is there a benefit for clipping or coiling. A recent meta-analysis of three randomized clinical trials including ISAT did not show a significant difference in outcomes between patients treated with these two options.11

Despite limitations of ISAT, this is a well-executed trial that highlights the necessity of long-term follow-up in aneurysmal SAH patients. The increased rate of rebleeding in untreated and de novo aneurysms underscores that clipping or coiling does not eliminate the underlying pathogenesis of cerebral aneurysms and that aggressive management of secondary risk factors is essential.

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Mammalian Target of Rapamycin (mTOR) Activity Promotes Neuronal Survival in Stroke With or Without Ischemic Postconditioning

Ischemic postconditioning (IPC), a concept derived from myocardial ischemic models, confers neuroprotection in various models of experimental stroke.1 Following a series of occlusion and reperfusion periods after the initial ischemic insult, IPC improves glucose uptake, reduces free radical generation, inhibits inflammation, and promotes protein activity in the phosphatidylinositol 3-kinase/Akt pathway.2-4 Although the exact relationship between mammalian target of rapamycin (mTOR), a member of the phosphatidylinositol 3-kinase-related kinase family, and IPC is still unclear, it is known that modulation of mTOR by IPC promotes cell metabolism, growth, differentiation, development, and cell survival.5

Xie et al6-8 created an in vivo stroke model incorporating IPC by generating focal cerebral ischemia through bilateral common carotid artery occlusions and permanent distal middle cerebral artery occlusion in male Sprague-Dawley rats. IPC was performed immediately after bilateral common carotid artery occlusions with 30 seconds of reperfusion followed by 10 seconds of temporary reocclusion. This sequence was repeated 3 times. Because Xie and colleagues were unable to clone the mTOR gene in a plasmid backbone, they constructed a lentiviral vector expressing S6K1, a downstream protein of mTOR and indicator of mTOR activity. To inhibit mTOR activity, the authors used rapamycin and a lentiviral vector containing mTOR short hairpin RNA (shRNA) to reduce mTOR expression. Rapamycin (5 μL, 1 mmol/L) was infused into the ventricular space ipsilateral to the ischemic side 1 hour before occlusion with a microsyringe pump. Lentiviruses were injected into the left cortex 5 days before occlusion, and infarct size was measured 2 days after ischemia.

The authors went on to subject mixed neuronal cultures derived from rat fetal brains to oxygen-glucose deprivation (OGD). Nine to 11 days after preparation, 6 hours of OGD was induced in a hypoxic chamber, followed by in vitro hypoischemic postconditioning (HPC). HPC was achieved through 3 cycles of 15-minute restoration of glucose and oxygen and 15 minutes of OGD. Lactate dehydrogenase levels were used to quantify cell death 18 hours after OGD.

Initial experiments demonstrated that IPC promotes the phosphorylation and activation of mTOR and other mTOR-related proteins (S6K1, S6, and 4EBP1). The authors showed reduced levels of protein phosphorylation in stroke models without IPC. In the penumbra, phosphorylation of such proteins was elevated in IPC models and reduced in non-IPC models. Furthermore, rapamycin, a known mTOR inhibitor, was found to exacerbate infarct volumes and to lower phosphorylated proteins in common carotid artery occlusion models with or without IPC. Likewise, transfection of shRNA worsened ischemic injury and reversed the protective effects of IPC, whereas gene transfer of S6K, a downstream protein of mTOR, inhibited neuronal death. In vitro, rapamycin worsened cell death induced by OGD and abolished the protective effects of HPC (Figure).

Postischemic neuronal injury occurs through multiple mechanisms, including the disruption of cell growth, a decrease in protein activity, and the creation of a proinflammatory state. Since the discovery of the protective benefits of IPC after myocardial ischemia, neuroscientists have tried to obtain equally positive results and to understand which proteins are affected by IPC in the setting of cerebral ischemia. The ability to successfully promote mTOR phosphorylation and to accelerate its downstream protein production may ultimately represent a novel therapeutic strategy for patients with stroke.

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A Previously Unidentified Mechanism of Immune Evasion in Glioblastoma

Despite gradual advancements in surgical technique, chemotherapy, and radiotherapy, current treatments for glioblastoma multiforme (GBM) still have only limited efficacy. One evolving strategy is the development of immunotherapies that upregulate or activate host immune function to target and destroy GBM cells. There is evidence, however, that patients with GBM have suppressed immune function, which may limit the success of immunotherapy.

Natural killer (NK) cells, an important component of the innate immune system, typically express NKG2D receptors on their cell surface. These receptors bind specific ligands (eg, MICB, ULBP-1) on target cells of interest, and binding triggers the release of cytotoxic granules and inflammatory cytokines, ultimately causing target cell death. Interestingly, it has been observed that NK cells have downregulated the expression of NKG2D in patients with GBM.

Myeloid-derived cells, including circulating monocytes and tumor-infiltrating macrophages, are believed to be an important driver of tumor-mediated immune invasion. Crane et al recently studied myeloid-lineage cells from patients with GBM and found that these cells overexpressed the NKG2D ligands MICB and ULBP-1 on their cell surfaces compared with myeloid cells from control subjects without GBM.

Next, the investigators studied several GBM cell lines (U87, SF767, U251) and determined that both lactate dehydrogenase 5 (LDH5), a tetrameric metabolic enzyme produced by

Figure. Rapamycin blocked the neuroprotective effects of hypoxic postconditioning (HPC) and ischemic postconditioning (IPC) both in vitro and in vivo. A, effects of rapamycin and HPC on neuronal death as measured by lactate dehydrogenase (LDH) release in vitro. LDH release was measured 18 hours after oxygen-glucose deprivation (OGD). All data from cultures without OGD were normalized to the values of control, non-OGD samples treated with vehicle that did not contain rapamycin (n = 16 per group). B, representative coronal sections of ischemic brain stained by the cresyl violet method. Infarct regions are traced. C, average infarct size measured from 5 coronal sections (n = 8 per group). *P < .05 vs the vehicle of the indicated group; #P < .05, ##P < .01 between the 2 indicated groups. Reprinted with permission from Xie et al.