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Regenerative rehabilitation of the musculoskeletal system

Riccardo Gottardi, PhD[1] and **Martin J. Stoddart, PhD**[2,3]

[1]Center for Cellular and Molecular Engineering, Department of Orthopaedic Surgery, University of Pittsburgh, Pittsburgh, PA, USA

[2]AO Research Institute Davos, Switzerland, Fondazione Ri.MED, Palermo, Italy

[3]G.E.R.N. Tissue Replacement, Regeneration & Neogenesis, Department of Orthopedics and Trauma Surgery, Medical Faculty, Albert-Ludwigs-University of Freiburg, Germany

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 little explored[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. Differently, in tissue engineering, cellular mechanobiology is more often studied to promote the maturation and the three-dimensional organization of engineered constructs, ranging from aligned muscled fibers to the zonal organization of chondrocytes. Regenerative rehabilitation can then be appreciated as an approach to translational mechanobiology, where 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 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 repair[5] and to regulate angiogenesis[6] so if the axial loads across bone defects can be monitored[7] and related to vascularization and repair[8] this would allow to design fixation strategies that transfer loads[9] and ambulatory exercises so as to promote regeneration and ideally accelerate a patient full recovery. The stability of the fracture fixation has a direct influence on whether fracture repair is 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, where scaffolds are combined with

Address for correspondence: Riccardo Gottardi, Center for Cellular and Molecular Engineering, Department of Orthopaedic Surgery, University of Pittsburgh, 450 Technology Dr., 15219, Pittsburgh, PA, USA.

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 beta (TGF-β). Within native cartilage this is believed to be strongly influenced mechanically at the superficial zone[12], 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 TGF-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.

Considering the joint as whole, however, we are looking at more than just articular cartilage. We are in fact faced with an organ comprising multiple tissues – bone, cartilage, synovium, meniscus, ligaments, infrapatellar fat pad – all of which interact and influence each other[20,21]. More generally, as we consider the musculoskeletal system, we are moving beyond looking at each tissue in isolation, but we should rather 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 pro-regenerative rehabilitation regimens should then account for load transduction across tissue interfaces[20] and for the different mechanobiological responses of each tissue.

Overall, physical therapy has been employed 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 these underlying mechanisms would allow to design 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 pro-regenerative mechanoactivation stimuli, could greatly enhance the research in regenerative rehabilitation and the delivery of personalized regenerative treatments.

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