Tyrosine Kinase and Mitogen Activated Protein (MAP) Kinase Pathway on Cerebral Vasospasm after Aneurysmal Subarachnoid Hemorrhage

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Abstract

Cerebral vasospasm is a severe complication after an aneurysm rupture. Many efforts have been done to understand the complexity signaling pathways involved in this condition. MAP kinase has been suggested to be one of the most important signaling pathways involved in cerebral vasospasm. This pathway is clinically important as it has both outcome and therapeutic implications.

Keywords: MAP kinase; Tyrosine kinase; Signaling pathways; Cerebral vasospasm

Introduction

Cerebral vasospasm is the most important complication following the subarachnoid hemorrhage (SAH) [1,2]. Despite current medical treatment, including hemodynamic therapy and calcium block channels medicines, up to 15% of surviving patients develops severe complications from vasospasm, making cerebral vasospasm the most important issue in outcome of patients after an aneurysm rupture [1-4]. Cerebral vasospasm involves a complex multiple signaling pathways. Many authors have been identified MAP kinase as the most important signaling pathway on vasospasm regards proliferation, inflammation, cell death, smooth muscle phenotype changes, vascular remodeling, and vascular contraction [2-6]. This mini review describes some important point in this pathway and tries to introduce the new molecular specific targets in selective treatment on vasospasm.

Tyrosine Kinase and MAP Kinase

Contraction of cerebral arteries is directly controlled by MAP kinase, involved in Ca++ regulation on cerebral smooth muscle cells. After an aneurysm rupture, hemoglobin, vasoactive agents (endothelin-1) and free radicals of blood clot enhance and activate MAP kinase expression in vascular smooth muscle cells [2,7,8].

Also, fibroblasts compaction is another important pathway involved in cerebral vasospasm. Some authors determined that Tyrosine kinase is responsible for this mechanism, activated by G-protein coupled receptor agonist and growth factors [1,2]. Di Savio et al. founded increased levels of G-protein receptor agonist such as adenosine triphosphate and endothelins, growth factors, and their receptors in cerebrospinal fluid and cerebral arteries in experimental models [7]. Other substrates were described after tyrosine kinase activation, such as Ras protein and phosphatidyl inositol-3 kinase tyrosine kinase. Ras is increased after spasm stimulation, and phosphatidyl-inositol-3 kinase is enhanced after vasospasm in animals. In experimental models, sumarin (tyrosine kinase inhibitors) reduced vasospasm. By the other side, this response was not obtained with phosphatidylinositol-3-kinase inhibitors (Figure 1) [2,7,8].

Conclusion

Pathogenesis of cerebral vasospasm involves multiple signaling pathways in proliferation, in inflammation, cell death, smooth muscle phenotype changes, vascular remodeling, and contraction. Understanding pathways in vasospasm might offer new possibilities for selective treatment of cerebral vasospasm in the future. Additional research is required to clarify the roles of these pathways and agents in vasospasm.

References


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Received December 28, 2015; Accepted January 19, 2016; Published January 23, 2016

Citation: Romero FR, Zanini MA (2016) Tyrosine Kinase and Mitogen Activated Protein (MAP) Kinase Pathway on Cerebral Vasospasm after Aneurysmal Subarachnoid Hemorrhage. Brain Disord Ther 5: 205. doi:10.4172/2168-975X.1000205

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