

# Phosphothreonine

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## summary

Phosphothreonine is a phosphorylated derivative of the amino acid threonine, formed by the addition of a phosphate group to the hydroxyl group in its side chain.

This post-translational modification is predominantly facilitated by protein kinases, enzymes that transfer a phosphate group from ATP to threonine residues within proteins. Phosphothreonine plays a vital role in regulating various cellular processes, including signal transduction, cellular responses to stimuli, and the modulation of protein activity, making it a critical component in the intricate network of cellular signaling pathways.[\[1\]\[2\]\[3\]\[4\]](#)

The significance of phosphothreonine extends to its impact on protein conformation and interactions, with phosphorylation often resulting in conformational changes that activate or inhibit proteins involved in essential biological functions, such as cell growth, survival, and differentiation. Notably, dysregulation of phosphothreonine signaling has been implicated in numerous diseases, including cancer, neurodegenerative disorders, and metabolic diseases, highlighting its potential as a therapeutic target for drug development and disease management.[\[5\]\[6\]\[7\]\[8\]](#)

Research into phosphothreonine also encompasses its synthesis, detection, and analysis, with various methodologies developed to incorporate this modification into peptides and proteins, as well as advanced techniques like mass spectrometry and immunoassays used to detect phosphorylated residues. These techniques are crucial for understanding the phosphorylation status of proteins within the context of disease states and cellular dynamics.[\[9\]\[10\]\[11\]](#)

Despite advancements in understanding phosphothreonine's role, challenges remain in synthesizing and analyzing its complex interactions, which require continued innovation in research strategies. The ongoing exploration of phosphothreonine not only contributes to our knowledge of fundamental biological processes but also offers insights into potential therapeutic interventions across a spectrum of diseases.[\[12\]\[13\]\[14\]](#)

## Chemical Structure

Phosphothreonine is a phosphorylated derivative of the amino acid threonine, characterized by the addition of a phosphate group to the hydroxyl (-OH) functional group present in its side chain. This post-translational modification occurs predominantly through the action of specific enzymes known as protein kinases, which facilitate the

transfer of a phosphate group from ATP to the hydroxyl group of threonine residues in proteins[\[1\]\[2\]](#).

## Structural Characteristics

The core structure of threonine includes a hydroxyl group, which is crucial for its phosphorylation. The addition of a phosphate group to this hydroxyl creates phosphothreonine, which can be denoted as phospho-Thr[\[3\]\[4\]](#). The resulting compound features a negatively charged phosphate moiety that can significantly alter the physical and chemical properties of the protein, influencing its conformation, stability, and interaction with other biomolecules.

## Functional Implications

Phosphothreonine is vital in various biological processes, including signal transduction pathways and cellular responses to environmental stimuli[\[2\]\[5\]](#). The phosphorylation status of threonine can modulate protein activity, either enhancing or inhibiting function depending on the specific context of the signaling pathway involved[\[6\]\[3\]](#). This reversible modification allows for dynamic regulation of protein interactions and activities within the cell.

## Synthesis

### Overview of Phosphothreonine Synthesis

The synthesis of phosphothreonine presents unique challenges due to the necessity of incorporating phosphorylated residues into peptides and proteins. Researchers have developed several methodologies to facilitate the efficient synthesis of phosphoforms, including phosphothreonine, utilizing various chemical strategies and technologies[\[6\]](#).

### Methods of Incorporating Phosphothreonine

#### Use of Dehydroalanine

One effective method for introducing phosphate-analogous structures in fully assembled peptides is through the use of dehydroalanine (DHA), which can be generated from cysteine or phosphoserine. This approach leverages the unique reactivity of DHA as an electrophile, allowing for high chemoselectivity in reactions[\[6\]](#). For instance, a bisalkylation-elimination protocol converts cysteine to DHA, which can subsequently undergo further transformations to introduce phosphothreonine analogs.

#### Thioester-Based Approaches

Innovations such as the bis(2-sulfanylethyl)amido linker allow the synthesis of thioesters that can be employed in the formation of phosphothreonine-containing

peptides. The incorporation of a latent thioester, created through resin functionalization and subsequent cleavage, enables transthioesterification with other thiols, ultimately facilitating the introduction of phosphothreonine[6]. This method has yet to be extensively applied to phosphopeptides but showcases the potential for future developments.

## Radical-Induced Reactions

The introduction of phosphothreonine can also be achieved via radical-induced methodologies. This approach has expanded the toolkit available for peptide synthesis, enabling the incorporation of various phosphoforms[6]. Such techniques are essential as they provide alternatives for constructing peptides that require specific modifications, like phosphorylation at threonine residues.

## Challenges in Phosphothreonine Synthesis

Despite advancements, synthesizing phosphothreonine and its corresponding phosphoforms remains a significant challenge. Researchers face the dual difficulty of incorporating multiple phosphorylated residues and generating a comprehensive array of phosphoform combinations for each protein sequence. These complexities highlight the need for continued innovation in synthetic strategies to enhance the efficiency and effectiveness of phosphothreonine synthesis[6].

## Biological Functions

Phosphothreonine, a phosphorylated form of the amino acid threonine, plays a crucial role in the regulation of various biological processes within cells. Its phosphorylation affects protein structure, function, and protein-protein interactions, thereby controlling diverse biological functions such as signal transduction and cell cycle regulation[7][8].

## Role in Cellular Signaling

Phosphothreonine is a key regulatory mechanism within cellular signaling pathways, modulating not only the activity of proteins but also their interactions and subcellular localization[8]. For instance, the addition of phosphate groups to proteins often results in conformational changes that activate enzymes and receptors, which is vital for the proper functioning of physiological and pathological processes like neural activity and cellular communication[9]. Protein kinases, the enzymes responsible for the phosphorylation of threonine residues, serve as critical molecular switches that initiate and propagate signals within the cell[10][11].

## Regulation of Cellular Responses

The cellular responses mediated by phosphothreonine involve complex regulatory mechanisms, including feedback loops, reversible phosphorylation, and compartmentalization[12]. For example, pathways such as MAPK (Mitogen-Activated Protein

Kinase) can promote cell growth and division, while PI3K/Akt pathways are pivotal in enhancing cell survival by inhibiting programmed cell death (apoptosis)[\[12\]](#). Additionally, phosphothreonine participates in signal amplification, where a single extracellular signal can trigger a cascade of intracellular events leading to a robust cellular response[\[12\]\[13\]](#).

## Impact on Disease

Dysregulation of signaling pathways involving phosphothreonine has been implicated in various diseases, particularly cancer. Aberrant phosphorylation events can lead to uncontrolled cell proliferation and survival, contributing to tumorigenesis[\[14\]](#). Therefore, understanding the biological functions of phosphothreonine is crucial for elucidating the mechanisms underlying many diseases and for developing targeted therapeutic strategies[\[15\]](#).

## Detection Methods

Phosphothreonine detection involves various advanced techniques that allow researchers to study the phosphorylation status of proteins, particularly in the context of signaling pathways and disease states. These methods are essential for understanding the role of phosphothreonine in cellular processes and its implications in diseases such as cancer.

### Mass Spectrometry

Mass spectrometry is a primary method used for the detection and characterization of phosphothreonine. It enables the identification of phosphorylation sites within proteins and offers quantitative data regarding their phosphorylation levels. Techniques such as high-energy collision dissociation (HCD) and electron transfer dissociation (ETD) are particularly useful for analyzing phosphopeptides, as the phosphorylation modifies the mass of the peptide, facilitating its detection [\[5\]](#). Moreover, the incorporation of differential isotope labeling techniques, like stable isotope labeling by amino acids in cell culture (SILAC), has advanced the relative quantification of changes in phosphorylation, including phosphothreonine [\[10\]](#).

### Immunoassays

Fluorescence-based immunoassays are another approach used to detect phosphothreonine in proteins. These assays utilize specific antibodies that recognize phosphorylated threonine residues, allowing for the visualization and quantification of phosphorylated proteins within complex mixtures. This method is advantageous for studying protein interactions and dynamics in live cells [\[5\]](#).

### Chemical Enrichment Techniques

Chemical enrichment techniques, such as the use of phosphoprotein enrichment kits, facilitate the isolation of phosphorylated proteins from cell lysates. These methods

typically involve affinity purification steps that selectively capture phosphothreonine-containing proteins, enhancing the sensitivity and specificity of downstream analysis [\[10\]](#).

## Computational and Text Mining Approaches

In addition to experimental techniques, computational methods and text mining are increasingly being utilized to predict and analyze phosphothreonine interactions and modifications. These approaches leverage publicly available biomedical databases to extract and predict protein-protein interactions (PPIs) related to phosphothreonine, providing insights into its functional implications in various biological contexts [\[1\]](#).

## Research Applications

### Drug Development

In the context of drug development, phosphothreonine modifications have been recognized as essential for elucidating the mechanisms behind drug resistance. By analyzing the biochemical pathways influenced by phosphothreonine, researchers can identify potential targets for novel therapeutics that may overcome resistance phenomena [\[16\]\[17\]](#). Furthermore, the role of 14-3-3 proteins, which are known to interact with phosphorylated threonine residues, has been highlighted in various malignancies, suggesting their potential as targets for new cancer therapies aimed at improving patient outcomes [\[15\]](#).

### Cancer Therapy

Phosphothreonine plays a significant role in the understanding and treatment of cancer, particularly regarding drug resistance. The ability of cancer cells to develop resistance against chemotherapy is a major clinical challenge that often leads to uncontrolled tumor progression and relapse, ultimately reducing patient survival rates [\[17\]](#). The modulation of signaling pathways involving phosphothreonine can influence cancer cell behavior, particularly in enhancing drug resistance mechanisms. For instance, alterations in gene expression, including multidrug resistance (MDR) genes such as MDR1 and MDR2, have been shown to be linked to phosphothreonine modifications, which may exacerbate the challenges faced in effective cancer treatment [\[18\]\[19\]](#).

### Cancer Stem Cells

The cancer stem cell (CSC) model provides insight into tumor heterogeneity and the complexities of cancer progression. CSCs are critical for tumor initiation and can exhibit unique phosphothreonine signaling pathways that contribute to their self-renewal and differentiation, making them pivotal in understanding how tumors can resist therapies [\[2\]\[17\]](#). This understanding could aid in the identification of novel



therapeutic targets that specifically address the resilience of CSCs against anticancer agents.

## Mechanistic Understanding

The exploration of phosphothreonine in cancer research serves as a platform for generating hypotheses that can lead to a deeper mechanistic understanding of tumor biology. Such insights can guide the selection of diagnostic and therapeutic targets, ultimately enhancing the efficacy of cancer treatments and addressing the significant challenge of chemoresistance[\[20\]\[21\]](#). Understanding the interplay between phosphothreonine signaling and tumor biology may also lead to improved guidance for treatment approaches, helping to tailor therapies to individual patient needs[\[11\]\[2\]](#).

## Dysregulation and Disease

Dysregulation of signaling pathways involving phosphothreonine has been implicated in the pathogenesis of various diseases, highlighting its critical role in cellular processes and disease progression.

### Neurodegenerative Diseases

Aberrant phosphorylation, particularly in the context of tau protein and amyloid beta ( $A\beta$ ) accumulation, is a hallmark of neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. Dysregulated signaling pathways contribute to the hyperphosphorylation of tau, leading to neurofibrillary tangle formation, which is a characteristic feature of Alzheimer's disease[\[22\]\[12\]](#). Additionally, the MAPK signaling pathway, known for its regulation of critical cellular processes, has been implicated in the progression of neurodegenerative diseases, further linking phosphothreonine dysregulation to these conditions[\[12\]](#).

### Metabolic Disorders

In metabolic diseases like type 2 diabetes, altered kinase activity, often manifested through abnormal phosphothreonine levels, plays a significant role in the development of insulin resistance. The dysregulation of protein kinases and phosphatases that normally counterbalance each other's activity can lead to metabolic dysfunctions[\[22\]](#). Such alterations in kinase signaling pathways affect glucose metabolism and insulin signaling, establishing a direct connection between phosphothreonine dysregulation and metabolic disorders.

## Cancer

Cancer is significantly influenced by the dysregulation of protein kinases and their associated pathways. Mutations or overactivity of kinases can lead to uncontrolled cell proliferation and tumor formation. Aberrant phosphorylation, particularly involving the PI3K/Akt/mTOR and MAPK pathways, is critical for cancer cell survival, growth, and metastasis[\[12\]\[18\]](#). The involvement of phosphothreonine in these signaling

cascades emphasizes its importance in oncogenesis, where specific alterations can lead to aggressive tumor behavior and therapeutic resistance[16][2].

## Autoimmune Diseases

In autoimmune diseases, the dysregulation of signaling pathways in immune cells can lead to inappropriate immune responses against self-tissues. Aberrant signaling through receptors on T and B cells, which may involve phosphothreonine modifications, contributes to the pathogenesis of these conditions[12]. This highlights the role of phosphothreonine in modulating immune cell activity and maintaining self-tolerance.

## Cardiovascular Disease

Kinases and phosphatases that regulate signaling related to blood pressure and cardiac stress responses also involve phosphothreonine modifications. Dysregulation of these enzymes has been linked to the development of cardiovascular diseases, where altered signaling can lead to hypertension and heart failure[22]. The involvement of phosphothreonine in these processes underscores its potential as a target for therapeutic intervention in cardiovascular health.

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