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Foreword

Tyrosine phosphorylation is a rapid and reversible protein modification catalyzed by the activities of protein tyrosine kinases (PTKs) and their cellular counterparts, protein tyrosine phosphatases (PTPs). Although phosphorylation of proteins on tyrosine is relatively rare compared to phosphorylation on serine or threonine residues, the past 2 decades of research into PTP function have led to a great appreciation of the critical role PTPs have in regulating basic cellular processes. Among these important roles is the regulation of cellular signaling pathways related to metabolism. This volume contains chapters which highlight many aspects of PTP function in the context of metabolism. Given the growing obesity and diabetes epidemics in the United States and throughout the world, the desire to identify possible therapeutic targets for treatment of these diseases is a high priority. In many ways, PTPs may be attractive drug targets since they are amenable to targeting with small molecules; however many challenges abound in making PTP inhibitors.

PTPs are encoded by a large family of 107 genes, the majority of which can be broadly classified into classical phosphotyrosine-specific phosphatases or dual-specificity phosphatases (which display serine, threonine, and tyrosine phosphatase activity). More than half of identified PTPs have been implicated in human disease to date, with a growing number of PTPs now known to play major roles in metabolic disease. Many metabolic signaling pathways invoke a feed-forward cascade of tyrosine-phosphorylated proteins; thus, PTPs have emerged as critical regulators of these pathways, including the insulin and leptin pathways.

The activity of PTPs is regulated in many ways within the cell, most notably by reversible oxidation of the catalytic cysteine residue by reactive oxygen species (ROS). In Chap. 1, assays to quantify redox regulation of PTPs are discussed in the context of metabolic signaling. Subsequent chapters in this volume discuss quantitative modeling approaches that may be effective in modeling PTP behavior, and the importance of identifying novel substrates of PTPs. Several chapters highlight the role of PTPs known to regulate metabolic signaling, including PTP1B, SHP2, TC-PTP, and RPTP epsilon. Over the past decade, mouse models of PTP-deficiency have provided important insight into the precise tissue-specific functions of many PTPs including PTP1B, TC-PTP, SHP2, and PTEN (which also functions as an

inositol phospholipid phosphatase). Perhaps the most well-characterized PTP with a known metabolic role is the prototypical classical, non-receptor PTP, PTP1B. As such, several chapters in this volume are dedicated to the specific metabolic functions of PTP1B. More recently the MAPK phosphatases, or MKPs, have also emerged as important regulators of metabolic homeostasis. Finally, two chapters in this volume discuss the role of the low molecular weight class of PTPs (LMPTP) and the glycogen phosphatase laforin in human metabolic disease pathogenesis.

Overall, recent studies into PTP function in the context of metabolism highlight the importance of understanding the regulation/modifications of PTPs that affect activity, the subcellular localization of PTPs and how that affects their function, and the cell-type specificity of PTP functions. Going forward, it will be important to understand how PTPs function at the intersection of metabolic signaling and other pathways regulated by PTPs, including growth factor signaling and oncogenic signaling pathways, in order to sustain the growing interest in targeting PTPs for treating metabolic syndromes.

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Chapter 1
Redox Regulation of PTPs in Metabolism: Focus on Assays

Yang Xu and Benjamin G. Neel

Abstract Protein-tyrosine phosphatases (PTPs), along with protein-tyrosine kinases (PTKs), are the key regulators of phosphotyrosine signaling, and therefore are important contributors to normal metabolism and metabolic disease. Over the past 10 years, reactive oxygen species (ROS), which had long been viewed as toxic by-products of metabolism, have been recast as important second messengers, which act, at least in part, to regulate PTP activity by reversible oxidation. For example, ROS-catalyzed PTP oxidation can transiently inhibit PTP enzymatic activity and facilitate ligand-induced receptor tyrosine kinase (RTK) signaling. Identifying ROS-inactivated PTPs represents a key challenge to understanding the role of PTPs and redox regulation in physiology and pathology. Here, we briefly review ROS regulation of PTPs, focusing on existing assays and new approaches to identify and quantify PTP oxidation.

Abbreviations

ABP	Activity-based probe
AGE	Advanced glycation end product
Alk-β-KE	Alkyne β-ketoester
BBP-Biotin	α-Bromobenzylphosphonate biotin
BP1	Biotin-1,3-cyclopentanedione

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DSP	Dual-specificity PTP
DTT	Dithiothreitol
EGF	Epidermal growth factor
ER	Endoplasmic reticulum
FFA	Free fatty acid
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GPX	Glutathione peroxidase
GRX	Glutaredoxin
GSH	Glutathione
H_2O_2	Hydrogen peroxide
HFD	High-fat diet
IAA	Iodoacetic acid
IAM	Iodoacetamide
IAP-Biotin	Iodoacetylpolyethylene oxide biotin
IB	Immunoblot
IF	Immunofluorescence
IKK	Inhibitor of κB kinase
IL	Interleukin
IP	Immunoprecipitation
IR	Insulin receptor
IRS	Insulin receptor substrate
JNK	c-Jun NH_2-terminal kinase
LA	α-Lipoic acid
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
MAPK	Mitogen-activated protein kinase
MKP	MAPK phosphatase
MPB	3-(*N*-maleimido-propionyl)biocytin
MRM	Multiple reaction monitoring
NEM	*N*-ethylmaleimide
NF-κB	Nuclear factor-κB
NOX	NADPH oxidase
NRPTP	Non-receptor PTP
$O_2^{\bullet -}$	Superoxide anion
oxPTP Ab	Oxidized PTP active site antibody
PD	Pull down
PDGF	Platelet-derived growth factor
PI3K	Phosphatidylinositol 3-kinase
PKC	Protein kinase C
PROP	Purification of reversibly oxidized proteins
PRX	Peroxiredoxin
PTK	Protein-tyrosine kinase
PTP	Protein-tyrosine phosphatase
PTP1B-OX	Oxidized form of PTP1B
PV	Pervanadate
PVSN-N_3	4-(Azidomethyl)phenyl ethenesulfonate azide

ROS	Reactive oxygen species
RTK	Receptor tyrosine kinase
S^-	Thiolate
scFv	Single-chain variable fragment
SO_2H	Sulfinic acid
SO_3H	Sulfonic acid
SOD	Superoxide dismutase
SOH	Sulfenic acid
T2DM	Type 2 diabetes mellitus
TCA	Trichloroacetic acid
TCEP	Tris(2-carboxyethyl)phosphine
TNF-α	Tumor necrosis factor-α
TRX	Thioredoxin
VEGF	Vascular endothelial growth factor

Introduction

Tyrosine phosphorylation is one of the major regulatory mechanisms in signal transduction, and consequently, helps control many cellular processes, including cell growth, differentiation, migration, and metabolic homeostasis [1, 2]. The level of phosphotyrosine on any protein is regulated by the opposing actions of protein-tyrosine kinases (PTKs) and protein-tyrosine phosphatases (PTPs) [1–3]. Dysfunction of specific PTKs or PTPs is associated with several human diseases [4, 5], including metabolic disorders such as obesity, insulin resistance, and type 2 diabetes mellitus (T2DM) [6–9].

The PTP superfamily comprises 107 genes and can be subdivided into four families based on the amino acid sequence in their catalytic domains. Classes I, II, and III are cysteine-based PTPs defined by the consensus $HC(X)_5R$ motif, whereas class IV are aspartic acid-based PTPs [2, 3, 5]. The largest of these, the class I cysteine-based PTPs, containing 99 members, can be further divided into tyrosine-specific "classical PTPs" and dual-specificity PTPs (DSPs), which also can dephosphorylate Ser/Thr residues. The classical PTPs include 17 non-receptor PTPs (NRPTPs), and 21 receptor-like PTPs (RPTPs), each of which contains one, or for the RPTPs, often two, ~280 amino acid catalytic (PTP) domain(s), at least one of which contains a central, highly conserved signature motif [I/V]HCSXGXGR[S/T]G [10]. The invariant cysteinyl residue within the signature motif has a low *p*Ka (~4.5–5.5), enabling it to reside in the thiolate (S^-) state at physiological pH [11, 12]. This feature of the catalytic cysteine allows it to execute a nucleophilic attack on phosphotyrosine substrates [13], but also renders it highly susceptible to oxidation and inhibition by reactive oxygen species (ROS) [14, 15].

ROS have long been viewed as the toxic by-products of aerobic life and/or defense mechanisms used by phagocytic immune cells. However, studies over the past decade indicate that ROS, especially H_2O_2, also function as intracellular second