Dynamic computational models of cell-extracellular matrix and cell-cell interactions

Summary

This thesis explores cell-cell and cell-extracellular matrix (ECM) interactions in regenerative medicine. Tissue engineering and regenerative medicine field aims to develop cell culture systems and biomaterials that mimic native tissues. The extracellular matrix facilitates communication between cells and is vital for organismal well-being. As such, imbalances in cell-ECM and cell-cell interactions can lead to impaired regeneration, such as fibrosis, resulting in reduced tissue function.

The thesis utilizes a computational approach to understand cell decision-making affected by these interactions and comprises a review and four original research articles, each focusing on a different aspect of cell-cell or cell-ECM communication.

Chapter 2 provides an overview of integrins' role in cell-ECM interactions and existing computational models thereof. Challenges in studying integrins are discussed, emphasizing the need for more specific experimental data. Chapter 3 presents a computational model of integrin activity, considering ligand binding competition. The model results suggest that both the binding affinity as well as relative ligand abundance need to be considered for successful biomaterial design.

Chapter 4 combines the biochemical and mechanical interactions occurring during the formation of integrin clusters and adhesions. The model predicts the fraction of nascent adhesions that can become mature focal adhesions under different substrate stiffnesses. Chapter 5 explores the crosstalk between cadherin-11 and platelet-derived growth factor receptors (PDGFRs) using a computational model. The model reveals the need for additional crosstalk between signaling pathways for cadherin-11 to influence cell proliferation, as was shown experimentally.

Chapter 6 models the reversible fibroblast to myofibroblast transition (FMT) initiated by ECM tension at the tissue level. The model highlights the dynamic interactions between cells and the ECM, proposing that the tightly regulated production of new ECM can reverse the FMT process.

Overall, this thesis emphasizes the significance of understanding the exquisite regulation of cell-cell and cell-ECM interactions for regenerative medicine,

using computational modeling. By unraveling these complexities, the research presented in this thesis has established important building blocks to improve regenerative medicine strategies with computational modeling approaches.