Protein Kinases Read Braille

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Protein kinases recognize short contiguous sequences of residues within a protein, known as linear consensus motifs, and protein kinase specificity has been shown to be determined by the recognition of these motifs. However, phosphorylation often occurs within sequences that do not contain linear consensus motifs. One explanation is that this is due to the frequent localization of phosphorylation sites in non-structured regions. Recent studies show that phosphorylation in structured regions is as frequent as in non-structured regions. We identified a new protein kinase CβI (PKCβI) phosphorylation site in α-tubulin, Thr253. This phosphorylation is in a structured region of α-tubulin and is not within a linear PKC consensus motif, formed by flanking basic amino acids. Analysis of the three dimensional structure revealed that this site resembles a linear PKC phosphorylation site consensus motif however, it is structurally formed by basic residues found in different parts of the linear sequence which come together in the folded protein forming a PKCβI recognition motif. Mutations of these basic residues decreased substrate phosphorylation, confirming that the PKCβI recognition site is “structurally formed” and the importance of anchoring residues for the specific recognition and interaction of protein kinases with their substrates. Analysis of previously reported protein kinase A (PKA) and PKC substrates identified structurally formed consensus motifs in several other substrates. Thus, the concept of consensus phosphorylation site motif needs to be reviewed and include sites within structurally formed consensus motifs.

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