Preface

Reversible protein phosphorylation-based signaling forms the basis of various physiological functions. Reversibility of phosphorylation is dependent on the opposing yet balancing actions of protein kinases (that phosphorylate proteins) and protein phosphatases (that dephosphorylate these target proteins). While the protein kinases are reported to be derivatives of a common ancestor, the protein phosphatases have evolved from distinct mechanistic ancestors that were also structurally discrete. This book describes protein phosphatases in cellular signaling, and the role of their structural underpinnings in their catalytic cycle. The book has been divided into eight chapters that allow the reader to systematically plough through the structural and mechanistic basis of protein phosphatase function. Special emphasis has been given to the largest protein phosphatase gene family: the protein tyrosine phosphatases. This gene family has evolved from a common ancestor and shares a conserved catalytic domain and mechanism. Ten conserved motifs in the protein structure allow for defining the molecular details of its domain's biochemical function. Understanding of their molecular regulation is key to dissecting their role in various pathophysiologies.

The first chapter of this book focuses on the discovery of tyrosine phosphorylation and its immense impact on the understanding of cellular signaling. Noteworthy are the earliest experiments that un-covered protein phosphorylation, but failed to make a mark in understanding human disease. The road to exploration of protein phosphorylation-based signaling saw both planned and some serendipitous discoveries that have allowed researchers to study cell signaling in its present form today. This chapter also describes the structure and mechanistic role of protein tyrosine kinases using Src as the model system. The crucial role of phosphotyrosine-recognition domains including SH2, PTB and atypical phosphotyrosine-recognition domains has been described with regard to their structure.

The second chapter of this book illustrates the diversity of the protein phosphatases. Their structural distinctness allows for their categorization into seven groups. The protein phosphoserine/phosphothreonine phosphatases make three groups, namely the phosphoprotein phosphatases, the metal-dependent protein phosphatases and the aspartate-based phosphatases. The other four groups are the evolutionary distinct classes of protein tyrosine phosphatases. These include the cysteine-based class I, II and III protein tyrosine phosphatases and the aspartate containing, haloacid dehalogenase related, class IV protein tyrosine phosphatases. This chapter describes the structural and mechanistic features of each group of protein phosphatases (except class I protein tyrosine phosphatases that are covered in the following chapters). Conserved structural features, biochemical mechanism and biological function of each group and its example member has been illustrated.

The third chapter focuses on the molecular details of the conserved class I protein tyrosine phosphatase catalytic domain. The catalytic domain is an enzymatic machine

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of about 280 amino acids that has a central β-sheet that accommodates the catalytic cysteine. Using a two-step mechanism requiring the concerted action of a conserved acid/base aspartate with the nucleophilic cysteine, the protein tyrosine phosphatase catalytic domain transfers the phosphatase of a phosphotyrosine residue onto a water molecule. Conserved glutamines are required to activate these water molecules and a conserved aromatic amino acid defines the access of the phosphotyrosine substrate to this molecular machinery. This chapter details the key structural and mechanistic elements of the catalytic domain, and how they participate in the culmination of its catalytic cycle. Emphasis has been given to the structural details of biochemical evidences of the catalytic mechanism. The later part of the chapter also describes the differences in the catalytic mechanism of the cysteine-based class II and class III protein tyrosine phosphatases. The unique class IV aspartate-based protein tyrosine phosphatase catalytic domain and its catalytic mechanism is also explained.

The fourth chapter of this book is dedicated to the receptor protein tyrosine phosphatases. Eight types of receptor forms of protein tyrosine phosphatases have been described for their biological role and distinct features that allow for their classification. The extracellular domains of these proteins allow for their interaction with varied extracellular matrix components and modulate their role in cellular signaling. Each type of the receptor protein tyrosine phosphatase subgroup has been described and their most prominent members have been highlighted. The chapter provides a comprehensive insight into the varied roles of related receptor protein tyrosine phosphatases and also illustrates the role of mutations and polymorphisms in these proteins in human disease.

The fifth chapter of this book is about a special subset of receptor protein tyrosine phosphatases that harbor two catalytic domains in their cytosolic portions. Interestingly, phosphotyrosine phosphatase activity is almost always limited to the membrane proximal domains, whereas the membrane distal domains are inactive and serve as pseudophosphatases. This chapter explains the unique molecular evolution and role of these silent pseudophosphatase domains in regulating the role of their active, cognate catalytic domains in the bidomain receptor protein tyrosine phosphatases.

The sixth chapter focuses on PTP1B and TCPTP; members of the NT1 subclass of non-receptor protein tyrosine phosphatases. The nine subtypes of non-receptor protein tyrosine phosphatases are the cytosolic counterparts to the receptor forms of these enzymes that operate at the membrane. PTP1B is perhaps the most exhaustively studied protein tyrosine phosphatase and was also the first phosphotyrosine phosphatase to be discovered. The chapter focusses on the role of PTP1B in cancer and its overreaching impact as a therapeutic target. Molecular mechanism of substrate identification, role of a second aryl-binding pocket and sensitivity to oxidation of the active site of PTP1B have also been explained.

The seventh chapter is a continuation on detailing the non-receptor protein tyrosine phosphatases and explains the biological roles and molecular modes of the remaining subtypes. Each subtype has been explained for its reported mechanism, structure and biological function. Noteworthy is the understanding of specific features in the distinct catalytic domains of these subtypes that allow for their discretion. Emphasis has been laid on explaining the biological roles of these subtypes and how their sequence variation contributes to their molecular function.

The last chapter of this book is about various strategies of drug development that target the protein tyrosine phosphatases. The chapter documents the various natural and synthetic compounds that serve as effective inhibitors of these proteins. Binding modes and structural esthetics of reversible, irreversible, bidentate and allosteric inhibitors have been explained. The chapter ends with explaining biologics-based methods for therapeutic targeting of protein tyrosine phosphatases.

At present, this book explains the molecular details and structural elements that are key to the biochemical and biological function of protein tyrosine phosphatases. Emphasis has been given to providing a graphical illustration of these modes using the most relevant and recent protein structures from the protein data bank. In the present form of the book, research on protein dynamics and dynamics-based allostery of protein tyrosine phosphatases has not been covered. These concepts would provide the next level of understanding of these proteins and shall be included in future versions of this book.

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