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HINDLIMB UNLOADING INHIBITS MAMMALIAN DIGIT TIP REGENERATION

Abstract

Purpose Interplanetary space travel by humans is dependent on the ability to maintain astronaut health. However, prolonged mechanical unloading experienced by astronauts living in microgravity enhances degeneration of skeletal tissue, impairs wound healing, and disrupts stem cell proliferation and differentiation. Presently, it is unknown if mechanical unloading affects mammalian regeneration. Mice, as well as humans, are capable of regenerating the tips of their digits following injury. Digit tip regeneration is a complex process and occurs through sequential stages, which include inflammation, histolysis, epidermal closure, blastema formation, and redifferentiation to replace the amputated structures. In this study, a first for regeneration and space physiology, we investigate the role of mechanical unloading during mammalian digit tip regeneration.

Methodology We utilized hindlimb unloading (HU), a well established model in which the hindlimbs of mice are suspended such that they are no longer weight bearing. Three groups of mice were used: 1) amputated, non-HU mice were used as an amputation control, 2) non-amputated, HU mice were used as an HU control, and 3) amputated/HU (Amp/HU) mice as our experimental group. The distal tip of the terminal phalanx (P3) of the 2nd and 4th digits on both hindlimbs were amputated and mice were placed in HU for 26 days. P3 bone volume was monitored throughout the experiment using in vivo microCT. After 26 days post amputation (DPA) mice were terminated and digits analyzed using histological and immunohistochemical techniques. Each group consisted of 5 female, 8 week old, C57Bl mice (n = 5 mice/20 digits).

Results Hindlimb unloading completely inhibits digit tip regeneration. Histological studies reveal that epidermal wound closure, a requirement for regeneration, is incomplete in 95% of Amp/HU digits. At 26DPA Amp/HU mice had significantly less bone volume compared to 0DPA (59.02%; $P<0.0001$) and compared to amputation (49.1%; $P<0.0001$) and suspension (46.4%; $P<0.0001$) controls at 26DPA. Further, amputated bone has degraded, and in some instances degradation has exposed articular cartilage. Finally, cathepsin K-positive osteoclasts, a cell type absent during late regeneration stages, are significantly elevated in Amp/HU digits at 26DPA.

Conclusions and Areas for Discussion Mechanical unloading effects temporal and functional properties of regeneration in multiple tissues ultimately culminating in regenerative failure. These data are novel, and addressing how regenerative potential can be restored will be essential for restoring astronaut health in the event of a space flight injury. This research has been not presented at a previous meeting.