Phosphotyrosine Phosphatases in Cancer Diagnostic and Treatment

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Abstract: The activation of proteins by post-translational modification represents an important cellular mechanism for regulating most aspects of biological organization and control, including growth, development, homeostasis, and cellular communication. The complexity of protein modification includes phosphorylation and dephosphorylation, on proteins of different signaling pathways corresponding to growth, development, disease states, and aging.

Current patents in phosphotyrosine phosphatases signaling pathway are focusing in diagnosis, prognosis and treatment. Many, new diagnosis techniques detect changes in mRNA expression with microarray technologies and others introduced specific antibodies for detection proteins changes, introducing to Biomedicine at Transcriptomic and Proteomic era. Many recent invent development alternative therapy with antibodies and inhibitors to PTPs that demonstrate the need to deepen understanding of the molecular mechanisms involved in the development of cancer.

Keywords: Phosphotyrosine phosphatases, signaling pathway, diagnosis and treatment, cancer.

INTRODUCTION

The activation of proteins by post-translational modification represents an important cellular mechanism for regulating most aspects of biological organization and control, including growth, development, homeostasis, and cellular communication. Protein phosphorylation plays a critical role in the etiology of many pathological conditions and diseases, including cancer, developmental disorders, autoimmune diseases, and diabetes. In spite of the importance of protein modification, it is not yet well understood at the molecular level. The reasons for this lack of understanding are, first, that the cellular modification system is extraordinarily complex, and second, that the technology necessary to unravel its complexity has not yet been fully developed [1]. The complexity of protein modification includes phosphorylation and dephosphorylation, on proteins of different signaling pathways corresponding to growth, development, disease states, and aging [2]. The human genome encodes many kinases and phosphatases families, making them the most abundant class of enzymes known (Table **I**) [3].

Each of these kinases phosphorylates specific serine, threonine, or tyrosine residues located within distinct amino acid sequences, or motifs, contained within different protein substrates. Most kinases phosphorylate many different proteins, and many proteins are phosphorylated at multiple sites by different kinases [4].

Protein tyrosine phosphorylation is regulated in the cell by the opposing activities of two enzymes: protein tyrosine kinases (PTKs), which transfer phosphate from ATP to substrate proteins, and protein tyrosine phosphatases (PTPs), which remove it. Intercellular protein tyrosine phosphorylation is regulated by extracellular stimuli, such as cytokines, to control cell growth, differentiation and functional activities. This signaling mechanism depends on the interplay of protein tyrosine kinases, which initiate signaling cascades through phosphorylating tyrosine residues in protein substrates, and by protein tyrosine phosphatases that terminate signaling via substrate dephosphorylation. Functionally, the most important effect of tyrosine phosphorylation is to create high-affinity binding sites for other proteins containing small modular phosphotyrosine (pTyr)-binding domains, most notably Src homology 2 (SH2) domains [5]. Any deviation in balance between PTP and PTK can promote abnormal cell proliferation and differentiation thereby resulting in different kinds of diseases [6, 8]. SHP-1 (PTPN6) is one of the most important components from this equilibrium and decreased

Table I. Families of PTPs and Relation with Function

Type of PTP	Function	Examples
Receptor Classic PTP	Signaling pathways of immunological response	LAR, CDC45
Non Receptor Classic PTP	Signaling pathways of immunological response, proliferation, cell adhesion and differentiation.	SHP-1 (PTPN6), SHP-2 (PTPN11), PTP1B, PEST.
Duals PTP	Signaling pathways of differentiation, cellular cycling and apoptosis.	CDC25, MKP, VHR
Lipids Phosphotyrosine Phosphatases.	Signaling pathway of cellular surviving.	PTEN

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activity, gene mutation or gene deletion, leading to an increase in tyrosine-phosphorylated proteins in cells with pathological consequences [9-12].

Many phosphorylation sites regulate critical biological processes and may prove to be important diagnostic or therapeutic targets for molecular medicine [13]. Phosphorylation is important in signal transduction mediated by receptors via extracellular biological signals such as growth factors or hormones. For example, many oncogenes are kinases or phosphatases. In addition, a kinase or phosphatase can have its activity regulated by one or more distinct kinase or phosphatases, resulting in specific signaling cascades. The ability to identify phosphorylation sites on a wide variety of cellular proteins, and kinases and phosphatases involucrate in these processes, is crucially important to understanding the key signaling proteins and pathways implicated in cancer progression [14]. Oncogenic kinases such as ErbB2 and Jak3, widely expressed in breast tumors and various leukemias, respectively, transform cells to the oncogenic phenotype at least in part because of their ability to phosphorylate cellular proteins. Understanding which proteins are modified by these kinases will greatly expand our understanding of the molecular mechanisms underlying oncogenic transformation [15].

The usage of this knowledge can guide new diagnostics methods, prevention and treatment of cancer. For the other hand, recently new methods of treating cancer based in immune treatments which typically involve the administration of an antibody or antibody fragment, or alternatively new chemotherapeutic treatments are available with phosphotyrosine phosphatases. This review describes the most relevant patent respect this thematic (summarized in Table **II**).

PHOSPHOTYROSINE PHOSPHATASES SIGNALING PATHWAY AND DIAGNOSIS

Protein tyrosine phosphatases (PTPs) constitute a large family of signaling enzymes (>100 in humans) that are important for the regulation of cell proliferation, differentiation, metabolism, migration, and survival [16-17]. Dysfunction in PTPs results in aberrant tyrosine phosphorylation, which has been linked to the etiology of several human diseases, including cancer and diabetes [18].

Unlike protein kinases, where tyrosine specific and serine/threonine specific kinases share sequence identity, the PTPs show no sequence similarity with serine/threonine phosphatases, or the broad specificity phosphatases such as acid or alkaline phosphatases. The hallmark that defines the PTP superfamily is the active site amino acid sequence $C(X)_5R$, also called the PTP signature motif, in the catalytic domain. The PTPs can be broadly divided into two groups based on active site substrate specificity: the tyrosine-specific, and the dual specificity phosphatases, which hydrolyze pSer/Thr as well as pTyr. Despite variations in primary structure and differences in substrate specificity, key structural features in the active site and the mechanism of catalysis are conserved among all members of the PTP superfamily [19-20].

Although PTPs share a common catalytic mechanism, they have distinct (and often unique) biological functions in vivo. One of the major challenges in the field is to rapidly establish the functional roles for PTPs, in both normal physiology and pathogenic conditions. Gene knockout analysis is useful to assess the role of a number of PTPs in cellular signaling. However, this process is often tedious, and gene ablation in animals often results in compensatory changes through other mechanisms during embryonic development [21]. In addition, the one gene at a time approach is clearly inadequate to deal with the dynamics and complexity in the complement of proteins within a proteome. One attractive strategy for efficient analysis of PTP function is to characterize these enzymes collectively, rather than individually [22]. In this regard, DNA microarray methods provide significant insights into changes in the abundance of transcripts [23].

Cloning procedures aided by homology searches of expressed sequence tag (EST) databases have accelerated the pace of discovery of new genes, but EST database searching remains an involved and onerous task. More than 3.6 million human EST sequences have been deposited in public databases, making it difficult to identify ESTs that represent new genes. Compounding the problems of scale are difficulties in detection associated with a high sequencing error rate and low sequence similarity between distant homologues [24].

The analysis of gene expression within cells has been used to provide information on the state of those cells and importantly the state of the individual from which the cells are derived. The relative expression of various genes in a cell has been identified as reflecting a particular state within a body [25]. For example, cancer cells are known to exhibit altered expression of various proteins and the transcripts or the expressed proteins may therefore be used as markers of that disease state. The identification of quick and easy methods of sample analysis for diagnostic applications remains the goal of many researchers [26]. End users seek methods which are cost effective, produce statistically significant results and which may be implemented routinely without the need for highly skilled individuals. In this sense, WO2005118851A1 patent relates to oligonucleotide probes, for use in assessing gene transcript levels in a cell, which may be used in analytical techniques, particularly diagnostic techniques provides as kit form. Different sets of probes may be used in techniques to prepare gene expression patterns and identify, diagnose or monitor different cancers or stages thereof. A set of oligonucleotides for use in the methods includes the families of genes that have been identified as being differentially expressed in cancer patients may be summarized as follows: genes encoding proteins involved in protein synthesis and/or stability; and genes encoding proteins involved in the regulation of defense and/or chromatin remodeling. Preferably more than one oligonucleotide is selected from each family. The invention provides a kit comprising a set of oligonucleotide probes immobilized on one or more solid supports and each unique probe is attached to a different region of said solid support. Solid support is sheet, filter, membrane, plate or biochip. Optionally the kit may also contain information relating to the signals generated by normal or diseased samples, standardizing materials (e.g. mRNA or cDNA from normal and/or diseased samples for comparative purposes), and labels for incorporation into

Table II. Recent Patents in PTP Diagnosis, Treatment and Prognosis

Publication number	Title	Inventors
Recent in diagnosis of PTP signaling pathway		
WO 2009033293	Protein tyrosine phosphatase 1b and cancer technical field	Tremblay *et al.*, 2009.
US 0050233469	Activity-based probes for protein tyrosine phosphatases.	Zhang and Kumar, 2005.
WO 2005118851A1	Oligonucleotides for cancer diagnosis	Sharma and Lönneborg, 2005.
US 0050281743	Cancer associated protein phosphatases and their uses	Delaney, 2005.
US 0050181375	Novel methods of diagnosis of metastatic cancer, compositions and methods of screening for modulators of metastatic cancer	Aziz and Zlotnik, 2005.
Recent patents in antibodies compounds for PTP		
EP 1097944A1	Antibody against protein tyrosine phosphatase intracellular domains	Yamamoto *et al.*, 2008.
US20056933135	Antibodies specific for intracellular domain of protein tyrosine phosphatase	Yamamoto *et al.*, 2005.
US 0050233469	Activity-based probes for protein tyrosine phosphatases	Zhang and Kumar, 2005.
Recent patents in chemical compounds for inhibition of phosphatases		
WO2003050098A1	2-substituted thiazolidinone and oxazolidinone derivatives for the Inhibition of phosphatases and the treatment of cancer	Al-Shamma *et al.*, 2003.
WO2007067613A1	1,2,5-Thiazolidine derivatives useful for treating conditions mediated by PTP	Barnes *et al.*, 2007.
WO2003070158A2	Therapeutic compositions and methods useful in modulating protein tyrosine phosphatases cross-reference to related applications	Yi, 2003.
US20080176309	Inhibition of SHP2/PTPN11 protein tyrosine Phosphatase by NSC-87877, NSC-117199 and their analogs.	Wu *et al.*, 2008.

cDNA, adapters for introducing nucleic acid sequences for amplification purposes, primers for amplification and/or appropriate enzymes, buffers and solutions. Thus determination the gene expression pattern with this kit comprising at least the steps of: a) isolating mRNA from said cell, which may optionally be reverse transcribed to cDNA; b) hybridizing the mRNA or cDNA of step (a) to a set of oligonucleotide probes; and c) assessing the amount of mRNA or cDNA hybridizing to each of said probes to produce said pattern [27].

However, the measured mRNA levels do not always correlate with protein expression. Proteomic approaches address some of the gaps in genomic technologies by profiling and measuring bulk changes in protein levels. Unfortunately, current methodologies are only adequate for abundant proteins. Furthermore, the amount of protein is not always proportional to biological activity, which may subject to post-translational regulation. Thus, standard proteomics techniques are not optimal for tracking variations in protein activity. Because the function of a PTP depends on its phosphatase activity, the development of novel technologies for directly measuring the dynamics in PTP activity on a global scale is of tremendous interest [28].

United States Patent 0050181375 described methods and compositions that can be used for diagnosis and treatment of metastatic cancer. Also described herein are methods that can be used to identify modulators of metastatic cancer. The invention provides nucleotide sequences of genes that are up- and down-regulated in metastatic breast or metastatic lung cancer cells. Such genes and the proteins they encode are useful for diagnostic and prognostic purposes, and also as targets for screening for therapeutic compounds that modulate metastatic breast or lung cancer, such as antibodies. The methods of detecting nucleic acids of the invention or their encoded proteins can be used for a number of purposes. Examples include, early detection of breast or lung cancers, monitoring and early detection of relapse following treatment of breast or lung cancers including early detection of metastatic cancer, monitoring response to therapy of breast or lung cancers, determining prognosis of breast or lung cancers, directing therapy of breast or lung cancers, selecting patients for postoperative chemotherapy or radiation therapy, selecting therapy, determining tumor prognosis and the likelihood that a given cancer will metastasize or has metastasized, treatment, or response to treatment, early detection of precancerous conditions and early detection of metastasis. The most important aspect of the novel methods of diagnosis of metastatic cancer, compositions and methods of screening for modulators of metastatic cancer is that combines the detection at level of nucleic acids and proteins, contacting the compound with a metastatic breast cancer-associated polypeptide and determining the functional effect of the compound upon the polypeptide [29].

Other methods used only protein detection, such as United States Patent 0070161064 and 007192698, which

provides a method and kits for the detection and diagnosis of metastatic disease. More particularly, the methods and kits employ compounds that can detect EphA2, a specific epithelial cell tyrosine kinase that is overexpressed in metastatic tumor cells. In one embodiment the compound is an antibody capable of binding to an epitope of EphA2. A method for detecting the presence of metastatic cells in a cell population comprising the steps of: lysing at least a portion of the cell population, incubating the lysed cells with a monoclonal antibody that specifically binds EphA2 to allow antibody binding to EphA2, and detecting antibody-EphA2 binding; wherein the cell population comprises cancer cells selected from the group consisting of breast cancer cells, kidney cancer cells, prostate cancer cells, lung cancer cells, colon cancer cells and epithelial cancer cells, and wherein antibody-EphA2 binding is indicative of the presence of metastatic cells in the cell population [30-31].

Recently, a chemical approach has emerged that allows the consolidated detection and identification of collections of enzyme activities in complex proteomes [32-33]. Such an approach employs specific chemical probes that are directed to enzyme active site for covalent modification in an activity dependent fashion. Activity-based probes have been used for proteomic analysis of the cysteine and serine hydrolases, providing new insights into our understanding of these two families of proteases in cell biology and in diseases. However, little success has been achieved in targeting specifically to the PTP family with activity-based probes [34-35]. The United States Patent 0050233469 represent invention satisfies that utilized activity-based probes targeted to recognize proteins of PTP superfamily. The inventors have identified activity-based probes that covalently bind to all members of the protein tyrosine phosphatase (PTP) superfamily. These probes are useful for isolating and identifying PTPs in tissues, cells, cellular extracts or biological fluids. Additionally the method evaluate whether a substance is an inhibitor of a PTP. The methods comprise combining the patented compound and a possible inhibitor with the PTP; and determining whether one substance (possible inhibitor) is bound to the PTP. In these methods, a reduction in or lack of binding of the patented compound to the PTP indicates that the substance is an inhibitor of the PTP [36].

Despite a long-felt need to understand and discover methods for regulating cells involved in various disease states, the complexity of signal transduction pathways has been a barrier to the development of products and processes for such regulation. Accordingly, there is a need in the art for improved methods for detecting and modulating the activity of such genes and for treating diseases associated with the cancer and signal transduction pathways. The role of a protein tyrosine phosphatase 1B (PTP 1B) are an example of this. Previous studies of PTP1B activity and expression in various cancer cells and tumors have revealed variable expression levels and conflicting effects of this phosphatase in oncogenesis, however, the exact role of PTP1B in tumorigenesis has remained unclear. It would therefore be desirable to understand the role of PTP1 B in cancer development and tumorigenesis, for example in human breast cancer, prostate cancer and lung cancer. Any breast and prostate cancers coursed with high levels of PTP1B. It would also be desirable to have therapeutic agents for the treatment and/or prevention of cancer [37]. The patent WO20090-33293 presents a method for identification using (PTP1 B) as a marker gene useful in the diagnosis and prognosis of breast cancer and prostate cancer. In addition, provides methods for determining the course of treatment of a patient with cancer and to screening for PTP 1B inhibitors therapeutics [38].

Other phosphatases and kinases can have used for screening of a cancer associated changes, wherein said targets are associated with signal transduction in cancer cells, the method comprising: comparing the pattern of gene expression or protein phosphorylation in a normal cell, and in a tumor cell characterized by up-regulation [39]. In the past decades, kinases were focus of the major of studies and may be a focusing of new therapy with inhibitors. For example WO2008066498A1 relates to mutant protein kinases, nucleotide sequences encoding the mutated protein kinases, their use for the diagnosis and treatment of various kinase-related diseases and conditions and the design and identification of novel protein kinases inhibitors. The protein kinase is one of FGFR4, FGFRl, Tyro3, TEC, CSK and Ackl [40]. However, many researchers have been described PTPs with antiproliferative agents. In this sense, United States Patent Application 0050281743 present methods and compositions relating to agents those specifically bind to phosphatases MKPX, PTP4A1, PTPN7, FEM-2, DKFZP66K0524 or FLJ-20313 for treatment and visualization of tumors in patients [41].

DETECTING PHOSPHORYLATION SITES WITH SPECIFIC ANTIBODIES

The efficient identification of protein phosphorylation sites relevant to disease has been aided by the recent development of a powerful new class of antibodies, now available commercially, called motif-specific, context-independent antibodies, which are capable of specifically binding short, recurring signaling motifs comprising one or more phosphorylated amino acids in many different proteins in which the motif recurs [42]. More recently, a powerful new method for employing such motif-specific antibodies in immunoaffinity techniques coupled with mass spectrometric analysis to rapidly identify modified peptides from complex biological mixtures has been described. Such techniques will enable the rapid elucidation of protein activation and phosphorylation events underlying diseases, like cancer, that are driven by disruptions in signal transduction [43].

The United States Patent 0050233469 patent relates to compositions and methods of specifically labeling proteins. More particularly, the inventors have identified activity-based probes that covalently bind to all members of the protein tyrosine phosphatase (PTP) superfamily and describe compositions that probe, and methods for using those compositions for tracking PTP activity and for identifying and isolating PTPs. These probes isolate and identify PTPs in tissues, cells, cellular extracts and biological fluids [36].

Mechanisms involving in the onset of many diseases have been gradually elucidated, and risk factors thereof have been identified. Thus the therapeutic treatments have been extensively carried out [44]. Clinically common pathology of these disease states is the signaling pathway that consists in tyrosine kinases receptor activation. Antibodies to intracel-

lular domains of two or more kinds of protein tyrosine phosphatases, methods for generation thereof and cells producing these antibodies are disclosed [45]. The antibody describes in United States Patent 6933135 patent may have specificity to intracellular domains of phosphatase subunits of both of LAR and CD45, and may be useful for analysis and quantitative determination of PTPs, identification and detection of novel PTPs, and for obtaining novel phosphatases by cloning and the like, as well as for developing useful diagnostic methods of insulin resistance, for prophylaxis and diagnosis of various disease states of syndrome X that is based on insulin resistance, and for prophylaxis and diagnosis of onsets of arteriosclerosis and cardiac diseases [46]. EP 1097944A1 have similar fundaments and including agonist and antagonist antibodies [47].

The meaning of fundament of antibodies treatment may be that the similar therapies upon the uptake of other pathologies such as cancer.

CHEMICAL COMPOUNDS ASSOCIATED WITH PROTEIN TYROSINE PHOSPHATASES

Chemical compounds that modulate the activity of protein tyrosine kinases or phosphatases can induce cellular changes through affecting the balance of intracellular protein tyrosine phosphorylation and redirecting signaling. Such compounds can be of value as experimental tools and, importantly, as potent therapeutic reagents. [48]

Few specific inhibitors of protein tyrosine phosphatases have been reported despite extensive efforts in the last decade to identify them. Although a number of chemicals that broadly inhibit protein tyrosine phosphatases are known, including sodium orthovanadate and iodoacetic acid, their usefulness as therapeutic agents is severely limited due to their general toxicity in vivo [49]. In 2001, WO2003070158 (A2), claim a group of compositions and methods useful in modulating the activity of protein tyrosine phosphorylation. These chemical compounds that modulate the activity of protein tyrosine kinases or phosphatases can induce cellular changes through affecting the balance of intracellular protein tyrosine phosphorylation and redirecting signaling. The invention provides for a method for the prophylactic and therapeutic treatment of diseases associated with protein tyrosine activity or abnormal activity. For example, sodium stibogluconate (also known as sodium antimony gluconate, Stibanate, Dibanate, Stihek, Solusti-bostam, Solyusurmin, Pentostam or Glucantime), a penta-valent antimonial used for the treatment of leishmaniasis, as a potent inhibitor of protein tyrosine phosphatase SHP-1.

Sodium stibogluconate targets the catalytic domain of SHP-1 and forms stable complexes with SHP-1 in vitro, also augments the opposite effects of GM-CSF and IFNa on TF-1 cell growth. Potassium antimonyl tartrate lacks inhibitory activity against PTPases. Compositions for use of WO 0307-0158(A2) inventive method preferably comprise a pharmaceutically acceptable carrier, the amount of the therapeutic composition sufficient to treat the particular disease prophylactically or therapeutically and the route of administration. It can be formulated as polymeric compositions, inclusion complexes, such as cyclodextrin inclusion complexes, liposomes, microspheres, microcapsules. [50]

Many thiazolic compounds were described for PTP inhibition. In this sense WO 2007067613(A1) that presents pharmaceutical thiadiazolidinone derivatives for treating conditions mediated by protein tyrosine phosphatases, in particular PTP1B and T-cell PTPase. The compounds of the invention may be employed to treat cancer (such as prostate or breast cancer) and many disease mediated with PTPases pathways such as osteoporosis, neurodegenerative and infectious diseases, and diseases involving inflammation and the immune system. [51]

Also, WO 03050098A1 provides compounds that are useful to treat diseases of uncontrolled proliferation, for example, for the treatment of cancers and precancerous conditions. The invention relates to a series of substituted heterocyclic compounds, including 2-substituted thiazolidinone and 2-substituted oxazolidinone compounds, which show unexpectedly potent anti-cancer activity *in vitro* and/or *in vivo*. The therapeutic target of the novel heterocyclic compounds has been Cdc25, with the effect of inhibiting cancer cell growth, and/or causing the apoptosis of cancer cells. Accordingly, the heterocyclic compounds disclosed herein are useful in the treatment of diseases of uncontrolled proliferation, such as cancer and precancerous conditions, particularly those found in mammals. These compounds can be used in the inhibition of certain inflammatory mediators such as, for example, TNFa and/or nitric oxide synthase (NOS). Compounds provided herein are useful in the treatment of diseases related to uncontrolled cellular proliferation, such as cancer or precancerous conditions. Therefore in view of their ability the compounds can also be useful for the control of inflammatory diseases such as arthritis. [52]

Wu *et al.* (US20080176309) patent compounds and associated methods for inhibiting a protein tyrosine phosphatase SHP2/PTPN11 in a cell comprising the step of contacting the cell with an effective amount of a described compound. These compounds are NSC-87877, NSC-117199 and their analogs, have been identified as specific SHP2 PTP inhibitors. Significantly, NSC-87877 is active in cell-based assays and has no detectable off-target effects in the EGF-stimulated Erk1/2 activation pathway. Additionally, a number of analogs of NSC-117199 exhibit enhanced protein tyrosine phosphatase inhibition and are found to be potent and/or selective inhibitors of SHP1 and/or SHP2 protein tyrosine phosphatases. Interestingly, the patented method is applicable to diseases with elevated protein tyrosine phosphatase activity associated with a selected disease group consisting of Noonan syndrome, juvenile myelomonocytic leukemia, Noonan-like disorder with multiple giant cell lesion syndrome, LEOPARD syndrome, acute lymphoblastic leukemia, acute myelogenous leukemia, H. pylori-associated gastritis and gastric cancer. [53]

CURRENT & FUTURE DEVELOPMENTS

The recent publication of the sequence of the human genome will accelerate the discovery of new genetic susceptibility factors for human disease, leading to the development of novel diagnostics and therapeutics. The exhaustive analysis of the human genome sequence will be the focus of the biomedical research community for many years to come.

In particular, current patents in phosphotyrosine phosphatases signaling pathway are focusing in diagnosis, prognosis and treatment. Many, new diagnosis techniques detect changes in mRNA expression with microarray technologies and others introduced specific antibodies for detection proteins changes, introducing to Biomedicine at Transcriptomic and Proteomic era. Simultaneously, many recent invent development alternative therapy with antibodies and inhibitors to PTPs.

All these findings demonstrate the need to deepen understanding of the molecular mechanisms involved in the development of complex diseases like cancer.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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