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

Chapter 7

Impact

In this chapter, we discuss the (potential) impact of the research results described in the thesis on the state of the art scientific knowledge and applications within and across disciplines of tissue engineering and regenerative medicine. In addition, we also discuss the societal and economic relevance of our research findings.

By combining principles from cell biology, engineering, and materials science, the field of tissue engineering and regenerative medicine provides unprecedented opportunities to restore, maintain, or improve the functions of injured tissues and organs damaged by aging, cancer and other diseases [1, 2]. It aims to engineer functional tissues/constructs that can be implanted into the body to promote natural healing processes, and ultimately improve patients' quality of life. In 2006, the first engineered tissue, specifically an engineered bladder, was successfully implanted into human patients [3]. The engineered bladder was created using a combination of the patients' own cells and a biodegradable scaffold, allowing it to grow and integrate with the natural tissues in the body [4]. This groundbreaking achievement marked a significant milestone in the field of regenerative medicine and tissue engineering, and has further spurred the development of experimental therapies and increased public expectations. Enthusiasm about the far-reaching potential of tissue engineering created a gap between expectations and the (speed of) translation of experimental technologies into clinical practice. Currently, there are still many challenges to overcome in the process leading from bench to bedside. Specifically, creating biomaterials and tissue engineered constructs with tailored and controllable interaction with the biological environment of the body remains a core challenge. To address this challenge, it is of utmost importance to obtain a full understanding of how cells interact with their environment. This knowledge could help researchers engineer better biomaterials that mimic the native environment or adopt to it, improving tissue and organ repair and regeneration, and offering potential treatments for various degenerative diseases and injuries. Therefore, we anticipate that the contributions of this thesis to the understanding of how ligand immobilization strategies influence stem cell-material interactions may be valuable to a broad scientific community and will eventually accelerate the clinical translation of regenerative medicine products.

Since the discovery of fibronectin and the role it plays in cell adhesion, there has been increasing interest in the use of ECM proteins for promoting cell adhesion in tissue engineered constructs. In particular, RGD, which has been

identified as the minimal binding domain of fibronectin, has become the most widely used ligand for material functionalization to improve cell adhesion [5]. However, other cell adhesion peptides (CAPs), have also been investigated. CAPs including RGD, represent an interesting alternative to the use of natural ECM macromolecules, because they are easy to manufacture at a high purity in automated peptide synthesizers, and are well characterized. As such, CAPs have had a great impact on the design of cell culture platforms, implants, and wound dressings. Despite their potential, the full scope of functions exhibited by various CAPs is not yet comprehensively understood [6]. Biointerfaces with the capability to present biomolecules specifically and flexibly such as the one developed in Chapter 3 (DNA modified MSN films), are promising platforms to systematically study their biological functions. By finely controlling the presentation of these ligands, researchers can gain insights into cell adhesion mechanisms, signaling pathways, and cellular responses, ultimately contributing to the advancement of regenerative medicine and tissue engineering strategies by the creation of new biomaterial design rules.

The MSNs used in this study can also be used themselves in biomedical applications as coatings or components in biomaterials. Surface coating technology is a promising strategy for the creation of highly biocompatible and functional biomaterials, including medical devices and scaffolds for regenerative medicine. For example, coating techniques have been used to improve the osteoconductivity of bone implants and bone fillers. Silica nanoparticles could be used as potential coating materials [7]. In the past few years, silica nanoparticles have entered clinical trials for a variety of biomedical applications, including oral drug delivery, diagnostics, plasmonic resonance and photothermal ablation therapy. Preliminary results indicate the safety, efficacy and viability of silica nanoparticles under these clinical scenarios [8]. In this thesis, the synthesized silica nanoparticles have only been used for coating glass surfaces. However, considering their good biocompatibility and potential drug delivery capacity, MSN may be suitable for coating a wide range of biomaterials. Especially, in Chapter 4, we developed MSN functionalized with highly clustered of RGD ligands, which has been shown to enhance stem cell adhesion. Such MSN coatings may thus be used to enable proper cell adhesion to biomaterials and enhance their integration with the surrounding tissue. In addition to the coating approach, MSN can also be incorporated into biomaterials as chemical crosslinkers to increase their bioactivity or mechanical properties [9, 10], which are crucial for their clinical applicability. For

example, hydrogels are a promising class of materials in tissue regeneration [11]. However, hydrogel often lacks the mechanical strength required for load-bearing applications like bone regeneration. Several studies have reported that incorporating MSN into the hydrogel matrix allows for the development of hybrid material with improved structural integrity and mechanical properties [12, 13]. Additionally, another interesting study has demonstrated that RGD-modification of MSN remarkably enhanced cell adhesion on an alginate hydrogel compared to a MSN-NH2- incorporated hydrogel [14]. Therefore, the functionalized MSN developed in the thesis holds the potential for a wide range of applications, such as serving as a coating material for biomedical devices or as additives to create hybrid biomaterials with additional functionalities, demonstrating their potential clinical and economic impact.

The study of cells on surfaces is relevant in several scientific disciplines. In the current thesis, we empathize the usefulness of synthetic biointeraces in understanding stem cell-material interactions in the regenerative medicine field. In Chapter 5, we explored a novel strategy based on DNA hybridization to create a dynamic biointerface. This paves the way towards the fabrication of advanced ECM-mimicking biomaterials with dynamic complexity associated with complex cell processes. Beyond regenerative medicine, dynamic platforms also hold high potential to be used for other applications such as cell-based disease diagnosis. Work performed by Lei and co-workers nicely demonstrated this concept [15]. In this work, a flexible dynamic interface was developed. Different peptides were successfully introduced for various applications from dynamic modulation of stem cell adhesion behavior to selective isolation of tumor cells. Currently, most dynamic systems are focused on in vitro studies. There is still a long way to go to translate the dynamic systems to clinical applications. To speed up the translation process, further efforts should be directed towards evaluation of the efficacy and long-lasting operation of the dynamic platforms both in vitro and in vivo, as well as their cost and scalability [16].

References

[1] S. Mantha, S. Pillai, P. Khayambashi, A. Upadhyay, Y. Zhang, O. Tao, H.M. Pham, S.D. Tran, Smart Hydrogels in Tissue Engineering and Regenerative Medicine, Materials 12(20) (2019) 3323.

[2] F. Berthiaume, T.J. Maguire, M.L. Yarmush, Tissue Engineering and Regenerative Medicine: History, Progress, and Challenges, Annual Review of Chemical and Biomolecular Engineering 2(1) (2011) 403-430.

[3] E. Jacques, E.J. Suuronen, The Progression of Regenerative Medicine and its Impact on Therapy Translation, Clin Transl Sci 13(3) (2020) 440-450.

[4] A. Atala, Tissue engineering of human bladder, British Medical Bulletin 97(1) (2011) 81-104.

[5] N. Huettner, T.R. Dargaville, A. Forget, Discovering Cell-Adhesion Peptides in Tissue Engineering: Beyond RGD, Trends Biotechnol 36(4) (2018) 372-383.

[6] Q. Chen, S. Yu, D. Zhang, W. Zhang, H. Zhang, J. Zou, Z. Mao, Y. Yuan, C. Gao, R. Liu, Impact of Antifouling PEG Layer on the Performance of Functional Peptides in Regulating Cell Behaviors, J Am Chem Soc 141(42) (2019) 16772-16780.

[7] X. Lin, J. Chen, Y. Liao, J.L. Pathak, H. Li, Y. Liu, Biomimetic Calcium Phosphate Coating as a Drug Delivery Vehicle for Bone Tissue Engineering: A Mini-Review, Coatings 10(11) (2020) 1118.

[8] T.I. Janjua, Y. Cao, C. Yu, A. Popat, Clinical translation of silica nanoparticles, Nature Reviews Materials 6(12) (2021) 1072-1074.

[9] A. Zengin, J.P.O. Castro, P. Habibovic, S.H. van Rijt, Injectable, self-healing mesoporous silica nanocomposite hydrogels with improved mechanical properties, Nanoscale 13(2) (2021) 1144-1154.

[10] A.K. Gaharwar, C. Rivera, C.J. Wu, B.K. Chan, G. Schmidt, Photocrosslinked nanocomposite hydrogels from PEG and silica nanospheres: structural, mechanical and cell adhesion characteristics, Mater Sci Eng C Mater Biol Appl 33(3) (2013) 1800-7.

[11] S. Cascone, G. Lamberti, Hydrogel-based commercial products for biomedical applications: A review, Int J Pharm 573 (2020) 118803.

[12] S. Yang, J. Wang, H. Tan, F. Zeng, C. Liu, Mechanically robust PEGDA–MSNs-OH nanocomposite hydrogel with hierarchical meso-macroporous structure for tissue engineering, Soft Matter 8(34) (2012) 8981-8989.

[13] X. Sun, Z. Ma, X. Zhao, W. Jin, C. Zhang, J. Ma, L. Qiang, W. Wang, Q. Deng, H. Yang, J. Zhao, Q. Liang, X. Zhou, T. Li, J. Wang, Three-dimensional bioprinting of multicell-laden scaffolds containing bone morphogenic protein-4 for promoting M2 macrophage polarization and accelerating bone defect repair in diabetes mellitus, Bioactive Materials 6(3) (2021) 757-769.

[14] N.S. Kehr, E.A. Prasetyanto, K. Benson, B. Ergün, A. Galstyan, H.-J. Galla, Periodic Mesoporous Organosilica-Based Nanocomposite Hydrogels as Three-Dimensional Scaffolds, Angewandte Chemie International Edition 52(4) (2013) 1156-1160.

[15] L. Liu, X. Tian, Y. Ma, Y. Duan, X. Zhao, G. Pan, A Versatile Dynamic Mussel-Inspired Biointerface: From Specific Cell Behavior Modulation to Selective Cell Isolation, Angew Chem Int Ed Engl 57(26) (2018) 7878-7882.

[16] W. Li, Z. Yan, J. Ren, X. Qu, Manipulating cell fate: dynamic control of cell behaviors on functional platforms, Chem Soc Rev 47(23) (2018) 8639-8684.