Pseudophosphatases in Disease

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Pseudophosphatases are important regulators, and their proper regulation is important for maintaining homeostasis and preventing diseases.

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1. Introduction

Over the past decade, the relevance of pseudoenzymes has been elevated and solidified as important signaling regulators. These modes of action and their roles in various cellular processes serve as an idea link for the roles of pseudoenzymes in pathologies and diseases. Misregulation of pseudoenzymes has been implicated in the etiology of various diseases such as cancer, obesity, and neurological disorders [1][2][3][4][5]. This review highlights the signaling pseudophosphatases and their implications in diseases, while demonstrating some of their essential roles in preventing or causing such diseases.

Pseudophosphatases of PTPs are widely accepted as having mutations within their signature active site motif (HCX5R) They maintain the three-dimensional fold and the ability to bind phosphorylated proteins [1][6][7]. Recent reports have advanced the field, complicating the mutated sequence definition [6][8] and the “grab and hold on” perspective, where pseudophosphatases stably interact with phosphorylated residues, thereby competitively inhibiting active phosphatases or kinases [6][7]. For example, the histidine domain containing protein tyrosine phosphatase (HD-PTP) is reported as a pseudophosphatase [1][2][9][10][11][12][13] and an active phosphatase [1][2][14][15][16].

This dual and contradictory functionality of HD-PTP highlights the complexities of investigating pseudophosphatases. Wishart and Dixon defined pseudophosphatases as STYX domains, and demonstrated a loss of function of dephosphorylating phosphorylated substrates [17]; thus, they defined the prototypical STYX domain beyond pure bioinformatics [17]. The analysis of pseudophosphatases through a combination of sequencing and functional experiments —dephosphorylation assays with appropriate substrates and contextual situations (localization, substrates/interactors, or abundance of interactor or pseudphosphatase—will provide more of an insight into the full spectrum [1][2][3]. Nevertheless, the roles of pseudophosphatases as regulators in many cellular processes such as spermatogenesis, stress response, neuronal differentiation, cell fate, migration, ubiquitylation, demyelination, oocyte-to-zygote transition, transcription, and apoptosis [1][18][3][7][11][13][19][20] have led to interest into their apparent roles in diseases.

The increased interest in pseudophosphatases resulted in the discovery of their relevance in many diseases. provided a useful framework for pseudophosphatases’ linkage to diseases [3]. Mutations of these molecules or their misregulation leads to diseases such as leukemia, breast cancer, colorectal cancer, hepatocarcinoma, glioblastoma, other cancers, Charcot-Marie-Tooth (CMT) disease (abnormal nerve myelination), obesity, diabetes, chronic obstructive pulmonary disease (COPD), and nephrotic syndrome [2][3][21][22][23][24][25][26][27]. A comprehensive list of the known functions of pseudophosphatases and their implications in diseases is provided in **Table 1**.

Table 1. Pseudophosphatase Functions and Roles in Disease.

Pseudophosphatase Name	Alternative Names	Normal Function	Role in Disease
MTMR5 (Myotubularin-related protein 5)	**SBF1**	• Heterodimerizes with and increases phosphatase activity of MTMR2 [28]	• Mutations in MTMR5 cause CMT4B3 [29] • Male mice with MTMR5 knockout are infertile [30]
MTMR9 (Myotubularin-related protein 9)		• Heterodimerizes with and increases phosphatase activity of MTMR6, MTMR7, and MTMR8 [31] • Negative regulator of autophagy [31] • Negative regulator of apoptosis [31]	• An MTMR9 SNP is positively associated with obesity [32] • Mutated MTMR9 is implicated in epilepsy [33]
MTMR10 (Myotubularin-related protein 10)		-	• MTMR10 expression decreased in the esophageal mucosa of sufferers of esophageal achalasia [34]
MTMR11 (Myotubularin-related protein 11)		-	• The expression of MTMR11 is reduced in acute myeloid leukemia [35] • Abnormal expression levels in HER2 breast cancer cells [36]
MTMR12 (Myotubularin-related protein 12)	**3-PAP**	• Dimerizes with and stabilizes MTM1 [37] • Dimerizes with MTMR2 [38]	-
MTMR13 (Myotubularin-related protein 13)	**SBF2**	• Heterodimerizes with and increases phosphatase activity of MTMR2 [24]	• Mutations in MTMR13 are the causative factor of CMT4B2 [39]
STYX (Serine/threonine/tyrosine -interacting protein)		• Major positive regulator of spermatogenesis. Interacts with CRHSP-24 [17] • Anchors ERK1/2 in the nucleus and reduces its phosphorylation [40] • Binds to FBXW7 and reduces its association with the SCF ubiquitin ligase complex [41]	• Drives tumor growth and metastasis in colorectal cancer [22] • Expression increased in breast cancer [42] • Downregulates FBXW7 to drive endometrial cancer [43]

Pseudophosphatase Name	Alternative Names	Normal Function	Role in Disease
MK-STYX (Mitogen-activated protein kinase phosphoserine/ threonine/tyrosine-binding protein)	**STYXL1, DUSP-24**	• Antagonizes stress granules, and interacts with G3BP1 [44][45] • Promotes mitochondrial dependent apoptosis by reducing the activity of PTPMT1 [46] • Promotes cellular changes associated with neuronal differentiation [47][48][49] • Alters nuclear localization of HDAC6, and increases the detyrosination of tubulin [50]	• Overexpressed in Ewing's sarcoma [5] • Commonly amplified in glioma and enhances glioma growth, migration, and metastasis [51] • MK-STYX expression elevated in hepatocellular carcinoma (HCC). Has pro-proliferative and anti-apoptotic effects on this cancer. [27] • Expression increased in breast cancer cells subjected to proton beam therapy [52] • MK-STYX expression is elevated in human prostate cancer [53]
STYXL2 (Serine/threonine/tyrosine-interacting-like protein 2)	**DUSP-27 (duplicated)**	• Expressed in muscle tissue and may be important for myofiber development [54]	• Mutation in STYXL2 causes muscular dysfunction [54]
TAB1 (TGF-beta-activated kinase 1 and MAP3K7-binding protein 1)	**MAP3K7IP1**	• Activates TAK1, a MAP3K, during TGFβ signaling [55] • TAB1 activates p38 MAPK and changes its localization [56] • TAB1 blocks MDM2′s inhibition of p53 [57]	• Cleaved by the Enterovirus 71 virus that causes hand, food, and mouth disease (HFMD) [58] • TAB1 levels reduced in ovarian cancer [57]
Tensin 1	**TNS1**	• Serves as an adaptor between integrin receptors and actin filaments in focal adhesions [59] • Upregulates cell migration [60]	• A common tensin 1 SNP is positively associated with COPD [26] • Increased expression augments proliferation and metastasis in colorectal cancer [61] • Tensin 1 inhibits cdc42 to reduce invasion and metastasis in breast cancer [62] • A MaTAR25/PURB complex activates tensin 1 to drive breast cancer [63]

The proteins here all contain alterations in their catalytic active site motifs that are associated with loss of phosphatase function.

Furthermore, those that have not been linked to diseases have functions that may allude to a possible role in diseases. The diversity of these diseases, such as various types of cancer, COPD, CMT, obesity, diabetes, etc. Furthermore, their diverse range, while validating the intricate roles of pseudophosphatases in signaling cascades, also makes understanding their many functions in diseases more complicated. Considering this special edition focused on the roles of protein tyrosine phosphatases in signaling, with an emphasis on therapeutic strategies, the pseudophosphatases' signaling mechanisms linked to diseases, myotubularins, tensins, and STYX pseudophosphatases, was discussed in more detail.

2. Myotubularin in Diseases

Six of these genes produce pseudophosphatases, which form complexes with their active homologs [21][64][65] (**Figure 1**A). This dimerization is context dependent, resulting in complex stability, enhancement of catalytic function (increased phosphatase activity), and regulation of the subcellular localization of the active phosphatase [66][67]. The coupling of active and inactive MTMs to form heterodimers is common; however, self-association to form homodimers also occurs among both active and inactive MTMs (**Figure 1**A) It is of interest that some MTMs have not been reported to interact directly as dimers [65].

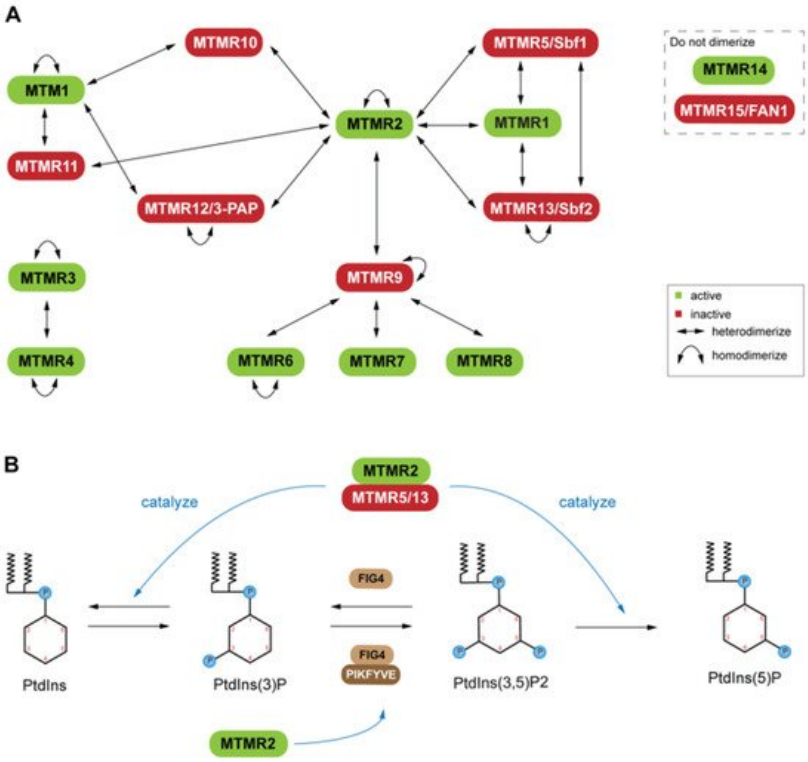

Figure 1. Dimerization states of the myotubularin (MTM) family: (**A**) Active and catalytically inactive forms are indicated in green and red, respectively. Active and inactive coupling (heterodimerization) is common; however, self-association (homodimerization) has also been reported among both active and inactive MTMs. MTMR14 and MTMR15 are not known to dimerize. (**B**) Phosphorylation schema for phosphatidylinositol (PtdIns), a molecule important for endosomal-lysosomal membrane trafficking, with example PtdIns kinases (PIKFYVE) and non-MTM phosphatases (FIG4), along with active and inactive MTMs (labelled green and red, respectively). Heterodimerization of an active (MTMR2) and inactive (MTMR5, MTMR13) leads to a stabilized complex with PtdIns phosphatase potential. MTMR2 and FIG4 interactions have been implicated in vivo, though further characterization is necessary.

For example, mutations of MTMR2 and MTMR13 leads to misregulation of the AKT signaling in Type 4B Charcot-Marie-Tooth (CMT4B) disease [68]. Overexpression of MTMR2 prevents sustained activation of epidermal growth factor, which leads to sustained AKT activation in transgenic mice [68]. PtdIns(3)P and PtdIns(3,5)P2are important molecules for endosomal-lysosomal membrane trafficking [69], which is tightly regulated by PtdIns kinase and phosphatase activity. MTMs have also been linked to X-linked centronuclear myopathy (XLCNM)

(phosphatase) forms heterodimers with MTMR13 (pseudophosphatase) or MTMR5 (pseudophosphatase), and heterodimers with MTMR13 (pseudophosphatase) or MTMR5 (pseudophosphatase), and Genetic studies in mice revealed that MTMR12 interacts with another phosphatase, polyphosphoinositde phosphatase (FIG4) MTM pseudophosphatase: phosphatase heterodimer signaling complexes are required for cellular processes such as differentiation, membrane trafficking, endocytosis, and survival [70][21][71][69].

3. STYX Pseudophosphatases in Disease

The term “STYX” (phosphoserine/threonine/tyrosine-interacting protein) was coined to designate the phosphotyrosine binding domain that has no catalytic activity, or “dead” phosphatases or pseudophosphatase [17]. These “dead” or STYX domain phosphatases allude to the Greek mythological STYX river of the dead [6][7]. Usage of a point mutation to “restore” catalytic activity in the STYX domain has proved to be a helpful tool to initiate the process of investigating molecules that contain STYX domains. STYX domain phosphatases are pseudophosphatases; therefore, the authors have referred to them as STYX pseudophosphatases, as previously reported [6].

They are all members of the dual specificity protein tyrosine phosphatase (DUSP) family; however, they belong to different subfamilies [2]. These domains vary both from the active site signature motif and each other (**Figure 2**B,C). Of note, all these STYX domain proteins have glycine, isoleucine, serine, and arginine in the active site motif (**Figure 2**B,C). Furthermore, early reports classified glycine as a conserved residue of the active site motif, HCxxGxxR [70][16].

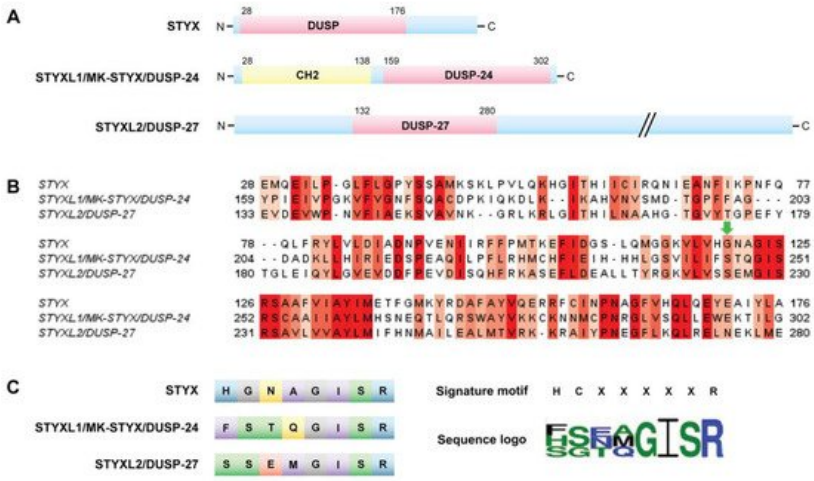

Figure 2. STYX pseudophosphatases: (**A**) Structure of STYX pseudophosphatases. STYX has an N-terminal DUSP domain. MK-STYX features an N-terminal CH2 domain and a C-terminal DUSP domain. STYXL2 contains an N-terminal DUSP domain. (**B**) Sequence alignment of the phosphatase domains of the STYX pseudophosphatases (Clustal Omega 1.2.4). Conserved residues are shown in red, where darker red indicates higher conservation (Jalview 2.11.14 with a threshold of >5.5). The green arrow indicates where the essential active-site cysteine residue would be located in a catalytically active PTP (HCX_5R). (**C**) The left-hand side of the panel compares the active site sequences of the STYX pseudophosphatases. Amino acid color indicates chemical property. Polar amino acids are shown in green, neutral in yellow, basic in blue, acidic in red, hydrophobic in purple, and glycine in grey. The right-hand side of the panel shows the sequence of the consensus active signature motif of PTPs compared to the sequence logo of the three STYX pseudophosphatases. The sequence logo was built by WebLogo 3.7.4 with a 2.0-bit scale.

STYX and MK-STYX have been shown to be important signaling regulators in cellular processes such as cell cycle, spermatogenesis, cell-fate decisions, cell migration, ubiquitylation and protein degradation, apoptosis, and neuronal differentiation [19][20][46][47][49][72][73], alluding to their roles in the etiology of various diseases. Furthermore, these STYX pseudophosphatases have roles in cancer such as colorectal, Ewing sarcoma, and hepatocarcinoma [4][22][27]. In addition, STYX promotes oncogenesis in colorectal cancer by inhibiting FBXW7, blocking the degradation of cyclin E and c-Jun Therefore, free (unbound) cyclin E and c-Jun are able to promote proliferation in colorectal cancer.

MK-STYX lacks the critical cysteine in the active site signature motif (HCX5R) An increase in MK-STYX expression also promotes hepatocellular carcinoma (**Figure 3** (Bii)) mRNA expression results in upregulation of PI3K (phosphatidyl 3-kinase)/AKT pathway proteins and an enhancement of proliferation, while reducing apoptosis in hepatocellular carcinoma STYXL2 is a downstream target of the Janus activated kinase/Signal transducers and activators of transcription signaling pathway [74], suggesting that STYXL2 has important roles in signaling cascades.

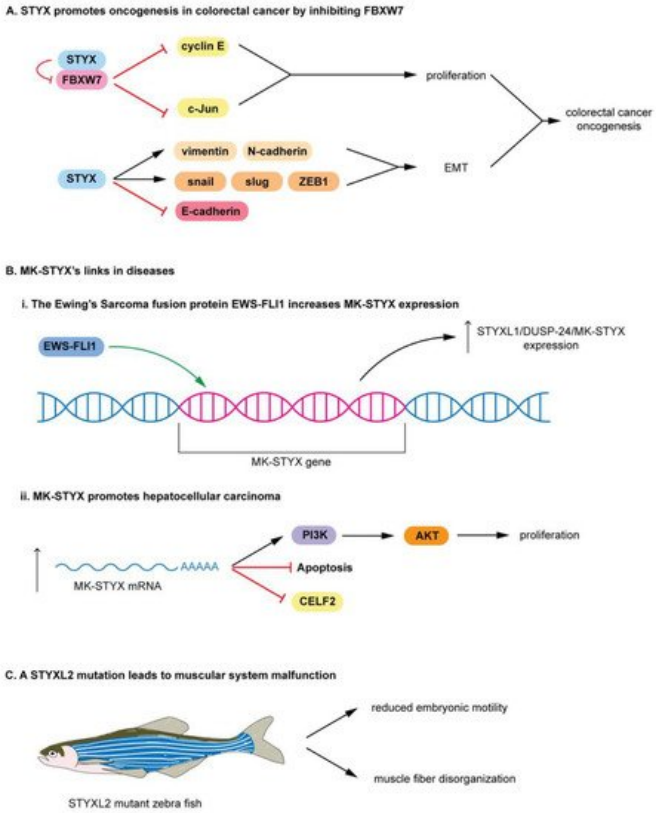

Figure 3. Roles of STYX domain pseudophosphatases in disease: (**A**) Prototypical STYX roles in colorectal cancer. STYX promotes oncogenesis in colorectal cancer by inhibiting FBXW7. STYX binds FBXW7, preventing other interactions of FBXW7, which is a substrate recruiter for a ubiquitin protein ligase complex. Thus, STYX prevents the degradation of cyclin E and c-Jun, promoting proliferation in colorectal cancer. STYX overexpression increases the expression of vimentin, N-cadherin, snail, slug, and ZEB1, but reduction in E-cadherin. These proteins support EMT; STYX may promote the oncogenesis of colorectal cancer by positively regulating EMT. (**B**) MK-STYX's links in diseases. (**i**) The Ewing's sarcoma fusion protein EWS-FLI1 increases MK-STYX expression. The EWS-FLI1 oncoprotein binds an ETS binding motif within the MK-STYX gene and increases the MK-STYX's expression. (**ii**) MK-STYX promotes hepatocellular carcinoma. An increase in MK-STYX mRNA expression leads to upregulation of PI3K/AKT pathway proteins and an enhancement of proliferation in hepatocellular carcinoma, while inhibiting apoptosis and CELF2. (**C**) STYXL2 mutation leads to muscular system malfunction. A transgene integration into the STYXL2 gene reduces STYXL2 expression in zebrafish, resulting in reduced embryonic motility, low spontaneous coiling movements, and severely reduced touch response, as well as major muscle fibers disorganization.

In addition, a transgene integration intoSTYXL2reduces STYXL2 expression in zebrafish, resulting in muscular system malfunction (**Figure 3**C) [2][74]. STYXL2 mutants have reduced embryonic motility (low paralysis), displaying low spontaneous coiling movements and severely reduced touch response (**Figure 3**C) [74]. Furthermore, STYXL2 mutants have a major disruptions in the contractile apparatus of their muscle fibers–disorganized muscle fiber formation (**Figure 3**C) [74].

4. Atypical Pseudophosphatases

This review focused on the less contradictory pseudophosphatases' signaling in diseases, with DUSP27/STYXL2 as the exception; Reiterer et al. encompasses such contradictory pseudophosphatases [2]. In addition, the D2 domains, which are catalytically inactive and recognize substrate [70], of the PTP receptor molecules were excluded. Recently, the protein tyrosine phosphatase receptor U (PTPRU) was classified as pseudophosphatase [75], both its DUSP domains, D1 and D2, were considered as pseudophosphatase domains [75]. In addition, tensin 2 is thought to have possible activity by dephosphorylating insulin receptor substrate-1 [76].

Some pseudophosphatases were reported as having catalytic activity [1][2][3]. Phosphatase of regenerating liver-3 (PRL3) phosphatase is an example of the concept of a pseudo-pseudophosphatase, which recognizes the catalytic activity and the importance of the noncatalysis in signaling cascades [2][77][78]. In studies with PRL3 mutants specifically defective in

either binding the substrate of PRL3 substrate, CBS domain divalent metal cations transport mediators (CNNM) or phosphatase activity [78] demonstrated that the phosphatase activity is dispensable [78]. Moreover, phosphatase activity prevents PRL3-CNNM interaction, which is necessary and sufficient for tumor metastasis [78].

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