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Profiling post-translational modifications of proteins that regulate gene expression

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Background

The aggregation of over 100,000 non-redundant, experimentally-determined post-translational modification sites on human proteins in PhosphoSitePlus (PSP) has enabled system-wide analyses of modification sites on proteins that regulate gene expression. The location of modification sites within specific domains or motifs, their distribution on subsets of proteins and in specific locations within the cell presumably underlie the flow of information within signaling networks that regulate gene expression. We will present the results of analyses of the structure, location and distribution of phosphoryl, acetyl, ubiquitinyl, and methyl modification sites on proteins that regulate transcription. The goals of this work are to gain an overview of protein modifications and identify novel modification sites that may regulate gene expression.

Materials and methods

Sequences of modification sites are analyzed using PSPlogo (Figure 1a), a variant of a commonly used graphical method for discovering patterns in sets of aligned sequences. Molecular visualization of proteins and their modification sites curated into PSP is performed using the Astex viewer customized to display modified residues. Protein sequences and associated information about experimentally observed human phosphosites and the sequence logo tool are from PhosphoSitePlus (PSP). Subcellular compartment and protein type assignments in PSP are from GO and from manual assignments, respectively. All tools and data described here are available at PhosphoSitePlus (http://www.phosphosite.org).

Results

Analyses of the PSPlogo profiles of modification sites differ significantly between subsets of proteins that regulate gene expression, presumably reflecting differential signaling networks, and implicating different enzymes in these various networks. For example, the profile of all phosphoserine sites in nucleosomal proteins (Figure 1a) indicates that multiple kinase families are active in this

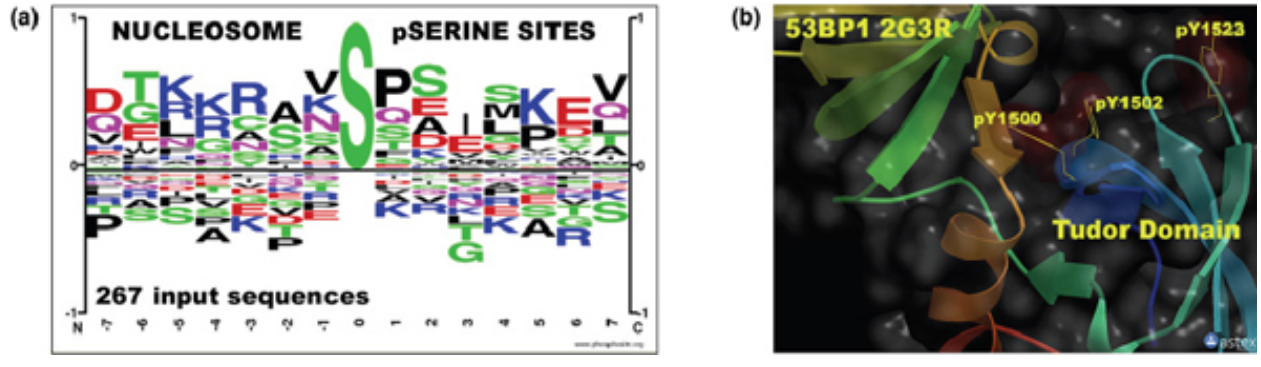

Figure 1 Profiling protein phosphorylation sites with tools in PhosphoSitePlus. Analyses of modification sites on proteins that regulate gene expression. (a) PSPlogo analysis of phosphoserine sites on nucleosomal proteins. (b) Molecular visualization of the 3 phosphotyrosine sites at the mouth of the dimethyl-binding cage in the Tudor domain of 53BP1.

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compartment (proline-directed, DNA damage, and AGC kinases). Molecular visualization software allows for the identification of modification sites that may regulate gene expression such as the three phosphotyrosines at the mouth of the H4-K20me2-binding cage of 53BP1 (Figure 1b).

Conclusion

Post-translational profiling using the data and algorithms available in PSP can be a useful tool for developing testable hypotheses about protein modifications that might regulate gene expression.

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