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# THE ROLE OF INTRINSIC AND EXTRINSIC MECHANICS ON ENDOTHELIAL CELLS AND FIBROBLASTS ORGANIZATION DURING EARLY BONE HEALING: AN IN SILICO STUDY

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**Summary:** The initial phase of bone healing is a critical window for the ultimate healing outcome. During this phase, fibroblasts (FBs) and endothelial cells (ECs) are known to invade the healing region and self-organize reaching complex patterns. In vitro observations suggest the existence of a complex mechanical interplay between ECs and FBs through cells internally generated traction forces which in turn influence collective FBs organization and ECs sprout patterning; however, the details of this interaction in early healing remain largely unknown since mechanical signals are very dynamic and challenging to measure or investigate experimentally. Moreover, the mechanical environment within the fracture is substantially influenced by the external loading and the fracture fixation chosen. The aim of this in silico study is to investigate the individual and collective contribution of intrinsic and extrinsic mechanical cues on ECs and FBs organization during the early stages of bone healing. Exemplarily, a mouse model of fracture healing was selected and an in silico model of FBs and ECs organization within the healing region of an osteotomy stabilized with a rigid vs. semi-rigid fixator developed. Finite Element Models, to compute mechanical signals within the healing region, were coupled to Agent-Based Models, describing ECs and FBs activity [Checa et al., Ann Biomed Eng., 2009][ Checa et al., Biomech Model Mechanobiol., 2015]. A feedback loop was implemented to account for the specific responses of ECs and FBs to local mechanical signals (e.g. durotaxis) and also include the effects of cell traction forces on the local matrix deformation. The iterative nature of the model allowed to obtain results at discrete time points simulating the first week post-osteotomy. Predictions at day 7 were compared to dedicated ex vivo histological data. After model validation, the in silico analyses were used to explore the relevance of alterations in cell traction forces and mechano-responsiveness. Vessels fragments, consisting of multiple ECs, were predicted to gradually align towards the lateral direction (i.e. perpendicular to the bone long-axis) while approaching the osteotomy gap, as observed experimentally. Furthermore, the lack of vascularity within the gap observed for the semi-rigid fixator was mimicked by the in silico analyses and could be explained by high mechanical strains locally. FBs were less prone to invade the osteotomy gap with the semi-rigid fixation as compared to the rigid one. Moreover, FBs were predicted to orient along preferential directions, in agreement with the direction of collagen fibres experimentally observed at later healing stages. The computer model predicted an altered cellular organization after cell mechano-response removal, while the inhibition of cellular traction forces did not produce a visible change. To our knowledge, this is the first in silico study that analyses collective ECs and FBs organization during early bone healing and comprises both cell internally generated traction forces and externally applied loads. Collectively, our results identified external loads as the main player driving early ECs and FBs organization, suggesting that initial mechanical stability determines early cell patterning. The knowledge gained in this work should enable to support the development of strategies to foster bone regeneration.