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Peptide-based biosensors: From self-assembled interfaces to molecular probes in electrochemical assays☆

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ABSTRACT

Redox-tagged peptides have emerged as functional materials with multiple applications in the area of sensing and biosensing applications due to their high stability, excellent redox properties and versatility of biomolecular interactions. They allow direct observation of molecular interactions in a wide range of affinity and enzymatic assays and act as electron mediators. Short helical peptides possess the ability to self-assemble in specific configurations with the possibility to develop in highly-ordered, stable 1D, 2D and 3D architectures in a hierarchical controlled manner. We provide here a brief overview of the electrochemical techniques available to study the electron transfer in peptide films with particular interest in developing biosensors with immobilized peptide motifs, for biological and clinical applications.

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1. Introduction

Peptides are probably the most versatile tools in the development of supramolecular and flexible frameworks due to their inherent ability to self-assemble in highly-ordered 1D, 2D and 3D structures. Due to their tunable physio-chemical properties, peptides are able to fold in compact structural motifs shaping nanosized architectures in monolayers, bilayers, fibers, micelles, tubes, and strips [1,2]. Peptide self-assembly is driven by noncovalent intermolecular interactions (electrostatic, hydrogen bonding, hydrophobic, aromatic π-stacking and van der Waals) through molecular recognition [3,4]. The secondary structure of peptides (α- and, 3_{10} helices, β-sheets and β-hairpins) can be easily modulated by engineering the amino acid (AA) sequence in order to optimize the

Abbreviations: AA, amino acid; Fc, ferrocene; MB, methylene blue; AMP, antimicrobial peptide; CPP, cell-penetrating peptide; Aib, α-aminoisobutyric acid; SAM, self-assembled monolayers; ADNT, aromatic dipeptide nanotubes; ET, electron transfer; CV, cyclic voltammetry; SWV, square wave voltammetry; ACV, alternating current voltammetry; DPV, differential pulse voltammetry; EIS, electrochemical impedance spectroscopy; SWCNT, single-walled carbon nanotube; DWCNT, double-walled carbon nanotube; EGFR, epidermal growth factor receptor; DGP, deamidated gliadin peptide; PDDA, poly(diallyl dimethyl) ammonium chloride; PNW, peptide nanowire; AuNP, gold nanoparticle; GN, grapheme nanoparticle.

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interactions between adjacent peptides [5,6]. The helical conformations provide intrinsic electron transfer and conductive properties, leading to the idea that peptide scaffolds might be used for building materials with electronic/photoelectronic functions [6]. Moreover, short peptides (up to 10 AA residues) [3,7] can be easily obtained by standard synthesis methods, avoiding complex, laborious and time-consuming procedures, as in the case large proteins [2,8]. They are also biocompatible, and therefore excellent candidates for stabilizing labile macromolecules such as enzymes, antibodies and nucleic acids used in biosensors and bionanodevices [2,9]. Peptide-based biosensors have been developed for the detection of various analytes, including cells [10] proteins [11] ions [12,13] or small molecules.

The 20 natural amino acids (Fig. 1) are the building blocks in peptide synthesis. All natural amino acids, except glycine (G), are chiral adopting the $_{L}$-configuration. They have the same basic structure and vary only in the R-group at the central carbon (C_{α}) position of the molecule. Peptides adopt specific configurations, depending on which R-groups are near one another in a peptide chain [14]. AA sequences ensure the primary structure, usually designated with one-letter code (Fig. 1).

The nature of the R group dictates the peculiarity of each AA residue, which can be categorised as hydrophobic, hydrophilic, charged, or "other" [15,16]. The hydrophobic residues can be divided in two groups: the aliphatic residues, A, I, L, M, V and the aromatic residues F, W and Y. The aliphatic residues generally provide a hydrophobic environment. Aromatic residues are usually involved in π–π stacking, where p-orbitals in π-conjugated system overlap [1,6]. These interactions are mainly involved in peptide folding [17,18]. The hydrophilic, polar residues participate to hydrogen bonding, either via OH (S, T) or CONH (N, Q) groups. The ionisable residues can be positively charged, H, K, R, and have pK_a values of 6.5, 10 and 12, respectively, or negatively charged, D, E, and both have similar pK_a of 4.4 [14]. The oppositely charged residues may promote the formation of peptide assemblies through their electrostatic attraction, while equal charges prevent

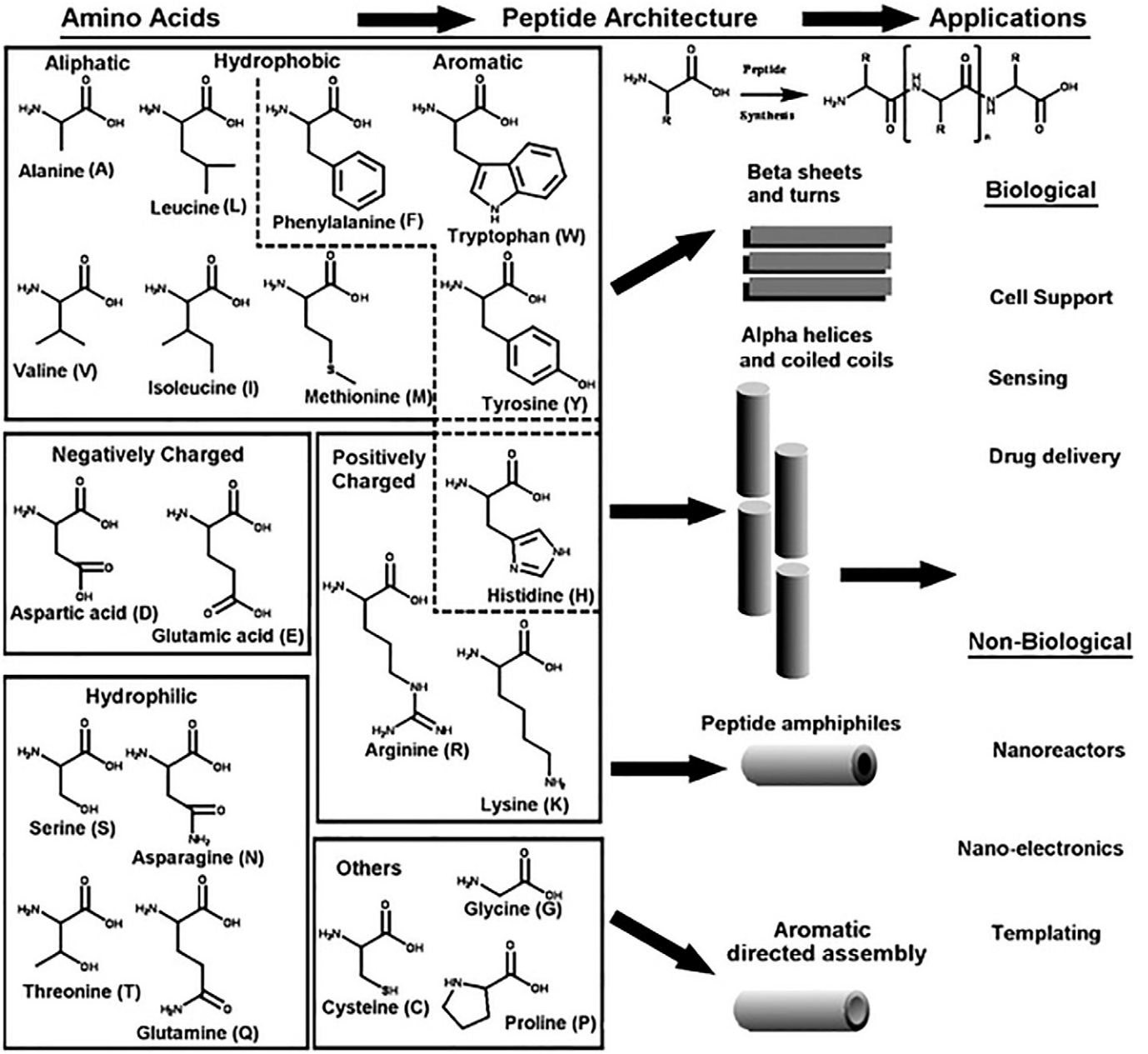

Fig. 1. Basic structures of amino acids are displayed along with their common name and the one letter abbreviations. The main architectures derived from peptide sequencing are presented with their potential applications in nano-biomedicine and nano-electronics. Reproduced from [14] with permission of RSC Publishing.