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Regenerative Physiotherapy: Definition, Concepts and Perspectives

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Abstract

The term "regenerative physiotherapy" (RPt) characterizes an emerging and little-known area of physiotherapy aimed at the study, scientific/technological development and application of physiotherapy principles and techniques as an adjuvant to recent approaches in regenerative medicine (RM). Due to the emergence and accelerated advancement of RM, a multidisciplinary science that has been presenting promising and revolutionary results in the treatment of previously untreatable injuries and diseases, "regenerative" physiotherapy has come to represent a powerful complementary alternative, considering that it shares the same regenerative principles and strategies of the newly established area. Recent scientific evidence, based on preclinical research, reinforces the potential of RPt. On the other hand, it also demonstrates the risks associated with the improper use of its techniques. This review aims to briefly explain the definition and basic concepts of physiotherapy and regenerative medicine, providing an update and creating awareness among physiotherapists about the benefits and risks associated with its use.

Keywords: Regenerative Physiotherapy; Regenerative Rehabilitation; Regenerative Medicine; Physical Therapy; Mechanotherapy; Electrophysical Resources; Cell-Based Therapy; Cell Signaling

Introduction

Regenerative medicine (RM) is an emerging area of medicine, with a scientific, technological, and clinical nature, designed to maximize the body's tissue repair process, resulting in more efficient structural and functional restoration levels of damaged tissues and organs [1,2]. Its central strategies are the application of cells, signaling biomolecules, and scaffolds, used alone or in combination, to favorably influence the microenvironment of a lesion site, accelerating and enhancing the pathophysiological intrinsic events of the repair process [3]. Thanks to technological and scientific advances, and promising preclinical and clinical results from the last 3 decades of research, RM has been explored clinically and gradually integrated into the therapeutic arsenal in several areas of medicine [4]. A natural consequence of the growing insertion of RM is the need to identify and characterize the type of interference exerted when associated with conventional therapeutic approaches, ensuring that the benefits achieved by the interference are constructive.

Physiotherapy (Pt) is among the areas impacted by the advancement of RM. Sharing the same objectives as RM (intervening in the repair process to restore the structure and function of tissues and organs) but using mechanical and electrophysical resources, the advantageous possibility of combining the two techniques became evident [5]. The expectation, which has already been scientifically supported, is that the integrative influence of these modalities will provide results superior to those expected from an isolated approach. The insertion of knowledge linked to the principles, methods, and techniques of RM in the context of Pt determined the spontaneous emergence of a new sub-area, regenerative physiotherapy (RPt). The expectation is that the scientific and technological development of RPt, in parallel with the development of RM, will increase the efficacy and therapeutic success of treatments for tissue and organ damage associated with the most diverse pathological conditions [6]. Furthermore, the development of these areas is also expected to establish the limits and restrictions associated with the combined use of therapies, conditions that, if not respected, are potentially critical for patients [7].

Background

Tissue Injury and Repair

Biological tissues have a widely differentiated function conferring a high specificity to the organs and systems they comprise. They have a peculiar structural characteristic, a diverse and specialized cellular contingent immersed in an abundant and complex structure constituted by the extracellular matrix it produces. To maintain the functionality of these organs and systems, the structure of the tissue must be preserved or restored in cases where tissue damage has occurred. Tissue restoration after injury is an inherent phenomenon to all biological tissues, of an intrinsic and spontaneous nature. This process is based on a sequence of highly orchestrated cellular events that result in tissue neoformation. On the other hand, the efficiency of this process concerning the quantity and quality of the tissue formed is not similar, varying from the recovery of the original tissue (regeneration) to the formation of a replacement tissue (healing), with a direct impact on its function [8].

The main determining factors for the efficiency of the tissue repair process include the type and severity of the injury, the intrinsic regenerative potential of the tissue (related to the characteristics of the constitutive cellular contingent), and the influence exerted by external stimuli applied to the tissue during the repair. Unfavorable conditions such as those related to more extensive injuries and/or those manifested in tissues with limited regenerative potential often result in irreversible impairments, significantly impacting quality of life levels even with the conventional therapeutic approaches available. For these cases, science seeks new strategies to improve the therapeutic results [9].

Regenerative Medicine

MR is a contemporary interdisciplinary area of science aimed at scientific and technological advancement applied to medicine. Its main objective is to develop and consolidate principles, methods, and therapeutic techniques capable of maximizing the regenerative process of damaged tissues and organs, restoring their structure and function optimally. It is considered a frontier area of medical science, with the potential to revolutionize therapeutic approaches concerning its ability to provide a definitive cure for certain diseases currently treated only by controlling symptoms.

The basic principle of MR consists of modulating the function of cells involved in the inflammatory and fibroproliferative phases of the repair process, seeking to maximize their function (viability, proliferation, differentiation, and modulation of the microenvironment), and respecting the normal course of intrinsic events to improve the quality of the newly formed tissue. The term MR is highly representative of this principle, aiming at the full reconstitution of the structure of a tissue (regeneration) through specific medical approaches, determining your full functional recovery [10].

To achieve this goal, MR uses 3 basic strategies: cell-based therapy (CBT), signaling biomolecule-based therapy (SBBT), and support-based therapy (SBT), administered alone or in combination.

Cell-Based Therapy

Cell-based therapy (CBT), the most relevant of the MRI strategies, consists of administering healthy cells to an injury site so that they can increase the repair cell contingent. The expectation is that this contingent, now in a higher number, has greater ease in exercising the regulatory functions of regenerative events and tissue repopulation with specialized cells. CBT can involve the use of either differentiated or undifferentiated cells (stem cells - SC) [11].

SCs represent the main source used in CBT, given their exclusive potential for self-renewal (proliferation), cell differentiation, and microenvironment modulation. In synchrony and synergy with the tissue cells, they more effectively reconduct the peculiar events of the initial formation of the tissues (regeneration), enabling the restoration of the original structure and function [12]. The effectiveness of this technique depends on several factors, including the intrinsic repair potential of the target tissue, the source of obtaining the cells (embryonic, somatic, or induced), the number of cells administered, association with other MR strategies (biomolecules and/or scaffolds), association with external stimuli (Pt), and the age and clinical condition of the patient [13].

Signaling Biomolecule-Based Therapy

Cells play a central role in controlling the processes of genesis, maintenance, and repair of tissues and organs. This control depends on a complex mechanism of intercellular communication, enabling an orchestrated cellular action responsible for the success of each process. Among the mechanisms involved in intercellular communication, the chemical one stands out, in which signaling biomolecules produced by the cells, such as growth factors and cytokines, disperse after release and interact with neighboring cells (paracrine or autocrine control) or even at a distance (endocrine), exercising their regulatory functions [14].

In the natural sequence of the repair process, these biomolecules are produced and released in a strictly controlled and orchestrated manner, determining the correct sequence of specific events in each of the phases of repair (inflammatory, fibroproliferative, and remodeling). Aware of the possibility of contributing to this control mechanism, MR proposes the administration of exogenous signaling biomolecules obtained by extraction from the individual (autologous), produced by molecular biology techniques (recombinant molecules), or even by synthetic routes. It is important to note that this contribution, to be effective and beneficial, needs to occur in synergy with intrinsic events [15].

One of the technologies most explored by MR in this topic, already with extensive scientific basis including clinical research, is platelet-derived growth factors (PGF) [16]. PGFs are obtained simply and inexpensively from small samples of the individual's blood. These samples, subjected to different centrifugation protocols for platelet concentration and activation, provide a solution (plasma or serum) enriched with several growth factors. The objective is to make these biomolecules amplify the cellular events responsible for the regeneration process [17,18].

Scaffold-Based Therapy

The extracellular matrix (ECM) is a crucial part of biological tissues. It provides support for cells and is responsible for determining the shape and size of tissues and organs due to its three-dimensional structure. The ECM is made up of basic components such as proteins and polysaccharides, which are produced by the cells themselves. The composition and organization of the ECM vary from one type of tissue to another.

Recent scientific advances have shown that the ECM does not only perform a support function but is also capable of establishing a "dynamic interaction" with resident cells, influencing basic functions such as viability, proliferation, differentiation, and even cell death. Consequently, RM has utilized SBT to enhance the tissue repair process. To this end, it uses biomaterials, of natural or synthetic origin, to create a biomimetic three-dimensional structure that artificially and provisionally reproduces the ECM, conducting, inducing, and guiding regenerative cellular events [19,20].

Physiotherapy

Pt is a branch of applied medical science aimed at studying, maintaining, preventing, and restoring the function of tissues and organs compromised by genetic disorders, trauma, or acquired diseases. Considering the concept that "structure governs function", Pt, to interfere with function, must initially interfere with the structure of the tissues and organs. This interference occurs through external stimuli applications capable of influencing cellular function. To achieve this objective, it uses resources of mechanical [21] (e.g. therapeutic exercises and ultrasound) and electromagnetic nature (LASER and LED photo biomodulation, short waves, and electrical fields) that are assimilated by cells, modulating their functions (viability, metabolism, proliferation, differentiation and synthesis of biomolecules). Examples of the success of this approach, with extensive scientific evidence, are the results achieved by Pt in the treatment of traumatic and degenerative injuries of the musculoskeletal system, such as muscle, tendon, bone, and chondral injuries. In these cases, these external stimuli are expected to maximize the intrinsic cellular events of the repair process, appropriately restoring the structure and, consequently, the function [22].

Regenerative Physiotherapy

RPt is defined by the American Physical Therapy Association as "the integration of principles and approaches from rehabilitation and regenerative medicine, with the ultimate goal of developing

innovative and effective methods that promote the restoration of function through tissue regeneration and repair" [23]. Over the past decade, numerous scientific studies have emphasized the potential of RPt, leading to increased research efforts aimed at advancing methods and techniques for future clinical application, ensuring both effectiveness and safety [24]. Examples of conditions explored by RPt include the use of mechanotherapy (exercise) and/or bio stimulating electrophysical resources (LASER photo biomodulation and ultrasound) after CBT or SBBT approaches in bone, tendon, and muscle repair [24]. The expectation is that the spectrum of conditions benefited by RPt will increase with the scientific and technological progress of this new therapeutic approach. On the other hand, studies also highlight the risks of deleterious effects, reinforcing the need for extensive research before these techniques are routinely applied [5].

It is also worth highlighting the need for adjustments in the training process of professionals interested in working in this area, considering that the principles of RPt are not yet addressed in the professional training process [25].

Conclusion

RPt represents an applied, emerging, and promising science of PT, resulting from scientific and technological evolution and the possibility of convergent integration with the concepts and principles of MR. It is based on the administration of external stimuli of various natures, capable of maximizing the results triggered by MR strategies in search of tissue and organ regeneration. Considering the current level of scientific evidence, RPt should be viewed as a promising science that is still experimental, requiring scientific advancement and professional training prior to the effective implementation of its clinical application.

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Conflict of Interest

The authors have no competing interests to declare that are relevant to the content of this article.

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