New pathophysiological function of protein phosphatase 2A?

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Online publish-ahead-of-print 12 August 2008

This editorial refers to ‘Diastolic dysfunction in alveolar hypoxia: a role for interleukin-18-mediated increase in protein phosphatase 2A’ by Larsen et al.,1 pp. 47–54, this issue.

In this issue of the Journal, there is an interesting study by Larsen et al.,1 which provides evidence that in pulmonary hypoxia a new mechanism might be operational that explains the deterioration of heart function in primary pulmonary hypertension. The authors chronically exposed mice to 10% oxygen to mimic hypoxia in patients. The authors had noted in previous studies that this degree of pulmonary hypoxia leads to slower cardiac relaxation, putatively due to reduced phosphorylation of phospholamban on amino acid serine 16. In the present report, they provide evidence that the activity of phosphatase 2A but not phosphatase 1 is enhanced in sarcoplasmic reticulum-enriched membranes from these hearts. This led to reduced phosphorylation of phospholamban, which could explain reduced cardiac contractility. Surprisingly, a similar increase in phosphatase activity was noted in left ventricular as well as in right ventricular preparations. On the basis of the model and the clinical feature of pulmonary hypertension, one would have expected an increase in phosphatase activity only in right ventricular preparation. This could indicate that a humoral mechanism, such as altered interleukin levels, increases transcriptional activity of the PP2A gene.

The role of serine/threonine phosphatases in the heart has gained considerable attention. For instance, it is well known that increased activity of calcineurin, also known as phosphatase 2B, leads to cardiac hypertrophy. If the animals are treated with an inhibitor on the enzyme (cyclosporine A), this hypertrophy is prevented. Also, if transgenic animals are engineered with additional overexpression of modulatory calcineurin-interacting protein, a protein inhibitor of calcineurin, this hypertrophy can also be antagonized (for review2). Moreover, there is evidence that increased expression of the catalytic subunit of PP1α occurs in human heart failure3,4, and mice with overexpression of the catalytic subunit of PP1α also exhibit hypertrophy, fibrosis, and increased mortality.5 If the phosphatase activity is reduced by use of an adenovirus, the phenotype of the animals is rescued.6 On the other hand, if the protein inhibitor of PP1, namely I-1, is knocked out, an increased PP1 activity and cardiac hypertrophy is noted.5 Similarly, if I-2 of PP1 is overexpressed, the heart exhibits a hypercontractile state under basal conditions, probably because the phosphorylation of phospholamban is enhanced.6

Some studies have also been performed on the cardiac role on PP2A, which occurs as a dimer or trimer (Figure 1; for review7). For instance, overexpression of a dominant negative mutant of the structural A-subunit of PP2A increases the PP2A activity, and this leads to cardiac hypertrophy.8 The function of the regulatory B-subunit has not yet been studied by overexpression in the heart (Figure 1). Moreover, inhibition of PP2A with a drug such as fostriecin protected rabbits’ hearts against ischaemia.9 If the catalytic subunit of PP2A is overexpressed, this leads to cardiac

Figure 1 PP2A is composed of three catalytic subunits (A, B, and C). Heart failure and/or hypoxia lead to increased expression of the C subunit and thereby increased phosphatase activity, which results in decreased phosphorylation and hence decreased function of cardiac regulatory proteins. For further details, see text.

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hypertrophy, impaired cardiac function, and decreased phosphorylation of cardiac regulatory proteins like phospholamban and the inhibitory subunit of troponin. In addition, in at least some animal models of cardiac hypertrophy, increased activity of PP2A has been observed. Thus, it is interesting that PP2A can apparently also be regulated by hypoxia (see Figure 1). One can speculate that a drug such as festrin that is able to decrease the PP2A activity might be beneficial in primary pulmonary hypertension. However, this drug is usually used in patients suffering from carcinoma. In fact, festrin has other effects besides phosphatase inhibition, including effects on topoisomerase.

Hence, PP2A might be an interesting target for future pharmaceutical research to design organic compounds that selectively inhibit this enzyme. Although it is well established that proteins like I-1PP2A or I-2PP2A exist, it cannot be predicted whether these would be useful for gene therapy of primary pulmonary hypertension or chronic obstructive pulmonary disease as they are known to increase the PP1 activity to some extent. In summary, the paper by Larsen et al. opens a new field of research into a pathophysiological role of PP2A.

References