Proteins at Interfaces: at the Core of Biomaterials Science

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In this Founders Award presentation I will discuss the contributions of our knowledge and understanding of proteins at interfaces to the discipline of biomaterials. Since proteins at interfaces has been the overriding theme of my career (thus far) the presentation will have a strong personal flavor. It is of interest to note that as of 1966 when I began working in biomaterials, there were only a few papers on this topic and none that was directly relevant to biomaterials. Early on I wrote a review on the subject; published in 1971 it has the title "Adsorption of Proteins and Lipids to Nonbiological Surfaces" [1]. There are 127 references in total and of these, only 67 are papers reporting original research on protein adsorption. In a recent search of Pubmed under "protein adsorption" I found a total of 19,983 papers, ranging from 3 to 8 per year in the 1950s to over 1000 in 2008 (Fig 1). As can be seen, the field "took off" in the 1960s and has continued to grow over the ensuing 40 plus years.

My own work began with studies of protein adsorption in blood contact situations, specifically vascular implants and hemodialysis. That theme has continued to the present time and indeed it motivated the majority of researchers who contributed to knowledge of proteins at interfaces in the early days. However it soon became apparent that such knowledge was crucially important in many other situations, indeed in any situation where a solid-fluid interface exists in a biological system. Over the years the list has come to include: contact lenses, dental prostheses, biosensors implantable and otherwise, protein purification, therapeutic apheresis, biomicrofluidic systems, drug delivery, solid phase immunoassays, and biofouling including non-biomedical areas such as marine fouling and bio/food processing.

Much of this research has focused on phenomenology and includes theoretical as well as experimental studies. The main "fact" or axiom of proteins at interfaces is that proteins are highly surface active: they adsorb. This is attributable to their macromolecular and amphipathic properties. Besides adsorption itself, interactions include desorption (at some interfaces), re-orientation with respect to the interface, exchange of adsorbed and dissolved proteins, diffusion of adsorbed proteins over the interface, aggregation, conformational change, and denaturation. Much of the early work was done in systems of one or two proteins so very little was learned about how proteins compete with one another at an interface. However at the level of real biological fluids like blood or tears, knowledge of competitive adsorption is crucial since this determines the composition of the adsorbed layer, with certain proteins being desirable and others decidedly undesirable. The quest to determine the "proteome" of adsorbed proteins has been pursued in several labs in recent years (including at McMaster), but much remains to be done.

In broad brush terms our knowledge of proteins at interfaces can be summarized as follows: adsorption occurs in monolayers even at high concentration and follows, at least empirically though not mechanistically, the Langmuir isotherm and Langmuir kinetics; adsorption is irreversible on a "realistic" time scale at most interfaces; hydrophobic surfaces adsorb more extensively and more "avidly" than hydrophilic ones; proteins probably adsorb (and desorb) in sequence from multiprotein fluids (Vroman effect); adsorbed proteins tend to undergo conformational change (although direct evidence for this remains elusive); protein adsorption precedes cell interactions and determines the response of cells to the interface.

Beginning in the 1980s additional impetus for research on proteins at interfaces came from the need for "protein resistant surfaces", and the discovery that certain hydrophilic polymers (notably polyethylene oxide) incorporated at the interface could inhibit adsorption. This has become a major focus and the number of papers published recently on this topic is impressive.

In my view the major driving force for studying proteins at interfaces in the context of biomaterials is the need for "control". Given that adsorption is ubiquitous and inevitable and leads to adverse consequences such as biofouling, blood coagulation, the foreign body reaction, and thrombosis (indeed it has been proposed that nonspecific protein adsorption is "the enemy" of biocompatibility), we need to control it; i.e. we need to design the interface to adsorb the "right" proteins in their native state. This implies two requirements: attracting the right proteins and keeping the others away.

Reference:

[1] Brash JL and Lyman DJ. In: The Chemistry of Biosurfaces v1, ML Hair, ed., Marcel Dekker, NY, 1971.

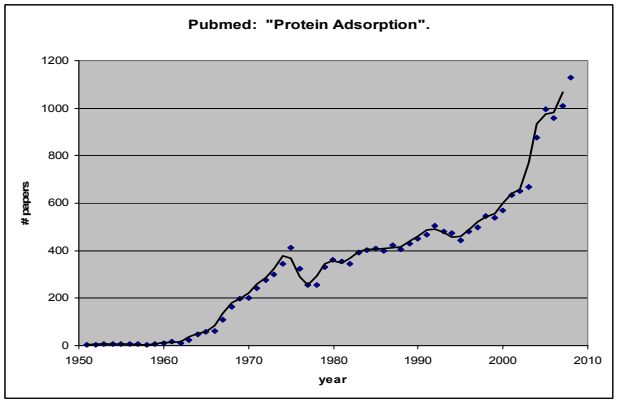

Figure 1. Publications on protein adsorption 1950-2008. (Data Source: Pubmed).