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# Tyrosine phosphatase Epsilon - a multi-faceted 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 families of enzymes - the protein tyrosine kinases and tyrosine phosphatases (PTPs). Both enzyme families are considered master regulators of physiological processes.

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 through mechanisms involving use of alternative promoters, translational control, and post-translational proteolytic processing. All forms of PTPe share the same catalytic domains, but have unique amino termini. This fact determines their individual subcellular locations and physiological roles.

Along these lines, we have shown that the receptor-type form of PTPe (tm-PTPe) is an accessory factor in Neu-mediated mammary tumorigenesis in mice. tm-PTPe is specifically expressed in this type of mammary tumors, and expression of tm-PTPe in transgenic mice causes massive mammary hyperplasia and associated tumorigenesis. In agreement, mammary tumors induced by Neu in mice genetically lacking PTPe have distinct morphologies, grow slower in culture, and produce smaller tumors upon implantation in nude mice than do similar tumors of PTPe-expressing mice. At the molecular level, tm-PTPe 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 tm-PTPe this process is less efficient and the resulting tumor cells are less 'well off'.

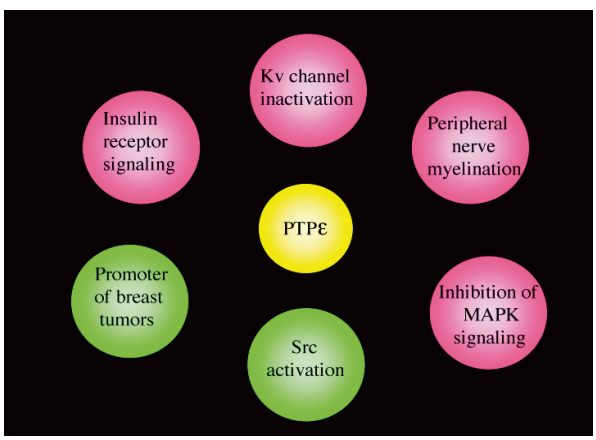


***Fig. 1*** *PTP Epsilon activates (green) or inactivates (pink) distinct processes.*

A second, distinct isoform of PTPe, cyt-PTPe, is predominantly a cytosolic molecule. Absence of this molecule from Schwann cells leads to hyperphosphorylation and increased activity of a class of voltage gated potassium channels, exemplified by the Kv1.5 and Kv2.1 channels. Using substrate-trapping technology we have shown that Kv2.1 is a substrate of PTPe, and that dephosphorylation of Kv2.1 by PTPe counters Kv2.1 phosphorylation and activation by the Src and Fyn tyrosine kinases. These findings correlate with a severe transient hypomyelination phenotype 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.

Other studies conducted in our lab have shown that tm-PTPe and cyt-PTPe can down-regulate transcriptional activity induced by Elk1 following activation of the ERK 1/ERK2 MAP kinase cascade in NIH3T3 cells. In a manner distinct from its role in mammary tumorigenesis, PTPe apparently performs a growth-suppressing role in this system. We have also shown that PTPe can bind the adaptor molecular Grb2, invoking a molecular mechanism by which the SH2 domain of Grb2 binds a specific phosphotyrosine residue located near the C-terminus of PTPe. In all, these and other studies conducted in our lab 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 is dependent upon the specific context examined.

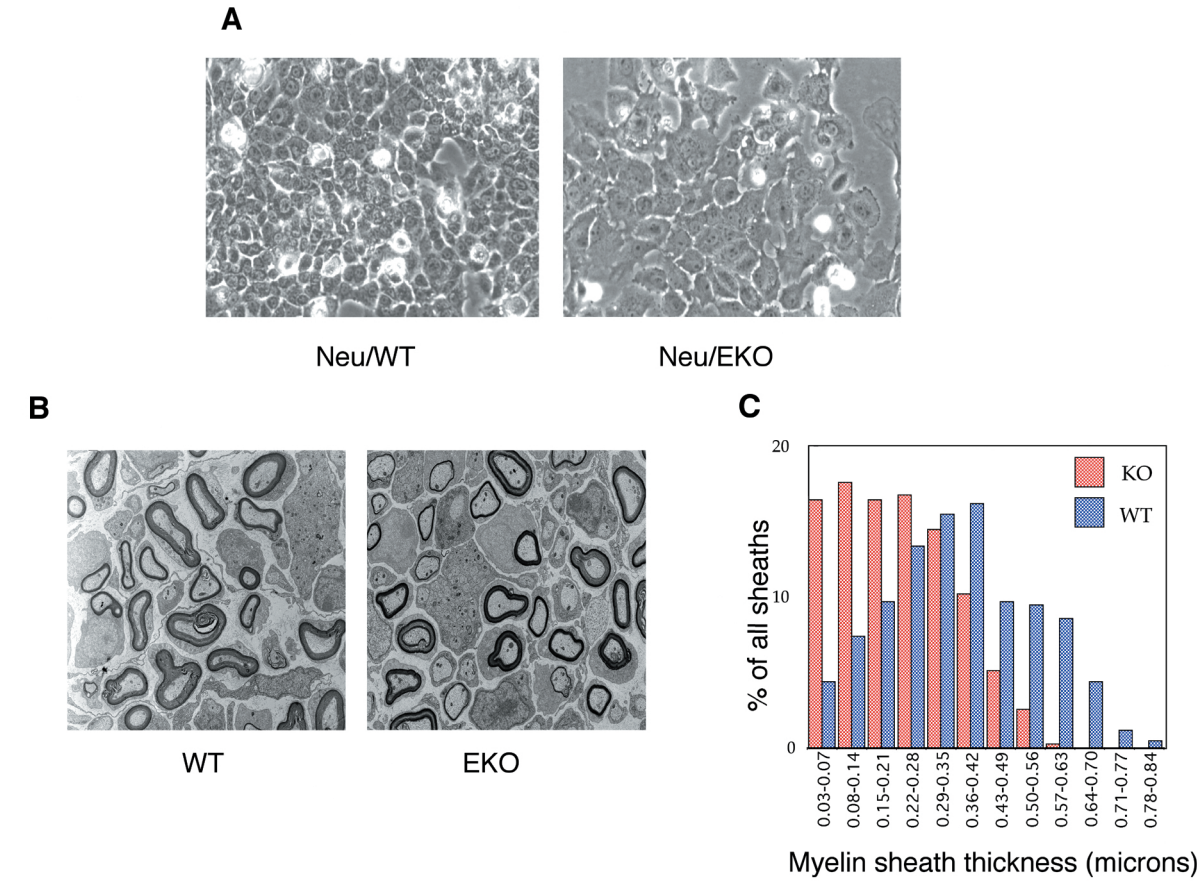


***Fig. 2*** *Loss of PTPe affects various cell types in PTPe-deficient mice. A. Neu-induced mammary tumor cells are larger and flatter in PTPe-deficient mice (Neu/EKO) than in WT mice (Neu/WT). B. Morphology of PTPe-knockout (EKO) and wild-type (WT) mouse sciatic nerves. Closed circles are axons ensheathed by Schwann cells. 3400X; Photo by Dr. Vera Shinder, WIS. C. Myelin sheath thickness distributions of both genotypes. n=456 sheaths (WT), n=526 sheaths (KO); p<0.0001, Mann-Whitney test.*

***Selected Publications***

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Peretz, A*., Gil-Henn, H*., Sobko, A., Shinder, V., Attali, B and Elson, A. (2000) - Hypomyelination and increased activity of voltage-gated potassium channels in mice lacking protein tyrosine phosphatase e. EMBO J. 19 (15) 4036-4045 (* - equally contributing first authors).

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Web page: http://www.weizmann.ac.il/molgen/scientists/elson2.html