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Regenerative rehabilitation: A call to action

INTRODUCTION

We have battled against disease since the beginning of time. As science and technology have evolved, so have the weapons in our antidisease arsenal improved. Indeed, in the last 50 years, the sheer volume of knowledge about human biology has doubled every 8 years. This means that the foundation on which the design and delivery of healthcare is built is 1,000 times stronger at the end of our lives than at the beginning. In the next century, we will add therapies that can restore lost function to ailing tissues and organs to the arsenal of health-aging technologies. This "regenerative medicine" will eventually open the door to battling crippling diseases like diabetes, Parkinson, and heart failure, as well as the impacts of traumatic injury. Success in the laboratory, where all such endeavors must begin, will drive the commercial activities toward products that subsequently become available to patients.

Regenerative medicine is a multidisciplinary field incorporating expertise from engineers, biologists, and chemists, to name a few. The goal of regenerative medicine is to restore tissue and organ function lost as a result of aging, injury, or disease. It uses a variety of tools to divert the default pathways of wound healing in humans, which typically result in a patchwork of scar tissue, toward pathways that recapitulate restoration of original tissue/organ architecture and function. Regenerative medicine scientists seek to harness tissue and organ regeneration that was once only possible as a fetus or newborn.

We believe that rehabilitation science and technology will be critical in the success of any regenerative therapy and therefore the two fields must pay increasingly more attention to each other. We suggest herein a variety of mechanisms for the rehabilitation community to be the enablers of regenerative therapies. Because regenerative therapies are outcome-driven rather than technology-specific, the community needs to engage in this interdisciplinary cross-fertilization with an understanding of the different tools that can be used to restore lost organ and tissue function.

Our ability to restore damaged tissues and organs today relies on three large categories of interventional approaches: (1) medical devices/artificial organs, in which tissue function is replaced with entirely synthetic constructs and machines; (2) tissue engineering and biomaterials, in which temporary scaffolds are used to bridge large tissue-gap defects; and (3) cellular therapies, including the transplantation of stem cells and genetically manipulated cells for the repair of damaged or diseased tissue.

The **Figure** illustrates the concept of vertical integration of rehabilitation and regeneration. Traditionally, regenerative medicine and rehabilitation have

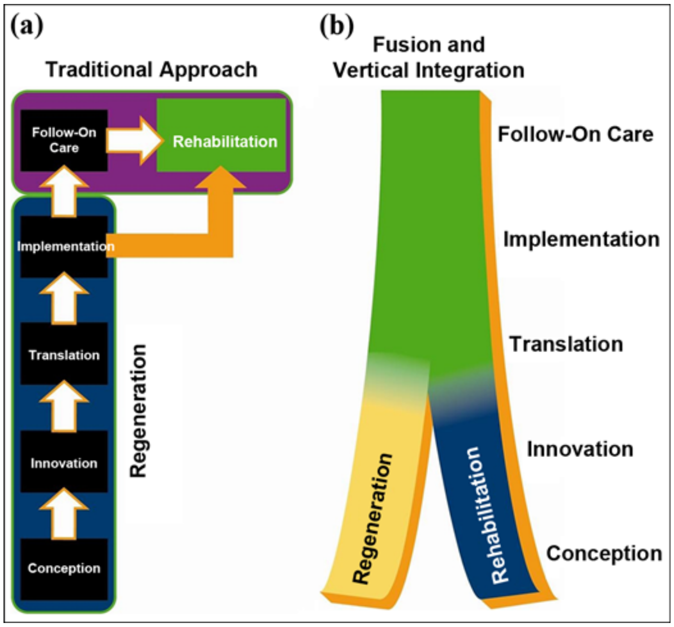

Figure.
(a) Traditional approach is contrasted with **(b)** fusion of regeneration and rehabilitation.

existed as serial processes in patient treatment and care plans, despite common end points. In contrast, we propose that the vertical integration of rehabilitation and regeneration, in which the two tracks are "fused" at the onset of therapeutic development, will allow us to achieve functional goals faster and more effectively. Conjoined education in these disciplines must be the vehicle through which each field can learn where the overlaps exist and how to exploit opportunities.

Here, we provide an example of how the treatment of skeletal muscle injury could be affected by regenerative medicine and optimized by regenerative rehabilitation.

TREATMENTS TO PROMOTE SKELETAL MUSCLE REGENERATION FOLLOWING ACUTE INJURY

Muscle injury, defined as "a prolonged impairment of the ability of a muscle to produce force" [1], can greatly impair an individual's function and ability to participate in recreational and occupational activities. The four interrelated phases of healing, irrespective of the cause of injury, have been well characterized in both animals and models and consist of degeneration, inflammation, regeneration, and fibrosis (reviewed by Huard et al. [2] and Järvinen et al. [3]). While minor injuries typically heal well and with little residual dysfunction, the regeneration of severe or aged skeletal muscle damage is often incomplete and ultimately results in scar tissue formation or fibrosis. Any factor, including scar tissue deposition, that decreases contractile capacity of the muscle, will decrease energy-absorbing capabilities of the muscle, increase likelihood for reinjury [4], and decrease functional capacity. As long as the scar persists, complete muscle regeneration is not possible.

Rehabilitation Approach

Unfortunately, although our scientific understanding of the underlying mechanisms relating to muscle regeneration has made significant strides over the last several decades, clinically available treatment protocols largely lack a scientific basis. A majority of the rehabilitation approaches used clinically are predominantly centered on minimizing an inflammatory response and pain immediately following injury. Most commonly, the "RICE" principle— rest, ice, compression, and elevation—is implemented, with the prevailing intention of minimizing inflammation, hematoma formation, and the accumulation of interstitial fluid at the injury site [3,5]. Despite RICE being the treatment intervention of choice for several decades, no direct empirical evidence supports its clinical efficacy [5], and randomized controlled clinical trials have never been performed. Similarly, therapeutic ultrasound is also commonly used clinically for the treatment of muscle injuries, with an underlying rationale that high-frequency ultrasound waves elicit a micromassage to injured tissues. This rationale, however, has also never been confirmed scientifically. Electrical stimulation is another modality used frequently for the treatment of tissue injuries, despite that it is severely limited by the lack of clearly delineated timing and dosing regimens to optimize therapeutic benefit.

Pharmacological interventions, such as the use of nonsteroidal antiinflammatory drugs (NSAIDs), are also commonly used for minimizing pain and discomfort following an injury, therefore allowing for a faster return to activity. However, recent studies have demonstrated long-term detriments to the use of NSAIDs and suggest that a muted inflammatory response to injury may actually inhibit functional myofiber regeneration [6–9].

Regenerative Medicine Approach

Scientists in the field of regenerative medicine have taken a different approach toward the treatment of acute skeletal muscle injuries and have largely focused on modulating the latter phases of healing to promote myofiber regeneration and inhibit the formation of scar tissue. To inhibit fibrosis formation following severe injury, attributed in large part to the secretion of transforming growth factor (TGF)-β1 [10], researchers have investigated the administration of TGF-β1 specific inhibitors, such as relaxin [11], decorin [12], and suramin [13–15]. In animal models, the presence of TGF-β1 antagonists has significantly decreased fibrosis while concomitantly improving myofiber regeneration [11,16]. Ultrastructural changes were further associated with an increased force-producing capacity of the injured muscle [13]. Of these agents, suramin, clinically trialed for use as an anticancer agent (reviewed by McGeary et al. [17]), offers the additional advantage of being FDA approved. However, the feasibility of administration of this agent in humans is questionable, because intramuscular injection of suramin is very irritating and only recommended in the absence of reasonable alternatives (http://home.intekom.com/pharm/bayer/suramin.html/). Additionally, suramin doses administered in animal models exceed permitted doses in humans. Together, the adverse effects of suramin administration or other TGF-β1 inhibitors to enhance healing are likely to outweigh the benefits.

Cellular therapies have also been investigated in the laboratory as a means to boost the regenerative potential of injured skeletal muscle. Muscle stem, or satellite, cells are localized to the myofiber periphery [18], and under the stress of injury, these normally quiescent cells become activated to regenerate damaged myofibers [18]. In the case of elderly individuals, an impaired healing response following skeletal muscle injury has been largely attributed to age-related dysfunction of these muscle stem cells. Circulating factors typical of aged microenvironment drive the differentiation of muscle stem cells from a myogenic-to-fibrogenic lineage [19], ultimately increasing fibrosis formation characterizing aged skeletal muscle. Additionally, a decreased proliferative capacity of aged muscle stem cells severely depletes the reservoir of cells available for regeneration. For replenishment of the stem cell supply, and therefore enhancement of the regenerative potential of aged skeletal muscle, the transplantation of young muscle stem cells has been proposed. Unfortunately, functional outcomes following transplantation have been less than desirable, and even embryonic stem cells, once transplanted into an aged milieu, rapidly decline in their regenerative potential [20]. The rejuvenation of the aged skeletal muscle niche may be a prerequisite to the successful transplantation of stem cells for the treatment of skeletal muscle injuries.

Fusion Approach

We propose that maximal functional benefits in the treatment of skeletal muscle injuries may be best achieved when regenerative medicine and rehabilitation approaches are simultaneously applied. Mechanical stimulation is a promising method for communicating with cells following transplantation and dictating their in vivo behavior. Rodent studies from our laboratory have demonstrated that a treadmill running protocol, initiated shortly after stem cell transplantation into severely contused muscle, increases the myogenic contribution of donor cells 5 weeks after transplantation [21]. Similarly, findings from our laboratory suggest that a combination therapy comprised of stem cell transplantation and neuromuscular electrical stimulation significantly increases the force-generating capacity of injured skeletal muscle when compared with the administration of electrical stimulation alone (F. Ambrosio, PhD, MPT; unpublished data, December 2009). These laboratory findings suggest a synergistic effect between physical therapeutics and cellular therapies for the treatment of acute muscle injuries. Elucidation of the underlying mechanisms by which mechanotransductive signals may enhance the regenerative potential of donor and host cells will allow us to refine treatment protocols and maximize therapeutic benefit.

In addition, arguably, muscle contractile activity alone is a powerful tool for rejuvenating the regenerative potential of aged muscle. Even exercise programs initiated late in life may enhance the ability of muscle to heal itself after severe injury while concomitantly decelerating tissue degeneration. Preliminary murine findings from our laboratory have demonstrated that the application of targeted muscle contraction protocols enhances molecular, cellular, and tissue functioning (F. Ambrosio, PhD, MPT; unpublished data, February 2010). This type of stem cell therapy, even in the absence of stem cell transplantation, suggests that the most powerful regenerative medicine tool—physical activity—has been in our toolbox since the beginning of time. A better understanding of the underlying mechanisms controlling the antiaging effect of exercise is critical if we intend to put this tool to good use.

NECESSARY STEPS TOWARD VERTICAL INTEGRATION

One of the greatest barriers to implementing a fusion approach lies in the decreased communication that results because the two fields speak very different languages. Traditional rehabilitation training programs focus on whole body and physiological responses to mechanical loading and/or modalities, yet largely neglect mechanotransductive principles guiding cellular and molecular behavior. Conversely, regenerative medicine scientists often target modulation of molecular, cellular, and histological properties through the development of cutting-edge technologies while overlooking clinically available tools that may elicit similar responses.

Investigators working in the field of rehabilitation science are also largely unaware of regenerative medicine breakthroughs and vice versa. Therefore, rather than benefitting from transdiscipline advances, we are duplicating our efforts.

One can envisage many ways to reduce or eliminate barriers between regenerative and rehabilitative science and technology. Communication between experts and those who are passionate about the interface between the fields is clearly the best starting point. We therefore are initiating a series of steps and are using this editorial to mobilize our communities into action. At the outset, we will—

- Develop an annual International Regenerative Rehabilitation Symposium to bring together scientists in both fields and initiate new collaborative efforts.
- Dedicate considerable course work in physical and occupational therapy educational programs to understanding orthopedic and neurological procedures, including the underlying principles of regenerative medicine.
- Consider new physical therapy specializations, such as “Cellular Rehabilitation.”

Regenerative rehabilitation is difficult but inevitable, and now is the time to prepare specific, science-based protocols for patients who will expect that we have responded to these new exciting opportunities as they have arisen.

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DOI:10.1682/JRRD.2010.03.0021