The idea that exposure to sublethal ischemia could confer protection against a subsequent ischemic insult goes back at least as far as 1989, when Miyazaki and Zipes (13) reported that a sequence of four 5-min coronary occlusions reduced the autonomic denervation produced by a subsequent coronary occlusion in dog hearts. This idea rapidly gained popularity, and, in 1994, Kato et al. (10) reported that prior exposure to ischemia also conferred ischemic protection in the brain. That same year, Gidday et al. (8) also reported this preconditioning effect in neonatal rats. In the time elapsed since these early observations, several thousand published studies of ischemic preconditioning in the heart and brain have revealed a complex interplay of multiple mechanisms that appear to be highly specialized among the different cell types involved.

Whereas much of the work done to identify the pathways involved in ischemic preconditioning have focused on the parenchymal cells of the heart and brain, it quickly became clear that blood vessels are important players in the preconditioning process. In 1994, Richard et al. (16) found that ischemic preconditioning improved postischemic attenuation of coronary vasoreactivity in rat heart, and two years later Wang et al. (19) observed that preconditioning ameliorated postischemic vasospasm in rat skeletal muscle. By the year 2000, the potential involvement of cerebral arteries in the effect of ischemic preconditioning on the brain was also recognized (6).

As in coronary arteries (16), much of the early interest in the cerebrovascular contribution to ischemic preconditioning focused on the endothelium. Correspondingly, ischemic preconditioning was first shown to reduce postischemic brain edema in the rat (12). In cultured mouse endothelial cells, preconditioning with oxygen-glucose deprivation (OGD) enhanced resistance to subsequent bouts of OGD, as revealed by lactate dehydrogenase release and expression of intercellular adhesion molecule-1 (2). Then, in 2004, Hashiguchi et al. (9) reported their fundamental observation that in the gerbil hippocampus, ischemic preconditioning upregulated the expression and activity of endothelial nitric oxide synthase (eNOS) through a phosphatidylinositol 3-kinase (PI3-kinase) and Akt-dependent pathway. Equally important, these authors also reported the provocative observation that inhibition of either eNOS or PI3-kinase ablated the effects of preconditioning. The ability of eNOS inhibition to eliminate the effects of ischemic preconditioning in rat brain has also been reported by Vlasov et al. (18).

In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, the most recent study by the Gidday group (21) introduces yet another potentially important role for the PI3-kinase/Akt pathway in the effects of ischemic preconditioning on cerebrovascular endothelium. Using cultured human brain microvascular endothelial cells, these investigators have shown that hypoxic preconditioning reduces the ability of a subsequent bout of OGD to induce apoptosis in this human cell line. Most importantly, the effects of preconditioning could be blocked by treatment with wortmannin, an inhibitor of PI3-kinase. Prima facie, this is not a surprising outcome given that ischemic insults have long been associated with increased rates of apoptotic conversion, and ischemic preconditioning has been shown to attenuate the myocardial apoptosis induced by coronary occlusion in the rat heart (15).

Similarly, the idea that ischemia could induce cerebral apoptosis was suggested by Chen and Simon (4) in 1997 and later demonstrated by Bossemeyer-Pourie et al. (3) in rat brain. In gerbil brain, the ability of ischemic preconditioning to attenuate postischemic apoptosis has also been attributed to activation of the PI3-kinase/Akt pathway (20). Nonetheless, postischemic apoptosis has not been well studied in the arteries of any vascular bed, and thus the new results from Zhang et al. (21) emphasize that increased vascular apoptosis is also an important consequence of ischemic insults and that ischemic preconditioning mitigates this effect as well.

Notwithstanding their demonstration of the effects of preconditioning on endothelial apoptosis, perhaps the most unique and potentially most important aspect of the study by Zhang et al. (21) concerns the role suggested for the antiapoptotic protein survivin. Even though the multiple pathways that converge to determine how a cell undergoes a controlled pattern of nonnecrotic cell death have been heavily investigated, the manner in which these pathways are recruited by ischemia remains uncertain (11). Interestingly, a growing body of evidence suggests that caspase-independent mechanisms of programmed cell death may contribute significantly to ischemia (17). One critical signaling molecule in the caspase-independent pathways is apoptosis-inducing factor (AIF), which can be released from the mitochondria following activation of the nuclear enzyme poly(ADP-ribose) polymerase in response to oxidative stress and DNA damage (14). Opposing the proapoptotic actions of AIF is the small homodimer protein survivin, which in turn is a member of the inhibitor of apoptosis gene family (1). This protein serves multiple functions related to both cell survival and cell division within many cell types and only recently has come under study in relation to ischemia in either the heart (7) or brain (5). The recent results by Zhang et al. (21) add a new role to the functions assigned to survivin and demonstrate that this protein is a target for the PI3-kinase/Akt pathway, can antagonize the effects of AIF to ameliorate apoptosis, and thereby may help mediate the antiapoptotic effects of ischemic preconditioning.

As for many interesting new findings, the realization that survivin may play a key role in ischemic preconditioning opens many questions. For example, what is the half-life of activated survivin, and how does this correlate with the longevity of the
protection afforded by ischemic preconditioning? How do cell history and time since the last cell division influence survivin levels and their ability to be phosphorylated by activated Akt? What other kinases can phosphorylate and activate survivin, and might any of these also participate in ischemic preconditioning? Is the role of survivin in ischemic preconditioning equally important in all cell types, or is this role unique to vascular endothelium? Hopefully, the interest that will undoubtedly be stimulated by the recent findings of Zhang et al. (21) will motivate efforts to address these and other related questions in the very near future.

REFERENCES