＜シンポジウム 06―1＞脳血管障害治療の次のブレークスルーを目指して

Regulating the Responses of the Neurovascular Unit to Focal Ischemia

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During focal cerebral ischemia, cerebral microvessel and their recipient neurons, as well as other components of the neurovascular unit (NVU), suffer a sequence of consistent and complex changes. The NVU is both a structural and conceptual framework that recognizes functional interactions among the cells and their environment, during normal conditions and following injury. This conceptual unit consists of microvessels (endothelial cells-basal lamina matrix-astrocyte end-feet [and pericytes]), astrocytes, neurons and their axons, and other supporting cells (e.g., microglia and oligodendroglia) that are likely to modulate the function of the unit. This also provides a framework for considering potential bidirectional communication between neurons and their supply microvessels with the participation of intervening astrocytes.

The failure of "neuroprotectant" agents, intended to "protect" the neurons during ischemic injury, to bring clinical benefit can be explained by targeting of only one component of the neurovascular unit. On the contrary, maintenance or restitution of blood flow to the unit appears to produce benefit to the NVU.

Among the numerous potential interrelationships among cells and components of the neurovascular unit, the contributions of astrocytes and microglial cells to the integrity of the unit during injury have not been rigorously explored. For instance, the now well-described responses of the gelatinases (pro-MMP-2 and pro-MMP-9, and their activated products) have been shown to increase variously in small and large animal models of focal cerebral ischemia, and in various settings in ischemic stroke patients. A rigorous examination of that data suggests inconsistencies among the clinical reports that have been left unexplained, and the exact cellular sources are not named. As the potential window for treatment with large artery recanalization techniques increases the possible ill effects of these proteases on the NVU become more important to understand.

A critical examination of the roles of astrocytes and microglia in NVU responses to ischemia can resolve many of these clinical inconsistencies. (pro-) MMP-2 and (pro-) MMP-9 generation in non-human primate tissue with regions of ischemia and plasma leakage, and primary murine microglial cells and astrocytes, have been assayed by immunocytochemistry, zymography, and real-time RT-PCR. Ischemia-related hemorrhage was associated with microglial cell activation in tissue, and the leakage of plasma fibronectin (FN) and vitronectin (VN). In strict serum-depleted primary cultures, pro-MMP-9 was generated exclusively by microglia exposed to VN and FN found in plasma (not in the normoxic CNS) and was enhanced by experimental ischemia (oxygen-glucose deprivation, OGD). Primary astrocytes generated exclusively pro-MMP-2, and not pro-MMP-9, which decreased on each matrix substrate during OGD. Microglia-astrocyte contact enhanced pro-MMP-9 generation in a cell-concentration-dependent manner under OGD. Limited studies have indicated that activated microglial cells do not produce sufficient local activity to alter matrix integrity. Hence, asytrocytes alone do not generate pro-MMP-9. It is likely that the resting microglia in brain, upon encountering plasma or blood during focal ischemia, generate MMP-9. But, it is unclear whether either gelatinase is responsible for increased microvascular permeability as has been asserted.

This is relevant to the broadening window for the use of the plasminogen activator rt-PA as asserted by ECASS-III, recently published. Here, patients could be safely treated at 3.0-4.5 hours after stroke onset. The safety relative to treatment within a 6.0 hour window in other studies could represent refined patient selection in ECASS-III, to reduce the risk of increased microvessel permeability. This choice suggests that the status of the NVU depends upon patient selection.

These observations support a number of implications about how stroke acutely injures both non-vascular and vascular tissues within the brain. They also have implications for the manner in which components of the NVU may com-

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municate with one another, and their roles in the matrix environment during focal ischemia. It is of interest how patient selection, reperfusion, and cellular protection are intertwined and could improve the outcomes of ischemic stroke at the level of the neurovascular unit.