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Polymer hydration and stiffness at biointerfaces and related cellular processes

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Abstract

The direct and indirect (by changing mechanical properties) effects of hydration at interfaces on cellular processes and tissue diseases are reviewed. The essential effect of substrate stiffness on cellular processes was demonstrated in the last decade. The combined effect of surface stiffness and hydration at interfaces has garnered much less attention, though hydration and dehydration play important roles in biological processes. This review focuses on the studies that demonstrate how hydration affects biological processes at interfaces. Elevated sodium and dehydration stimulate inflammatory signaling in endothelial cells and promote atherosclerosis. Various types of implant and blood contacting device coatings with varied surface stiffness and hydration have been reported. Effect of hydration on polymer modulus of elasticity and viscoelasticity was discussed taking into account cells adhesion, migration, proliferation, differentiation on surfaces with various degree of hydration. Future directions of research were considered, including the use of nanotechnology to regulate the hydration degree.

Key words: Polymer; Hydration; Stiffness; Biointerface; Cellular processes

Water is an integral part of various biological molecules and biopolymer systems. Water is the most abundant molecule in the body and water is essential for life. This review focuses on effect of polymer hydration/dehydration on the processes at the cell–biomaterial interface and cell–extracellular matrix interactions.

Ventre and Netti[1,2] consider that "a thorough understanding of the cell-material crosstalk has not been achieved yet". It is known that biological cues, topography, and mechanical properties control cell fate and functions. It has been suggested in the recent review[3] that cells respond to elasticity and topography of biomaterials by generating tractional forces on their adhesive contacts. Muzzio et al[4] observed that cells adhere better on relatively smoother annealed substrates. So they suggested that surface roughness is not the most relevant factor in the interaction of adherent cells with solid surfaces. The influence of surface stiffness on the adhesion of cells can be considered as a more important factor. Balance of chemistry, topography, and mechanical properties at the cell–biomaterial interface was analyzed by Wong et al[5] in 2004 and the authors stated that "effect of substrate elasticity on cell behavior is still a relatively unexplored research field". More knowledge has been generated during the last decade, and at present already surface stiffness can be considered as a more important factor compared to a surface topography. Huang et al[6] note that "it is not clear whether the surface chemistry or topography is the main factor on modulating cellular behavior, because the commonly used surface modification techniques for titanium-based implants simultaneously modify surface topography and chemistry".

Abbreviations: ECM, extracellular matrix; PEG, polyethylene glycol; PEO, poly(ethylene oxide); PEMs, polyelectrolyte multilayers; FN, fibronectin; PGs, proteoglycans; BMSCs, bone marrow stromal cells; Hap, hydroxyapatite; Cap, carbonate-substituted hydroxyapatite; PEO, poly(ethylene oxide); PSS, poly(sodium 4-styrenesulfonate); PDADMAC, poly(diallyldimethylammonium) chloride; ECs, endothelial cells; SMCs, smooth muscle cells; PRX, polyrotaxane; iPS cells, pluripotent stem cells; α-CD, α-cyclodextrin; CNWs, cellulose nanowhiskers; SBR, poly(styrene-co-butadiene); PBD, polybutadiene; PVOH, poly(vinyl alcohol); hMSC, human mesenchymal stem cells; ESL, endothelial surface layer; NO, nitric oxide; pSBMA, poly(sulfobetaine methacrylate); DSC, differential scanning calorimetry; DTA, differential thermal analysis; LbL, layer-by-layer; PIPAAm, poly(*N*-isopropylacrylamide); PSBMAm, poly(sulfobetaine methacrylamide); BSA, bovine serum albumin.

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Human bone marrow derived mesenchymal stem cells (BMSCs) were cultured to form cell sheets by researchers at Nanyang Technological University, Singapore.[7] Collagen formation within the cell sheet was enhanced on substrates with lower stiffness, higher hydrophobicity and roughness. Li et al[8] in experiments with rat bone marrow mesenchymal stem cells found that substrate stiffness is the main factor in regulating cell proliferation and differentiation, but topography plays a lesser role in directing cell differentiation. No statistically significant influence of surface roughness on osteoblast proliferation and cell viability was detected by Cai et al.[9]

Layer-by-layer (LbL) assembly based on the alternating adsorption of polyelectrolytes on surfaces allows for designing multilayer architectures with nanometer precision. Nanocoatings can be used in biomedical applications. The role of the surface stiffness of polyelectrolyte multilayers (PEMs) in interaction with cells is generally recognized.[10–13] It is important to control the adhesion processes of mammalian and bacterial cells at interfaces in such biomedical applications as polymer coatings of implants and biosensors, antifouling and antibacterial coatings, tissue engineering.[14] Adhesion affects other cell functions, such as spreading, migration, proliferation and differentiation.[15] The correlation between cell viability and surface energy (wettability), modulus (matrix stiffness), and surface charge of the polyelectrolyte multilayer coatings has been studied and the authors at McGill University, Montreal, Quebec, Canada concluded that stiffness has the highest impact on cells survival.[16] In other publication it was observed that surface hydration can play a stronger role in comparison with surface stiffness in the control of platelet adhesion.[17]

The mechanical properties of extracellular matrix (ECM) to a great extent depend on properties of ECM component collagen, and the conformation and mechanical properties of collagen depend on water molecules that through water bridges stabilize triple-helical conformation of collagen.[18,19] It has been widely believed for the past several decades that structure of water in collagen fibrils is very different from bulk water.[20–23]

This review focuses on the effect of combination of surface stiffness with surface hydration, which is still underestimated aspect with a direct effect on cells adhesion, migration, proliferation, growth and differentiation.

States of water in polymers

Hydration water structure depends on the architecture of hydrated polymer chain.[24,25] Dynamics of hydration water plays an active role for proper functions of proteins.[26] Non-freezing water, freezing water and free water can be observed by the methods of differential scanning calorimetry (DSC) and differential thermal analysis (DTA).[27,28] The states of water have been reported as a tightly bound water, loosely bound water and bulk water. The concept of intermediate water, with the properties similar to freezing water, or loosely bound water, has been also proposed.[29] The water is tightly bound to macromolecules provided the water content in a polymer is lower than a certain water content threshold.[30–32] The value of this threshold depends on polymer macromolecule chemical structure.

The macromolecules change the properties of water. Water is an integral part of various biomolecular complexes.[33] The distribution and binding energy of water molecules to biopolymers was investigated for food products, such as bread[28,34–44] and meat.[45–47] Water-holding capacity of pork increases during aging due to degradation of the cell cytoskeleton.[47] Protein oxidation increases hydration but decreases water binding in pork.[48] Hydration water is essential in biological processes and plays a major role in actin–myosin binding.[49–51]

There is essential change of water properties in confined conditions. Goertz et al[52] observed effective viscosities that are $\sim 10^6$ times greater than that of bulk water for nanometer-scale interfacial separations.

The influence of polymer chain architecture of polysaccharides on the structuring of confined hydration water has been reported by researchers of Dutcher Lab at the University of Guelph, Canada.[24,53] They studied phytoglycogen, a highly branched, water-soluble polymer of glucose with dendrimeric or tree-like structure and remarkable capacity to retain water. They found similarities between water structuring in two linear polysaccharides, hyaluronic acid and chitosan, and significant differences between the linear molecules and highly branched phytoglycogen. Quasi-elastic neutron scattering measurements revealed a significant slowing down or retardation of the hydration water relative to bulk water by an average factor of ~5.8. The hydration water in the phytoglycogen nanoparticles is significantly more highly ordered and tightly bound than in the linear polysaccharides, as indicated by the large peak at ~3200 cm^{-1} in the phytoglycogen infrared spectra.[24,54] They found a correlation between the structural rearrangement of the hydrogen-bonding network of the tightly bound hydration water and the interchain separation in the highly branched phytoglycogen nanoparticles.[25]

It was reported that polyvalent dendrimer glucosamine conjugates prevent scar tissue formation.[55] So it would be interesting to confirm the relation of water retention to ability to prevent scar formation or to show that such processes are not interdependent.

Design principles and clinical applications of dendrimers in nanomedicine have been recently reviewed.[56]

Hydrated polymer coatings and surfaces

Cell biology and biomaterials science are related. Polymer materials are used in implants and in many cases polymers mimic the properties of living tissues. Biopolymers are used in the design of scaffolds for regenerative medicine. Similar behavior of cells can be expected on the surfaces of biocompatible polymers and on the surfaces of living tissues with the similar physical properties.

PEG coatings

Hydrophilic polyethylene glycol (PEG) with molecular structure $H–(O–CH_2–CH_2)_n–OH$ can tightly bind water molecules to form a surface hydration layer, which can resist nonspecific protein adsorption and platelet adhesion.[57] PEG can also affect protein conformational changes.[58] Molecular simulations demonstrated the