Topography-mediated Control of Cellular Response: Migration, Intracellular Crowding, and Gene-delivery

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DOI:
10.33612/diss.146106454

Publication date:
2020

SUMMARY

With the vigorous development and major breakthroughs of regenerative medicine technology, biomaterials occupy a very important position for providing a suitable therapeutic option for obtaining a higher quality of life. The cell-material interactions, especially the physicochemical (topography and stiffness) effects of materials, determines cell functions like cell adhesion, spreading, proliferation, alignment, migration and differentiation. In this thesis, to explore topography-mediated alterations and investigate subcellular behaviors, we demonstrate the important role of topography modulating cell migration, and identify the topography influence on macromolecular crowding in living cells. Furthermore, the topography stimuli were investigated for the control and enhancement of gene delivery capacity of stem cells.

Cells are living in a highly dynamic and extremely complicated three-dimensional microenvironment, which not only serves as structural support but also provides diverse biochemical and biophysical cues, that regulate cell functions and development. In **Chapter 1**, we introduce the cellular microenvironment such as the extracellular matrix, cell-cell contact, biochemical cues, physicochemical parameters (e.g., mechanical property, topography) and highlight the important role of topography for modulating cell behaviors. Furthermore, the modulation of cell migration in wound healing procedure, macromolecular crowding sensor and gene delivery were introduced.

In **Chapter 2**, we introduce the influence of physicochemical (e.g., topography, stiffness, roughness), and (bio)chemical properties (e.g., material composition and proteins) of high-throughput screening (HTS) platforms on various cell behaviors (e.g., cell spreading, proliferation, adhesion, and migration). High-throughput methods provide an ideal strategy to analyze thousands of combinations of interactions between cells and biomaterials on one substrate, thereby serves as a potential tool to elucidate the relationships between biomaterial properties and cell behavior.

To take the advantage of high-throughput screening methods as mentioned above, in **Chapter 3** the topographically patterned substrate of variable local wavelength and amplitude in a single substrate was fabricated for investigating the modulation of fibroblast migration in in vitro wound healing procedures. The wavelength/amplitude decoupled guidance effect was investigated for the first time. The results indicated that the topographic dimensions of surface wrinkles have an impact on cell migration behaviors. The fibroblast migration behaviors are not only influenced by the topographical wavelength and amplitude but also the topographical orientation. These findings suggest that for in vitro wound healing procedure the topography of materials is essential, and the topography of substrates may give guidance in designing biomedical implants and optimal wound dressings and skin engineering scaffolds.

In **Chapter 4**, topographic substrate with variable nano- or macro-scale size induced macromolecular crowding inside living HEK293T cells and various cell behaviors of the material-cell interfaces were investigated. The results demonstrated that the topography dimension has an influence on cell macromolecular crowding. The increased macromolecular crowding was found to be correlated with increased proliferation, which is induced by the topography. Furthermore, cell spread area and nuclei area were altered by the wrinkle surface and the topography that induced higher macromolecular crowding was associated with higher metabolic activity, increased proliferation, protein expression, increased focal adhesion and myosin tension but not YAP-TAZ transduction. These findings provide key insights in topography-triggered macromolecular crowding and provides useful information to better understanding interfaces between cells and materials and many new insights may be elucidated for tissue engineering and regenerative medicine approaches.

In **Chapter 5**, topographically patterned surfaces of variable wavelength and amplitude were applied to study the guidance of gene transfection of hBM-MSCs and myoblast cells. The results indicates that the topography dimension has an influence on cell spreading, elongation, proliferation, and transfection behaviors, and that the responses are dependent on cell type. Higher transfection efficiency was achieved on the substrates with wavelengths of 2 μm for hBM-MSCs and 10 μm for myoblast cells as compared to the transfection efficiency on Flat substrates. The increased gene delivery ability was found to be most likely related to quicker release or quicker nuclear entry of lipoplexes, which was found to be associated most likely to enhanced cell proliferation. Our findings highlight the importance of surface topography on cell stimulation for gene delivery and provides useful information on in vitro gene delivery, which have therapeutic applicable potential for non-viral gene transfer.

Chapter 6 is the general discussion of the role of topography in regulating cell spreading, proliferation, migration, macromolecular crowding, and gene delivery in this thesis. The topography and its sub-parameters such as direction, wavelength, and amplitude have an important influence on fibroblast migration in wound healing procedure. Different wrinkle features induce different intracellular macromolecular crowding phenomena that is associated with other subcellular activities. In addition, wave-like topography-mediated enhancement of non-viral gene delivery of stem cells. The obvious influence of topography on cell spreading, proliferation, migration, macromolecular crowding, and gene expression highlights its importance as a design parameter for the application of biomaterials. Furthermore, the perspective of topography combining other parameters were discussed to regulating cell functions.

Overall, the work presented in this thesis is to explore topography-mediated alterations of cell behaviors and investigate cell-material interface-induced subcellular behaviors like cell morphology alteration, cell migration in wound healing, intracellular macromolecular crowding, and topography-modulated gene delivery of stem cells. The work demonstrates that the topography plays an important role in modulating cell behaviors, which provides useful information to better understanding material-cells interfaces and many new insights may be elucidated for tissue engineering and regenerative medicine approaches.