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A computational tissue repair model identifies an early transient decrease in fiber cross-linking that unlocks regeneration in adult mammals

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In adult mammals, scar formation predominates over tissue regeneration, often leading to dysfunction due to the disrupted relationship between tissue architecture and function. Addressing this challenge is crucial in regenerative medicine. The restricted regenerative capacity in mammals suggests the presence of inhibitory factors established early in life. Our previous studies, using a model of massive subcutaneous adipose tissue (AT) resection, suggest that regeneration in adult mammals may be governed by self-organizing principles similar to those in salamander limb regeneration. We developed an agent-based model (ABM) showing that AT architecture may emerge from simple mechanical interactions between growing adipocytes and the extracellular matrix (ECM). This ABM considers three mechanisms involved in ECM mechanical properties: synthesis, degradation, and fiber cross-linking. We extended this ABM to use it as a predictive model of tissue repair, mimicking both regeneration and scar healing-like architectures. We performed high-throughput multiparametric simulations in which each ECM parameter was independently varied over a wide range of values and used machine learning models to reveal that ECM cross-linking was the most important parameter explaining tissue repair outcomes in silico. Temporal calibration of the ABM with in vivo AT regeneration revealed a six-day window post-injury during which ECM cross-linking modulation significantly impacts repair outcomes. In vivo experiments confirmed these findings: inhibiting cross-link formation within this window promoted regeneration, while inducing cross-linking led to scarring. Taken together, these results showed that the final tissue architecture after an injury emerges from mechanical interactions between cells and ECM, and that modifying ECM cross-linking during the first days after injury guides tissue repair toward regeneration. Our results also show that our ABM represents a significant step toward developing a digital twin of the repair process.

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