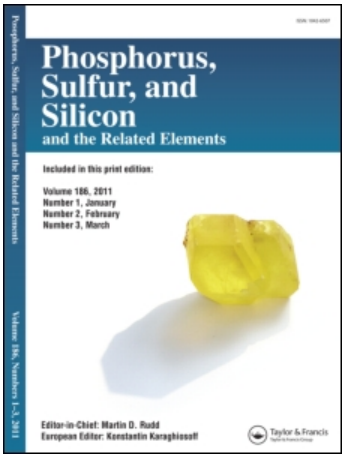

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The Effects of Reversible Phosphorylation on Peptide and Protein Local Structure

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The Effects of Reversible Phosphorylation on Peptide and Protein Local Structure

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Protein phosphorylation is one of the most important forms of protein post-translational modifications. Reversible phosphorylation is related to most physiological and pathological processes. Some of our recent results concerning how phosphorylation participates in modulating protein local structure and adjusting protein properties were summarized in this article.

Keywords Protein phosphorylation; protein local structure; protein function

INTRODUCTION

Phosphorus plays an irreplaceable role in life. Phosphorus is involved in the absorption and metabolization of carbohydrates and fat, and it keeps acid-base balance and energy transfer. As the building block of nucleic acids, phosphoric acid is specially adapted for its role in DNA and RNA.[1] Phospholipids bilayer is the mainly component of cell membrane. Here we will focus on another form of phosphorus participating in life, protein phosphorylation.

Protein phosphorylation is one of the most important forms of protein post-translational modifications. It is the process that phosphoryl group is transferred from ATP onto specific sites of proteins—mostly on serine, threonine, and tyrosine residues of proteins—by protein kinase. Actually, most cellular processes are regulated by reversible phosphorylation and at least 30% of proteins have such modification.[2,3] The structure and function of proteins will change under phosphorylation regulation. In 1992, E. H. Fisher and E. G. Krebs received

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the Nobel Prize in honor of physiology and medicine because of their contribution in researches of protein reversible phosphorylation as a biological regulatory mechanism (information available at http://nobelprize.org/nobel_prizes/medicine/lanreatos/1992/index.html).

Phosphorylation Modulates Protein Properties and Functions

Phosphorylation on the first microtubule-binding repeat domain of tau protein (R1) has been studies by Zhou and her coworkers.[4] Extracellular amyloid plaques and the intracellular neurofibrillary tangles (NFTs) are the two hallmarks of Alzheimer's Disease.[5,6] Analysis of NFTs has found that abnormally phosphorylated tau is the major component of NFTs.[7,8] Hyperphosphorylation of tau is also common to all diseases with tau filaments.[9] Whether the hyperphosphorylation is the cause or the result of tau aggregation, however, is still under discussion. Zhou and her coworkers studied the effects of phosphorylation of R1 on its self-assembly ability.[4] The aggregation dynamics of R1 and Ser^{262} phophorylated R1 (pR1) was monitored by turbidity. It was found that phosphorylation at Ser^{262} could speed up the process of assembly although R1 and pR1 were capable of self-assembly into fibrils. TEM results showed that fibrils formed by R1 was long and smooth while fibrils formed by pR1 was short.[4]

Another interesting phenomenon is that the reciprocal roles of phosphorylation and glycosylation—which is also an important form of protein post-translational modifications—have similar processes.[10] While in the case of the nuclear-localization sequence (NLS) of viral Jun (v-Jun) protein, phosphorylation and *O*-GlcNAcylation of serine residues would cooperate to negatively regulate nuclear import via the v-Jun NLS.[11] NLS silencing could be achieved by the introduction of a negatively charged residue, like phosphate, or a bulky uncharged residue like GlcNAc.[11]

Phosphorylation Changes Protein Comformation

Protein function being modulated by phosphorylation has been well accepted. However, it is still unclear at the molecular level that how phosphorylation can induce differences in functional behavior. Chen et al.[12] tried to give an explanation by utilizing model peptides from the N terminus of murine estrogen receptor β (mER-β). It was found that the introduction of *O*-phosphorylation brought more flexibility to this region while *O*-GlcNAcylation promoted the content of type II β-turn-like conformation.[12] It was postulated that the hydrogen bond was

formed between amide proton of pSer16 and the phosphate group of pSer16. The key process for protein possessing its function is adopting proper conformation; therefore, we propose that protein phosphorylation regulates protein function and activity by changing protein local conformation.

Phosphorylation Induces Changes in Protein Conformation and Function via Specific Hydrogen Bonds

The activity of a protein can be modulated by post-translational covalent modifications. Reversible phosphorylation and dephosphorylation on serine or threonine side chains are a feasible way introduced for this purpose. Yet relatively little is known about how phosphorylation modulates protein structure in molecular level, which in turn results in the alteration of biological activity.[13] Efforts have been made by Du and his coworkers;[14] they explored the possible causes of phosphorylation/dephosphorylation mediated protein function changing. It is found that during the process of deprotonation of phosphate group with increasing the pH, formation of a low-barrier hydrogen bonds between a serine and a phosphate group may contribute to the stabilization of local structure.[14] This reversible protonation of the phosphate group, which changes both the electrostatic properties of the phosphate group and the strength of the hydrogen bond, provides a credible mechanism in regulating protein function.[14] This finding also gives a new aspect to understand enzyme activity regulated by protein phosphorylation. In those cases when an enzyme-substrate complex is formed, it can be stabilized by a hydrogen bond formed between phosphate groups from the enzyme, for example, and amino acid residue from substrate with lower energy barrier.

CONCLUSION

Since E. H. Fisher and E. G. Krebs discovered the reversible phosphorylation in 1950s,[15] protein phosphorylation has achieved great progress in recent years and is becoming a popular field of research. One of the most important roles of reversible protein phosphorylation is adjusting a protein's biological function by changing protein local structure.[16–18] Reversible phosphorylation is related to most physiological and pathological processes, including cellular signal transduction, occurrence of tumor, metabolic regulation, nervous activity, and muscle contraction, as well as the proliferation, development and differentiation of cell.[19] Detailed studies of why phosphorylation can regulate the protein properties and how phosphorylation modulates protein function

are significant to better understanding the phosphorylation-dependent process in life.

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