Differential regulation of TSP-1 and TSP-2 following focal cerebral ischemia-reperfusion.

許重義
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Abstract

Angiogenesis occurs after cerebral ischemia, and the extent of angiogenesis has been correlated with survival in stroke patients. However, postischemic angiogenesis is short-lived and may be completely terminated within a few weeks after ischemic insult. The molecular mechanism underlying the dissolution of postischemic angiogenic processes is poorly understood. Although the expression of angiogenic genes has been studied in ischemic stroke models, the activation of angiostatic genes after cerebral ischemia has not been investigated. Thrombospondin (TSP)-1 and TSP-2 are naturally occurring angiostatic factors, which inhibit angiogenesis in vivo. The aim of the present study was to explore the expression of TSP-1 and TSP-2 in relation to the evolution of angiogenic process in a focal ischemia model in rats.

Methods— Rats underwent cortical ischemia in the middle cerebral artery territory for 60 minutes and reperfusion for up to 2 weeks. Northern and Western blot analysis were used to study the temporal profile of TSP-1 and TSP-2 expression at the mRNA and protein level, respectively. In situ hybridization and immunohistochemical studies were used to examine the spatial expression patterns. Double immunostaining was applied to define the cellular origins of TSP-1 and TSP-2.

Results— A biphasic expression of TSP-1 was noted after ischemia, peaking at 1 and 72 hours. Endothelial cells in the leptomeninges were the only source of the first TSP-1 peak, whereas endothelial, glial, neuronal, and macrophage cells contributed to the second peak of TSP-1 expression. TSP-2 expression occurred much later and in a monophasic manner, peaking 2 weeks after ischemia. TSP-2 immunoreactivity was observed in endothelial, neuronal, and macrophage, but not glial, cells. TSP-1 was expressed before the peak of angiogenesis, whereas robust TSP-2 expression occurred at the peak of angiogenesis and continued into the period when angiogenesis had completely resolved.

Conclusions— Robust expression of TSP-1 and TSP-2, 2 major angiostatic factors, was noted in the ischemic brain with different temporal expression profiles from different cellular origins. The expression of these angiostatic factors, especially TSP-2, likely contributes to the spontaneous resolution of postischemic angiogenesis. Further studies are needed to explore the molecular mechanisms that regulate the balance of angiogenic and angiostatic factors in the ischemic brain.