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SHORT COMMUNICATION

A Potential Role for PTEN in the Diabetic Heart

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Introduction

Type 2 diabetes mellitus is associated with malfunction of the intracellular insulin signalling pathway [1]. This signalling pathway—the PI3 kinase/Akt pathway, is also essential in cell survival and it has been demonstrated that, when activated, protects the myocardium against ischaemia/reperfusion damage [2].

Phosphatase and tensin homologue on chromosome 10 (PTEN) is a relatively recent discovered enzyme. It is a dual protein and lipid phosphatase, responsible for negatively regulating PI3 kinase pathway [3]. In summary PI3 kinase activation phosphorylates the phosphatidyl-inositol PtdIns(4,5)P2 (PIP2) into the secondary messenger PtdIns(3,4,5)P3 (PIP3). This metabolite mediates downstream signaling via recruiting and activating PDK-1 which is followed by the activation of PKB/Akt. Akt is demonstrated to be able to phosphorylate a multitude of targets, resulting in the activation of prosurvival substrates in addition to inhibiting specific proapoptotic effectors. PTEN has the ability to dephosphorylate PIP3 into its precursor, PIP2, thereby blocking the cascade of events generated by the accumulation of this secondary messenger in the plasmalemma. PTEN is ubiquitously present in all cells and its activity is reflected by its cellular level, which can be modulated by transcription.

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There is not much information about the role of this phosphatase in the pathology of the ischaemic myocardium. In spite of the theoretical interest for investigating this phosphatase [4], the lack of specific inhibitors makes these investigations difficult. However, recently it has been shown that PTEN down regulation may be one of the mechanisms responsible for ischemic preconditioning protection in normal hearts [5].

Although in the normal rat heart one cycle of ischaemic precondition can significantly protect the myocardium this is not the case for the diabetic heart. In this regard we have recently shown that in the diabetic heart (Goto Kakizaki rat) three cycles of preconditioning ischaemia are required in order to elicit the same protection [6].

Interestingly, in the diabetic rat heart the level of total Akt was not different from the normoglycemic rat but the capability of this enzyme to be phosphorylated, hence activated, by protective mechanisms (in this case preconditioning) was reduced [6]. Based on these results, we went on to hypothesise that this decrease in the level of Akt phosphorylation we observed in diabetic hearts is due to the presence of an increased level of PTEN in the myocardial tissue.

Materials and methods

To verify our hypothesis we compared PTEN levels extracted from normal (Wistar rats) and diabetic (Goto Kakizaki rats) animals. The animals were heparinised (300 IU) and anaesthetised with pentobarbital (55 mg/kg i.p). Deep anaesthesia was confirmed by the disappearance of the plantar reflex. The chest was opened, the

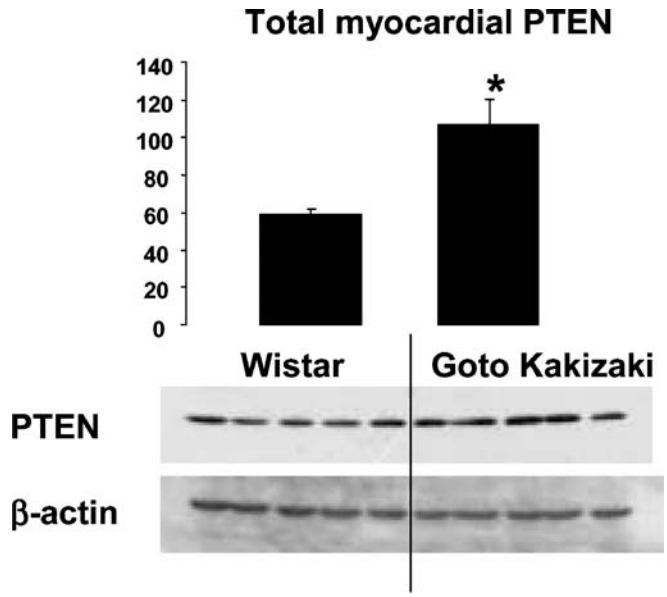

Fig. 1 Total PTEN in normal (Wistar) and diabetic rats (Goto Kakizaki). The data are presented in arbitrary units after normalization to the total b-actin content.

hearts quickly removed into cold buffer and snap frozen for Western blot analysis. The tissue samples were homogenised, and the protein samples were prepared and proceeded as previously described [7]. Primary antibodies for PTEN and secondary antibodies were purchased from Cell Signalling Ltd.

Results

The data, presented in Fig. 1, demonstrate that in the Goto Kakizaki rat hearts there is a significant increased level of total PTEN. This may explain the difficulty to precondition the diabetic heart with only one cycle of ischaemia-reperfusion, as previously demonstrated [6].

Discussions

The importance of PTEN in down regulation of protection is supported by recent data from our group [7] as well as from others [8]. In this regard, it has been demonstrated, in normoglicemic rat hearts, that a chronic treatment with a drug which protects against ischaemia, by up regulating the PI3 kinase/Akt pathway, namely atorvastatin, loses its protective effect following a chronic treatment [7]. Importantly an increased level of PTEN was found in these hearts.

This result can be explained as a normal reaction of the cellular regulatory mechanisms against chronic Akt activation which is usually associated with hypertrophy and malignancy. Moreover, recent studies have now confirmed this situation in the case of another statin, lovastatin [8] in a cell-based model.

Importantly there are now data becoming available which link PTEN with the pathological state of diabetes. In this regard, it has been demonstrated that the inhibition of PTEN expression in diabetic mice is associated with reduction in blood glucose [9] and may regulate islet development [10]. Our data supports this finding that diabetes may be associated with increased PTEN levels, at least in the myocardium. Therefore any protection which is associated with an up regulation of the prosurvival kinase (RISK) pathways [2] could be negatively effected by changes in PTEN levels.

As such we would suggest that much care and further investigations are necessary in order to extrapolate the results obtained in normoglicemic models over diabetic conditions.

Our results point out the significance of considering PTEN an important target for improving diabetes and the cardiac pathology associated with it.

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