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Effect of peptide secondary structure on adsorption and adsorbed film properties

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ABSTRACT

Protein adsorption at the biomaterial–tissue interface is of utmost importance to the widespread application of engineered materials. The present study asked what role the secondary structures of peptides play in their adsorption, as well as how these structures affect the physicochemical properties of the final adsorbed layer. To this end, α-helices and β-sheets were induced in poly-L-lysine, and their adsorption to Au surfaces was monitored using quartz crystal microbalance with dissipation. It was observed that secondary structures played an important role in governing both the adsorption process and the final film properties. Higher initial adsorption rates were obtained for α-helices compared with β-sheets, regardless of solution salt concentration. Adsorption half-time for β-sheets was greater than that for α-helices, and the final amount adsorbed on β-sheet was significantly higher than that on α-helix. The adsorbed amount and adsorption half-time decreased with increasing salt concentration, suggesting that electrostatic interactions played a role. It was found that the differences in Zeta potential coupled with the apparent effect of surface contact area differences between α-helix and β-sheet conformations are ultimately responsible for these different peptide adsorption behaviours at the Au interface. The initial adsorption rate of α-helix increased with salt concentrations up to 50 mM, whereas β-sheet initial adsorption rates increased with salt concentrations up to 500 mM. Viscosities for films formed from α-helices were about twice those of β-sheets films, regardless of solution ionic strength. It was evident that the peptide secondary structures influence all aspects of their adsorption, as well as affecting the adsorbed film properties.
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1. Introduction

Spontaneous and non-specific adsorption of proteins at the interface between physiological fluids and materials is a major problem that continues to challenge the broad application of most biomaterials [1–5]. Specifically, the consequences of protein fouling at the tissue–material interface may include compromised implant performance, adverse host responses (inflammation, immune and thrombotic), implant failure and patient infection—situations that ultimately impair patient health, device efficiency and increase the cost of treatment [6]. Although there are numerous studies investigating protein adsorption and its mechanism, systematic studies of individual aspects of proteins are difficult, as each protein has a unique chemical composition as well as secondary and tertiary/quaternary structures that may allow for preferential adsorption at surfaces of different physiochemical properties. Moreover, it is understood that the strength and range of protein–surface interactions are dependent on the protein (amino acid sequence [7], molecular weight [8] and isoelectric point [9,10]), solution (pH [11], ionic strength [12] and temperature [13]) and surface (roughness [14], structure [15], hydrophobicity [16] and chemical nature [17]) properties. Although the effect of many protein attributes (pI [9,10], size [8] and hydrophobicity [18]) on non-specific protein adsorption have been investigated, there have been very few systematic studies [19] elucidating the effect of secondary structure composition on protein adsorption and the resulting adsorbed layer properties.

Although each protein has a 'unique' physical and chemical structure, determined by its amino acid sequence, several structural features are common among all proteins. In general, proteins have a compact three-dimensional structure with little internal space. Moreover, there are a relatively limited number of secondary structures (e.g. α-helix, β-sheet) periodically occurring throughout the main protein chain, where ~50% of the protein sequence is devoted to α-helix and β-sheet formation [20,21]. Secondary structure formation has been attributed to hydrogen bonding between neighbouring amino acids in the protein's sequence, and can directly influence the protein's physicochemical properties, such as shape, size, apparent hydrophobicity, charge

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and function. In an α-helix chain, each amine group from the backbone forms a hydrogen bond with the carbonyl group of amino acid four places earlier in the primary sequence. In the case of β-sheets, two strands form hydrogen bonds via the carbonyl group in the backbone of one strand with the amine group from the opposing backbone of a neighbouring strand. The α-helix has a more compact structure than the β-sheet, owing to the formation of hydrogen bonds between immediate neighbouring amino acids. For a poly-L-lysine (PLL) chain (Fig. 1), 3.6 residues form a full helical turn with 0.54 nm pitch and 26° pitch angle [22]. The distance between two adjacent strands in a β-sheet motif has been reported to be 10.08 Å [23]. For a given molecular weight of PLL, geometric differences between different secondary structures result in a β-sheet structure that is 2.3 times longer than an α-helix.

The protein adsorption literature is too vast to review in its entirety here. Suffice it to say that several investigations have looked at protein adsorption mechanisms via experiments using a known protein or multi-component protein solutions for a wide variety of surfaces [24,25]. From bulk solution to a substrate surface, diffusion moves proteins towards the surface, and adsorption occurs due to the influence of intermolecular and surface forces that can affect proteins from ∼1 to ∼10 nm away from the surface [26]. The relatively low energy barrier between conformational states of various protein domains yields an overall native conformation that is highly susceptible to structural changes induced by environmental disturbances, i.e. the introduction of a surface [27]. Near a surface, the interactions between the surface and protein might alter the balance of intramolecular non-covalent interactions responsible for secondary structure formation (hydrogen bonds, hydrophobic interactions, electrostatic interactions and van der Waals) and, consequently, lead to non-specific protein adsorption and surface-induced denaturing.

In fact, the adsorption of proteins on a surface may cause a perturbation in protein conformation. This conformational change may expose hydrophobic domains of the protein, resulting in the formation of multiple contact points between the proteins and surface that yield a tight adhesion to the biomaterial surface [28–32]. It has been reported that conformational changes of adsorbed proteins can be responsible for adverse host responses such as accumulation of inflammatory cells, foreign body response and coagulation [28,33–35]. Despite the apparent influence that secondary structures have on protein properties, very few investigations have tried to systematically evaluate their influence on protein adsorption. Bonekamp reported that the secondary structure of PLL (random coil and α-helix) does not affect the amount adsorbed on polystyrene latex [19]. Further to this, it was reported that these secondary structures were perturbed upon adsorption on a polystyrene surface. However, it is important to note that inconsistent solution pH conditions used in these studies convolute the interpretation of the results, as PLL secondary structure strongly depends upon solution pH. In this previous work, the conformation of adsorbed PLL was indirectly deduced via analysis of proton titration data as opposed to direct determination using techniques such as circular dichroism (CD). It is still largely unknown how these secondary structures will interact with the surface, and how it may lead to surface-induced unfolding of the secondary structures, layer viscoelasticity and adsorbed mass surface-density.

Thus, the purpose of the present work is to systematically investigate the influence that protein secondary structure has on adsorption and adsorbed film properties. To better understand the effect of secondary structure of proteins on non-specific protein adsorption, PLL is used as a model peptide. The rationale behind this choice is that, while maintaining a constant overall molecular charge profile, PLL can adopt both α-helix and β-sheet structures, depending on solution pH and temperature (Fig. 1) [36]. PLL chains in exactly the same physicochemical solution condition may have a specific, pre-induced secondary structure, depending on the solution preparation path (thermal history). It has been reported that 75% α-helix content can be induced in a PLL solution by increasing pH; heating this α-helix PLL solution will transform these chains into β-sheet (i.e. complete transformation of α-helix to β-sheet) [37]. The formation of an adsorbed layer in this work will be monitored using a quartz crystal microbalance with dissipation (QCM-D), providing kinetic information about absorbed film thickness, adsorbed mass and adsorbed film viscoelastic properties (i.e. shear viscosity) [38]. QCM-D allows for the formation and growth kinetics of a protein layer on a quartz crystal

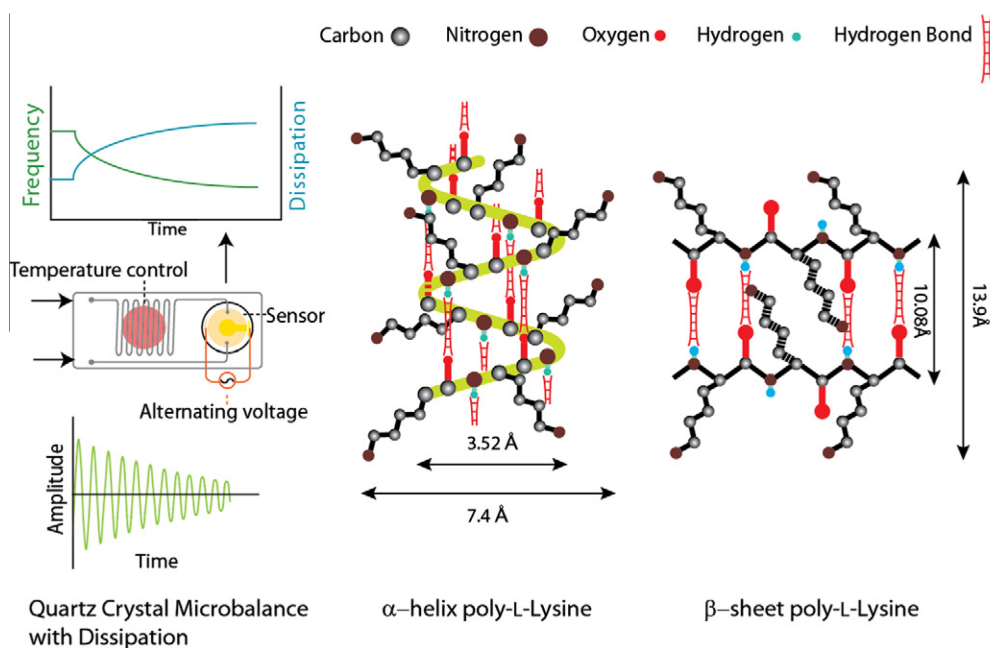

Fig. 1. Schematic drawing of experimental setup of QCM-D and PLL in α-helix [21] and β-sheet [22] conformation.

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