Applications of Constrained Peptides to Various Biological Processes

Peptides play a crucial role in many cellular processes, however short peptides are devoid of well defined structures while in solution. In addition, the short half life in vivo due to rapid proteolytic degradation and poor cell permeability, remains a challenge to their therapeutic applications.[1] Thus common strategies aiming at improving receptor affinity, receptor efficacy, enzyme stability and pharmacokinetic properties are an active field of research.

Side chain to side chain cyclization of peptide is one common method applied whereby amino acid residues which have been identified as not involved in the receptor interaction are linked via lactam formation[2] or ring closing metathesis[3]. This method has been shown to mimic and stabilize α-helix structures which play an essential role in protein-protein interactions (PPI).

For instance, hydrocarbon stapled peptides mimicking BCL-2 domain (an important family of proteins that regulates apoptosis) showed increased protease resistance and cell permeability due to stabilized helical conformation[4]. This modification was further applied to NOTCH 1 transcription factor resulting to peptides with increased binding affinity towards NOTCH transactivation complex. NOTCH proteins have been shown to play a pivotal role in cellular differentiation, proliferation and apoptosis and their mutations have been linked with diseases like T-cell acute lymphoblastic leukemia.

These few examples show the potential of constrained synthetic peptides in PPI's [5].

References:

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