Design of PPI inhibitors by peptide mimics with high membrane permeability

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Inhibitors of protein-protein interactions (PPIs) are among the most promising drug candidates. In particular, peptides that recognize large surface areas of proteins are expected to be a good modality for PPI inhibitors. Advances of in vitro selection techniques have made it possible to develop peptide inhibitors with high binding affinities, such as nM and even pM. However, peptide-based PPI inhibitors often suffer from low membrane permeability, and improving the membrane permeability of peptides has been a challenge in this field.

Peptoid (oligo-N-substituted glycine), wherein the side chain at the Cα position is changed to the N position, is a new chemical component for designing membrane-permeable peptide-like molecules. We recently achieved a conformationally-strained peptoid (oligo-N-substituted alanine: NSA) that can be used as a scaffold to develop peptoid-based PPI inhibitors.[1] The NSA retains a rigid backbone in water,[2] which was successfully used to design PPI inhibitor in cells.[3] We are proposing NSA as a peptide-based molecular scaffold with a minimal structure and a high density of functionalizable sites.[4]

Here in this talk, I will present the advantages of NSA, including recent progress.

References

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