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Review Article

Potential Role of Physical Therapy in the Field of Genetic and Cellular Rehabilitation: A Review of Literature

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ABSTRACT

This literature review proposes the future scope of biotechnology & physical therapy in the field of cellular & genetic rehabilitation. Multiple articles were searched using the key words "genetic regeneration", "cellular rehabilitation" on various online search engines. Today a majority of the rehabilitation approaches used clinically are predominantly centered on minimizing an inflammatory response and pain immediately following injury but not working towards scientific ways that can regenerate the lost or damaged muscle. Our ability to restore damaged tissues and organs today relies mainly on interventional approaches. However, with constantly evolving technology, the scientific community needs to engage in interdisciplinary cross-fertilization with an understanding of different tools that can be used to restore tissue functions more holistically.

Key words: genetics, rehabilitation, biotechnology, physical therapy.

INTRODUCTION

This paper proposes the future scope of hybridization of biotechnology & physical therapy in the field of cellular & genetic rehabilitation. Studies have indicated that genetics appear to influence not only risk for disease, but also progression, outcomes and response to rehabilitation interventions. Not only do advances in this genomic era promise to alter our understanding of physiological processes, but these advances also open doors to future medical professions.

The Human Genome Project (H.G.P) was started in 1990 with a goal of identifying all the genes in human body by 2005. The project was completed before time in April of 2003 with 99.99% accuracy unraveling an estimated 20,000- 25,000 genes in the human body. [1] Another such large scale human genome project was HapMap. It was an organization that aimed to develop a haplotype map (HapMap) of the human genome to describe the common patterns of human genetic variation. It started off in 2002 October and completed the set target in October 2005. A haplotype is a group of specific genes within an organism that are inherited together from a single parent. It also refers to the inheritance of a cluster of single nucleotide polymorphism (SNPS) which are variations at a single position in a DNA sequence among individuals. HapMap is used to find the genetic variants affecting health, disease and responses to drugs and environment factors. It has been estimated that there is 99.9% similarity among human DNA sequences, indicating that as species we are remarkably similar in our genetic makeup.

The Human Genome Project and HapMap and many such undertakings have revolutionized developments in medical field. We are now able to take blood, saliva,

hair, or other DNA samples from patients and provide necessary information of medical inheritance, including risk of future diseases. Many medical conditions and impairments dealt by physical therapist have genetic underpinning , including diseases such as stroke, arthritis, heart diseases and cancer to name a few. Studies have shown that genetic factors influence many diseases commonly encountered in clinical practice by physical therapist. For example a study shows that the presence of Trp2 allele in the collagen IX alpha-chain gene (COL9A2) is associated with a 4-fold increase in the risk of developing annular tears at 30-39 years old, and a 2.4-fold increase in the risk of developing degenerative disk disease and end-plate herniations at 40-49 years. [2] Heritability refers to the proportion of total phenotypic variance attributable to genetic factors. Heritability estimates range from 0% (no influence of genes) to 100% (total genetic influence). Family and twin studies show that many common performance measures, impairments and conditions encountered in clinical practice are influenced by genes. These include postural sway (35%), lumbar range of motion (flexion, 64%), trunk flexibility (sit-and-reach, 64%) and grip strength (48%), fast gait speed over 10-meters (16%) and 6 minute walk test (20%). [3]

REVIEW OF LITERATURE

Regulation of gene expression includes a wide range of mechanisms that are used by cells to increase or decrease the production of specific gene products (protein or RNA). Complicated programs of gene expression are widely observed in biology. One such pathway is external trigger, where human body responds to environmental stimuli (stress). Gene expression can be modulated, from transcriptional initiation, to RNA processing, and to the post-translational modification of a protein. Often, one gene regulator controls another, and so on, in a gene regulatory network. In multicellular organisms, gene regulation drives cellular differentiation and morphogenesis in the embryo, leading to the creation of different cell types that possess different gene expression profiles from the same genome sequence. This explains how evolution actually works at a molecular level, and is central to the science of evolutionary developmental biology.

Cancer is the second biggest killer after heart disease in India. More people are dying of cancer than ever before, with cancers accounting for 15% of all deaths in 2013, up from 12% in 1990, reports the Global Burden of Cancer 2013. Breast cancer took the most lives of women, while lung cancer was the biggest cause of deaths in men in India. Doxorubicin (DOX), a quinone-containing anthracycline antibiotic, is a highly effective chemotherapeutic agent widely used in the treatment of solid tumors and hematologic malignancies. Unfortunately, the clinical use of this valuable anticancer drug is limited due to life-threatening side effects. Specifically, DOX treatment can promote heart failure in patients due to a severe dose-dependent cardiotoxicity. In addition, DOX can cause skeletal muscle myopathy that can lead to both respiratory and locomotor muscle dysfunction and impaired quality of life. Several studies have demonstrated that physiological doses of DOX induce a significant elevation of mitochondrial ROS production in cardiac myocytes and skeletal muscle fibers. [4-6] In this regard, it has been reported that DOX stimulates ROS generation by mitochondrial NADH dehydrogenase leading to the generation of a free radical cascade with potent oxidizing potential. Elevated levels of ROS production could activate the forkhead-box O (FoxO) signaling pathway. This amplified FoxO signaling is important because increased FoxO nuclear translocation results in amplified transcription of FoxO target genes [e.g., atrogin-1 (also called muscle atrophy F-box; MaFbx), muscle ring finger-1 (MuRF-1), and BCL2/adenovirus E1B 19 kDa protein interacting protein (BNIP3)] involved in muscle catabolism. Regulation

of FoxO transcriptional activity is complex, but evidence indicates that increased peroxisome proliferator- activated receptor-gamma coactivator-1 alpha (PGC-1expression can protect myocytes by inhibiting FoxO transcriptional activity. It has been shown that endurance exercise training is an effective intervention for protecting both heart and skeletal muscle from DOX-induced damage. Nonetheless, the specific mechanisms responsible for exercise-induced protection against DOX-induced cardiac and skeletal muscle atrophy remain unknown. [7,8]

Common epigenetic changes induced by exercise also include histone modifications, such as methylation and acetylation, DNA methylation and expression of different types of microRNAs (miRNAs). Histone acetyltransferases (HATs) and histone deacetylases (HDACs) are enzymes that regulate DNA acetylation, with HATs adding acetyl groups and HDACs removing them from DNA. Histone lysine acetylation is a reversible process which is associated with the transcriptional activation. DNA methylation is also a reversible epigenetic process which is catalyzed by a family of DNA methyltransferases (DNMTs). These enzymes add a methyl group, through a covalent modification, primarily on CpG dinucleotides. The CpG island is a short stretch of DNA in which the frequency of the CG (Cytosine-guanine) sequence is higher than other regions. It is also called the CpG island, where "p" simply indicates that "C" and "G" are connected by a phosphodiester bond. The presence of multiple methylated CpG sites in CpG islands of promoters causes stable silencing of genes. Silencing of a gene may be initiated by other mechanisms, but this is often followed by methylation of CpG sites in the promoter CpG island. In cancers, loss of expression of genes occurs about 10 times more frequently by hypermethylation of promoter CpG islands than by mutations, but this methylation also cause activation of certain metabolic genes. However, the promoter demethylation and the activation of associated genes depend on the intensity of the exercise; high intensity exercise causes a reduction in the promoter methylation of genes such as peroxisome proliferator-activated receptor gamma (PPAR-γ), coactivator 1 alpha (PGC-1a), transcription factor A mitochondrial (TFAM), pyruvate dehydrogenase lipoamide kinase isozyme 4 (PDK4) and MEF2A, immediately after exercise, as well as a reduction in the promoter methylation of peroxisome proliferator-activated receptor delta (PPAR-δ), 3 hours after exercise. [9,10]

In addition, exercise can lead to changes in the action of cytosolic messengers such as Ca2+ and AMP, both in humans and mice, which result in the activation of signaling cascades and eventually to alterations in gene transcription. These alterations occur through the activation of Ca2+/Calmodoulin-dependent protein kinase (CaMK) and AMP-dependent protein kinase (AMPK). AMPK can change the expression of genes, such as the glucose transporter type 4 (GLUT4) and mitochondrial genes, by activating cellular transcription factors and coactivators in mammalian skeletal muscle in type 2 diabetic patients. [11,12] Thus, exercise may have a beneficial effect on the prevention and confrontation of type 2 diabetes and other metabolic disorders. .

It is well known that exercise is associated with inflammatory responses, the methylation of its CpG island surrounding exon is inversely correlated with ASC protein expression. [13] It has been shown that chronic moderate exercise up-regulates the methylation status of ASC (Apoptosis-associated speck-like protein containing a caspase recruitment domain), resulting in a decreased activity of the gene in human monocytic cells and, thus, preventing the activation of inflammatory cytokines, such as interleukins and tumor necrosis factors (TNF). [14] Thus, exercise can protect the cell from an inflammatory environment,

which could favor carcinogenesis or the development of several age-related diseases. Changes in individual miRNAs result in multiple effects, such as interactions between different types of miRNAs and a greater T-cell responsiveness along with reduced susceptibility to infection, regulation of toll-like receptors (TLRs) in monocytes and T-regulatory lymphocytes and down-regulation of DNA methylation in CD4+ T-cells. All these effects are induced by exercise and can alter the pathogenesis and progression of diseases, such as systematic lupus erythematosus and rheumatoid arthritis. [15,16] The response of immune cells to physical activity is of growing interest because some of the key health effects of exercise, both beneficial (e.g., reduction of cardiovascular disease risk) and detrimental (e.g., exercise- induced asthma), may well be mediated through the activity of circulating leukocytes. In humans, relatively brief episodes of exercise can activate neutrophils, but the ultimate impact of exercise on neutrophil function varies and depends on the duration and intensity of the exercise challenge. An intriguing emerging aspect of neutrophil biology is the mounting data that these cells play a role in tissue repair, remodeling, and growth. Neutrophils act as an elegant paracrine type of hormonal system - the cells are attracted from the central circulation to a specific tissue (e.g., a wound or injured muscle) and then are induced to secrete mediators that impact tissue growth. In many cases, such as exercise-induced asthma, anaphylaxis, and chronic diseases like arthritis, there is mounting evidence that neutrophils play a pathologic role. Several studies had shown that TBX21 and Gata 3 have been associated with an asthma or atrophy phenotype. [17] This subset of neutrophil genes that are both influenced by exercise and altered in disease states may prove as useful targets for further investigations into how physical activity acts to prevent or exacerbate disease. [18]

Studies have demonstrated that high-intensity interval training (HIT) induces numerous physiological adaptations that resemble traditional endurance training, despite a low total exercise volume. [19] For example, 2 weeks of HIT was similar to 2 weeks of endurance training leading to increase in exercise performance as well as the maximal activity and protein content of the mitochondrial enzyme cytochrome-c oxidase (COX). [20] Low-volume HIT has also been shown to promote improvements in markers of metabolic control and vascular endothelial function which are comparable to endurance training. HIT is a potent and time-efficient strategy to induce skeletal muscle metabolic adaptations and improve functional exercise capacity. Low-volume HIT may represent an alternative to endurance training to improve metabolic health and reduce the risk for chronic diseases, in times where lack of time for exercise is an issue.

There are multiple mechanisms by which physical activity promotes health; however, recently there has been an interest in defining the contribution of circulating proteins secreted by skeletal muscle, called as the myokines. They are autocrine, paracrine, or endocrine stimuli that may guide local skeletal muscle remodeling, repair, and maintenance or steer systemic adaptation related to physical activity. A subset of myokines whose production and secretion into systemic circulation are stimulated by physical activity, have shown to modulate skeletal muscle and systemic metabolism, angiogenesis, growth, and inflammation. [21]

Aging is a natural process that is usually associated with numerous pathologies and homeostatic deregulations. It is known that epigenetic mechanisms are involved in the pathogenesis of some of the age-related diseases. Studies have shown that a general demethylation pattern, causing genomic instability, is associated with the aging process. The essential role of microRNAs in the aging process has been also indicated, in regard to the manifestation of many pathological situations. [22] Furthermore, aging is usually associated

with great shortening of telomeres that can lead to cellular damage. Telomeres are sequences of nucleotides at the ends of chromosomes that protect their integrity and are shortened with each successive cell division. It has been shown that telomeres are transcribed in order to express non-coding RNAs that may regulate telomere length and chromatin status, indicating that epigenetic modifications can alter telomeres' length. There are studies, both in animal models and in humans, suggesting that physical exercise is an inducer of telomerase activity and gene transcription, coding for proteins that stabilize telomeres, through epigenetic mechanisms. Another family of molecules related to aging is sirtuins. Sirtuins constitute a highly conserved family of proteins with a possible key role in cell survival, since they are associated with a variety of cellular functions, such as cell cycle regulation, cell survival and life span extension. [23] Sirtuins not only deacetylate histones and several transcriptional regulators in the nucleus, but also modulate specific proteins in the cytoplasm and in mitochondria. Studies have shown that chronic exercise training may reduce the expression of pro inflammatory cytokines through epigenetic modifications and, therefore, help against chronic inflammatory diseases. Lastly, although aging is usually related to increased frailty, as a result of the aging of muscles, however, epigenetic mechanisms induced by exercise regulate the expression of myogenic regulatory factors, such as Myogenin, MyoD, Myf5 and MRF4, which are associated with muscle atrophy prevention and muscle growth. [24,25]

Various studies in the last few years have revealed new evidence that strongly indicate an important role of exercise on brain plasticity and cognition. Effects of exercise are mainly mediated through the actions of brain-derived neurotrophic factor (BDNF), a neurotrophin which is highly expressed in hippocampus and contributes to neuronal development. [26] It has been shown that BDNF is associated not only with the effect of exercise on brain plasticity, but also is involved in neuronal excitability, and particularly in the functions of learning and memory. Moreover, it can act as a mediator between metabolism and brain plasticity, because it is regulated by protein molecules, such as AMPK, which have shown to be up-regulated by physical exercise in rats. Researches have shown that physical exercise alleviates the symptoms of ADHD. It has been previously indicated, that it has a beneficial effect on remodeling the chromatin region which contains BDNF gene, making it accessible to the indispensable transcriptional factors and, thus, inducing the expression of BDNF. In this way, physical exercise, regardless of its type (i.e., endurance or resistance exercise), can partially restore the decreased levels of BDNF, improving both the neurobehavioral deficits and the biomarkers associated with ADHD. [27,28] With regard to the REM sleep deprivation, exercise increases synaptic integrity and neuroplasticity in the brain, and simultaneously improves memory, learning and stress responses.

Physical exercise exerts also a great impact on cardiovascular system. The molecular mechanisms that promote the necessary cardiovascular adaptations include an increase in free radicals in association with improved antioxidative activity, alterations in the composition and the architecture of the extracellular matrix, and epigenetic modifications. It has been shown that epigenetic modifications caused by physical exercise regulate the activity of genes which are responsible for the expression of pro-inflammatory cytokines, such as the ASC gene, the methylation of which is increased by exercise. Deregulation of HAT/HDAC ratio, or of their function, can also lead to modified expression of matrix metalloproteinases (MMPs), which are related to pathological alterations of vascular walls, to altered proliferation of endothelium myocytes in heart and vessel, and even to lethal cardiomyopathy. Regular physical exercise can have a protective role against cardiovascular diseases, by restoring

HAT and HDAC activity to the normal condition, and by regulating these epigenetic mechanisms. Exercise training causes a non-pathological increase of the myocardial mass, resulting in cardiac hypertrophy and neo-angiogenesis – "the athlete's heart". During the exercise-induced cardiac hypertrophy, new sarcomeres are added both in parallel and in series, increasing the length of the cardiac cells. This results in an increased ventricular stroke volume and cardiac output, which improves aerobic capacity. It has been shown that aerobic exercise training modulates numerous miRNAs, which in turn regulate their target mRNAs and, thus, provoke the physiological cardiac hypertrophy, through different signaling pathways. [29]

ROLE OF PHYSICAL THERAPY IN CELLULAR REGENERATION

Advances in regenerative medicine allow for the restoration of injured, diseased, or degenerated tissues to a more functional state. These therapies are particularly important to the field of Physical Therapy as they strive to improve an individual's functional capacity, which is often limited by persistent deficits stemming from processes such as scar tissue deposition, reduced muscle mass or loss of innervation. By partnering with technologies that regenerate tissues (including bone, muscle, cartilage, ligaments, and nerves), therapists-through rehabilitation-may be able to increase the functional gains made by patients following injury or disease, and ultimately improve their quality of life.

Vibration and compressive loads are mechanical stimuli that have a powerful influence on biological tissues. Studies in animal models demonstrate that certain types of mechanical load regulates bone, fat , skeletal muscle and nerve tissues. [30] In addition, it is also well known that "over exposure" to mechanical stimuli is damaging to tissues. The underlying need to study the value of therapeutic stress in humans is well grounded in the literature. For example, Wolff's law supports that bone tissue (osteocytes) exposed to high loads triggers osteogenesis. [31] Subsequent studies verified that exerting high strain in a dynamic fashion to bone tissue was more effective than delivering a sustained strain. For many years, the dynamic delivery of high stress to bone was considered the primary mechanical method to up-regulate osteogenesis. Localized limb vibration modulates several central nervous system and muscle signaling pathways in people with and without spinal cord injury. [32,33] Research has also shown that deficiencies in postural control are associated with brain activity during localized vibration of the foot. [34] However, at present there are no existing devices that can provide isolated mechanical loading to a human limb by delivering controlled vibration and/or compression. Many of the existing devices for humans are commercial vibration platforms that are inherently noisy and typically used for whole body vibration and not localized vibration.

In another study, muscle contractions consistently increased the expression of transcription factors: peroxisome proliferator-activated receptor gamma, coactivator 1 alpha(PGC-1α), nuclear receptor subfamily 4 group A member (NR4A3), interferon-related developmental regulator (IFRD1), actin binding Rho activating protein(ABRA), early growth response (EGR1), and myostatin (MSTN). [35] These genes are linked to regulating oxidative metabolism (PGC-1α and (NR4A3), mitochondrial dynamics (IFRD1), and muscle hypertrophy (ABRA and EGR1), while suppressing a potent regulator of muscle atrophy (MSTN). In yet another study, active muscle exercise repressed MSTN to a greater degree than that of vibration. [36] Based on the findings from the study, regulating the MSTN gene would be most effective if the stress was induced through active muscle exercise rather than using a vibration plate. However, if the individual is unable to activate their skeletal muscle (CNS injury) or they are

restricted from activating the muscle (fracture, surgery, ligament repair), vibration may provide an alternative method to regulate MSTN and potentially attenuate skeletal muscle atrophy. Passive vibration may offer a unique mechanical stimulus to influence the skeletal muscle phenotype. An interesting finding from the study was that whole-body heat stress suppressed the expression of PGC-1α. PGC-1α is down regulated in skeletal muscle in people with long-standing diabetes and correlated with a shift from an oxidative muscle to a glycolytic muscle. [37] The short-term suppression of PGC-1α because of heat stress may indicate a shift in substrate utilization at the skeletal muscle level. In support of this view, skeletal muscle blood flow decreases and shunts the blood to the skin capillary beds to attenuate core body temperature. Recent works by scientists support that blood glucose increases after passive whole body heat stress. Thus, whole body heat stress may trigger the exact opposite of what typically occurs with long duration exercise. That is, during exercise, an increase in PGC-1α regulation inhibits glucose oxidation to favor fatty acid oxidation and glycogen synthesis. Conversely, during heat stress, there is a decreased need for ATP in the skeletal muscle that may trigger a less efficient energy utilization strategy. It is proposed that a shift in substrate utilization may trigger a more suitable environment for muscle repair after muscle damage from exercise or disease processes. Skeletal muscle repair, including proliferation of satellite cells, may depend on the energy utilization state of the skeletal muscle. The duration and intensity of heat stress (dose) on skeletal muscle recovery after injury are important areas for continued examination. Understanding optimal methods to support skeletal muscle health, using non-pharmacologic interventions, will be instrumental in identifying new regenerative medicine rehabilitation protocols in the future.

Muscle injury, defined as "a prolonged impairment of the ability of a muscle to produce force", 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 human models and consist of degeneration, inflammation, regeneration and fibrosis. [38] 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 re-injury, and decrease functional capacity. As long as the scar persists, complete muscle regeneration is not possible. 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. 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 non-steroidal anti-inflammatory 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. [39] Muscle stem, or satellite, cells are localized to the myofiber periphery, and under the stress of injury, these normally quiescent cells become activated to regenerate damaged myofibers. 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. [40,41] Circulating factors typical of aged microenvironment drive the differentiation of muscle stem cells from a myogenic-to-fibrogenic lineage, 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. 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. The rejuvenation of the aged skeletal muscle niche may be a pre-requisite to the successful transplantation of stem cells for the treatment of skeletal muscle injuries. [42] In addition, 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. Studies have demonstrated that the application of targeted muscle contraction protocols enhances molecular, cellular, and tissue functioning. 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 anti-aging effect of exercise is critical if we intend to put this tool to good use.

Limitations

Cross-hybridization of biotechnology and physical therapy 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. The challenges that lie for both the fields are many. Some of the greatest concerns regarding the use of genetics in medicine and healthcare surround the possibility that genetic information may be used for discriminatory purposes. But carrying out researches taking a wider prospective help us understand the limits of human exercise capacity that can lead to the development of treatments for a range of diseases like cancer and cardiovascular disease. There exist almost no common medium of communication between the two fields. Both speak and comprehend different medical and scientific language. This makes taking up of research work difficult for both the parties. Also, most of the studies done previously have been conducted on animals. Thus, validity and reliability of such studies on humans is still uncertain. Ethical clearance for human trials is also a challenging task for the researchers. Lastly, awareness of possible roles of hybridized biotechnology and physical therapy is very minimal within both the fields. Investigating genetics, acknowledge a public concern about genetic research and scientists need to engage in public in debates about the potential benefits of their researches.

DISCUSSION

Recently, an international team of scientists at Baylor College of Medicine, The Telethon Institute of Genetics and Medicine in Naples, Italy and other institutions have discovered that the gene TFEB is a major regulator of muscle function during exercise. [43] The functions of this gene include those involved in

glucose use, insulin sensitivity and function of the mitochondria. This work may lead to the design of future treatments for conditions such as diabetes, obesity and metabolic syndrome. The study appeared in Cell Metabolism. Another study discovered circadian clocks in muscle tissue that control the muscle's metabolic response and energy efficiency depending on the time of day. [44] According to the study, the capacity for a muscle cell to perform its most important functions, to contract, vary according to the time of day. When the scientists manipulated the clock genetically in nocturnal mice, they noticed there were profound abnormalities in the muscle. Since these genes also exist in humans, this suggests humans may also be able to respond better to exercise during the daytime. The muscle clocks control the metabolic response by interacting with proteins called HIFs that change metabolism when oxygen concentrations get too low in order to allow muscle cells to continue to make energy.

Similar to this, an Australian company has already offered the first genetic performance test (for the ACTN3 gene) which has been linked to sprint and power performance. [45] The report authors highlight two dangers of genetic performance tests. Firstly, Not all people may want to know, while young that they are at increased risk of cancer by early middle age, but they might inadvertently become aware of that just because they had a sport gene test. Secondly, genetic performance tests can be performed even before birth and this may lead to the selection of foetuses or to abortions based on athletic potential.

While advances such as tissue-engineered bladders and vascular grafts are the headline-grabbers of regenerative medicine, far more common is a simpler procedure involving injections of platelet-rich plasma (PRP). The procedure, involves a series of injections of a patient's own blood after it has gone through a multistage centrifugation process that increases platelet concentration to 5-8 times its normal level. Once administered, the PRP simulates an injury at the site of the injection, which in turn triggers the body's healing response. APTA defines regenerative rehabilitation 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. [46]

CONCLUSION

Multiple studies have shown the potential role of physical exercises in regulation of genes. Rehabilitation science and biotechnology will be critical in the success of any rehabilitative therapy and in counteracting the epidemic of lifestyle disorders. We propose that further researches should be undertaken in the field of cellular rehabilitation. The power of combining emerging technologies and new knowledge in both disciplines could be transformative for patients with previously untreatable disorders or injuries. The scientific community needs to engage in this interdisciplinary cross-fertilization of biotechnology and physical therapy with an understanding of different tools that can be used to restore tissue function.

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