MSN based biointerfaces to advance knowledge on ligand-stem cell interaction

Summary

ECM-mimicking 2D biointerfaces that offer high control over surface properties are an important tool to improve our understanding of stem cell-material interactions. In this thesis, we focus on the design and fabrication of a new type of synthetic 2D biointerface based on mesoporous silica nanoparticles (MSN) to study how ECM adhesive ligand presentation parameters influence stem cell regenerative processes. Chapter 2 describes a literature review on the development of synthetic biointerfaces to study (stem) cell adhesion processes. This review focuses on the design of static biointerfaces with predefined biochemical signals and how these can be optimized towards the creation of dynamic biointerfaces that can spatiotemporally control ligand display. In the future outlook of Chapter 2, we highlight that one core challenge in the design of biointerfaces is to mimic the dynamicity and nanoscale features of natural ECM ligand presentation. In Chapters 3-5, we present novel strategies to address this challenge using MSN to tune the dynamic and clustered RGD ligand presentation at the nanoscale. To ensure specific interaction of the bioactive ligands with stem cell integrin receptors, the effect of PEG length on its anti-fouling property and RGD presentation is investigated in Chapter 3. The results demonstrated that RGD ligand immobilized on a longer PEG chain length is more favorable in terms of reducing non-specific cell attachment without negatively affecting RGD-cell interaction. Based on this result, a long PEG chain length was selected to prepare MSN films for the following studies. Next, in Chapter 4, we investigated the influence of RGD clustering level on stem cell morphology, adhesion and differentiation. We found that a higher RGD ligand clustering level led to enhanced focal adhesions and osteogenic differentiation of human mesenchymal stromal cells (hMSCs) even when the global RGD density remained consistent. In Chapter 5, we increased the MSN biointerface complexity to mimic the dynamicity of the ECM. A novel strategy based on DNA hybridization was explored to control ligand display kinetics. High RGD kinetics showed a negative effect on stem cell adhesion and migration. In Chapter 6, we summarize the main findings obtained in this thesis, give a general discussion of the results and provide future perspectives. In the last part of the thesis, we explore the scientific and social impact of our findings and potential future commercial applications of the system developed in this thesis.

In conclusion, the results described in the present thesis shed light upon the importance of adhesive ligand parameters for the regulation of stem cell adhesion, survival, migration and differentiation. Increased understanding on these processes will improve the clinical translation of stem cell–based therapies by helping tissue engineers to rationally design better performing bioactive biomaterials. Furthermore, this thesis also provides valuable insights into strategies to tune adhesion ligand presentation, which is a step forward toward uncovering the mechanisms underlying integrin-mediated cellular signaling pathways.