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Peptides in Biology and Biomedicine: Walking towards the future

Biochemistry textbooks classify peptides just as short proteins. However, apart from having a myriad of biological functions, peptides show some structural differences with proteins, and their sequences can contain a diversity of non-natural amino acids. All areas of research related to peptides are receiving an increasing interest in recent years. On one hand, thousands of naturally occurring peptides have been identified, and these are often important players in intracellular communications and effectors of most biological processes [1]. As such, they are essential tools for understanding the physical-chemical basis of life and the molecular events behind biomolecular recognition [2]. On the other hand, their therapeutic potential is growing rapidly, with about 60 peptide-drugs that have reached the market, while several hundred are under preclinical and clinical development as future therapeutics for addressing a rising variety of medical challenges [3, 4]. Moreover, peptide-based conjugates are also being used for disease diagnosis and to modify other pharmaceutical agents for specific targeting or to facilitate cellular membrane permeability [5]. Peptide biomaterials and their applications in controlled drug delivery and tissue engineering are more recent expansions of the field [6]. In this scenario, we consider it is time to put together a set of reviews covering a broad range of peptide-related topics, from structure to function and different applications.

A few reviews deal mainly with **structural aspects** of peptides, helping in deciphering protein folding and stabilizing intramolecular interactions, or assisting in the study of the preferred organization in contact with lipidic bilayers. Thus, **Paula Morales & M. Ángeles Jiménez** [7] offer us a fascinating revision, with high formative value, in which the fundamentals for stabilizing α -helices and β -hairpins in water-soluble linear peptides are clearly explained and compiled. They describe the geometry features contributing to peptide conformational stability, including intrinsic propensities, dependence on specific residues and their location, particular capping motifs and side-chain interactions. Moreover, they also contemplated the influence of solvents/micelles on peptide stability, comment on some selected approaches for *in silico* design, and define the general guidelines for the structural characterization. Scientists interested in designing stabilized β -hairpin and helical peptides should consider this review as an essential reference article. To deepen our current understanding about β -hairpin stability, **Radhakrishnan Mahalakshimi** [8] nicely shows us the great stabilisation

power of non-covalent interactions between aromatic residues, particularly those involving tryptophanes. A few illustrative instances are selected to highlight how the importance of interactions between aromatic rings was discovered. Interestingly, the selected examples comprise both water-soluble and water-insoluble β -hairpin peptides, which indicates that the stabilising contributions of aromatic interactions are mostly solvent-independent. As it is the geometry of interacting aryl pairs, in which a T-shaped arrangement of the rings predominates. Incorporation of aromatic pairs is an outstanding current strategy to get stable peptide scaffolds with diverse functionality, which is expected to grow in the future, and to expand by incorporating non-natural aromatics. Next, the nice review by **Nicolas Inguibert & coworkers** [9] covers most recent articles on peptaibols, a family of naturally occurring peptides that contain non-proteogenic α -aminoisobutyric acid residues and a terminal hydroxyl group. Their particular primary and secondary structures have positioned these peptides as invaluable gadgets for studying different synthetic and conformational aspects, as model of choice for studying interactions with lipid bilayers to develop artificial membrane pores, and as the source of innovative foldamers. The contribution of peptaibols to the development of materials and drugs of the future is an open question. The structure-related topics can not be closed without noticing that a thorough understanding of peptide folding, not yet achieved, should lead to accurate structure prediction. Therefore, in their well-written review, **Panagiota S. Georgoulia & Nicholas Glycos** [10] give us a fine overview about how molecular dynamics simulations are advancing on the way towards the goal of achieving accurate structure prediction of peptides. The review provides us a historical perspective of the most commonly used force fields as well as their performance. Among the challenges for the future, the problematic of disordered peptides is emphasized.

As the most abundant class of molecules in biological systems, peptides represent invaluable **research tools** in chemical biology. In the form of microarrays, as biomarkers, drug delivery systems or as conjugates to enhance permeability, some of the most important applications of peptides as molecular probes are covered by several reviews in this Issue. Thus, **Rebekka Mauser & Albert Jeltsch** [11] present an appealing review about the modified histone peptide arrays (PTMs) and its applications in chromatin research, mainly directed to study the specificity of antibodies, reading domains and enzymes. They introduce the peptide array technology and provide a

comparison of the commercially available PTM arrays, containing histone peptides with several post-translational modifications in many different combinations, and differing in peptide synthetic approaches, immobilization methods, and peptide and PTM coverage. Although here particularized to histone arrays and their specific applications, an ample relevance of peptide array methodologies in other fields could be envisaged. Meanwhile, **Marc Vendrell & coworkers** [12] write an attractive article on the design, preparation and application of fluorescent peptides as probes for shedding “light” on fungal infections. They have been used for accelerating the comprehension of fungi-related biological processes and their mechanisms of action, and for enabling novel diagnostic and treatment strategies. Considering that fungal infections are a major burden to our society, it is expected that the development of new fluorescence-based reporters in general, and fluorescent peptides, in particular, could contribute to innovative medical imaging strategies and to mechanistic studies related to different microbe-induced infections. On the other hand, the seminal review by **A.M. Papini & coauthors** [13] provide the readers with recent advances in structural and functional aspects of glycoreplica peptides, as glycan mimetic probes for autoimmune diseases diagnosis and, possibly, for future treatments. These mimetics, which can be prepared more easily than oligosaccharides, could be promising tools for studying autoimmune mechanisms and for detecting autoantibodies. In addition, if successful results in animal models could be satisfactorily translated into humans, their upcoming application in autoimmunity diagnostics and therapeutics can be definitely predicted. Therefore, peptide scientists have here an emerging hot topic to face. Next, **David Andreu & coworkers** [14] tackle the vast area of the cell-penetrating peptides (CPPs), whose ability to diffuse across cell membranes makes them very good “transport media” to carry and deliver drugs to their target. After providing us a splendid perspective on the latest advances within this broad and diverse field, they focus on three interesting aspects: how to efficiently transport drug into the brain, how to deliver disruptors of G protein-coupled receptor complexes related to various diseases, and how to achieve internalization of drugs into parasites.

Finally, natural bioactive peptides represent exceptional starting points for innovative therapeutics, given their selectivity, efficacy and relative safety. Diverse emerging peptide technologies are also behind the increased interest in **peptide therapeutics** for the treatment of different unmet medical needs. Some descriptive advances in the field

are also covered by several reviews in this Special Issue. Thus, the review by **Paolo Grieco & Isabel Gómez-Monterrey** [15] describes the current state of the art of urotensin, urocortins and adrenomedullin vasoactive peptides, with important implications in the cardiovascular system. It is a comprehensive compendium, including a complete description of specific receptors, particular effects on cardiovascular processes, clinical studies and potential as biomarkers for each peptide. In addition, these peptides have been the base for the preparation of analogues with improved properties, which could help in controlling vascular tone or stabilize blood pressure, and could constitute future treatments for life threatening cardiovascular disease states like congestive heart failure, atherosclerosis, and coronary artery disease, among others. Subsequently, the well-written **Luca d'Andrea & co-workers'** review [16] starts with a clear-cut background about angiogenesis, which is an essential process in healthy organisms and of great therapeutic relevance, since both insufficient and excessive angiogenesis can cause or aggravate diverse pathologies. Next, the review describes the role of vascular endothelial factor (VEGF) and its receptors on angiogenesis; to finally be focused on proangiogenic VEGF-derived peptides, which constitute a worthwhile alternative therapeutic strategy in cardiovascular diseases and regenerative medicine. Afterwards, **Luis Rivas & Verónica Rojas** [17] drive reader's attention into the potentiality of cyanobacterial peptides as antiparasitic agents, which have been scarcely examined up to now. This review is an outstanding summary of the chemical diversity of cyanobacterial peptides, which is remarkably high, including cyclation and methylation, as well as the presence of non-proteinogenic amino acids, and heterocyclic rings. They also comment on the nowadays knowledge about the mechanisms of their antiparasitic action. Then, **Kalkena Sivanesam & Niels H. Andersen** [18] report on the hot topic of amyloid inhibitors from an interesting point of view. Their inspiring review concentrates in two proteins, α -synuclein and human amylin, and examines those peptides able to inhibit their amyloidogenesis processes. These common inhibitors might be universal amyloid traps, which as stated in the review "could lead to the development of a therapy that is applicable for all amyloid diseases". Following, the superb review by **Rosario González-Muñiz & co-authors** [19] prompt readers to ask themselves whether peptides will allow us to live in a pain-free world. The review summarizes non-opioid analgesic peptides, some of them already in the clinics or under clinical trials, according to their targets: different ion channels and several receptors in nociceptive pathways. These non-opioid analgesic peptides are alternatives to the

therapeutic drugs of current clinical use, which have undesired side effects and do not effectively treat all pain types. Finally, in the excellent account-type review by **Hazel Szeto & Shaoyi Liu** [20], we find out a family of penetrating peptides (SS-peptides), discovered by serendipity, targeting cardiolipin in the mitochondria and increasing ATP production. These peptides, which show an exceptional safety profile, are able to rejuvenate mitochondrial bioenergetics, ameliorate diverse age-related conditions, and are currently under clinical studies for the treatment of multiple age-related chronic diseases. Therefore, a question arises: will SS-peptides contribute to unveil the secret of eternal youth? We are expectant for the forthcoming answer.

As a whole, this Special Issue offers the readers with a compendium of interesting reviews covering different facets of peptides, including the accumulating knowledge on structural aspects, and the increasing use of peptides and derivatives as valuable tools to understand biological processes. A better understanding of the promiscuous role of peptides in biological systems, both under physiological and pathological conditions, has advanced their use as therapeutic probes for different diseases. Without being exhaustive, the included reviews pretend to give an idea of recent progress in all these aspects, and predict the continuous advancement in the field in the near future.

As Guest-Editors, we would like to warmly thank all our colleagues who have participated with their outstanding articles, making this Special Issue possible. For the many colleagues developing an extraordinary activity in this field that do not participate in it, for one reason or another, our sincere apologies. We would also wish to extend our thanks to the referees for their wiliness, comments and suggestions that have positively contributed to greatly improving each review. To finish, we would like to express our gratitude to the Editorial staff of *Archives in Biochemistry and Biophysics*, specially to Dr. José Luis Neira, Assistant Editor, first, for inviting us to guest-edit this Special Issue, and then, for his continuous assistance, facilitating our work and making it a pleasant experience.

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