋亡的機制。希望此計劃的完成可進一步瞭解樣澱粉 beta 調控腦內皮細胞凋亡的機轉，並且發展出治療樣澱粉 beta 誘發腦血管疾病的治療方針。利用 MTT 測分析，我們發現樣澱粉 beta 會濃度依賴性的降低腦內皮細胞的細胞存活率。而進一步利用流式細胞儀分析發現選擇性的 p38MAPK 和 JNK 抑制劑，SB203580 及 SP600125 可以抑制樣澱粉 beta 所引起的腦部內皮細胞凋亡。這結果指出澱粉 beta 可能是透過活化 p38 MAPK 和 JNK 而使得腦部內皮細胞進行細胞凋亡。再者，樣澱粉 beta 會顯著增加 p38MAPK 和 JNK 的活性。利用 MBP 當作受質，我們發現樣澱粉 beta 可以在短時間內增加 apoptosis signal-regulating kinase 1(ASK1)的活性而後回復到基礎？(basal level)，相對地，可負向調控 ASK1 的蛋白激？Akt 的活性在樣澱粉刺激下而降低，這意味著樣澱粉 beta 可能透過抑制 Akt 而活化 ASK1 使得腦部細胞凋亡。再者，當細胞轉殖不活化態的 dominant-negative ASK1(dn-ASK1)會顯著的阻斷樣澱粉 beta 所增加 p53 在胺基酸殘基 ser15 位置的磷酸化以及增加 p53 蛋白的安定性。在 p53 所調控的基因中，我們發現樣澱粉 beta 會增加 bax 表現，而這增加的現象會被 dn-ASK1 所抑制。已有報導指出 ASK1 可以透過 p38 訊息傳遞路徑促使細胞凋亡，因此在本年度的研究中我們推測樣澱粉 beta 可能是透過活化 ASK1/p38MAPK/p53/Bax 訊息傳遞路徑而引起細胞凋亡。

- 英文摘要

The amyloid beta peptide (Abeta) has been linked to both neuronal and vascular degeneration in Alzheimer's disease (AD). Amyloid deposition in cerebral vessels (cerebral amyloid angiopathy, CAA) is also a major cause of hemorrhagic and ischemic stroke in the elderly with or without AD. Recent studies have found that cerebral endothelial cells (CECs) exposed to Abeta die with features suggestive of apoptosis. However, the molecular mechanism through which Abeta exerts its apoptotic effect remains to be elucidated. Here, we investigated the molecular mechanisms underlying Abeta-induced cell death in cerebral endothelial cells. Using MTT assay, we show here that Abeta decreased cell viability in a dose-dependent manner. Selective p38 MAPK inhibitor, SB203580, and JNK inhibitor SP600125 blocked Abeta-induced cell cycle accumulation on the sub-G1 phase as determined by flowcytometry. This indicated that activation of p38 MAPK and JNK might be critical in Abeta-induced cell death. Moreover, Abeta treatment significantly resulted in the activation of p38 mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinase (JNK) in apoptosing cells. An important role for apoptosis signal-regulating kinase 1 (ASK1) in Abeta apoptotic effect was also demonstrated by ASK1 kinase activity assay using MBP as substrate. We showed the ASK1 kinase activity was transient increased upon Abeta treatment and then declined to basal level after 1 hour. The increased ASK1 activity was correlated with the decrease of Akt activity which play an inhibitory role in ASK1 regulation. In the other hand, p53 might lay downstream of ASK1 signaling pathway since cells transfected with dominant-negative ASK1 (dn-ASK1) significantly diminished Abeta-induced p53 phosphorylation at Ser15 and Abeta-increased p53 protein level. We also found that the upregulation of p53-target gene, Bax was suppressed by dn-ASK1 in Abeta-treated cells. However, activation of ASK1 has been reported might occur upstream of p38MAPK signaling pathway leading to cell apoptosis. Taken together, these findings suggest that Abeta might induce cell apoptosis through ASK1/p38MAPK/p53/Bax signaling cascade.