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Review article

Cell sensing of physical properties at the nanoscale: Mechanisms and control of cell adhesion and phenotype

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ABSTRACT

The chemistry, geometry, topography and mechanical properties of biomaterials modulate biochemical signals (in particular ligand-receptor binding events) that control cells-matrix interactions. In turn, the regulation of cell adhesion by the biochemical and physical properties of the matrix controls cell phenotypes such as proliferation, motility and differentiation. In particular, nanoscale geometrical, topographical and mechanical properties of biomaterials are essential to achieve control of the cell-biomaterials interface. The design of such nanoscale architectures and platforms requires understanding the molecular mechanisms underlying adhesion formation and the assembly of the actin cytoskeleton. This review presents some of the important molecular mechanisms underlying cell adhesion to biomaterials mediated by integrins and discusses the nanoscale engineered platforms used to control these processes. Such nanoscale understanding of the cell-biomaterials interface offers exciting opportunities for the design of biomaterials and their application to the field of tissue engineering.

Statement of significance

Biomaterials design is important in the fields of regenerative medicine and tissue engineering, in particular to allow the long term expansion of stem cells and the engineering of scaffolds for tissue regeneration. Cell adhesion to biomaterials often plays a central role in regulating cell phenotype. It is emerging that physical properties of biomaterials, and more generally the microenvironment, regulate such behaviour. In particular, cells respond to nanoscale physical properties of their matrix. Understanding how such nanoscale physical properties control cell adhesion is therefore essential for biomaterials design. To this aim, a deeper understanding of molecular processes controlling cell adhesion, but also a greater control of matrix engineering is required. Such multidisciplinary approaches shed light on some of the fundamental mechanisms via which cell adhesions sense their nanoscale physical environment.

Abbreviations: μCP, micro contact printing; AFM, atomic force microscopy; ALP, alkaline phosphatase; ARP, actin-related proteins; CL, colloidal lithography; DPN, dip-pen nanolithography; EBL, electron-beam lithography; ECM, extracellular matrix; ERK, extracellular-signal-regulated kinases; FA, focal adhesion; FAK, focal adhesion kinase; FC, focal complex; FIB, focused ion beam; FLIP, fluorescence loss in photobleaching; FMOC, fluorenylmethoxycarbonyl; FRAP, fluorescence recovery after photobleaching; FRET, Förster resonance energy transfer; GAG, glycosaminoglycan; HA, hyaluronic acid; hESC, human embryonic stem cell; HSQ, hydrogen silsesquioxane; IJP, inkjet printing; ILK, integrin-linked kinase; MAPKs, mitogen-activated protein kinases; MSCs, mesenchymal stem cells; NEB, high resolution chemically amplified negative resist; NIL, nanoimprint lithography; NRVMs, neonatal rat ventricular myocytes; NSCs, neural stem cells; PAA, polyacrylic acid; PAAm, poly(acrylamide); PALM, photo-activated localisation microscopy; PAN, polyacrylonitrile; PCL, poly(3-caprolactone); PDMS, poly(dimethyl siloxane); PE, polyethylene; PEA, poly(ethyl acrylate); PEG (or PEO), polyethylene glycol; PES, polyethersulfone; PET, poly(ethylene terephthalate); PLA, polylactic acid; PMA, poly(methyl acrylate); PMMA, poly(methyl methacrylate); POR, porin; PP, polypropylene; PS, polystyrene; PVA, poly(vinyl acetate); PVC, poly(vinyl chloride); PVP, polyvinylpyrrolidone; Rap1, ras-proximate-1; rBM, reconstituted basement membrane; RGD, arginylglycylaspartic acid; RhoA, ras homolog gene family, member A; ROCK, rho-associated, coiled-coil-containing protein kinase; STORM, stochastic optical reconstruction microscopy; TCPS, tissue-culture polystyrene; TEM, transmission electron microscopy; TIRF, total internal reflection fluorescence; VASP, vasodilator-stimulated phosphoprotein; VEGF, vascular endothelial growth factor; ZEP, high performance positive EB resists.

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1. Introduction

In recent years, the reconstruction and regeneration of human tissues that have been damaged by accident or are seriously compromised by diseases such as cancers or cardiovascular and neurodegenerative diseases, has been the focus of significant efforts from the biomedical community. Tissue engineering and regenerative medicine aim to develop scaffolds combining biomaterials and cells that mimic some of the characteristics of the tissue they are replacing. Despite the fast progress in the range and quality of materials used, our understanding of the interface between cells and their microenvironment (in this context at cell-material interfaces) remains incomplete. This is an important point in the quest for the design of devices that closely mimic the extracellular matrix and the cell microenvironment and control and facilitate the growth and proliferation of cells and their remodelling of the matrix, leading to tissue reconstruction.

Cell adhesion to neighbours and to extracellular matrix (ECM, a complex network of proteins and polysaccharides secreted and assembled by cells) is essential to maintain tissue structure and mechanical integrity. These interactions are mediated by transmembrane cell–cell and cell-matrix adhesion molecules, providing a direct connection between neighbouring cells or ECM proteins and the cell cytoskeleton. Such molecular networks are not only fundamental to confer an architecture to cells and tissues (their shape, structure and mechanical strength), control the orientation and localisation of subcellular organelles and cell polarity, but also for signal transduction [1–3]. The signals transduced from the exterior of the cell and the cytoplasm (as well as the nucleus) through a variety of pathways regulate cell behaviour and associated patterns of gene expression. In addition, an increasing number of reports provide evidence that physical properties of the cell microenvironment such as matrix rigidity, topography and geometry modulate biochemical cues mediated by these molecular networks. Understanding the detailed mechanism via which molecular interactions allow cells to sense such physical properties is essential to the design of artificial ECM and biomaterials for tissue engineering and regenerative medicine applications. This review will focus on our understanding of the mechanisms underlying the sensing of the physical cellular environment at the nanoscale, with an emphasis on integrin mediated processes. In Section 2, molecular mechanisms controlling the formation of integrin-mediated adhesions and their anchorage to the cell cytoskeleton are presented as their understanding is essential to the study of cell response to nanoscale physical properties of matrices. In Section 3, we briefly present the design and main fabrication strategies used to prepare important engineered matrices. Understanding how nanoscale properties are controlled in such platforms is essential to discuss and identify mechanisms underlying cell sensing at this scale. In Section 4, we review more specifically the mechanisms that are known to regulate nanoscale sensing of matrix geometry, topography and mechanics, and discuss how these parameters impact on cell phenotype. We made distinction between these different nanoscale.

2. Nanoscale architecture and dynamics of the cytoskeleton and integrin-mediated adhesions

The formation of cell adhesions, whether to natural extracellular matrix or to synthetic biomaterials, relies on the self-assembly of molecular complexes that are inherently structured at the nanoscale although often extending in size up to the microscale. These adhesions are often associated with nanoscale sensing of surface properties, although other mechanisms have also been highlighted. Hence understanding the molecular processes underlying cell adhesion, the architecture of relevant complexes and their dynamics is essential to understand the response of cells to nanoscale physico-chemical properties of biomaterials.