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Review Paper

PROTEIN PHOSPHATASES-OCCURRENCE, CLASSIFICATION AND AS DRUG TARGETS IN HUMAN DISEASES

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Abstract

A phosphatase is an enzyme that removes a phosphate group from its substrate by hydrolyzing phosphoric acid monoesters into a phosphate ion and a molecule with a free hydroxyl group . Protein phosphatase catalyzes the dephosphorylation of post translational modified serine/threonine and tyrosine residues in phosphoproteins. Protein kinase catalyzes the phosphorylation in which the addition of a phosphate group takes place from energetic molecules such as ATP, to a protein usually at a serine/threonine, tyrosine or histidine residue . Protein kinases and Protein phosphatases in different organisms can be assembled in the 'kinome' and 'phosphatome' respectively. Protein Phosphatases are structurally and functionally diversified enzymes and play an important role in a number of signal transduction pathways in animal and yeast systems. It has been found that the deregulation of protein phosphatases enzyme can cause a number of severe diseases. So the present study shows that how these enzymes may be the noble drug target.

Key words: Protein phosphatase (PPase), Protein kinase (PKase), Protein threonine phosphatase (PThPase), Protein tyrosine phosphatase (PTPase), Protein serine phosphatase (PSPase), Protein phosphorylation, Mitogen activated protein kinase (MAPKase).

INTRODUCTION

Protein phosphatases (PPases):

Among different kinds of protein modifications, phosphorylation and dephosphorylation play a significant role in a wide range of processes. The reversible phosphorylation of proteins controlled by PKases and PPases (**Fig.1**) is a major regulation mechanism in all eukaryotic cells [1,2]. Protein phosphorylation is the most common and important form of reversible protein post translational modification

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(PTM) up to 30% of all proteins being phosphorylated at any given time. Inorganic phosphate (Pi) is an essential, but limiting macronutrient that plays critical roles in plant metabolism and development [3]. Post-transduction modification of proteins, such as phosphorylation and glycosylation is a universal mechanism for regulation diverse biological functions. In addition, many cellular proteins are reversibly phosphorylated in response to external stimuli or intracellular signals. An earlier emphasis on functional characterization has recently been complemented by biochemical and structural investigations of protein tyrosine phosphatase (PTPase) and protein serine/threonine phosphatase (PSThPase) families, giving rise to major advances in mechanistic understanding [4-6]. Taylor *et al,* (2019) studied the development of a light activated protein phosphatase named dual specificity phosphatase 6 (DUSP6) [7]. On the basis of phosphorylated amino acids used as substrate, PPases are classified as (**Fig.2**):

(1) Protein Serine/Threonine Phosphatases (PSThPases):

PSThPases (E.C. No.-3.1.3.16) are the enzymes that reverse the actions of PKases by cleaving phosphate group from serine/threonine residues. They are structurally and functionally distinct from the family of PPases encompassing the tyrosine and dual specificity phosphatases.

About 150 genes in the human genome encode PPases, include approximately 40 PSThPases. PSThPases control key biological pathways including early embryonic development, cell proliferation, cell death, circadian rhythm, cancer and play an essential role in the cellular signaling, metabolism, and cell cycle control promiscuous catalytic subunits [8].

According to distinct amino acid sequences and crystal structures, the PSThPases are classified into the following families.

(2) Protein tyrosine phosphatases (PTPases):

PTPases consist of a very large family of enzymes that dephosphorylate the tyrosine residues. A further classification of PTPase is based on their overall structure. More than 100 PTPase have been cloned till now. Tyrosine phosphorylation is known to be a control mechanism for growth, differentiation, metabolism, cell cycle regulation and cytoskeletal function [9]. Unique three-dimensional structure of catalytic domain and lack of sequence homology with PSThPase, indicate that PTPase evolved independently [10]. PTPases catalyze the dephosphorylation of phosphotyrosine, a central control element in mammalian signal transduction [11]. The PTPases are

classified into receptor protein tyrosine phosphatase (RPTPase), non-receptor protein tyrosine phosphatase (NPTPase) and the dual-specific phosphatase (DSPase).

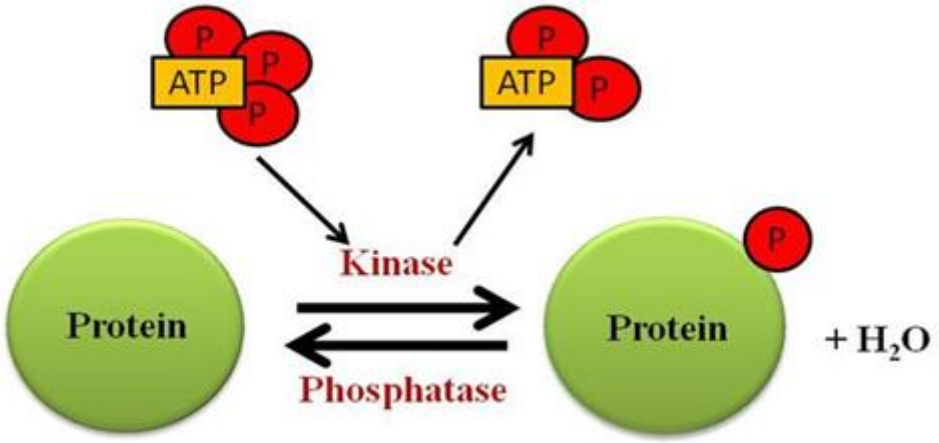

Fig. 1: **Reversible protein phosphorylation involves the function of protein kinases and protein phosphatases.**

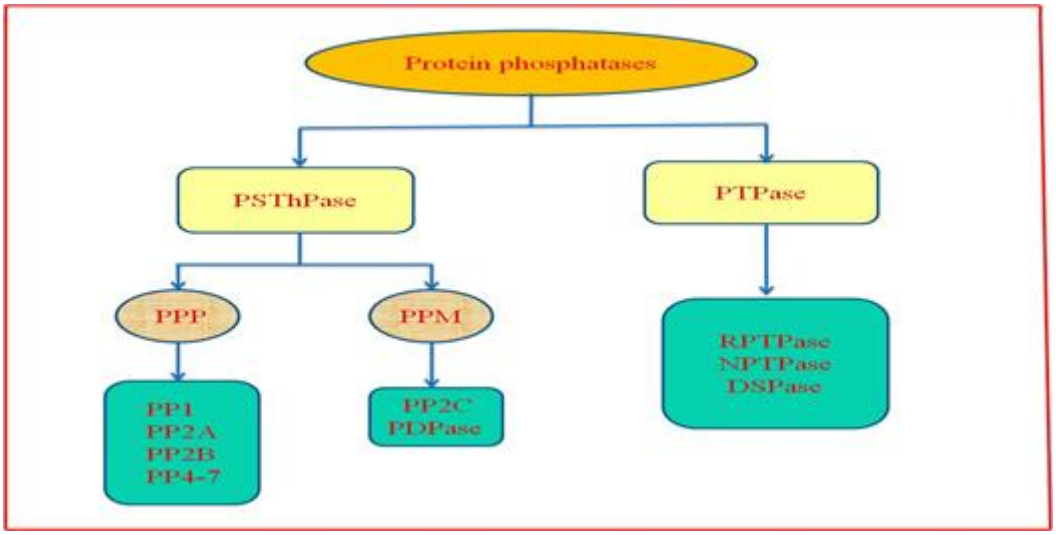

Fig.2 Classification of protein phosphatases

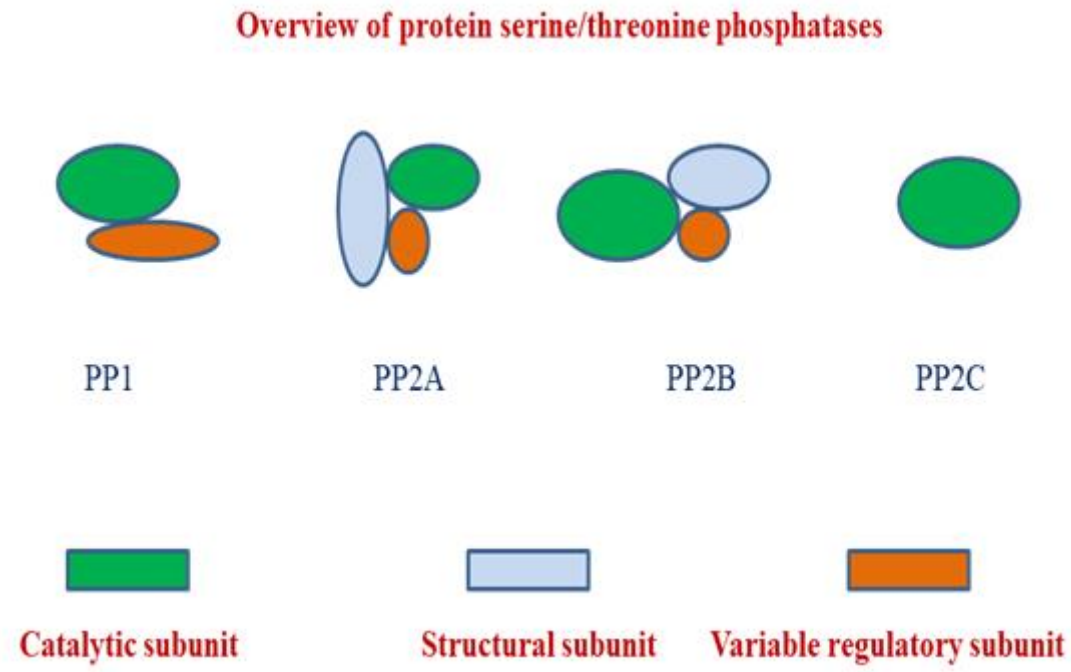

Fig 3: Holoenzyme assembly of the four most abundant serine-threonine phosphatases.

OCCURANCE OF PROTEIN PHOSPHATASES:

In eukaryotes, these enzymes are categorized based on their substrate specificity. PPases activities have been reported in most sub-cellular components, e.g., mitochondria, chloroplasts, nuclei and cytosol various particulate functions. Many of the plant PPases are only poorly characterized, for instance of the unique plant enzymes, chloroplast thylakoid PPases are very poorly characterized. In plants, PPases constitute a large gene family and are reportedly involved in the regulation of abiotic stress responses and plant development.

Using substrates for mammalian PPases and the same pharmacological agents (e.g., okadaic acid), PPP family enzymes such as PP1 and PP2A have been detected in plants such as**,** pea, carrot, and maize [12], *Brassica napus* [13]. In addition to substrate specificity and pharmacological properties, the primary structure of PPases is also highly similar to that of the mammalian enzymes. This became obvious after genes encoding members of PP1, PP2A, and PP2C type phosphatases were cloned from a number of plant species.

PP4 is found in the cytoplasm and to a higher extent in the nucleus of all mammalian cells. PP5 is a PSThPase abundant in the nucleus and cytoplasm of

mammalian, *Drosophila* and yeast cells [14]. PP6 is a PP2A like PSThPase initially identified in yeast cells. PP7 is abundant in the retina.

PROTEIN PHOSPHATASES AND HUMAN DISEASES:

The deregulation of these enzymes has been implicated in a variety of diseases e.g., cancer, diabetes, cardiac hypertrophy, and neuro degeneration. Emerging therapeutic strategies have focused on the design of drugs that affect the biological actions of kinases and phosphatases. Many observations support a role for PP2A in the pathology of human diseases, such as cancer, Alzheimer's, spinocerebellar ataxia, AIDS, malaria and Opitz syndrome. PP2A plays an important role in the regulation of apoptosis . It has been therefore assumed, that PP2A suppresses tumor development through its involvement in cell cycle regulation and cellular growth control. In addition, PP2A inhibits nuclear telomerase activity in human breast cancer cells and human leukemia cells [15]**.** PP2A is indispensable in development, and deficits of PP2A and deterioration of neuronal axons have been observed in several neurodegenerative disorders, but the direct link between PP2A and the neuronal axon development is still missing [16,17].

Alzheimer's disease (AD) is a common neurodegenerative disorder characterized by the presence of two histopathological hallmarks called senile plaque formation and neurofibrillary tangles. PP2A has unique functions in neuronal cells. The role of PP2A in Alzheimer's disease has been studied extensively in various transgenic mouse models. PP2C and PP2C like phosphatases largely function as negative regulators of stress activated pathways. Cerebellar dysfunction is a hallmark of different neurodegenerative disorders, like Spinocerebellar Ataxias (SCAs), but many also include abnormalities in other regions of the central and peripheral nervous system [18].

PROTEIN PHOSPHATASES AS DRUG TARGET:

With the recent clinical success of drugs targeting PKase activity, drug discovery efforts are focusing on the role of reversible protein phosphorylation in disease states. The activity of PPase enzymes that oppose PKase activity can also be manipulated to alter cellular signaling for therapeutic benefits. Discussing past successes, current challenges, and future strategies for modulating phosphatase activity, the PPases may be presented as viable therapeutic targets. Numerous cellular processes, including metabolism, immune response, synaptic plasticity, cell growth and proliferation, and apoptosis, are controlled by intricate signal transduction networks composed of

molecules and macromolecular protein complexes that are responsive to biological or chemical stimuli in the cell's immediate environment.

PKases have become increasingly popular drug targets, constituting 30% of several pharmaceutical manufacturers' drug discovery programs. The approval of rapamycin for immune suppression, imatinib for chronic myelogenous leukemia and gastrointestinal tumors, and gefitinib for non–small cell lung cancer has paved the way for development of additional kinase-targeted drugs that are currently under evaluation of clinical trials. Indeed PSThPases catalytic subunits are already established as drug targets. It was later determined that several of these compounds (e.g.,cyclosporin A(CsA), FK506, cantharidin, and fostriecin) specifically bind and inhibit PSThPases catalytic subunits [19,20]**.** The PP5 promoter contains an estrogen response element, and estradiol has been reported to increase PP5 expression by 50% in estrogen-dependent breast carcinoma cells [21]. Because decreased PP5 activity restricts estrogen-dependent cell growth, small-molecule inhibitors of PP5 could be useful for treating breast cancers resistant to selective estrogen receptor modulators. Ellgaard *et al,* (2017) purified the turocofocog alfa in a CHO cell line with minimal virus contamination [22]**.**

Treatment of severely diabetic rats with *d*-chiroinositol-galactosamine enhanced insulin signaling and decreased blood sugar levels, presumably as a result of increased PP2C dephosphorylation and activation of glycogen synthase and pyruvate dehydrogenase. Because allosteric activation of PP2C correlates with increased sensitivity to insulin, PP2C may also prove to be a desirable target for the design of new diabetes drugs [23].

CONCLUSION

Aberrant PPases activity has been linked with several pathological states, including diabetes, cardiovascular disorders, cancer, and Alzheimer's disease. Therefore, the pharmacological manipulation of phosphatase activity is an attractive strategy for the treatment of such conditions. There is two different approaches for PPases drug development: (1) targeting phosphatase catalytic subunits and (2) targeting specific phosphatase complexes (i.e., phosphatase oligomeric holoenzymes and phosphatase-substrate complexes). Both strategies are being actively pursued and have produced multiple compounds that are worthy of clinical testing. Molecular

targeted drug design requires a thorough knowledge of the enzyme's structure and catalytic mechanism.

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