Rehabilitation Considerations in Regenerative Medicine

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KEYWORDS

• Regenerative rehabilitation • Mechanotransduction • Mechanotherapy
• Physical therapy • Platelet-rich plasma • Stem cell therapy

KEY POINTS

- Regenerative rehabilitation pairs exercise principles with regenerative therapies to facilitate the regeneration and repair of bone, muscle, cartilage, ligaments, tendons, nerves, and other musculoskeletal tissues.
- Mechanotherapies form one of the largest groups of interventions prescribed by physical therapists with nearly every intervention used introducing mechanical forces.
- A basic understanding of mechanotransduction and the impact of mechanical loading on cellular biology can guide the development of appropriate rehabilitation programs after regenerative therapies.
- Regenerative rehabilitation guides protocols for when to start therapy, types of stimuli administered, and graded exercise programs, taking into account biological factors and technologies designed to optimize healing potential.

INTRODUCTION

Regenerative medicine is an emerging, interdisciplinary field that combines advances in molecular biology, gene therapy, cellular therapy, and tissue engineering to replace or regenerate human cells, tissues, or organs.[1,2] The goal of regenerative medicine is to restore or establish normal function after loss from any cause, including congenital defects, injury, disease, or aging.[2,3] Given that physical rehabilitation shares the same goal, the combination of the 2 approaches may serve to enhance the desired treatment outcomes and could be transformative for individuals with previously untreatable injuries or disorders.[3,4]

Regenerative rehabilitation is defined by the American Physical Therapy Association as "the integration of principles and approaches from rehabilitation and regenerative

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medicine, with the ultimate goal of developing innovative and effective methods that promote the restoration of function through tissue regeneration and repair."[5] Regenerative rehabilitation pairs exercise principles (eg, loading, intensity, frequency, duration), with regenerative therapies to facilitate regeneration and repair of bone, muscle, cartilage, ligaments, tendons, nerves, and other musculoskeletal tissues. This concept requires an interdisciplinary approach between scientists, clinicians, and physical therapists (PTs). In addition, it requires PTs to develop an understanding of the impact of exercise on cellular and molecular biology.

After tissue injury, PTs use targeted exercise therapy to enhance the efficiency of the body's innate healing potential.[6] Properly designed rehabilitation programs can play a critical role in optimizing the incorporation of regenerative therapies into the native tissues. The role of PTs should not be confined to restoring function after tissue regeneration or repair has occurred, because we should also play an active role in facilitating regeneration and repair during the healing process.[1]

MECHANOTHERAPY

The term "mechanotherapy" was initially coined in the 19th century, and defined in the Oxford English Dictionary as "the employment of mechanical means for the cure of disease."[7,8] In 2009, Khan and Scott[7] proposed to update the definition to "the employment of mechanotransduction for the stimulation of tissue repair and remodeling" to highlight the cellular basis of therapeutic exercise prescription for tissue healing. This definition also recognized that injured and healthy tissues may respond differently to mechanical loads.[7]

In 2016, Thompson and colleagues[1] proposed to once again update the definition to "any intervention that introduces mechanical forces with the goal of altering molecular pathways and inducing a cellular response that enhances tissue growth, modeling, remodeling, or repair." This definition highlights the responsiveness to mechanical signals at a multisystem level (ie, molecular level, cellular level, and tissue level) and recognizes the influence of mechanical forces on the processes responsible for tissue development, maintenance, healing, and regeneration.[1]

Mechanotherapies form one of the largest groups of interventions prescribed by PTs. Nearly every intervention used in the practice of physical therapy introduces mechanical forces.[1] Such interventions, including but not limited to, exercise prescription, joint mobilization, soft tissue mobilization, muscle stretching, and even neuromuscular electrical stimulation, provide mechanical stimulation at both the cellular and tissue levels.[7,9] Developing insight into the molecular and cellular responses to the forces used in daily practice will allow PTs to increase understanding of therapeutic dosing and potentially improve clinical outcomes in patients undergoing regenerative therapies.

MECHANOTRANSDUCTION

Mechanotransduction refers to the physiologic process by which cells convert mechanical stimuli into cellular responses.[1,7,10] These cellular responses will, in turn, promote structural adaptation. Mechanotransduction consists of 3 distinct phases: (1) mechanocoupling, (2) cell–cell communication, and (3) the effector response. Mechanocoupling refers to a mechanical stimulus or load that causes physical perturbation to cells.[7] The perturbation may be direct or indirect and can trigger a variety of cellular responses depending on the type, magnitude, frequency, and duration of the load.[11–13] Cells may be exposed to an array of mechanical forces, including tension, compression, shear, hydrostatic pressure, vibration, and fluid shear. The tissue in