

# Amyloid beta peptide-activated signal pathways in human platelets

馮琮涵

Shen MY;Hsiao G;Fong TH;Chen HM;Chou DS;Lin CH;Sheu

JR;Hsu CY

摘要

## Abstract

Amyloid beta peptide (amyloid- $\beta$ ), which accumulates in the cerebral microvessels in an age-dependent manner, plays a key role in the pathogenesis of cerebral amyloid angiopathy. Platelets are an important cellular element in vasculopathy of various causes. Amyloid- $\beta$  may activate or potentiate platelet aggregation. The present study explored the signaling events that underlie amyloid- $\beta$  activation of platelet aggregation. Platelet aggregometry, immunoblotting and assays to detect activated cellular events were applied to examine the signaling processes of amyloid- $\beta$  activation of platelets. Exogenous amyloid- $\beta$  (1 – 2  $\mu$ M) potentiated platelet aggregation caused by collagen and other agonists. At higher concentrations (5 – 10  $\mu$ M), amyloid- $\beta$  induced platelet aggregation which was accompanied by an increase in thromboxane A2 (TxA2) formation. These amyloid- $\beta$  actions on platelets were causally related to amyloid- $\beta$  activation of p38 mitogen-activated protein kinase (MAPK). Inhibitors of p38 MAPK and its upstream signaling pathways including proteinase-activated receptor 1 (PAR1), Ras, phosphoinositide 3-kinase (PI3-kinase), or Akt, but not extracellular signal-regulated kinase 2 (ERK2)/c-Jun N-terminal kinase 1 (JNK1), blocked amyloid- $\beta$ -induced platelet activation. These findings suggest that the p38 MAPK, but not ERK2 or JNK1 pathway, is specifically activated in amyloid- $\beta$ -induced platelet aggregation with the following signaling pathway: PAR1  $\rightarrow$  Ras/Raf  $\rightarrow$  PI3-kinase  $\rightarrow$  Akt  $\rightarrow$  p38 MAPK  $\rightarrow$  cytosolic phospholipase A2 (cPLA2) $\rightarrow$  TxA2. In conclusion, this study demonstrates amyloid- $\beta$  activation of a p38 MAPK signaling pathway in platelets leading to aggregation. Further studies are needed to define the specific role of amyloid- $\beta$  activation of platelets in the pathogenesis of vasculopathy including cerebral amyloid angiopathy.