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Soft materials and medical devices designed for blood-contacting applications have been practically implemented for many years. When the soft materials comprising these devices encounter blood, the body's innate defense mechanisms recognize them as foreign. The foreign body reactions via blood coagulation on soft material surfaces proceed through a sequence of events (**Fig.1**): 1) sorption of water molecules from blood, leading to material hydration; 2) nonspecific adsorption of plasma proteins; 3) conformational changes in adsorbed proteins, exposing cell adhesion sites; 4) platelet adhesion and activation; and 5) subsequent blood cell deposition and fibrin network formation. Water plays a crucial role in biointerfacial interactions, including protein adsorption and cell adhesion on biomaterials¹⁾.

However, water is often the neglected medium at the interface between materials and biology²⁾. To understand the role of water in the interaction of proteins and cells at biological interfaces, it is important to compare states of hydration water with various physicochemical properties of hydrated soft materials. Here, we discuss the fundamental concepts for determining the interactions of proteins and cells with hydrated soft materials along with selected examples corresponding to our recent studies³⁾, poly(2-methoxyethyl acrylate) (PMEA), PMEA derivatives, poly(ethylene glycol) (PEG), poly(*N*-vinyl-2-pyrrolidone) (PVP), and poly(2-oxazoline)s, zwitterionic polymers, and other polymers including biopolymers.

The states of hydration water were analyzed by differential scanning calorimetry, time-resolved *in situ* attenuated total reflection infrared spectroscopy, solid-states NMR, surface force measurements, and wide variety of analytical techniques. The hydration water can be classified into three types: free water (scarcely bound water), intermediate water (loosely bound water), and non-freezing water (tightly bound water). Among these, intermediate water (IW) was found in hydrated biopolymers and hydrated biocompatible synthetic polymers. We found that IW is a key indicator of the biocompatibility of material surfaces in physiological conditions. The amount of IW is influenced by the type of functional groups, local polymer configuration, and polymer chain mobility. The degree of denaturation of adsorbed proteins was influenced by IW contents. This concept of IW, which is common in hydrated biomolecules and synthetic biocompatible materials, offers a valuable framework for designing soft materials in aqueous environments.

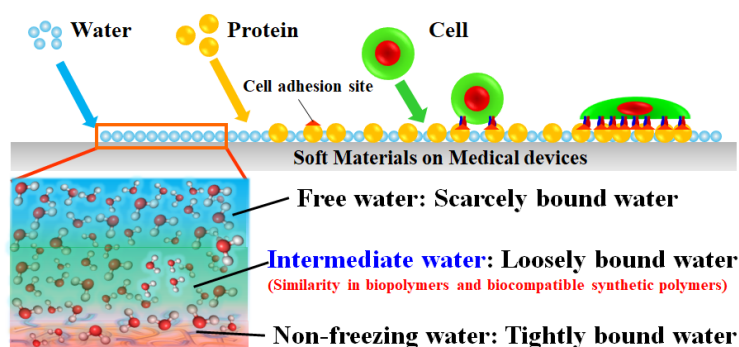


Fig. 1 Soft Material/Protein/Cell interactions at the Bio-Interface.

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