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Peptides and peptidomimetics as prototypes

Editorial overview

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Helma Wennemers HW received her master (Diploma) degree in chemistry from the University of Frankfurt in 1993 and her PhD degree from Columbia University New York in 1996. After two years as a postdoctoral researcher at Nagoya University, she joined the faculty at the University of Basel where she is now associate professor of chemistry. Her research focuses on the use of peptides in supramolecular assemblies and the development of peptides as asymmetric catalysts.

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Ronald T Raines RTR received ScB degrees in chemistry and biology from the Massachusetts Institute of Technology in 1980 and AM and PhD degrees in chemistry from Harvard University in 1982 and 1986, respectively. In 1989, after three years as a postdoctorate at the University of California, San Francisco, RTR joined the faculty at the University of Wisconsin–Madison, where he is now the Henry Lardy professor of biochemistry and professor of chemistry. His research is focused on the chemistry and biology of proteins.

Since the unraveling of the structure of the α-helix [1] and β-sheet [2] by smart modeling, the use of peptides and their mimetics has been a highly fruitful approach that continues to attract natural scientists. These molecules occupy a privileged place in chemical biology, being both readily accessible via chemical synthesis and directly relevant to complex biological systems. This issue of *Current Opinion in Chemical Biology* is devoted to the use of peptides and peptidomimetics to probe or manipulate natural systems. This approach is being employed by many researchers who began their research careers only recently. Their views are represented in this issue, alongside opinions from established scientists who have helped to shape research on peptides and their mimetics over the past decades. Four major topics are covered: (1) designing peptidic and peptidomimetic model systems for particular applications, (2) probing and manipulating protein folding with simple model systems, (3) using peptidic model systems to reveal the biological role of particular amino-acid residues, and (4) developing new synthetic tools for the efficient synthesis or selective modification of peptides and proteins.

Peptidic and peptidomimetic model systems

Laura Henchey, Andrea Jochim, and Bobby Arora review contemporary strategies to stabilize α-helices in short peptides and miniature proteins. They note that recent advances in the design of stabilized helices, helical foldamers, and helix-surface mimetics are testing basic principles of biomolecular recognition in complex settings, while providing new reagents for molecular biology and drug discovery.

Vera Martos, Pilar Castreño, Julián Valero, and Javier de Mendoza summarize approaches relying on the multivalent display of functional groups or ligands. The systems range from simple molecules with small molecular weight to larger dendritic molecules that are reminiscent of naturally evolved proteins. Remarkable levels of sophistication in interfering with protein–protein as well as protein–carbohydrate interactions have been achieved with both types of compounds.

Jutta Eichler describes how comparatively small peptidic systems consisting exclusively of natural α-amino acids are used to mimic binding sites within natural proteins. The article highlights how combinatorial as well as rational design approaches have helped to establish simple peptides that interfere with protein binding.

Peptoids – oligomers of *N*-substituted glycine residues – are an especially interesting class of peptidomimetics. Barney Yoo and Kent Kirshenbaum provide a synopsis of recent advances on the elaboration of sequence–

structure–function relationships for peptoids, drawing parallels to the (temporarily!) more developed field of peptides.

Chemical models of β-sheets are now emerging as valuable tools with which to understand and control two crucial phenomena: protein recognition and protein aggregation. Omid Khakshoor and James Nowick summarize recent uses of artificial β-sheets, focusing sharply on β-sheet folding and intermolecular β-sheet interactions.

Models of protein folding

Understanding the often subtle balance between the 'right fold' and a 'misfold' within a protein is at the heart of many diseases and is the focus of the review by Kevin Pagel and Beate Koksch. They describe how conformational switches can be induced deliberately by external triggers in carefully designed model peptides. Apart from a basic understanding of protein folding processes, research in this field is guiding the way to disease remedies.

Nearly a quarter of all human proteins are thought to contain disulfide bonds formed by the oxidation of two cysteine residues. Watson Lees reviews the exciting development of small molecules that catalyze oxidative protein folding. These organocatalysts accelerate both the rearrangement of incorrect disulfide bonds and the oxidation of protein thiols to form disulfide bonds, and have the potential to facilitate the production of insulin, erythropoietin, and numerous other proteins of interest.

Models of protein function

Kate Carroll and Khalilah Reddie summarize recent information on posttranslational modifications of cysteine residues to form sulfenic acids, sulfonic acids, and sulfones. Their review provides a lucid primer on the relevant redox chemistry as well as a context for understanding the biological function of different cysteine 'oxoforms'.

How electrons travel over distances as long as 40 Å within a protein is a fascinating topic that is understood only poorly. Bernd Giese, Michael Graber and Meike Cordes critically discuss the role of superexchange and multiple hopping steps for electron-transfer processes, and highlights how simple peptide models have helped to gain a deeper understanding of electron-transfer processes in enzymes such as ribonucleotide reductase.

New synthetic tools

Anouk Dirksen and Phil Dawson provide an overview of the methodologies that enable the chemical synthesis of peptides and proteins in sizes that were once accessible only via recombinant DNA technology. These chemical tools have enabled the introduction of nonnatural amino acids, site-specific isotopic labeling, and the site-specific attachment of affinity tags or labels for imaging. Recent advances include higher reaction rates, higher reaction yields, and greater biocompatibility, all of which increase the impact of peptide ligation reactions in chemical biology.

Equally as important and challenging is the establishment of synthetic tools that allow for the chemoselective modification of proteins. Joe Binder and Ron Raines highlight the use of one such tool – olefin metathesis – in chemical biology. Their article reports on the recent development of air-stable and water-stable ruthenium-based catalysts for a wide range of applications, including the modification of proteins at defined sites.

Envoi The diverse research on peptides and peptidomimetics covered in this issue showcases the importance of these model systems for modern chemical biology. With inspiration cascading from nature and a toolbox that is ever-growing, this field can look forward to a bright future.

References

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