Two Bites at the Apple: Design and Repair of Peptide Therapeutics

Krishna Kumar

Departments of Chemistry and Biomedical Engineering, Tufts University, Medford, MA 02115; Cancer Center, Tufts Medical Center, Boston, MA 02111
krishna.kumar@tufts.edu

The two incretin hormones GLP-1 and GIP are key regulators of glucose homeostasis and fat cell metabolism. The hormonal actions of these peptide ligands are mediated by binding and stimulation of the cognate receptors, GLP-1R and GIPR, followed by downstream signaling. Both peptides suffer from rapid inactivation by protease (DPP4) catalyzed hydrolysis. We have previously shown that N-terminal alkylation with a variety of chemical decorations can render the peptides refractory to enzyme action while simultaneously preserving receptor agonism. A new paradigm in molecular design of peptide therapeutics has been to fine tune the ability of a single molecule to activate both receptors with varying potencies (tirzepatide). We demonstrate it is possible to achieve this objective and retain resistance to DPP4 catalyzed hydrolysis *via* judicious N-terminal alkylation. In addition, we will discuss the design of small molecule agents that can 'repair' the truncated inactive peptide derived from GLP-1 into a full-length functional compound. These studies present complementary strategies to modulate the glucose maintenance system through molecular design.

[1] Sicinski, K. M.; Montanari, V.; Raman, V. S.; Doyle, J. R.; Harwood, B. N.; Song, Y.-C.; Fagan, M. P.; Rios, M.; Haines, D. R.; Kopin, A. S.; Beinborn, M.; Kumar, K. "A Non-Perturbative Molecular Grafting Strategy for Stable and Potent Therapeutic Peptide Ligands". *ACS Cent. Sci.* **2021**, *7*, 454-466.