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Biological responses to immobilized microscale and nanoscale surface topographies

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ABSTRACT

Cellular responses are highly influenced by biochemical and biomechanical interactions with the extracellular matrix (ECM). Due to the impact of ECM architecture on cellular responses, significant research has been dedicated towards developing biomaterials that mimic the physiological environment for design of improved medical devices and tissue engineering scaffolds. Surface topographies with microscale and nanoscale features have demonstrated an effect on numerous cellular responses, including cell adhesion, migration, proliferation, gene expression, protein production, and differentiation; however, relationships between biological responses and surface topographies are difficult to establish due to differences in cell types and biomaterial surface properties. Therefore, it is important to optimize implant surface feature characteristics to elicit desirable biological responses for specific applications. The goal of this work was to review studies investigating the effects of microstructured and nanostructured biomaterials on *in vitro* biological responses through fabrication of microscale and nanoscale surface topographies, physico-chemical characterization of material surface properties, investigation of protein adsorption dynamics, and evaluation of cellular responses in specific biomedical applications.

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Abbreviations: 3D, three-dimensional; AFM, atomic force microscopy; AAO, anodic aluminum oxide; ALP, alkaline phosphatase; ANSC, adult neural stem cell; AR, aspect ratio; BCP, block copolymers; BSA, bovine serum albumin; CEC, corneal epithelial cells; CHO, Chinese hamster ovary; CVD, chemical vapor deposition; DAE, dual acid-etched; ECM, extracellular matrix; EDS, energy dispersive x-ray spectroscopy; FIB, focused ion beam; HAEC, human aortic endothelial cells; HCAEC, human coronary artery endothelial cell; HEK, human embryonic kidney cells; hmVEC-d, human dermal microvascular endothelial cells; HSaVEC-c, human saphenous vein endothelial cells; HUVEC, human umbilical vein endothelial cells; ICP-MS, inductively coupled plasma mass spectrometry; IL-6, interleukin 6; IL-8, interleukin 8; FAK, focal adhesion kinase; LEC, lens epithelial cells; LEIS, low energy ion scattering; MAP2k1, mitogen-activated protein kinase kinase 1; MDCK, Madin-Darby canine kidney epithelial cells; MSC, mesenchymal stem cells; NaOH, sodium hydroxide; NCD, nanocrystalline diamond; OCN, osteocalcin; OPN, osteopontin; PCL, polycaprolactone; PCU, polycarbonate urea urethane; PDMS, polydimethylsiloxane; PEG, polyethylene glycol; PLGA, poly(lactic-*co*-glycolic acid); PLLA, poly-L-lactide; PMMA, poly(methyl methacrylate); POSS, polyhedral oligomeric silsesquioxane; PP, polypropylene; PRP, platelet rich plasma; PS, polystyrene; PU, polyurethane; PVD, physical vapor deposition; QCM-D, quartz crystal microbalance with dissipation monitoring; RF, radio frequency; RGD, arginine-glycine-aspartic acid; RIE, reactive ion etching; RMS, root-mean-square; SAM, self-assembled monolayer; SEM, scanning electron microscopy; SFK, Src family kinases; SIMS, secondary ion mass spectrometry; SMC, smooth muscle cells; STM, scanning tunneling microscopy; XRD, x-ray diffraction; TEM, transmission electron microscopy; TiO_2, titanium dioxide; UNCD, ultrananocrystalline diamond.

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1. Introduction

Nanotechnology is expected to critically impact the design, development, and manufacture of next-generation medical devices. Currently, nanomaterials are being investigated for use in novel medical applications, such as diagnostics, medical imaging, drug delivery, cancer therapy, tissue engineering, wound healing, and implantable devices. Examples of nanomaterial-enabled devices include tissue engineering scaffolds, dental filler materials, wound dressings and catheters with antimicrobial coatings, *in vitro* diagnostic kits for pathogens and cancer biomarkers, biosensors, and imaging contrast agents. Furthermore, functionalization or modification of medical device surfaces with nanotechnology, by modulating the chemistry to introduce preferred nanoscale topographies or by physically etching the surface to create nanoscale features, is being considered to provide enhanced tissue integration. Nanomaterials offer unique, size-dependent properties such as large surface area, optical properties, thermal behavior, magnetic capabilities, electrical performance, catalytic activity, and antimicrobial effects, making them attractive candidates for use in the medical device industry. For assessment of nanomaterials in biomedical applications, there are two primary areas of interest: (1) physical and chemical characterization to provide consistency in manufacturing, performance, and quality of nano-enabled medical products, and (2) appropriate and sufficient testing approaches to evaluate biological interactions of cells and tissues with nanomaterials to ensure safety and efficacy.

The two main classes of nanomaterials used in medical applications are shown in Fig. 1. The most widely investigated group of nanomaterials includes individually separate, unattached nanomaterials, referred to as discrete nanomaterials. Examples of discrete nanomaterials (or nano-objects) include nanoparticles, liposomes, quantum dots, nanotubes, and dendrimers (Fig. 1A) (Re, Gregori, & Masserini, 2012). Discrete nanomaterials may be high-aspect ratio structures, such as nanofibers, nanowires, nanorods, and nanotubes. Low-aspect ratio discrete nanomaterials include nanoparticles of various geometries, such as nanospheres, nanocubes, nanoshells, nanostars, and nanopyramids. The majority of the toxicological research in nanotechnology has focused on discrete nanomaterial systems. The use of nano-objects (e.g., nanoparticles) in medical applications and their effects on biological response have been reviewed elsewhere (Etheridge et al., 2013; Lewinski, Colvin, & Drezek, 2007; Wagner, Dullaart, Bock, & Zweck, 2006). This review will focus on the second class of nanotechnology, immobilized surface nanostructures (Fig. 1B) and their effects on cell—material interactions in medical device applications.

Immobilized surface nanostructures are imparted on biomaterials for implantable devices to improve interactions of the device with surrounding tissues. These nanoscale features may be etched, coated, functionalized, and/or hierarchically assembled on a biomaterial surface. Immobilized nanostructured biomaterials include nanoscale surface features such as pores, pits, grooves, pillars, electrospun fibers, and roughness. Examples of medical devices with immobilized surface nanostructures include cardiovascular stents, orthopaedic joint replacements, and dental implants. These nanoscale surface features may affect protein adsorption and cell adhesion dynamics which are critical in regulating cell signaling pathways that control cell function; therefore, it is important to first understand the biomolecular events occurring at the biomaterial-tissue interface in order to design implant biomaterials to optimize biological responses.

2. Biomolecular and biomechanical responses of cells to microscale and nanoscale surface topographies

2.1. Microscale and nanoscale structures of the extracellular matrix

Cellular response is strongly influenced by the surrounding physiological environment through complex interactions with mechanical forces, biochemical stimuli, and structural components of the extracellular matrix (ECM) (Fisher, Khademhosseini, Langer, & Peppas, 2010; Flemming, Murphy, Abrams, Goodman, & Nealey, 1999; Greiner, Richter, & Bastmeyer, 2012; Kriparamanan, Aswath, Zhou, Tang, & Nguyen, 2006; Martinez, Engel, Planell, & Samitier, 2009; Yim & Leong, 2005). The three-dimensional (3D) architecture of the ECM includes interwoven fibrillar proteins (e.g., collagens, elastins, fibronectins, and laminins) embedded within a network of proteoglycans (Alberts et al., 2007; Flemming et al., 1999). Collagens are a family of triple helical proteins and are the primary fibrous component of the ECM

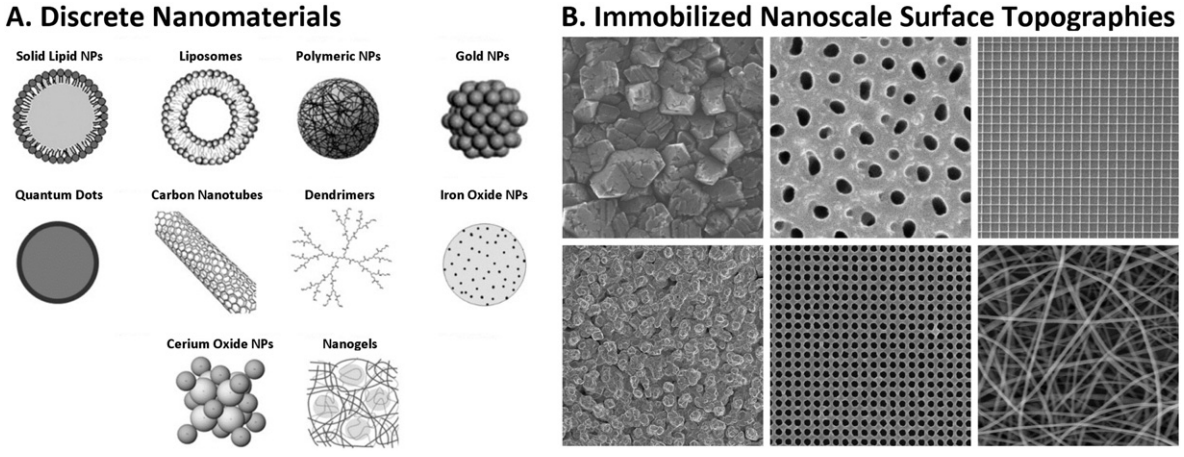

Fig. 1. Two classes of nanomaterials used in biomedical applications, discrete nano-objects, including nanoparticles (NPs), and immobilized surface nanostructures. (A) Different types of nanomaterials for biomedical use. Nanomaterials are commonly defined as objects with dimensions of 1–100 nm, which includes nanogels, nanofibers, nanotubes, and nanoparticles (NPs). Reprinted from *Nanomedicine: Nanotechnology, Biology, and Medicine*, 8, Re et al., Nanotechnology for neurodegenerative disorders, S51–S58, 2012, with permission from Elsevier (Re et al., 2012). (B) Representative electron micrographs of immobilized nanoscale surface topographies used in biomedical applications, including nanocrystalline coatings, nanoporous membranes, lithographically-patterned nanostructures, and nanofibers.