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"Evaluating limb regenerating capabilities of osteoprogenitor cells"

In the United States, 5.6 million fractures occur each year. About 5-10% of these fractures fail to properly heal resulting in invasive surgical intervention to treat nonunion, malunion, osteomyelitis, and chronic pain. For a bone fracture to heal, osteoprogenitor cells of the periosteum proliferate and form a cartilaginous callus which then undergoes endochondral ossification to become new bone. Osteoprogenitor cells are integral to this process, but sometimes fail to repair the bone resulting in non-union healing. To better understand regenerative failure, we use a comparative model of bone regeneration and non-regeneration.

The mouse, and similarly humans, can regenerate the distal ½ of digit tip (third phalangeal element or P3). An amputation proximal to this point (P2) results in a cartilaginous callus with no bone growth distal to the amputation plane and dermal scar formation. It is unknown if regenerative failure in P2 is due to specific factors intrinsic to the P2 osteoprogenitor cells or if environmental factors drive this healing difference.

When comparing osteoprogenitor cells in regenerative and non-regenerative species, for example in rabbit (regenerative) versus rat (non-regenerative), previous studies suggest regenerative osteoprogenitor cells overcome stress induced cellular senescence caused by reactive oxygen species (ROS) released upon injury better than non-regenerative counterparts. This resistance to stress corresponded to greater proliferative and regenerative abilities. Researchers theorize poor resistance to stress induced cellular senescence limits non-regenerative species from fully regenerating wounds.

To determine the intrinsic capabilities of osteoprogenitor cells derived from distinct anatomical regions of the body, we first analyzed the proliferative potential and cellular senescence characteristics of P2 and P3 osteoprogenitor cells in vitro. Our findings, though unexpected, shed light on the nuanced nature of these cells' behavior and provide insights into their regenerative capacities. Initially, we hypothesized that P3 osteoprogenitor cells would exhibit an inherent advantage in terms of proliferative ability and a reduced propensity for cellular senescence when compared to P2 osteoprogenitor cells due to the regenerative ability of the P3 phalangeal element. However, contrary to this hypothesis, our observations revealed a contrasting pattern. Specifically, P3 cells displayed an accelerated onset of senescence and a decelerated rate of proliferation compared to P2 cells. This finding suggests that P2 osteoprogenitor cells retain an intrinsic capability for proliferation, at least in vitro, and may be hindered by the in vivo environment.

Next, our study will investigate stress resistance. We hypothesize P3 cells will demonstrate heightened stress resistance in comparison to their P2 counterparts. This enhancement in stress resistance could potentially underscore the regenerative cells' ability to evade stress-induced cellular senescence, ultimately facilitating increased proliferative capacity following injury. Completion of this project will address if there are intrinsic differences in osteoprogenitor cells in different bones of the body and may help explain why some injuries in bone regenerate better than others.