TO THE EDITOR: Zinc is an essential heavy metal with multiple pleiotropic roles in biological systems. With regard to cell survival, it has been shown that zinc can have an antiapoptotic effect, acting either as an inorganic ion or as a key cofactor of many organic molecules (4). There are a number of zinc transporter systems in all cell membranes (10). Recently, a putative zinc receptor has been suggested (5) that may play an important role in cell survival by activating a number of prosurvival kinases (5). Furthermore, the addition of zinc ions to ischemic tissue seems to increase survival and improve recovery in different organs (1, 9).

In a recent issue of the American Journal of Physiology-Heart and Circulatory Physiology, Chanoit et al. (3) have demonstrated for the first time that the administration of ZnCl₂ at the onset of reoxygenation, following a period of ischemia in H9C2 cells, resulted in a significant reduction of the ischemia-reperfusion injury. They further investigated the mechanism of this protection, and their data support the hypothesis that cardioprotection is due to increased Akt activation, which in turn phosphorylates GSK-3β. Phosphorylated GSK-3β is incapable of inducing cell death since the opening of the mitochondrial permeability transition pore (mPTP) will be prevented. Although the relationship between Akt-Gsk3β-mPTP and cardioprotection has been previously established (6, 8), a significant question remains unanswered in this study, i.e., what is the missing link between zinc and Akt? In other words, how can this inorganic molecule increase Akt phosphorylation and prevent cell death? In this regard, there is strong evidence that zinc acts directly on the initiation of the phosphatidylinositol 3-kinase (PI3K)-Akt signaling cascade by inhibiting the negative regulators of this pathway, namely the protein tyrosine phosphatases (PTPases). Zinc ions are known to modify the activity of PTPases by reacting with specific cysteine residues localized in the active site of these enzymes. This reaction inactivates the phosphatase and can trigger the process of ubiquitination and proteosomal degradation (2). The most important PTPase in the downregulation of the PI3K/Akt pathway is the phosphatase and tensin homolog on chromosome 10 (PTEN) (7). Interestingly, it has already been shown in human airway epithelial cells and rat lungs that treatment with zinc results in a significant reduction of the levels of PTEN, parallel with an increased Akt phosphorylation (11). In addition to PTEN, but to a lesser extent, other tyrosine protein phosphatases (e.g., Src homology 2-containing inositol phosphatase 2) or protein phosphatases (e.g., PH domain leucine-rich repeat protein phosphatase and protein phosphatase 2A) can modulate the activity of the PI3K/Akt pathway, a pathway that needs strict regulation to avoid initiating uncontrolled tissue growth (Fig. 1).

It seems very likely that the protective effect of zinc on the PI3K/Akt pathway may be a result of the inhibition of regulatory phosphatases. In this respect, the cardioprotective role of zinc warrants further investigation.

REFERENCES

3. Chanoit G, Lee S, Xi J, Zhu M, McIntosh RA, Mueller RA, Norfleet EA, Xu Z. Exogenous zinc protects cardiac cells from reperfusion injury by targeting mitochondrial permeability transition pore through inactiva-

Fig. 1. Possible mechanism responsible for the activation of phosphatidylinositol 3-kinase (PI3K)/Akt by zinc. PI3K phosphorylates (activates) Akt, which, in turn, phosphorylates (activates) GSK-3β, and the mitochondrial permeability transition pore opening is blocked. Phosphatase and tensin homolog on chromosome 10 (PTEN) is the main negative regulator of this pathway and can be inactivated by the interaction with zinc ions. In addition, SHIP2, PP2A, and PHLP may also affect this prosurvival pathway but with less impact. There are no data regarding their possible inactivation by zinc. Gray lines, not known impact on PI3K/Akt and cardioprotection; gray dotted lines, hypothetical interactions.


