Taking Cell Adhesion to the Third Dimension: Photochemistry and Biofunctionalization for defined 3D Cell Culture Scaffolds

Martin Bastmeyer

Cell and Neurobiology, Faculty of Chemistry and Biosciences
Karlsruhe Institute of Technology (KIT), Karlsruhe, Germany

Cell behavior and differentiation are not only influenced by biochemical cues but also by physical properties like adhesive geometry, topography, and stiffness of the 3D extracellular environment [1, 2]. I will discuss how direct laser writing (DLW) into biocompatible photoresists can be applied to design 3D cellular microenvironments in the µm range with defined geometries and adjustable flexibility [3]. To achieve a precise and patterned functionalization with biomolecules in 3D three approaches are chosen:
(i) By sequential DLW of two different photoresists, composite-polymer scaffolds with distinct protein-binding properties can be fabricated and selectively bio-functionalised thereafter [4]. Cells cultured in these scaffolds selectively form cell-adhesion sites with the functionalised parts, allowing for controlling cell adhesion and cell shape in 3D. Since the elastic modulus of the scaffold material varies between E=140-350 MPa, measurements of cell adhesion forces in relation to adhesion geometry are also feasible. In addition, these scaffolds can be used to mechanically stimulate cells at single defined adhesion sites [5].
(ii) By combining two-photon polymerization with an efficient surface photochemistry, also amenable to two-photon activation, it is possible to generate structurally complex 3D microstructures with 3D resolved chemical patterns [6]. Microscaffolds with lattice constants of 10–20 microns are patterned with protein ligands with a resolution close to one micron using a phototriggered cycloaddition. By choosing maleimides with diverse functionalities, scaffolds with 2-3 different bio-functionalizations can be realized [7].
(iii) By writing two functional photoresists into one scaffold, a dual functionalization pattern can be obtained by a single irradiation step via orthogonal chemistry in the presence of adequate reaction partners via a self-sorting mechanism [8].

In summary, the above described 3D scaffolds enable to study the influence of spatial ligand-distribution on cellular differentiation, allow visualizing and measuring cell adhesion forces, and can be used to mechanically stimulate single cells at defined adhesion sites.

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