Doctoral Thesis

Molecular assembly patterning by lift-off at the micro- and nanoscale for applications in the biosciences

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MOLECULAR ASSEMBLY PATTERNING BY LIFT-OFF AT THE MICRO- AND NANOSCALE FOR APPLICATIONS IN THE BIOSCIENCES

A dissertation submitted to the SWISS FEDERAL INSTITUTE OF TECHNOLOGY ZURICH

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Abstract

A number of applications in the biosciences such as DNA-chips, protein microarrays and cell-based sensors rely on chemically patterned surfaces. Such surfaces are essentially characterized by bio-interactive and non-interactive areas. The ability to host single cells or ensembles of few cells in well controlled surface-microenvironments has proven to be useful to study the fundamental mechanisms involved in cell-substrate interactions. Several surface cues are known to steer cellular development into a particular phenotype, namely, the type and density of cell-binding ligands, the substrate stiffness, the topography/roughness and the cell spreading. The desire to unravel the complex interplay between these different factors has created a substantial need for improved surface and interface modification tools that allow a quantitative and precise control of individual surface cues as well as their combination.

This thesis describes the development and optimization of a novel, reproducible and cost-effective patterning process named Molecular Assembly Patterning by Lift-off (MAPL). The attractive features of the MAPL technique are its abil-
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ity: to quantitatively control type and surface density of the biointeractive ligands in the adhesive patches; to elicit highly specific and quantitative interactions with the biological medium while inhibiting non-specific interactions; to control the pattern geometry/size independently of the bioligand surface density; and to produce complex pattern geometries of dimensions ranging from hundreds of microns to 100 nm.

MAPL combines a top-down approach based on photolithography and a bottom-up strategy through the self-organization of multifunctional molecules: a photoresist pattern is transferred into the desired biochemical pattern by means of spontaneous adsorption of a biologically functionalized, polycationic PEG-graft copolymer, followed by photoresist lift-off. The background surface, between the biointeractive patches, is rendered non-fouling by a simple dip-and-rinse process to form a monolayer of the corresponding non-functionalized PEG-graft polymer. Each step of the process was extensively characterized by various ultrahigh vacuum, in situ and optical microscopy surface analysis techniques (XPS, ToF-SIMS, OWLS, ELM, AFM, CLSM and SNOM). MAPL patterns are shown to have precisely controlled bioligand surface density (e.g., biotin or cell-adhesive peptide) within the patterns, and minimal non-specific adsorption of biomolecules. Note that each pattern for a given MAPL surface contains the same type and surface density of ligands. The culture, in serum-containing media, of small cell populations as well as single cells in a predefined shape and location demonstrates that MAPL is suitable in the context of studying independently the effect of ligand surface density and cell-surface contact area ("footprint"). Surfaces patterned by the MAPL technique turned out to be a versatile platform for other bio-applications as well, namely, patterning of DNA-tagged vesicles, colloidal particles and proteins. Preliminary investigations demonstrated the feasibility of using MAPL surfaces to produce protein microarrays with well-defined spot
geometries that are defined by the pattern geometry rather than the spotting process. In addition, by combining nanoimprint lithography and MAPL we were able to produce functional nanopatterns in the 100 nm range. The nano-MAPL surfaces are promising platforms for the precise arraying of single protein and vesicles and for fundamental cell-surface investigations with the aim to study and control focal complex and focal adhesion formation at the level of single ECM/integrin clusters.

MAPL is demonstrated in this work to be a technique that is robust, compatible with large batch processing and applicable to comparatively large areas such as 10 cm wafers. Furthermore, it is compatible with the requirement of the transparent substrate materials for inverted, high-resolution microscopy and optical sensing applications. These aspects make MAPL a cost-effective technique with a substantial potential for industrial applications as well as fundamental research.