

On the Horizon From the ORS

Regenerative Rehabilitation of the Musculoskeletal System

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Regenerative rehabilitation is the convergence and integration of regenerative medicine and physical rehabilitation sciences.¹ Physical therapy (PT) is essential to support the return to function of a damaged or repaired tissue. However, the specific effects of PT down to the cellular level of regeneration are largely unexplored.² Conversely, when thinking of regenerative approaches, the mechanical environment that cells and scaffolds must withstand in orthopaedic repair is often regarded as a challenge that needs to be endured or overcome rather than as an opportunity that can be leveraged. In tissue engineering, cellular mechanobiology is more often studied to promote the maturation and the three-dimensional organization of engineered constructs, ranging from aligned muscle fibers to the zonal organization of chondrocytes. Regenerative rehabilitation can then be appreciated as an approach to translational mechanobiology, in which the mechanical cues driving cell differentiation and function are directed by rehabilitation routines to promote repair and regeneration.^{3,4}

Bone is well known to respond and adapt to changes in load (Wolff's law). However, during regeneration after fracture or critical bone defects, the picture becomes more complex, as there is not just the bone to account for but also a defect with associated instability, the repair tissue that bridges the defect, and vascularization that is required for effective healing. Ambulatory loads have been found to promote fracture repair⁵ and to regulate angiogenesis,⁶ so if the axial loads across

bone defects can be monitored⁷ and related to vascularization and repair,⁸ this would allow us to design fixation strategies that transfer loads⁹ and ambulatory exercises so as to promote regeneration and ideally accelerate a full patient recovery. The stability of the fracture fixation has a direct influence on whether fracture repair is achieved by way of endochondral ossification or direct intramembranous healing, and this can be modulated by the loads applied during the rehabilitation period.

When stem cells are used to support healing of muscle injury, exercise-driven mechanical activation supports proliferation of the transplanted stem cells and their effective repair of the injured muscle.⁴ For larger volumetric muscle loss, in which scaffolds are combined with stem cells for repair, exercise regimens enhance both force production and innervation of the engineered construct.¹⁰ Robotic platforms could then be developed to monitor muscle impairment and administer tailored training during the recovery process to enhance repair and overall motor performance.¹¹

Normal cartilage homeostasis is reliant on cyclical loading, and this has been associated in part with mechanical activation of matrix-associated transforming growth factor- β . Within native cartilage, this is thought to be strongly influenced mechanically at the superficial zone¹² but enzymically regulated in the deeper zones.^{13,14} Chondrogenic differentiation of human bone marrow-derived mesenchymal stromal cells, such as those that would be present during microfracture, can be induced

in vitro by mechanical forces alone,¹⁵ and a similar response has been observed in human articular chondroprogenitor cells.¹⁶ This is due to the production and activation of endogenous transforming growth factor- β , a process that, in part, is regulated by the application of shear.¹⁷⁻¹⁹ Such mechanistic knowledge at the protein and cellular level provides the opportunity to devise rehabilitation protocols based on a strong underlying scientific rationale.

The joint as a whole, however, consists of more than just articular cartilage. In fact, the joint is an organ comprising multiple tissues—bone, cartilage, synovium, meniscus, ligaments, and infrapatellar fat pad—all of which interact and influence each other.^{20,21} More generally, in considering the musculoskeletal system, one should not approach it as evaluating each tissue in isolation, but rather should regard it as a continuum of components, all tightly connected and transitioning from one to the next via the osteochondral junction, the enthesis, and so on.²² The development of proregenerative rehabilitation regimens should then account for load transduction across tissue interfaces²⁰ and for the different mechanobiological responses of each tissue.

Overall, PT has been used for years in orthopaedics to promote tissue repair and return to function. However, the cellular signaling and mechanistic relation between exercise and cellular responses are still far from being fully appreciated. Better understanding of these underlying mechanisms would allow us to design the rehabilitation protocol based on empirical data, focusing on the integration with regenerative medicine to enhance patients' outcomes.^{3,23} The development of assistive devices to monitor the progression of tissue repair and guide accordingly the delivery of proregenerative mechanoactivation stimuli could greatly enhance the research in

regenerative rehabilitation and the delivery of personalized regenerative treatments.

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