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Phosphomimetics

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As the name suggests, phosphomimetics is the amino acid substituted in place of the original amino acid so that it mimics a phosphorylated protein, thereby activating or deactivating the protein. Phosphorylation is how a protein is activated or deactivated as a form of regulation. Protein modification plays a vital role in regulating the cell environment by turning the downstream signaling network on or off, affecting the cellular process. Proteins are commonly modified at threonine, serine, and tyrosine amino acids by adding a phosphate group. However, some non-phosphorylated amino acids seem chemically similar to the phosphorylated amino acids.

Consequently, a higher protein activity level can be maintained by substituting the amino acid. For example, serine/threonine to aspartic acid or glutamic acid substitution; and tyrosine to glutamic acid substitution (Figure 1). Protein phosphorylation results in the addition of a net negative charge to the phospho-acceptor residue. Phosphomimetic mutations are used to examine the functional effects of phosphorylation.

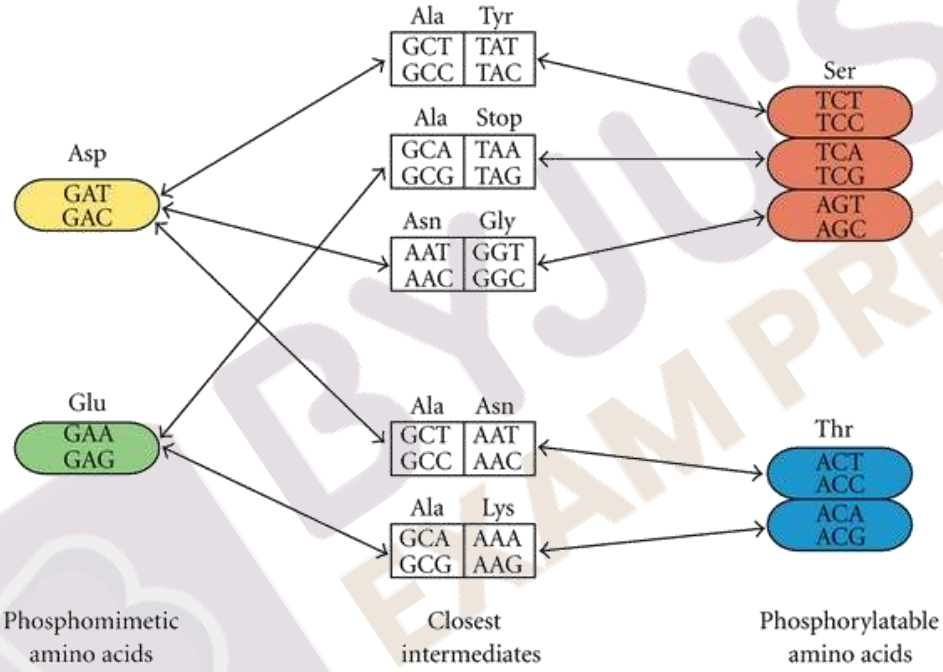

Figure 1: Transitions between phosphorylable and phosphomimetic amino acids through nonnegative charged intermediates

This chemical similarity in amino acids can be exploited for different purposes, such as cancer, where a protein can mutate to an "always-on," i.e. constitutively active state. A mutation replaces tyrosine, which requires phosphorylation to activate the protein, with aspartic acid that does not require phosphorylation. Phosphomimetics is artificially introduced with the help of recombinant proteins in order to study phosphorylation and protein activation.

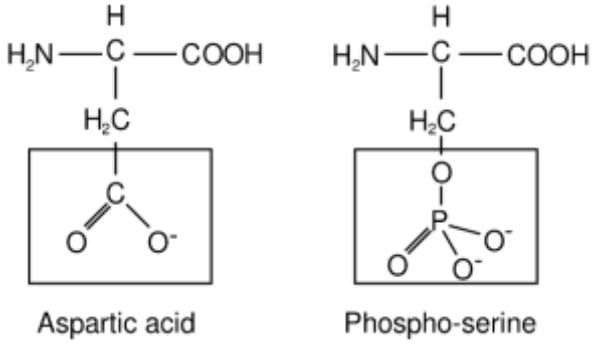

Figure 2. Aspartic acid and phosphoserine structure depict their phosphomimetic potential

The genetic code has been ordered so that transitions between phosphomimetic and phosphorylable amino acids comprise a transition state of an amino acid that is not negatively charged, except that between two serine and two aspartate codons involves a tyrosine residue. The biochemical properties of glutamic acid and aspartic acid mimic that of phosphorylated serine and phosphorylated threonine, except that their charge is not regulated.

Phosphomimetics are primarily used in "gain of function" mutation experiments. For example, to examine a gain of function mutation on a kinase related to Parkinson's disease, aspartate mutants were successfully used to analyze the biological function of phosphorylation of threonine residue in a ribosomal protein. It is also used to study the therapeutic potential of peptides or proteins. For example, phosphomimetic mutants use glutamate to mimic serine phosphorylation. Moreover, demonstrate that the phosphorylated glycoprotein can have more resilient anti-melanoma effects than the wild-type protein. This approach is constructive as up to three serine residues can be phosphorylated in that particular protein and help probe the function of individual phosphorylation.

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