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Tyrosine dephosphorylation of proteins as a regulator of physiological processes

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Phosphorylation of tyrosine residues in proteins is a major mechanism for regulation of protein structure and function. Tyrosine phosphorylation is a reversible process, and is controlled by the opposing activities of two major and entirely distinct families of enzymes - protein tyrosine kinases and tyrosine phosphatases (PTPs).

Our group studies two related PTPs - PTP Epsilon (PTPe) and PTP Alpha (PTPa). The four protein forms of PTPe are all produced from the single PTPe gene by steps regulated at the levels of transcription, translation, and post-translational proteolytic processing. All forms of PTPe share the same catalytic domains, but have unique amino termini that determine their individual subcellular locations and physiological roles.

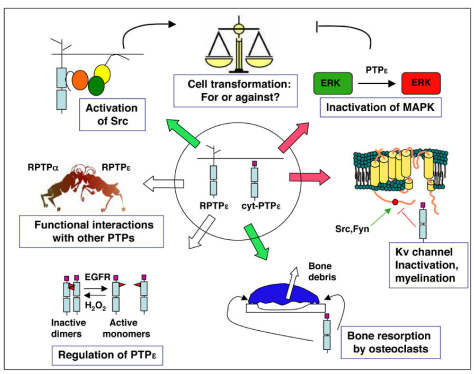

Fig. 1 *Involvement of PTPe in various physiological processes. Note that PTPe can activate some processes (green arrows), but inactivates others (red arrows).*

Along these lines, we have shown that the receptor-type form of PTPe (RPTPe) assists Neu-mediated mammary tumorigenesis in mice. RPTPe is specifically expressed in this type of mammary tumors, and expression of RPTPe in transgenic mice causes massive mammary hyperplasia and tumorigenesis. In agreement, mammary tumors induced by Neu in mice genetically lacking PTPe grow slower in culture and produce smaller tumors when implanted in nude mice than do PTPe-expressing tumors. At the molecular level, RPTPe dephosphorylates and activates the Src tyrosine kinase, a known collaborator of Neu in mammary cell transformation. Our data suggest that PTPe promotes Neu-induced mammary tumorigenesis by activating Src; in the absence of RPTPe this process is less efficient and the resulting tumor cells are less transformed. PTPe can inhibit transformation in other biological contexts, as recently shown in its ability to inhibit the transcriptional response following stimulation of MAP kinases.

A second, distinct isoform of PTPe, cyt-PTPe, is predominantly cytosolic. Absence of this molecule from Schwann cells leads to hyperphosphorylation and increased activity of the voltage gated potassium channels Kv1.5 and Kv2.1. Using substrate-trapping technology we have shown that Kv2.1 is a substrate of PTPe, and that dephosphorylation of Kv2.1 predominantly at Y124 by PTPe counters Kv2.1 phosphorylation and upregulation by the Src and Fyn tyrosine kinases. These findings correlate with severe transient hypomyelination observed in sciatic nerves of newborn mice lacking PTPe. Thus, cyt-PTPe might play an important role in regulation of myelination in the peripheral nervous system.

Cyt-PTPe is also expressed in osteoclasts, the cells that degrade bone matrix. Young female mice genetically lacking PTPe exhibit increased trabecular bone mass due to reduced function *in vivo* of osteoclasts. At the cellular level, this correlates with significant disruption of podosomes, the subcellular structures by which osteoclasts adhere to bone. We believe that cyt-PTPe is required for proper organization and function of podosomes in osteoclasts, and that in its absence

osteoclast adhesion to bone and subsequent bone resorption are abnormal.

Regulation of PTP activity is not properly understood at present. We have recently shown that PTPe activity can be inhibited by dimerization. PTPe phosphorylation and dimerization can be regulated by physiological processes, such as activation of the epidermal growth factor (EGF) receptor and increased oxidative stress, indicating it is a physiologically-relevant regulatory mechanism.

These and other studies indicate that the various forms of PTPe participate in diverse physiological processes. Furthermore, the nature of the role PTPe fulfills - activator vs. inhibitor - is not constant and depends on the specific context examined. Identification of additional molecular partners of PTPe will help us understand the full spectrum of its physiological roles in molecular detail.

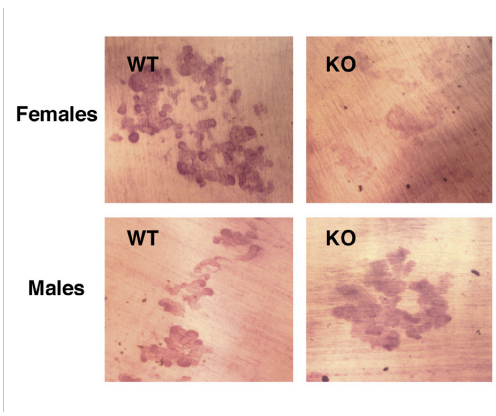

Fig. 2 *Reduced bone resorption by osteoclasts from young female mice lacking PTPe. Shown are pits excavated by WT or PTPe-deficient (KO) osteoclast-like cells from female (top) and male (bottom) mice following plating on dentine. Cells from KO females excavate pits that are smaller and shallower (reduced staining the female KO panel, top right).*

Selected Publications

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Granot-Attas, S. and Elson, A. (2004). Protein tyrosine phosphatase epsilon activates Yes and Fyn in Neu-induced mammary tumor cells. Exp. Cell Res. 294 (1), 236-243.

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