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Firing up Mitochondrial Activities with PTPMT1

Pagliarini et al. (2005) recently identified a new mitochondrial specific protein tyrosine phosphatase, PTPMT1. This report comments on its consequences for mitochondrial function and on its potential to act as a therapeutic target in diabetes and cancer.

The mammalian protein tyrosine phosphatase (PTP) gene family now consists of over 100 members (Andersen et al., 2004; Alonso et al., 2004). They have not only been found in all cells and tissues but in most organelles. In combination with various kinases, PTP enzymes provide exquisite balance to the levels of phosphorylation of key signaling proteins. Classical PTPs dephosphorylate only tyrosine residues, whereas dual PTPs also act on specific serine and threonine residues. Moreover, some members of the PTP family, such as PTEN and the myotubularins, have the ability to use phospholipids as substrates and modulate the cellular phosphoinositide content.

In a recent issue of Molecular Cell, Pagliarini et al. (2005) report the identification of a nuclear encoded PTP that resides exclusively in mitochondria (named PTPMT1 for tyrosine phosphatase localized to the mitochondrion). This localization is conferred by the presence of an N-terminal motif recognized by a mitochondrial translocase. PTPMT1 is anchored to the matrix face of the inner mitochondrial membrane, where the electron transport chain, proton pumps, and ATP synthase reside. This places PTPMT1 at the heart of the enzymatic machinery responsible for oxidative ATP synthesis. It also represents the first PTP to be exclusively located to this organelle.

PTPMT1 was originally cloned on the basis of the similarity of its catalytic site with that of the tumor suppressor phosphatase PTEN (Pagliarini et al., 2004). The members of the PTEN subfamily have poor phosphatase activity on proteins and prefer lipid substrates. PTPMT1 exhibits strong activity against the phosphoinositide PI5P in vitro, but the authors found no evidence of changes in the mitochondrial levels of PI5P following the knockdown of PTPMT1 (Pagliarini et al., 2005). The lipid phosphatase characteristics of PTPMT1 and its targeting to the inner mitochondrial membrane raise questions regarding its natural substrate and specific function in mitochondria.

Pagliarini et al. (2005) focus their functional studies on an insulinoma β cell line established from the pancreas, where PTPMT1 is abundantly expressed. Under normal conditions, β cells comprise most of the pancreatic islets and they respond to increasing glucose by secreting insulin (Lowell and Shulman, 2004). Glucose sensing and insulin secretion are tightly coupled to ATP generation. The knockdown of PTPMT1 in this insulin secreting cell line leads to an increase in the steady-state ATP/ADP ratio, and this is supported by the reduced amount of active AMP kinase (Pagliarini et al., 2005). It is not clear whether this reflects a greater mitochondrial substrate flux or better coupling between electron transport and ATP synthesis. It would be important to make a direct correlation between the activity of the different subunits of the ATP-dependent potassium channel and the function of PTPMT1 in future work.

The increased ATP production and its associated glucose-stimulated insulin secretion found by inhibiting PTPMT1 supports its relevance to type 2 diabetes. In this metabolic disease, the pancreas is unable to secrete sufficient quantities of insulin to overcome the insulin resistance from liver and skeletal muscle, thus causing hyperglycemia (Rhodes, 2004). On that basis, therapies based on inhibition of PTPMT1 could increase ATP production and insulin secretion. While such an approach is promising in the short term, one concern is whether benefits would last. This is because stimulation of insulin secretion with insulin secretagogues increases apoptosis (Rustenbeck et al., 2004). This is presumably mediated by endoplasmic reticulum stress (Araki et al., 2003), which adds to the proapoptotic hyperglycemic and inflammatory signals already impinging on the diabetic β cells (Rhodes, 2004). It is too early to assume that such a scenario will occur with PTPMT1 inhibition but it will have to be monitored.

A second potential benefit from inhibiting this phosphatase is that PTPMT1 mRNA is also expressed in skeletal muscle (Pagliarini et al., 2004), a major site of insulin resistance in type 2 diabetes. This resistance has been linked to intramyocellular lipid accumulation (Lowell and Shulman, 2004). Insulin-resistant but otherwise healthy children of type 2 diabetic patients have reduced mitochondrial oxidative phosphorylation, suggesting that this defect could account for intramyocellular lipid accumulation (Petersen et al., 2004). The exact mechanism whereby a reduction in PTPMT1 increases ATP production remains unknown, but if it involves increased substrate utilization, it could reduce intramyocellular lipid accumulation and also reverse skeletal muscle insulin resistance.

Modulation of mitochondrial ATP synthesis by PTPMT1 also suggests a novel approach for the treatment of pancreatic cancers, which represent some of the deadliest forms of human tumors. The gluttony of cancer cells for energy is well established, and with the development of a modulator of expression, one may hope that we could also achieve the synthetic induction of PTPMT1 expression. It would then be expected that this effect would attenuate, if not abolish, the growth of pancreas-derived tumor cells and support the establishment of a novel regimen for pancreatic cancers.

The potential clinical applications aside, the findings of the Dixon group (Pagliarini et al., 2005) bring another important focus to this organelle. It is important to point out that while the central function of all mitochondria is energy production, other metabolic activities are tissue (e.g., gluconeogenesis and ketone production in liver) and development specific. The developmental specialization is illustrated by the finding that mitochondria synthesize the formate needed for purine production during embryogenesis but not during adulthood. This

unique activity pattern is of great importance for the prevention of spina bifida (Di Pietro et al., 2002). Although most scientists working outside the mitochondrial field tend to consider mitochondria as homogeneous little factories, they are not. The tissue-specific expression of PTPMT1 is indeed a striking reminder of the plurality of mitochondrial biology.

The PTP field is still young and this is truly displayed by the ups and down in the collective efforts of the academic and pharmaceutical PTP community to develop reliable and specific PTP inhibitors. Similarly, it will definitely take more hard work to identify the true substrate(s) and mechanism of action of PTPMT1. This effort is obviously needed before specific inhibitors and activators can be designed. Since PTPMT1 seems to be expressed in many tissues—including liver and muscle—it is also premature to simply see it as a target for regulating insulin secretion. However, by locating PTPMT1 expression to the mitochondria, the Dixon's group provides the impetus to study further the unknown functions of the very diverse members of the PTP family and their roles in human diseases.

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