Peptides on the Rise

Guest Editorial for the Accounts of Chemical Research special issue on “Chemical Biology of Peptides”.

In nature and everyday life, peptides fulfill many different roles. Natural and synthetic peptides serve as hormones, neurotransmitters, snake and frog toxins, artificial sweeteners, antiwrinkle additives, and drugs against major diseases. This wide palette of disparate functions is enabled by the prodigious structural and functional diversity that can be accessed easily by linking different amino acids with each other. For example, 20 or 64 million distinct hexapeptides can be generated by combining 20 different amino acids.

The ensuing opportunities for drug development are evident and led decades ago to the development of numerous peptide-based therapeutics that are still important drugs (e.g., cyclosporine, octreotide, and glucagon). In comparison to small molecule-based drugs, peptides often exhibit extremely high potency, which in turn requires their administration in only low doses. In addition, the structural and functional features of peptides allow for highly specific targeting, which can be achieved otherwise only with “biologics” such as antibodies. Thus, the intermediate size of peptides combines highly desirable attributes of small molecules with those of large ones. Caveats such as the proteolytic degradation of peptides composed of natural α-amino acids and a lack of conformational control have become well-understood, and several effective remedies have been developed (e.g., cyclization, implementation of nonnatural amino acids and peptidomimetics, and grafting of active peptides onto stable scaffolds). As a result, the pipeline of peptides in clinical trials is rich, and the number of approved peptide-based drugs is likely to increase steadily in foreseeable years.

The increased interest in peptides as drugs has coincided with the development of numerous enabling tools for more and more effective peptide synthesis. Modern ligation methods have increased the length of synthetic accessibility far beyond the long-standing limit of about 50 amino acids and now allow for the chemical synthesis of polypeptides that contain more than 300 amino acids. In comparison to biotechnological synthesis, these synthetic tools are not limited to proteinogenic amino acids and entail less effort in the purification of the target peptide. Combinatorial methods allow for the effective synthesis of millions of linear and cyclic peptides consisting of essentially any desired amino acid building block. Such peptide libraries are, in combination with smart screening methods, powerful tools for the discovery of molecules with high utility. In addition, the uptake of peptides and peptide conjugates into cells and their use as shuttles to bring molecular cargo to desired locations is under intense study. This research could ultimately pave the way to a general method for drug delivery and enable the oral availability of drugs, which are major challenges. These advances in synthetic and screening methodology have been coincident with major developments in analytical chemistry. Modern mass spectrometric tools, in particular, are making the analysis of natural and synthetic peptides increasingly facile.

The rise of peptides is not limited to drug development. Numerous other disciplines are recognizing the opportunities afforded by the enormous structural and functional diversity of peptides, combined with their comparative ease of synthesis. Peptides have, for example, expanded the fields of materials science and asymmetric catalysis. In materials science, the ability of certain peptides to self-assemble has spawned biocompatible materials and electronic devices. For example, functionalized collagen-related peptides are attractive for applications in wound healing, acting as alternatives to immunogenic collagen preparations from natural sources. Conjugates between peptides and chromophores are promising to solve the challenge of ordered self-assembly of electron-rich moieties, which is key to the development of effective field-effect transistors and solar cells. In asymmetric catalysis, peptides have established themselves as alternatives to enzymes and low-molecular weight catalysts with properties that combine the best features of these two traditional types of catalysts. For example, peptidic catalysts can be tailored to function both in water and in organic solvents, and they can be highly chemo- and regioselective while retaining a broad substrate scope. Research in this field has not only yielded practical catalysts but also showed that the catalytic activity of amino acid-based compounds is not limited to enzymes, which in turn suggests that peptides might have played a crucial role in the evolution of enzymes.

The 21 articles in this special issue of Accounts of Chemical Research highlight these topics and more. The broad spectrum of science represented in this issue reveals that the traditional borders of peptide research have expanded considerably. Nowadays, conferences on peptides are populated by scientists from diverse backgrounds, including chemistry, biology, engineering, and medicine. The ensuing crosstalk is broadening the reach of peptide science and opening up still more avenues of engagement, ensuring an enduring rise.

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Notes
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