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Post-translational modification of protein and disease onset- recent advances

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Abstract

Proteins are the basis of cellular and physiological functioning in living organisms, and the physical and chemical properties of proteins dictate their activities and functions. The primary sequence of a protein is a main determinant of protein folding and final conformation as well as biochemical activity, stability, and half-life. Post-translational modifications (PTMs) are biochemical alterations of amino acids that extend the functional repertoire of proteins. PTMs regulate structural confirmations of proteins, protein-protein interactions and cellular signal transduction central in development. Alterations in the rate and extent of protein synthesis, accuracy, PTMs, and protein turnover are among the major molecular characteristics of some diseases. In this review, the incidence of PTMs disruption on certain disorders was evaluated.

Keywords: Post-translational modifications; Cancer; Diabetes; Cardiac disorders; Neurodegenerative diseases

1. Introduction

Posttranslational modifications (PTMs) are covalent processing events that change the properties of a protein by proteolytic cleavage and adding a modifying group, such as acetyl, phosphoryl, glycosyl and methyl, to one or more amino acids [1]. PTMs play a key role in numerous biological processes by significantly affecting the structure and dynamics of proteins [2]. Generally, a PTM can be reversible or irreversible. The reversible reactions contain covalent modifications, and the irreversible ones, which proceed in one direction, include proteolytic modifications. PTMs occur in a single type of amino acid or multiple amino acids and lead to changes in the chemical properties of modified sites [3]. PTMs usually are seen in the proteins with important structures/functions such as secretory proteins, membrane proteins and histones. These modifications affect a wide range of protein behaviours and characteristics, including enzyme function and assembly, protein lifespan, protein–protein interactions, cell–cell and cell–matrix interactions, molecular trafficking, receptor activation, protein solubility, protein folding and protein localization [4].

Therefore, these modifications are involved in various biological processes such as signal transduction, gene expression regulation, gene activation, DNA repair and cell cycle control [5]. PTMs occur in various cellular organelles including the nucleus, cytoplasm, endoplasmic reticulum and Golgi apparatus. Disruption in PTMs can lead to the dysfunction of vital biological processes and hence to various diseases.

2. Types of Posttranslational modifications

2.1. Phosphorylation

This process is an important reversible regulatory mechanism that plays a key role in the activities of many enzymes, membrane channels and many other proteins in prokaryotic and eukaryotic organisms [6]. Phosphorylation target sites

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are Ser, Thr, Tyr, His, Pro, Arg, Asp and Cys residues, but this modification mainly happens on Ser, Thr, Tyr and His residues [7]. This PTM includes transferring a phosphate group from adenosine triphosphate to the receptor residues by kinase enzymes. Conversely, dephosphorylating or removal of a phosphate group is an enzymatic reaction catalyzed by different [8]. Phosphorylation is the most studied PTM and one of the essential types of PTM, which often happens in cytosol or nucleus on the target proteins [9]. This modification can change the function of proteins in a short time via one of the two principal ways: by allostery or by binding to interaction domains. Phosphorylation has a vital role in significant cellular processes such as replication, transcription, environmental stress response, cell movement, cell metabolism, apoptosis and immunological responsiveness [10]. It has been shown that disruption in the pathway of phosphorylation can lead to various diseases such as cancer, Alzheimer's disease, Parkinson's disease and heart disease [11].

2.2. Acetylation

Acetylation is catalyzed via lysine acetyltransferase (KAT) and histone acetyltransferase (HAT) enzymes. Acetyltransferases use acetyl CoA as a cofactor for adding an acetyl group (COCH3) to the ε-amino group of lysine side chains, whereas deacetylases (HDACs) remove an acetyl group on lysine side chains [12]. There are three forms of acetylation: Nα-acetylation, Nε-acetylation and O-acetylation. Nα-acetylation is an irreversible modification, and the other two types of acetylation are reversible [13]. These three forms of acetylation occur on Lys, Ala, Arg, Asp, Cys, Gly, Glu, Met, Pro, Ser, Thr and Val residues with different frequencies, although the acetylation is more reported on Lysine residue. Nε-acetylation is more biologically significant compared to the other types of acetylation [13]. Acetylation has an essential role in biological processes such as chromatin stability, protein–protein interaction, cell cycle control, cell metabolism, nuclear transport and actin nucleation [14]. According to the available evidence, acetylated lysine is vital for cell development, and its dysregulation would lead to serious diseases such as cancer, aging, immune disorders, neurological diseases (Huntington's disease and Parkinson's disease) and cardiovascular diseases [15].

2.3. Ubiquitylation

This PTM has a major role in the degradation of intracellular proteins via the ubiquitin (Ub)–proteasome pathway in all tissues [16]. In ubiquitylation, a covalent bond befalls between the C-terminal of an active ubiquitin protein (a polypeptide of 76 amino acids) and Nε of a lysine residue of the protein [17]. Ubiquitin can occur in mono- or poly-ubiquitination forms on substrate proteins through specific isopeptide bonds by receptors containing ubiquitin-binding domains. Ubiquitylation is catalyzed by an enzyme complex that contains ubiquitin-activating (E1), ubiquitin-conjugating (E2) and ubiquitin ligase (E3) enzymes. Ubiquitinated proteins may be acetylated on Lys, or phosphorylated on Ser, Thr or Tyr residues, and lead to dramatically altering the signalling outcome [18]. Ubiquitylation modification in substrate proteins can be removed by several specialized families of proteases called deubiquitinases [18]. Ubiquitination plays important roles in stem cell preservation and differentiation by regulation of the pluripotency. Ubiquitylation has also played a vital role in many various cell activities such as proliferation, regulation of transcription, DNA repair, replication, intracellular trafficking and virus budding, the control of signal transduction, degradation of the protein, innate immune signaling, autophagy and apoptosis [19]. Dysfunction in the ubiquitin pathway can lead to diverse diseases such as different cancers, metabolic syndromes, inflammatory disorders, type 2 diabetes and neurodegenerative diseases [20].

2.4. Methylation

Methylation is a reversible PTM, which often occurs in the cell nucleus and on the nuclear proteins such as histone proteins [21]. Methylation occurs on the Lys, Arg, Ala, Asn, Asp, Cys, Gly, Glu, Gln, His, Leu, Met, Phe and Pro residues in target proteins [22]. However, lysine and arginine are the two main target residues in methylation, at least in eukaryotic cells [23]. One of the most biologically important roles of methylation is in histone modification. Histone proteins, after synthesis of their polypeptide chains, are methylated at Lys, Arg, His, Ala or Asn residues [24]. Nε-lysine methylation is one of the most abundant histone modifications in eukaryotic chromatin, which includes transferring the methyl groups from S-adenosylmethionine to histone proteins via methyltransferase enzyme. In eukaryotes, methylated arginine has been observed in histone and non-histone proteins [25]. Recent studies have shown that methylation is associated with fine tuning of various biological processes ranging from transcriptional regulation to epigenetic silencing via heterochromatin assembly. Defect in this modification can lead to various diseases such as cancer, mental retardation (Angelman syndrome), diabetes mellitus, lipofuscinosis and occlusive disease [26].

2.5. Glycosylation

Glycosylation occurs in multiple subcellular locations, such as endoplasmic reticulum, the Golgi apparatus, cytosol and the sarcolemma membrane [27]. In this modification, oligosaccharide chains are linked to specific residues by covalent bond. This enzymatic process, which is catalyzed by a glycosyltransferase enzyme, usually occurs in the side chain of

residues such as Trp, Ala, Arg, Asn, Asp, Ile, Lys, Ser, Thr, Val, Glu, Pro, Tyr, Cys and Gly however, it occurs more frequently on Ser, Thr, Asn and Trp residues in proteins and lipoproteins [3]. According to the target residues, glycosylation can be classified into six groups: N-glycosylation, O-glycosylation, C-glycosylation, S-glycosylation, phosphoglycosylation and glypiation (GPI-anchored) [28]. N-glycosylation and O-glycosylation are two major types of glycosylation and have important roles in the maintenance of protein conformation and activity. Glycosylation has a great role in many important biological processes such as cell adhesion, cell–cell and cell– matrix interactions, molecular trafficking, receptor activation, protein solubility effects, protein folding and signal transduction, protein degradation, and protein intracellular trafficking and secretion [29]. It has been shown that the defect in this process has a significant effect on the development of various diseases like cancer, liver cirrhosis, diabetes, HIV infection, Alzheimer's disease and atherosclerosis [30].

2.6. SUMOylation

Small Ubiquitin-Related Modifier (SUMOylation) takes place via SUMO that has a three-dimensional structure similar to ubiquitin protein and has been discovered in a wide range of eukaryotic organisms [31]. SUMOylation can occur in both cytoplasm and nucleus on lysine residues. SUMO family has three isoforms in mammals, four isoforms in humans, two isoforms in yeasts and eight isoforms in plants. SUMOylation occurs as a modifier in ε-amino group of lysine residues in target protein through a multi-enzymatic cascade [32]. In this reaction, SUMO is connected to a lysine residue in substrate protein by covalent linkage via three enzymes, namely activating (E1), conjugating (E2) and ligase (E3). Also, it is separated from the target protein by a specific enzyme protease-SUMO. Often, SUMOylation modifications occur at a consensus motif WKxE (where W represents Lys, Ile, Val or Phe and X any amino acid) [33].

2.7. Palmitoylation

These PTMs are taken place via a great variety of lipids like octanoic acid, myristic acid, palmitic acid, palmitoleic acid, stearic acid, cholesterol, etc. Myristoylation, palmitoylation and prenylation can be considered as the three main types of these lipid modifications. Palmitoylation is the covalent attachment of fatty acids, like palmitic acid on the Cys, Gly, Ser, Thr and Lys [3]. S-palmitoylation contains a reversible covalent addition of a 16-carbon fatty acid chains, palmitate, to a cysteine via a thioester linkage. Palmitoyl-CoA (as the lipid substrate) is attached to the target protein by a PAT and removed via acyl protein thioesterases. Mostly, S-palmitoylation occurs in eukaryotic cells and plays critical roles in many different biological processes including protein function regulation, protein–protein interaction, membrane–protein associations, neuronal development, signal transduction, apoptosis and mitosis [34]. Dysfunction of palmitoylation has been linked to many diseases including neurological diseases (Huntington's disease, schizophrenia and Alzheimer's disease) and different cancers.

2.8. Myristoylation

This modification is an irreversible PTM that occurs mainly on cytoplasmic eukaryotic proteins. Myristoylation has been reported in some integral membrane proteins as well [35]. In myristoylation after removal of the initiating Met, a 14-carbon saturated fatty acid, called myristic acid, is attached to the N-terminal glycine residue via a covalent bond [36]. This attachment is often observed in Met-Gly-X-X-X- Ser/Thr motif and is catalyzed by an N-myristoyl transferase (NMT) (there are at least two types of NMT enzymes, NMT1 and NMT2, in humans) [37]. Myristoylation occurs more frequently on Gly and less frequently on Lys residues [3]. Proteins that undergo this PTM play critical roles in regulating the cellular structure and many biological processes such as stabilizing the protein structure maturation, signaling, extracellular communication, metabolism and regulation of the catalytic activity of the enzymes [36, 37]. The role of myristoylation has been proved in the development and progression of various diseases such as cancer, epilepsy, Alzheimer's disease, Noonan-like syndrome, and viral and bacterial infections [38].

2.9. Prenylation

This is another important lipid based PTM, which occurs after translation as an irreversible covalent linkage mainly in the cytosol [39]. This reaction occurs on cysteine and near the carboxyl-terminal end of the substrate protein. Prenylation has two main forms: farnesylation and geranylation. These two forms contain the addition of two different types of isoprenoids to cysteine residues: farnesyl pyrophosphate (15- carbon) and geranylgeranyl pyrophosphates (20-carbon), respectively. In prenylated proteins, one can find a consensus motif at the C-terminal; the motif is CAAX where C is cysteine, A is an aliphatic amino acid and X is any amino acid [40]. This process is catalyzed by three prenyltransferase enzymes: farnesyltransferase (FT) and two geranyl transferases. The prenylation is known as a crucial physiological process for facilitating many cellular processes such as protein–protein interactions, endocytosis regulation, cell growth, differentiation, proliferation and protein trafficking [40]. Observations showed that disruption in this modification plays crucial roles in the pathogenesis of cancer, cardiovascular and cerebrovascular disorders, bone diseases, progeria, metabolic diseases and neurodegenerative diseases [41].

2.10. Sulfation

Often, the target residue of this PTM is tyrosine, which happens in the trans-Golgi network. N-sulfation or O-sulfation includes the addition of a negatively charged sulfate group by nitrogen or oxygen to an exposed tyrosine residue on the target protein [42]. Currently, PTS is observed mainly in secreted and transmembrane proteins in multicellular eukaryotes and have not yet been observed in nucleic and cytoplasmic proteins. This reaction is catalyzed by two transmembrane enzymes, tyrosyl protein sulfotransferases 1 and 2 (TPST1 and TPST2) [43]. TPSTs govern the transfer of an activated sulfate from 3-phospho adenosine 5-phosphosulfate to tyrosine residues within acidic motifs of polypeptides [42]. Recently, it has been observed that PTS has vital roles in many biological processes like protein–protein interactions, leukocyte rolling on endothelial cells, visual functions and viral entry into cells [44] This PTM involves in many diseases like autoimmune diseases, HIV, lung diseases and multiple sclerosis [45].

3. PTMs and Human Diseases

3.1. Cancer

Various PTMs can control, modulate, and regulated functions of IDPs and IDPRs. Therefore, human diseases can be caused by aberrant PTMs. In agreement with this hypothesis, all major PTMs, such as acetylation, glycosylation, methylation, palmitoylation, phosphorylation, proteolytic degradation, and ubiquitination, can be altered in various human maladies, including cancer [46], cardiovascular diseases, diabetes, and neurodegenerative diseases [47]. Systematic computational analysis revealed that ~5% of the disease-associated mutations in human proteins may affect known PTM sites, with most of the 15 PTM types being found to be disrupted at levels higher than expected by chance [48] Furthermore, the aforementioned Mtp-proteins were shown to be more prone to be involved in various human diseases than proteins carrying no known PTM site. Many malignancies [e.g., colorectal cancer (CRC) [49] are characterized by the abnormal glycosylation, which is commonly associated with the oncogenesis and cancer progression [50]. Many biomarkers used for diagnosis, prediction, and prognosis of various cancers are characterized by the aberrant N-linked glycosylation [51]. It was also shown that both gain and loss of phosphorylation target sites caused by the somatic mutations may play an active role in cancer pathogenesis. The distortion in the tightly controlled multiple modifications of the important nuclear IDPs, histones [52], is commonly found in malignancies. For example, CRC is characterized by the abnormal acetylation and methylation of specific histone residues [53], indicating the usefulness of the histone modification analysis for the diagnosis and prognosis in the CRC. Alterations of the PTMs of lysine residues (such as methylation, acetylation, sumoylation, and ubiquitination) of proteins involved in DNA repair are frequently associated with genomic instability, which is the major cause of different diseases, especially cancers [54]. Normal and pathological activities of one of the high-mobility group transcription factors, the Sry-containing protein Sox2, are controlled by normal and pathological phosphorylation, acetylation, ubiquitination, methylation, and SUMOylation [55]. Levels of a master transcriptional repressor REST/NRSF protein (RE-1 silencing transcription factor or neuron-restrictive silencer factor) that can serve as a tumor suppressor or oncogene are controlled by ubiquitination-deubiquitination cycles, with the abnormal upregulation of this protein being detected in glioblastoma, medulloblastoma, and neuroblastoma. Ectodomain shedding of syndecans, which is the proteolytic processing of cell-surface proteoglycans (PGs), is associated with the facilitation of cancer development. It also promotes cancer cell motility and invasion, thereby stimulating aggressiveness of various tumors [56].

3.2. Neurodegenerative diseases

In neurodegeneration, Huntington's disease (HD) is characterized by aberrant acetylation, methylation, phosphorylation, polyamination, and ubiquitination of histones (Moumne *et al.,* 2013). Furthermore, significant alterations in acetylation, palmitoylation, phosphorylation, proteolytic cleavage, sumoylation, and ubiquitination are reported for the HD causative protein, Huntingtin (Htt) [57]. In Alzheimer's disease (AD), levels and aggregation of the causative amyloid-β (Aβ) are affected by aberrant proteolytic cleavage of the amyloid precursor protein (APP). Pathogenesis of AD and other tauopathies is associated with altered sumoylation, abnormal hyperphosphorylation (Wang *et al.,* 2013), and abnormal truncations of the microtubule-associated protein tau. The pathogenesis of frontotemporal lobar degeneration (FTLD) is associated with the aberrant phosphorylation of a RNA/DNA binding protein TDP-43 (TAR DNA binding protein 43) [58]. In the transmissible spongiform encephalopathy (TSE) and other prion diseases, the infectious properties of the prion protein can be altered by changes in the glycosylation status of this protein [59].

3.3. Cardiac disorders

Acquired cardiac disorders, such as arrhythmias and heart failure, are associated with the aberrant functions of the voltage-gated sodium channel isoform 1.5 (NaV1.5) caused by its altered PTMs [60]. The myofilament dysfunction in

dilated cardiomyopathy (DCM) is associated with the aberrant phosphorylation of troponins I and T and myosin light chain, as well as with altered oxidation and glycation of sarcomeric proteins [61]. Deregulated phosphorylation and glutathionylation of nitric oxide synthases NOS1 and NOS3 represent an important contributing factor in the pathogenesis of cardiac hypertrophy and failure, myocardial infarction, myocardial ischemia, reperfusion injury, and vascular disease [62].

3.4. Diabetes

In diabetes and hyperhomocysteinemia, the aberrant glycation of fibrinogen [63] is associated with the increased atherothrombotic risk. Also, prolonged increase in the *O*-GlcNAcylation and sustained increase in the *O*-GlcNAc (*O*-linked *N*-acetylglucosamine) levels are associated with the insulin resistance and glucose toxicity [64]. This is due to the distortions in the complex interplay between phosphorylation and *O*-GlcNAcylation, since the rise in the GlcNAcylation levels can efficiently modulate the phosphate stoichiometry at most of the sites undergoing phosphorylation-dephosphorylation [65]. Curiously, 381 proteins affected by these diabetes-distorted dual modifications (phosphorylation and *O*-GlcNAcylation) were shown to have a multitude of biological functions, acting as metabolic enzymes, cytoskeleton regulatory proteins, chaperones, kinases, RNA processing proteins, or transcription factors [65].

4. Conclusion

PTMs have a vital role in almost all biological processes and fine-tune numerous molecular functions. Therefore, the footprints of disruption in PTMs can be seen in many diseases. Neurodegenerative disease is the major group of diseases, which is affected by the disruption in the PTMs (Alzheimer's disease, Parkinson's disease and Huntington's disease). Besides, cancer is also one of the most affected diseases. Consistently with this observation, the biological processes related to cancer are among the high-degree nodes (signaling, DNA repair, control of replication and apoptosis). Processes related to apoptosis, protein–protein interaction, signaling, cell cycle control, chromatin assembly, organization and stability, DNA repair, protein degradation, protein trafficking and targeting, regulation of gene expression and transcription control are the other high-degree biological processes. Moreover, we can say that ubiquitylation, prenylation, glycosylation, S-palmitoylation and SUMOylation have the most involvement in diseases. On the other hand, the PTMs with the highest number of interactions with biological processes are phosphorylation, ubiquitylation, methylation, acetylation and SUMOylation. Putting all together, we can conclude that the disruption in the pathways of these five PTMs has a great impact on the normal functioning of the cell and, as the result, on the organisms.

Compliance with ethical standards

Disclosure of conflict of interest

There is no conflict of interest in the publication of this article.

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