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Cancer Science 2020: Important crosstalk of post-translational modifications in diverse diseases - Zheng Wu - Capital University of Physical Education and Sports

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Multiple post-translational modifications (PTMs) can influence the actions of each other, termed as PTM crosstalk or PTM code. PTMs crosstalk could be divided into positive or negative relashionship, as well as within one protein (intra-protein) or across different proteins (inter-protein). With the development of molecular pathology, PTMs crosstalk has attracted increasing attention in association with chronic diseases, as well as drug therapy for patients. Numerous studies demonstrate that interplay between PTMs could influence tumorigenesis, neurodegenerative diseases, cardiovascular disorders, diabetes and related complications. Insight into the complexity of PTMs crosstalk will help us better understand etiology and provide novel targets for drug therapy.

1. PTM crosstalk in cancer: Among the diseases associated with PTM crosstalk, cancer has appeared to be the most widely studied. We focused on the crucial roles of PTMs crosstalk in multiple neoplastic diseases and demonstrate their functions by different types of modifications pairs, including the combinations of phosphorylation, acetylation, ubiquitination, SUMOylation and O-GlcNAcylation. For example, phosphorylation of ER-β at Ser16, β-catenin at Thr41 and c-Myc at Thr58 could result in protein degradation, while O-GlcNAcylation of these sites may lead to protein stability and contribute to cancer progress. No matter in intra-protein or inter-protein crosstalk, the modifications may influence cancer progress through activation or degradation of the substrates, thereby regulating the pathological development, metastasis, and resistance to chemotherapy of cancer diseases. PTMs crosstalk has been reported in various proteins associated with cancer diseases, such as oncoproteins, tumor suppressors, enzymes and transcription factors.

2. PTM crosstalk in neurodegenerative diseases: In neurodegenerative diseases, PTMs crosstalk could occur in critical proteins such as tau in Alzheimer's disease (AD) and α-synuclein in Parkinson's disease (PD). Tau is a key protein with multiple PTMs involved in the process of AD, including phosphorylation, acetylation, O-GlcNAcylation, methylation, SUMOylation, ubiquitination, oxidation, and truncation. In AD brains, hyperphosphorylated tau is unable to promote microtubule assembly and maintain the stability of the microtubules. Tau SUMOylation at Lys340 could reciprocally stimulate tau phosphorylation to decrease its solubility and inhibit the ubiquitination-mediated degradation in a competitive way. In addition, decrease of O-GlcNAcylation is related to the hyperphosphorylation of tau, suggesting that O-GlcNAcylation appears to protect tau against aberrant phosphorylation, while N-glycosylation may lead to the hyperphosphorylation of tau in AD brain, which is opposed to the function of O-GlcNAcylation. In contrast to tauopathy in AD, both O-GlcNAcylation and phosphorylation at the same residue in α-synuclein, Ser87, exerts a negative effect on the formation of neurofibrillary tangles via inhibiting α-synuclein aggregation, thereby slowing the progression of PD. However, modification on other sites may demonstrate different function. Phosphorylation of Ser129 in α-synuclein is the dominant pathological modification to promote α-synuclein aggregation, while O-GlcNAcylation at Thr72 inhibits protein aggregation to a larger extent compared with Ser87. These results suggest that the interplay between O-GlcNAcylation and phosphorylation in α-synuclein still remains to be clarified on a more complex level.

3. PTM crosstalk in cardiovascular diseases: Interplay between different types of PTMs has also been shown to participate in a variety of chronic cardiovascular diseases including hypertension, cardiac hypertrophy and heart failure. The prominent crosstalk in cardiovascular disorders is between phosphorylation and oxidation. Inhibition of ryanodine receptor (RyR2) phosphorylation can suppress sarcoplasmic reticulum (SR) Ca2+ leak in mouse hearts partly by reducing RyR2 oxidation, thereby reducing production of reactive oxygen species (ROS) and inhibiting pathogenesis of cardiac dysfunction. Evidence has shown that oxidation of Akt could influence Akt phosphorylation and further alter downstream pathways in several chronic diseases. In particular, oxidation and phosphorylation of PTEN could lead to the phosphatase inactivation and contribute to increased Akt phosphorylation and enhanced activation of PI3K/Akt signaling, resulting in neurogenic hypertension. Another typical type of PTMs crosstalk in cardiovascular diseases is O-GlcNAcylation and phosphorylation. For example, O-GlcNAcylation of endothelial nitric oxide synthase (eNOS) could inhibit its phosphorylation at Ser1177, leading to reduced activity of the enzyme and contributing to hypertension. In ischaemic heart failure, O-GlcNAcylation of troponin T (TnT) at Ser190 was shown to inhibit phosphorylation of TnT at Ser208, which might result from altered enzyme activity and function as an adaptive mechanism of cardiomyocyte protection.

Conclusions

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Depending on the modified targets and associated residues in signaling pathways, crosstalk between different proteins could provide abundant promising targets for drug therapy and rehabilitation, as well as biomarkers for clinical diagnosis and prognosis. Thus, it is imperative to identify and screen out the significant crosstalk related to specific diseases. Based on our previous studies which provide computational tools for predicting intra-protein or inter-protein PTM crosstalk, there are three possible ways to filter more important ones: 1) At least one of the sites in the crosstalk pair has crucial biological functions. 2) At least one of the sites in the crosstalk pair is affected by high frequency mutations. 3) The protein itself is vital in certain pathways or diseases.