Send Orders for Reprints to reprints@benthamscience.net

464 *Current Genomics,* **2020**, *21*, 464-477

REVIEW ARTICLE

Updated Understanding of the Degenerative Disc Diseases - Causes Versus Effects - Treatments, Studies and Hypothesis

Cristian Muresanu[1], Siva G. Somasundaram[2], Margarita E. Neganova[3], Elena V. Bovina[3], Sergey V. Vissarionov[4], Okom N.F.C. Ofodile[5,6], Vladimir P. Fisenko[7], Valentin Bragin[8], Nina N. Minyaeva[9], Vladimir N. Chubarev[7], Sergey G. Klochkov[3], Vadim V. Tarasov[7], Liudmila M. Mikhaleva[10], Cecil E. Kirkland[2] and Gjumrakch Aliev[3,7,10,11,*]

[1]Romanian Television, TVR Cluj, 160 Donath Street, Cluj-Napoca, CJ 400293, Romania; [2]Department of Biological Sciences, Salem University, Salem, WV, USA; [3]Institute of Physiologically Active Compounds Russian Academy of Sciences, Chernogolovka, 142432, Russia; [4]Department of Spinal Pathology and Neurosurgery, Turner Scientific and Research Institute for Children's Orthopedics, Street Parkovskya 64-68, Pushkin, Saint-Petersburg, 196603, Russia; [5]Center for Cardiovascular Research (CCR), Institute of Pharmacology, Charite, Universitaetsmedizin Berlin, AG: Theuring, Hessische Strasse 2-4, D-10115 Berlin, Germany, [6]Obie-Medical Corporate International LTD., Academic Section, 28 Oranye Street (American Quarters), Onitsha, Anambra State, Nigeria; [7]I. M. Sechenov First Moscow State Medical University (Sechenov University), Trubetskaya Str., 8, Bld. 2, Moscow, 119991, Russia; [8]Stress Relief and Memory Training Center, 3101 Ocean Pkwy, Suite 1A, Brooklyn, NY, 11235, USA; [9]National Research University Higher School of Economics, 20 Myasnitskaya Street, Moscow, 101000, Russia; [10]Research Institute of Human Morphology, 3, Tsyurupy Str., Moscow, 117418, Russia; [11]GALLY International Research Institute, 7733 Louis Pasteur Drive, #330, San Antonio, TX 78229, USA

ARTICLE HISTORY

Received: July 25, 2019
Revised: August 20, 2019
Accepted: March 16, 2020

DOI:
10.2174/1389202921999200407082315

Abstract: ***Background*:** In this review we survey medical treatments and research strategies, and we discuss why they have failed to cure degenerative disc diseases or even slow down the degenerative process.

***Objective*:** We seek to stimulate discussion with respect to changing the medical paradigm associated with treatments and research applied to degenerative disc diseases.

***Method Proposal*:** We summarize a Biological Transformation therapy for curing chronic inflammations and degenerative disc diseases, as was previously described in the book Biological Transformations controlled by the Mind Volume 1.

***Preliminary Studies*:** A single-patient case study is presented that documents complete recovery from an advanced lumbar bilateral discopathy and long-term hypertrophic chronic rhinitis by application of the method proposed.

***Conclusion*:** Biological transformations controlled by the mind can be applied by men and women in order to improve their quality of life and cure degenerative disc diseases and chronic inflammations illnesses.

Keywords: Biology, biological transformations, genome, mitochondria, degenerative disc disease, neurology, seminal secretions.

1. INTRODUCTION

Domenico Felice Antonio Cotugno reported the earliest research on lumbar disk hernia in the late 18th Century. His seminal work stimulated research by several French and German neurologists.

However, treatments were undertaken only in the beginning of the 20th Century, notably by Hermann Oppenheim and Fedor Krause. They performed surgical procedures on disc hernias that are followed even today [1]. Contributing to the increasing prevalence of disc herniation is greater life expectancy, which has risen to new heights: almost double since the Middle Ages [2].

Concomitantly, the number of Degenerative Disc Disease (DDD) cases have increased throughout the world and warrant immediate, sustained attention. The costs of healthcare for DDD in the United States alone total more than $90 billion dollars annually [3]. UK costs exceed £251 million pounds annually. Australia spends more than 9 billion dollars per year [4-6].

*Address correspondence to this author at the GALLY International Research Institute, 7733 Louis Pasteur Drive, #330, San Antonio, TX, 78229 USA; Tel: +440-263-7461; E-mails: aliev03@gmail.com and cobalt55@gallyinternational.com

The main problem associated with DDD has been presented as a chart in Fig. (**1**). The vertical scale is from macroscopic to nanoscopic and, finally, to invisible. The problems seen on the body level are generated at the tissue level. In turn, tissue level changes are generated by the extracellular level, which is a result of an outcome of intracellular changes. Molecular level changes modify the intracellular changes.

Molecular level changes may be affected by potential mind-level changes, which are invisible and can only be inferred. Thus, the complexity of DDD justifies the unusual object of study since DDD has implications in clinical, biochemical, histochemical and immunological investigations.

More unknown causes of DDD could be investigated due to the advancement of modern diagnostic technology. In this review, attempts have been made to introduce new enhanced physiology of the body, which is capable of creating a self-healing mechanism.

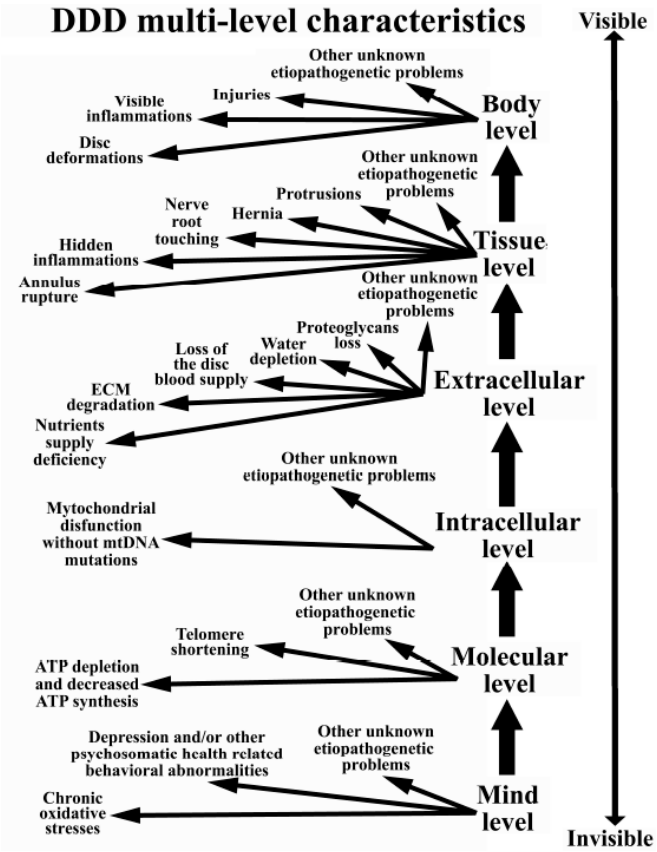

Fig. (1). Multilevel characteristics of degenerative disc diseases.

2. THE CAUSE AND EFFECT CHAIN IN DEGENERATIVE DISC DISEASE

Fig. (**2**) illustrates the chronological history of the cause and effect chain, proposed medical treatments, and research strategies for DDD. These have been common in various combinations for the past 100 years.

All vertical black arrows indicate a cause-effect pair, for example (b) pointing toward (a), (c) pointing toward (b) and so on. In reality, none of these are proved to be the ultimate cause of DDD: they remain unsolved or unknown. However, from a didactical point of view, there is a need to elaborate some causal or correlational relationships to help guide medication and other treatments. All horizontal gray arrows, from right to left, indicate the known or proposed strategies. All horizontal black arrows indicate the effects coming from one single method, named Biological Transformations Controlled by the Mind (BTCM), based on a single case published study [7].

2.1. The Present Conventional Treatments Problem of the Degenerative Disc Disease

In the past century, surgery has been the most common treatment for advanced stages of DDD. In Fig. (**2**), surgery is shown as number (1), along with physiotherapy and electrotherapy. These can be categorized as invasive and noninvasive methods, respectively. Noninvasive methods are less effective and require long-term use. Invasive methods are fast and more effective, but they also entail some risks and side-effects.

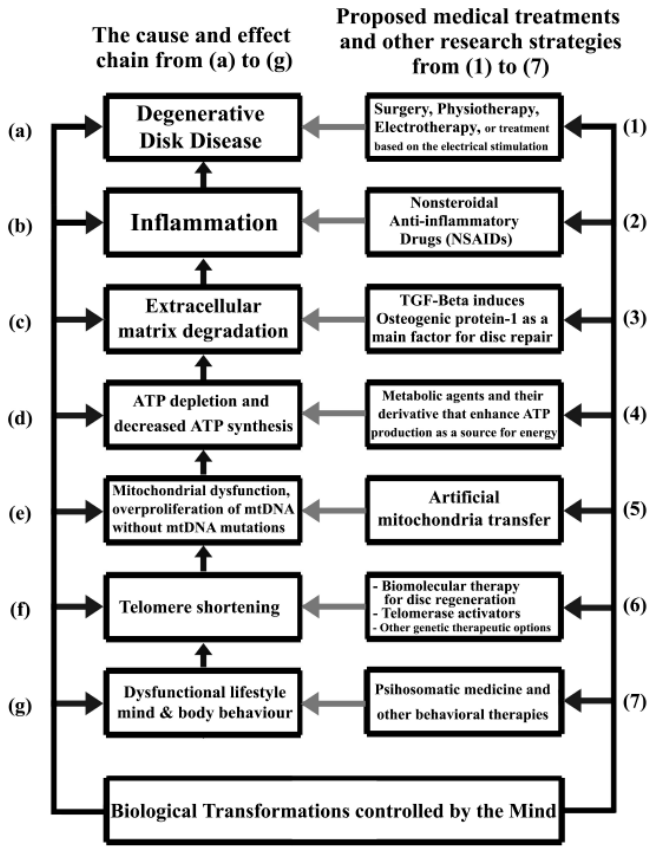

Fig. (2). The influence of biological transformations controlled by the mind over the cause and effect chain, from (**a**) to (**g**), in Degenerative Disc Disease, and the known medical treatments and other research strategies, from (**1**) to (**7**).

2.1.1. Invasive Methods

Surgical procedures include, without limitation, surgical implants, total disc replacements, devices for intervertebral assisted motion, disc arthroplasty, lumbar spine fusion, and so forth.

Some studies have highlighted the effects of psychosocial factors on pain levels and depression before and after sur-

gery in patients with degenerative lumbar and cervical vertebral disc disease [8]. We conclude that there is an association between social and demographic factors, pain perception, and depression that may persist despite surgical treatment for degenerative vertebral disc disease [8].

It is known that, even if surgery is considered successful, postoperative infections or allergic reactions to anesthesia are causes of increased morbidity, mortality, and cost [9]. Another study indicated that the extent of preoperative depression in patients is a predictor of functional outcome and patients' dissatisfaction, which is especially significant after revision surgery [10, 11].

There had been reported post-surgery complications, such as broken titanium screws that can irritate the nerve root or penetrate the endplate [12]. Researchers reported that more than 10% of cases had post-surgical complications, out of a population of 2233 consecutive patients treated for subaxial cervical disorders.

Other studies related to lumbosacral post-surgical complications revealed that the most common problems were late-onset discomfort or pain related to a pseudarthrosis or perhaps to the screws. These were associated with 1102 (23.0%) of the screws, used in 222 (24.3%) of the procedures. The symptoms necessitated the removal of the instrumentation with or without repair of the pseudarthrosis. A pseudarthrosis was found during 46 (20.7%) of the 222 procedures [13].

When surgery has been performed near the spine and spinal cord, there are other kinds of post-surgical complications that can be serious. Examples include thrombophlebitis (blood clots forming following many types of surgical procedures); hardware fracture of metal screws, plates, and rods before complete healing; implant migration; spinal cord injury during surgery; sexual dysfunction; pseudarthrosis' and many others [14].

In advanced stages of DDD, conventional surgery does not stop or even retard intervertebral disc degeneration. In simplest terms, it does not cure the disease. After performing a surgical intervention on a pair of degenerate discs, other discs may begin to show degenerative signs and often undergo degeneration. Finally, none of the known invasive medical procedures cure DDD.

2.1.2. The Noninvasive Non-pharmacological Methods

The group of noninvasive non-pharmacological methods is known as physiotherapy and includes a diverse array of rehabilitation techniques. Electrical stimulation therapies are used to calm pain and stimulate muscles to prevent atrophy. The most common electrotherapies are ultrasound therapy (however, analgesic effect of ultrasound is still under discussion [15]), electrical muscle stimulation, neuro-muscular electrical stimulation, and transcutaneous electrical nerve stimulation [16].

None of these methods cure DDD. Their effect is focused on pain relief. The International Association for the Study of Pain had been created for the specific propose of focusing worldwide research on pain management, especially musculoskeletal pain. One of the most common causes of musculoskeletal pain is nerve root compression during lumbar disc herniation, often accompanied by fibrous ring rupture and nucleus pulposus herniation.

All previously mentioned methods can reduce the pain degree, relieve the clinical symptoms and signs, improve the peripheral ROS level, and prevent the oxidative damage of myocardial tissues and other complications [17].

Other physical therapies, based on the use of mechanical force and movement (bio-mechanics or kinesiology), manual therapy, exercise therapy, and others can improve mobility. With the associated improved function, these are known to have positive effects on patient quality of life.

Statistical studies highlighted high levels of satisfaction with all components of physiotherapy treatment, except cost. Patients otherwise provide valuable feedback regarding their physiotherapy treatment for musculoskeletal pain [18].

This outcome should not be overestimated because in other cases physical therapists encounter patients who are competent but reluctant to mobilize. This situation leaves the physical therapist in an ethical dilemma: either accept the patient's right to refuse treatment or utilize other strategies (likely known to be less effective) to encourage the patient to follow a treatment plan [19].

Other manual therapies for pain relief include chiropractic manipulation and massage. Results depend upon the advancement of DDD. Success is more likely in an early stage of DDD. Sadly, most patients are not aware of the early signs of DDD onset and do not have routine medical checkups. Despite various efforts to improve diagnosis and best healthcare procedures, and despite lifespan increases, lower back pain has not been cured.

The positive effects of manual and mechanical therapies have been overestimated worldwide, as evidenced in popular and peer-reviewed articles. The word "cure" is not claimed. Instead, treatment is focused on symptoms, not on the underlying disease process. Absent curing the disease, symptoms invariably return sooner or later. The literature does not have sufficient analytical or methodological studies for manual therapies. The longer the use of manual therapies, the less effective and beneficial they are on the patient's life [20].

Some scientists have used meta-analysis to compare the effectiveness of manual therapies in treating low back pain. They concluded that, of 84% acute pain variance, 81% was from nonspecific factors and 3% from treatment. No treatment for acute pain exceeded placebos effectiveness [21].

This lack of effect does not preclude the use of manual therapies on DDD patients because the same study notes that treatments serve to motivate, reassure, and calibrate patient expectations. Thus, manual therapies may reduce medication and augment self-care. Exercise with authoritative support is an effective strategy for acute and chronic low back pain [21].

An important problem in approaching low back pain is the lack of clear diagnosis. Some researchers believe that the treatments offered to the patients tend to produce small effects, often only in the short-term, and none appear to be effective with respect to long-term prognosis [22].

However, DDD is not inevitably degenerative in all cases. The Institute for Chronic Pain presented several cases of DDD that indicate disc herniation may not occur with the passage of time, even if the patients fail to get better. This finding is contrary to what is expected, namely that the condition becomes more problematic. It has been found that the larger the disc herniation, the more it reduced [23]. A significant percentage of DDD patients without back pain did not get worse, while DDD often progresses in those with back pain.

Additionally, lumbar-related endplate changes are part of the DDD category. It has been observed that in few cases, patients with significant changes visible on magnetic resonance imaging (MRI) did not get worse; in a few cases, DDD even reversed back to normal [24-26]. These interesting findings should stimulate more research, despite the few or single cases because they might unlock a regenerative mechanism. Cases like these could help us understand DDD and how to cure them, instead of reducing symptoms.

2.2. The Chronic Inflammation Problem in Degenerative Disc Disease

About 2,000 years ago, Celsus, a Roman encyclopedist, defined inflammation in terms of calor, dolor, rubor, and tumor (heat, pain, redness, and swelling). Virchow added disturbance of function, *functio laesa*.

In their quest for a cure for DDD, scientists have found that degeneration of an intervertebral disc releases inflammatory proteins. These proteins, in turn, cause irritation of the surrounding nerves of the intervertebral disc. Although acute inflammation is a healthy response, it should subside in a few days. Anything longer than that is considered to be chronic inflammation and is a sign that the body is not healing properly [27].

Despite common knowledge that inflammation is not a cause of DDD, millions of patients are treated with at least three pharmaceutical groups of drugs. The first group is known as Nonsteroidal Anti-inflammatory Drugs (NSAIDs). These NSAIDs, such as Diclofenac, Ketonal, Voltaren, Ibuprofen, Piroxicam, and Naproxen, are known to have positive effects on pain relief, but long-term use has potential drawbacks, including risks of cardiovascular, gastrointestinal, and kidney problems [28].

For long-term use, NSAIDs are often prescribed with muscle relaxants, such as Clorzoxazone, Lorzone, Parafon Forte DSC. This group of drugs exhibits side effects, such as drowsiness, malaise, light-headedness, fainting, blurred vision, confusion, nausea, urinary retention, and gastrointestinal bleeding [29].

The third group of medications often is added to prevent or reduce the side effects of the first two groups. These act as gastric bandages. Examples include Ranitidine, Zantac, and Nizatidine. Ranitidine reduces the amount of acid secreted by the stomach, which may prevent stomach ulcers caused by NSAIDs [30]. Again, long-term therapy may induce other side effects such as constipation, diarrhea, dizziness, drowsiness, headache, nausea, trouble sleeping, and vomiting [31-34].

Moreover, taking these drugs will neither cure nor slow the progression of DDD. Their long-term side effects may create other health problems. While none of these drugs have negative health effects in the short-term use, DDD patients, especially those suffering from severe low back pain, may take them daily for months or years. In some cases, their effectiveness as pain relief diminishes over time. Long-term use has been shown to be harmful in several other cases, not just DDD.

Analyzing (Fig. **2**), we conclude that DDD is currently treated using the methods labeled in rectangles (1) and (2). A direct approach is indicated within the rectangle (1) and an indirect, purely symptomatic approach is indicated within the rectangle (2). The arrow pointing towards rectangle (b) is associated mainly with reducing inflammation.

2.3. Extracellular Matrix Degradation in Degenerative Disc Disease

It is a fundamental tenet of medicine that the sooner a problem is detected, the greater the chance of healing is. As advanced medical imagistic techniques were developed, scientists began to explore cellular behavior within the intervertebral discs. In DDD cases, chronic inflammation is commonly observed, but inflammation does not lead to DDD, as noted above.

The third level of medical approach indicated in Fig. (**2**) relates to extracellular matrix (ECM) degradation. Some theories postulate that DDD is a natural process associated with aging. However, there are far too many cases of younger patients with DDD. In addition, the multi-level characteristics of this process demonstrate acceleration greater than aging alone.

The main problem of ECM degradation in DDD is the loss of mechanical properties of the collagen network. This results in the impairment of the *anulus fibrosus* (AF) to resist forces delivered by compression of the disc [35].

Intervertebral disc degeneration also leads to the loss of disc matrix material, loss of chondrocyte-like cells of the nucleus pulpous (which leads to reduced structural integrity), hydration modification, decreased mechanical capacity, angiogenesis, and innervations modifications associated with the decrease of disc height, producing pain. The pain, in turn, reduces the patient's quality of life [36-39].

These points notwithstanding, ECM degradation is not beyond self-healing. Studies have shown that herniated discs from patients of various ages are able to produce vimentin, a structural protein responsible for maintaining cell integrity. If the cells from AF and nucleus pulposus (NP) are vimentin immune-positive, then the self-healing mechanism of the disc cells is producing oxytalan fibers to replace the disrupted elastic fibers. It had been demonstrated that injured intervertebral discs have endogenous resources that can stem the DDD progression by using oxytalan fibers. In addition, the induction of apoptosis suggests an increased cell turnover in response to repair needs [40].

Another cause for ECM degradation is the long-term lack of nuclear paraspeckle assembly transcript 1 (NEAT1) gene expression in the NP cells. According to several scientists,

the NEAT1-induced ECM degradation may involve ERK1/2-MAPK (mitogen-activated protein kinases, originally called ERK, extracellular signal-regulated kinases) signaling. NEAT1 produces a long non-coding ribonucleic acid (LncRNA). Thus, NEAT1 and LncRNA may represent a novel molecular target for intervertebral disc degeneration treatment by preventing NP ECM degradation [41]. But if other genes are expressed, such as micro-ribonucleic acid-132 (miR-132), also found in NP cells, then it promotes ECM degradation in human NP cells by direct targeting of growth differentiation factor 5 (GDF5). Hence, miR-132 represents a potential therapeutic target in the treatment of degenerative disc disease [42]. These studies have shown evidence that, *in vivo*, inhibiting the miR-132 gene attenuated the ECM degradation, as indicated by the value of quantitative real-time polymerase chain reaction (PCR) blood test.

To stimulate ECM synthesis and stop degradation, a novel hypothetical approach had been proposed that is correlated with a single-patient case study. The notion is that transforming growth factor beta 1 (TGF-β1) from seminal plasma secretions may contribute to releasing the osteogenic protein-1 (OP-1) that induces NP and AF cells in intervertebral discs for repairs [43-45].

It has been suggested that biological transformations controlled by the mind (BTCM) might naturally stimulate the release of the OP-1 without additional biochemical agents [43]. But for the patients who are unable to self-educate this novel physiology, the biochemical hypothesis might provide a possible cure for DDD. Transforming growth factor beta (TGF-β) belonging to TGF superfamily, is a multifunctional cytokine which has been shown to function as a chemoattractant [46-49]. It can regulate the synthesis or degradation of ECM [44, 50-56] and have key roles in the regulation of inflammatory processes [52-54].

Within the TGF-β family, other proteins have been discovered, such as growth differentiation factor 11 (GDF11) [57]. It declines with age and has been shown to play a role in tissue and muscle regeneration [58]. It has been called The Molecular Fountain of Youth. However, there is some skepticism that questions the claimed therapeutic effectiveness in lab animals [59].

It is known that GDF11 is important for the nervous and other organ systems, and may regulate aging. GDF11 protein is encoded by the corresponding GDF11 gene. This means that the human body already contains all of the tools necessary for ECM repair and tissue regeneration. The GDF11 gene is highly expressed in three tissues: the brain, the endometrium (part of the female reproductive system), and the prostate gland (part of the male reproductive system) [60].

The semen plasma and the endometrium contain insulin-like growth factor-1 (IGF-1), insulin-like growth factor-binding proteins (IGFBP), beta-nerve growth factor (NGF) and placental protein 14 (PP14). IGF-1 itself induces vascular endothelial growth factor (VEGF) expression, thus promoting angiogenesis. Seminal plasma also regulates vascular function [61].

Liver growth factor (LGF) is an albumin-bilirubin with hepatic mitogen activity. Its concentration increases markedly in the presence of any type of liver injury, and it shows *in vivo* therapeutic biological activity at extrahepatic sites. LGF had been found in the testes and may be related to spermatogenesis and Leydig cell physiology, since there is no active angiogenesis in the adult male. At present, researchers have not found a way to stimulate and transfer these transforming growth factors to promote ECM repair and tissue regeneration to cure DDD.

Our hypothesis regarding BTCM may hold the key for naturally transferring all these growth factors from semen and endometrium within the blood / lymph stream, providing the chance for self-healing. Once activated using the power of the conscious mind, the biological transformation process continues automatically, subconsciously controlled, transferring seminal fluid compounds and mitochondria toward other tissues and somatic cells of the entire body.

Activating or injecting precise quantities of these growth factors and proteins is risky and could result in serious problems. While BTCM can do this automatically, a therapeutic procedure cannot. To function properly with maximum efficiency, these special molecular complexes must be produced continuously and delivered to the cells in need. Once male individuals start to recirculate their seminal fluids and women no longer lose their endometrium and menstrual fluids (which is the essence of BTCM) all of these TGF proteins become available automatically. They contribute to tissue rejuvenation-repair or regeneration. A more complete methodology will be described in the second volume of this publication [7].

2.4. Adenosine Triphosphate Depletion and Decreased Adenosine Triphosphate Synthesis in Degenerative Disc Disease

In Fig. (**2**) the fourth level of the medical approach is indicated in a rectangle (4). Studies on ECM synthesis have led scientists to conclude that degeneration is caused by the inability to maintain extracellular matrix integrity. Extracellular matrix synthesis is related closely to the production of adenosine triphosphate (ATP) (*i.e.,* energy) by the cells [62]. According to the scientific paper entitled ATP Promotes the Extracellular Matrix Biosynthesis of Intervertebral Disc Cells, the authors concluded, based on animal cell cultures, that the ATP metabolism mediated by compressive loading and extracellular ATP accumulation, could be a potential pathway that regulates crucial biological activities in the intervertebral disc degeneration [63].

It is well known that maintenance of the ECM is a process that requires glucose and oxygen consumption to produce energy in the form of ATP. It has been discovered that some metabolic agents may enhance ATP production, such as glucose, oxygen, pyruvate, creatine, and Acetyl-L-Carnitine which improve cognitive functions. These agents are involved in generating ATP for the cell. The use of metabolic agents is a noninvasive method based on an appropriate diet [64].

These results may lead to a better quality of life and long-term cognitive performance improvement. Nutritional factors, in conjunction with other physical or chemical factors, affect epigenetic control, modulating gene expression for prevent or cure during the early stages of DDD. Advanced

cases may be ameliorated [65]. However, other factors, such as behavioral, could have a stronger influence on DDD that can be offset by a simple diet adjustment. Lifestyle and diet should be adjusted together to achieve better results.

2.5. Mitochondrial Dysfunction with no Pathogenic mtDNA Mutations in Degenerative Disc Disease

Another approach presented in Fig. (**2**), is indicated in a rectangle (5). ATP depletion or decreased ATP synthesis is correlated with mitochondrial function. Mitochondria are organelle known to be responsible for catalyzing the products of ATP that support most cell functions. Mitochondrial medicine has had amazing development in the past decade. Many degenerative diseases are associated with mitochondria behavior within the cells.

Based on the previous studies [62, 63], it has been found, using lab mice, that damaged mitochondria are replaceable with the condition of having their mitochondrial deoxyribonucleic acid (mtDNA) unaffected. Therefore, in the scientific paper entitled Mesenchymal Stem Cells Transfer Mitochondria to the Cells with Virtually no Mitochondrial Function but not With Pathogenic mtDNA Mutations, the authors concluded that human mesenchymal stem cells can transfer mitochondria to the cells with severely compromised function. The mitochondrial transfer is limited only by near total absence of mitochondrial function in the target [66, 67].

Other studies have demonstrated mitochondria transfer through vesicles. This finding highlights the idea that mitochondria are more dynamic than previously believed: Mitochondria or mtDNA can move between cells [68].

In the previously mentioned single-patient case study [7], the patient had a complete recovery from an advanced stage of lumbar bilateral discopathy. This therapeutic benefit can be related to a hypothetical model in which AF and NP cells might have lost their ATP production due to a total loss of mitochondrial activity with no other pathogenic mtDNA mutations. If this were true, then ATP production in AF and NP cells had been restarted via BTCM. If this hypothesis were verified using experiments on the patient, then BTCM can be related to transferring new, fully functional mitochondria from the patient's sperm cells to the other cells in need throughout the body.

The only way such transfer could be possible is through vesicles. The discovery of inter- and intra-cellular vesicle transport has been demonstrated by Rothman, Schekman, and Südhof, who won the Nobel Prize in Physiology or Medicine 2013 [69].

Experimental *in vivo* studies performed on mice also demonstrated mitochondria transfer using bone-marrow–derived stromal cells to repair tissue injury elsewhere. This finding suggests that rescue of injured cells through mitochondrial transfer may be an important process in curing many diseases. This conjecture is further supported by conclusive evidence that cells can communicate through the transfer of vesicles and particles carrying lipids, proteins, micro-ribonucleic acid (miRNA), messenger ribonucleic acid (mRNA), and deoxyribonucleic acid (DNA) [70].

Mitochondrial transfer is now recognized as a natural biological process that takes place in all mammals, including humans. As a consequence, donor cells, such as mesenchymal stem cells and fibroblasts can donate their organelles (*i.e.* mitochondria) for the benefit of other cells in need [71].

BTCM aims to highlight that sperm cells can play the role of donor cells for the benefit of other cells. There are extensive research findings regarding mitochondria, such as metabolic reprogramming (using mitochondrial transfer from stem cells) [72], immune response after acute injury [73-75], and mitochondrial extrusion, which allows the release of mitochondria or mitochondrial components from cells under specific conditions [76].

Recently, it has been proposed that a new approach for patients who require mitochondria transfer should be given Mitochondrial Replacement Therapy (MRT). MRT, also known as a mitochondrial donation, is based on the replacement of mitochondria in damaged tissue to restore the tissue to its functional state.

Unfortunately, mitochondria that come from a third party present a risk of epigenetic modification to DNA in the nucleus and mitochondria, caused by the procedure itself or by mito-nuclear interactions. MRT is experimental, but there is actually an extensive, but largely overlooked, body of experimental evidence that indicates mito-nuclear interactions are important in determining health outcomes in humans [77-90]. There also is evidence for mito-nuclear incompatibilities following a similar procedure of somatic cell nuclear transfer in cattle [91, 92]. We conclude that artificial methods for mitochondria transfer are not yet proved safe and, therefore, are not advisable.

The authors of the BTCM book strongly suggested that BTCM has many advantages that might provide new and heretofore unknown physiological mechanisms that contribute to increasing ATP synthesis in the AP and NF cells. In turn, these restored the function of ECM and stopped further degradation, as well as completely reducing various inflammations throughout the entire body. The single-patient case study reported that the patient had rhinitis for 15 years that was incurable with current pharmaceutical medications, but was cured by the BTCM method.

2.6. Telomere Shortening in Degenerative Disc Disease

The next research strategy for approaching DDD has been represented in Fig. (**2**), rectangle (6). Blackburn, Greider, and Szostak won the Nobel Prize in Physiology or Medicine 2009 for their finding that chromosomes are protected by telomeres and the action of telomerase enzyme. Since this discovery, a new branch of medicine known as telomerase-based medicine has shown promise. Beyond any reasonable doubt, the aging phenomenon, tissue and cell degeneration, and telomere length are closely related to each other. Telomere shortening may be a direct link to any degenerative process.

Beyond mitochondria functions in cells, an entire range of physiological processes are directly correlated (although not necessarily causally related) to telomere length. Worldwide research is underway to elucidate the role of disc cell senescence in intervertebral disc degeneration. According to

several researchers, senescent disc cells accelerate the process of intervertebral disc degeneration via their aberrant paracrine effects that cause senescence of neighboring cells and enhance matrix catabolism and inflammation [93].

It also has been confirmed that telomerase activity is inhibited or destroyed in the degenerating intervertebral disc cells. Therefore, the cells cannot maintain chromosome balance, leading to continuous shortening of the telomere in the replication process and promoting cell senescence and intervertebral disc degeneration [94-96].

A congress presentation of DDD, which took place in September 05-06, 2018 Auckland, New Zealand, had been mentioned in the Journal of Spine. Bill Andrews, the President and CEO of Sierra Sciences in Reno, Nevada, USA, also Advisor for Libella Gene Therapeutics in New Zealand, wrote that DDD correlates positively with the shortening of telomeres in intervertebral disc cells. The role of telomere shortening in aging related syndromes is called telomeropathies [97]. Regarding the biomolecular therapy for disc regeneration, Andrews added that recent breakthroughs in gene therapy, especially using vectors derived from the Adeno Associated Virus, have enabled means of delivering genes to human cells in a manner that is far safer than ever seen previously [97].

Other novel gene therapies have been proposed by Professor Michael Fossel of Stanford University in his most recent book, The Telomerase Revolution [98]. In his opinion, the telomere theory of aging can be associated with the functioning of mitochondria as follows: The mitochondria – which are the key to cellular energy - become fewer. Concomitantly, each of them individually becomes less effective. An overall decline in available energy - especially ATP - results from decreases in the protein turnover within the mitochondria. This is because most of the mitochondrial proteins depend on gene expression within the nucleus, and gene expression has slowed with aging. Accompanying these changes, the mitochondria show decreases in their oxygen uptake and in the activity of the enzymes responsible for oxidation. This is predictable: as protein turnover slows, the available proteins are more likely to be damaged proteins [98]. This description clearly illustrates the influence of telomere length *vis-à-vis* mitochondria function, thereby demonstrating a very good correlation.

Other gene therapies, such as biomolecular or cell-based therapies, and other medical strategies, including intervertebral disc replacement, might provide positive results in the near future. Several authors have opined that the inherent multi-factorial nature of DDD presents a challenge for optimal treatment strategies: biomechanical, immunologic, environmental, and genetic factors influence DDD, and their complex interactions have yet to be understood [99].

There are many debates and proposals for genetic therapy treatments, but most of these studies are still awaiting results from animal models experiments or toxicity tests. However, the effects of rejuvenation of derma, good health, and slower aging have been observed in the BTCM single-patient case study. However, telomere shortening is not the cause of DDD.

2.7. Dysfunctional Lifestyle - Mind and Body Behavior in Degenerative Disc Disease

Another approach to DDD treatment is shown in Fig. (**2**), rectangle (7). Although often neglected by patients and physicians, a dysfunctional lifestyle should be considered a major cause of low back pain and DDD. Several publications have tried to raise public awareness over the past three decades. The Newsletter of the American Institute of Stress, vol. 2, no. 7, 1989 on the 2nd International Montreux Congress on Stress, stated that almost 90 percent of patients with low back problems also had a history of other stress-related complaints. These included tension and migraines, heartburn, peptic ulcers, colitis, spastic colon, allergies, and other stress-induced disorders [100]. In his book on back pain, Dr. John Sarno wrote that when patients were treated more holistically there was an obvious improvement in the results of treatment. Sarno suggested it furthermore was possible to predict which patients would do well and which might not [101].

In the past few years, new discoveries have shown that chronic stress has a direct influence on telomere shortening. According to Elissa Epel from the University of California-San Francisco –who also directs the Center for Aging, Metabolism, and Emotion– the two most significant factors are chronological aging and genetics. Nevertheless, stress is one of the most consistent predictors of shorter telomere length ... the type of stress determines how big its effect is [102].

Other studies have presented evidence that psychological stress –both perceived stress and chronicity of stress– is significantly associated with higher oxidative stress, lower telomerase activity, and shorter telomere length. These factors are known determinants of cell senescence and longevity [103]. Many scientific papers highlighted the link between stress, telomere length, inflammations and other environmental factors [104-113].

For various stressors, mindfulness [114-120], meditation [121-123], and relaxation techniques are useful in overcoming or mitigating the adverse consequences. But for chronic DDD, more profound changes are required (which also are used in BTCM). These include balanced raw food, theoretical training, respect for the word and truth, pacing breath, and life consciousness [7]. In addition, BTCM is useful in reducing chronic inflammations and headaches. As illustrated in Fig. (**2**), using horizontal black arrows, BTCM can manifest a positive influence on all 7 stages of cause and effect chain in DDD. Behavioral psychology could reduce the impact of DDD, but BTCM implies that the psychic and the physiological must work together to achieve homeostasis along with an adequate diet and lifestyle.

Psychosomatic medicine (PM), also known as consultation-liaison psychiatry, has proved useful with comorbidity of psychiatric and medical problems. The patient is taught to understand his emotional trauma stress and his somatic problems before applying BTCM method. Earlier studies suggested that behavioral methods are helping individuals to self-manage low back pain through relaxation techniques and various coping techniques (such as visualization) [124].

In Fig. (**2**), it is shown that there are opportunities within grasp for introducing BTCM more widely. It is a novel self-

educated approach to physiology as well as a new branch of physiology that uses all available bodily resources (such as sperm fluids or ova menstrual fluids, female squirts, and ejaculation fluids) in order to help the body slow down aging and degeneration, which may cure DDD and other chronic inflammations that jeopardize world health.

3. A NOVEL SELF-EDUCATED PHYSIOLOGY FOR CURING CHRONIC INFLAMMATIONS AND ADVANCED LUMBAR DISCOPATHY

According to conventional medicine, the bad news is that while many treatment options exist, there is no cure for discogenic pain and DDD is not reversible [125]. However, in this paper, we have proposed BTCM as a new approach, demonstrated *via* a single-patient case study, which can reverse disc degeneration, revitalize the entire body, and cure inflammations without medication. The impact of BTCM is not that it halts degeneration, but instead, it creates a contra-process in opposition to degeneration, which we call the High-Speed Regeneration Process (HSRP).

3.1. Hypothesis About the Influence of Biological Transformations Controlled by the Mind in Self-Healing

BTCM aims to establish a relationship between classical medical science and an undiscovered or poorly understood biochemical and biophysical mechanisms of the human body. BTCM entails a new lifestyle, a natural healing method, and a philosophy of life. BTCM proposes a novel understanding of the seminal fluids and reproductive cells, adding a new role beyond the ones accepted by science (*e.g.,* perpetuation of the species, psychological relief, and entertainment). The newly discovered role of the mixture of substances and cells can provide vital new resources to support other somatic cells in need.

According to classical medical science, male ejaculation is a regular necessity, notwithstanding the inherent drive for procreation. In contrast, non-ejaculation is a medical condition that requires treatment. A review of the PubMed database found that papers analyzing semen loss are associated exclusively with sexually transmitted diseases or sexual health and dysfunction. All of them present cultural and religious aspects that can be traced from India, without emphasis on the benefits of semen transformation that are common knowledge but without scientific background [126].

Studies confirmed that semen plasma in 1 ejaculation contains the following substances: amino acids, citrate, enzymes, flavonoids, fructose, proteins, vitamins, zinc, acid phosphatase, citric acid, fibrinolysis substances, proteolytic enzymes, oxytocin, cholesterol and other major phospholipid classes, along with 200-500 million sperm cells [127].

BTCM aims to recirculate all these precious substances in the blood and lymph streams, when there are no more needs of procreation within an intimate relationship. Until this single-patient case study, we had no evidence of any beneficial outcome of the BTCM, until the patient had successfully cured three incurable defined medical conditions: a) 15-year-old case of bilateral lumbar L4–L5 DDD, b) 15-year-old case of hypertrophic chronic rhinitis and c) 25-year-old case of severe headaches and migraines.

The only logical observation was that, before BTCM, these conditions were incurable. Yet in fewer than 9 months from the start of BTCM, the patient's hypertrophic chronic rhinitis and migraines were cured and in less than 6 years his bilateral lumbar L4–L5 DDD was cured. The patient remains healthy 13 years after beginning BTCM. Several medical documents substantiate these claims. Clearly, these outcomes must have a scientific explanation, which we propose in the following hypotheses.

3.2. Hypothesis about the Physiological Mechanism of Biological Transformations Controlled by the Mind

In order to create 5 ml of seminal plasma, the male body needs to collect resources from food and marrow. BTCM aims to recirculate seminal fluid compounds into the blood and lymph streams. These compounds may contribute to several vital substances in the regeneration processes.

During BTCM, the patient needed at least five times less solid food per day; but consumed more liquids and water than before starting BTCM. That could be related to the supplemental of amino acids, citrate, enzymes, flavins, fructose, cholesterol and proteins provided by the seminal plasma.

During BTCM, some of the seminal compounds could have a positive influence on the brain, enhancing its capacity to use mind power to heal diseases [128]. It also is known that ordinary people or patients, with no self-educated BTCM, can heal some illnesses using their mind power. However, in this single-patient case study, the patient practitioner required only four hours of sleep per night, and it had no adverse effects on his brain for more than 13 years since he started BTCM.

A audacious hypothesis, which needs to be tested, proposes that, during BTCM, the reproductive cells have been broken into small pieces and parts (such as acrosome, enzymes, mitochondria, DNA) which then had been surrounded by nano-vesicles (formed out of the original membrane) and then began to circulate towards the cells in need. Except for the mitochondria (which can be transferred from one cell to another), the recirculation of sperm cell parts within nano-vesicles remains unknown.

3.3. Hypothesis about the Manifestation of High Speed Regeneration Process, Before and After Biological Transformations Controlled by the Mind

The medical literature is correct about degenerative processes: they cannot be stopped. However, regenerative processes are natural and can be stimulated under certain conditions. For example, the human body can reduce the loss of vital substances in order to have resources to perform new tasks. Natural implications and uneducated regeneration are already present in the patient's body, but cannot compete with the speed of degeneration. The evolution over time of the degeneration-regeneration mechanism can be described in several stages.

Stage 1: A mature 18-20 years old healthy body has a regeneration speed (Rs) that is about equal to degeneration speed (Ds): Rs ≈ Ds. This means, all cells, and cell organelles are having the best turn over and the entire body's maintenances processes are at an optimal level.

Stage 2: After 18-20 years old, the body begins a very slow aging process. Ds slightly increases while Rs remains relatively constant (Ds ≥ Rs). Inflammations might occur, and acute short back pains may occur.

Stage 3: At a given point in time, a degenerative process or a persistent inflammation many be manifest with repeated symptoms. In most cases, ordinary X-ray investigations highlight intervertebral disc problems. The patient is not able to increase Rs, while Ds continues to increase obtaining Ds > Rs). Rs simply cannot keep pace.

Stage 4: After several more years, the patient began to use prescribed medication for ongoing pain and inflammations episodes. At that time he might be willing to help the body recover by increasing Rs; but, unfortunately, the degeneration process is now too advanced and tends to further increase over time, obtaining Ds » Rs.

With Ds much greater than Rs, it becomes an insurmountable barrier. Most DDD patients live the remainder of their lives in this stage, without any hope for a cure. Their quality of life depends on advancements in medical technologies and pharmaceutical therapies. To date, no one has ever been cured of DDD.

Stage 5: The single-patient case study stimulated a hypothesis based on the patient's medical records. This suggested that BTCM had stimulated or created a high speed regeneration process (HSRP). The effect is to increase Rs faster than Ds. As Rs increases, various tissue repairs become more effective. Cell and cell organelle turnover improves, symptoms decrease, inflammation reduces, and a real curing process can start. This stage is only possible during a self-educated BTCM.

Stage 6: In this stage, the most logical understanding of the effects of BTCM leads to the hypothesis that Rs and Ds now have nearly an equal speed (Rs ≈ Ds) again, which at about 18-20 years of age. But this does not mean DDD had been cured. The curing process is still in progress simultaneously with the degeneration process. The process appears to have stopped the advancement of DDD, but the degeneration and regeneration processes are in relative equilibrium. The disease is not yet cured.

Stage 7: After several more years of BTCM, the HSRP continue to increase Rs until it exceeds Ds (Rs ≥ Ds). This is the only logical situation for compensating for an ongoing degeneration process. The HSRP also cures already damaged tissue. The novel hypothesis of anti-aging research is to find a means to reverse (*i.e.,* stop or slow down) aging. Biological laws do not forbid reversing the aging process; however, we simply do not yet have the necessary means to achieve this outcome.

Stage 8: After six years of practicing BTCM, the patient presented three magnetic resonance images that showed evidence of an advanced healing process. These images included one before starting BTCM and two after starting BTCM. In this stage, BTCM may either slightly lower Ds, continued to increase Rs, or both. The net effect is that Rs > Ds creates healing. The third MRI showed additional, slight improvements in the patient's health. The patient no longer reports having any back pain, inflammations, headaches, rhinitis, or other symptoms.

Stage 9: After 13 years of practicing BTCM, the patient observed a usual but also logical process of HSRP, which can be understood as a side effect of BTCM over healthy tissue and cells (Rs » Ds). It seems that some of them are having rejuvenation, while others might undergo a slow aging process. Patient's photos, taken with a professional video camera, present skin rejuvenation, a slight reduction of face wrinkles, slightly improved skin color, and almost constant gray hair over the past 10 years.

The MRI investigations highlighted the enduring effects of BTCM, improving health and even showing slow aging. The patient continues with BTCM, which in now uninterrupted for more than 13 years. None of the patient's earlier medical conditions repeated itself or reappeared.

CONCLUSION

The main propose of this report is to demonstrate that DDD may be treated effectively with a new supplemental approach, without neglecting the benefits of other scientific developments and medical treatments. Even if there were to be only a few results, if the results improved the patient's quality of life, then the gain is worthwhile. Future research, built on analyses of this single-patient case study, might provide more examples of using BTCM to cure DDD and improve the quality of life.

As shown in Fig. (**2**), another advantage of BTCM is the possibility of using it at any level, from (a) to (g) to improve the effectiveness of any of treatment from (1) to (7). BTCM does not require animal model research, toxicity testing, FDA approval, or clinical trial tests. BTCM can be applied directly by the patient through personal self-education.

In the case of the single-patient case study, BTCM was shown to be useful in curing all of his medical problems. He also reported improved mental focus for job work; better balance in his emotional and intimate life; and, ultimately, enhanced meaning in his life.

BTCM itself is not a cure, although it has shown enhanced healing effects. BTCM is more of a way of life or of personal development. It has the potential to contribute significantly to improved therapeutic effects and patients' overall sense of well-being. Improved quality of life should not be ignored as intangible: It is enormously valuable –perhaps invaluable– to those whose suffering is reduced or eliminated.

We believe that BTCM reasonably should be taken into consideration for future research in DDD and other inflammatory diseases. The immediate goal would be to demonstrate that the human body has resources –such as men's sperm cells and sperm plasma, and women's menstrual fluids– that potentially have a secondary, previously undiscovered role in rejuvenation and healing. BTCM still faces many challenges to achieve proper personal education. It may also be shown to have additional as-yet-undiscovered healing properties. We are confident that future detailed research will be able to support our working hypotheses.

AUTHORS' CONTRIBUTIONS

Cristian Muresanu (CM) and Gjumrakch Aliev (GA), discussed the manuscript topic, analyzed the data; CM, Siva

G. Somasundaram (SGS) Margarita E. Neganova (MEN), Elena V. Bovina (EVB), Sergey V. Vissarionov (SVV), Okom N. F. C. Ofodile (ONFCO), Vladimir P. Fisenko (VPF), Valentin Bragin (VB), Nina N. Minyaeva (NNM), Vladimir N. Chubarev, (VNC) Sergey G. Klochkov (SGK), Vadim V. Tarasov (VVT), Liudmila M. Mikhaleva (LMM), Cecil E. Kirkland (CEK), and GA wrote the paper. All authors have reviewed the manuscript.

CONSENT FOR PUBLICATION

The first author of this paper, Cristian Muresanu, also known in the paper as "the patient", has freely offered his personal data and personal medical files for use in this review article and has made them available for other authors and co-authors, without any present or future demands, any potential claims or retribution, and he has signed a consent letter addressed to the journal staff.

FUNDING

This work was supported by the Russian Academic Excellence project "5-100" for the Sechenov Medical University, Moscow, Russia. This research also was financially supported by the Ministry of Science and High Education of the Russian Federation; state contract 14.613.21.0086; unique identifier of the project: RFMEFI61318X0086.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Brunori, A.; De Caro, G.M.; Giuffrè, R. Surgery of lumbar disk hernia: historical perspective. *Ann. Ital. Chir.,* **1998**, *69*(3), 285-293. PMID: 9835099

[2] Bongaarts, J. Human population growth and the demographic transition. *Philos. Trans. R. Soc. Lond. B Biol. Sci.,* **2009**, *364*(1532), 2985-2990. http://dx.doi.org/10.1098/rstb.2009.0137 PMID: 19770150

[3] Luo, X.; Pietrobon, R.; Sun, S.X.; Liu, G.G.; Hey, L. Estimates and patterns of direct health care expenditures among individuals with back pain in the United States. *Spine,* **2004**, *29*(1), 79-86. http://dx.doi.org/10.1097/01.BRS.0000105527.13866.0F PMID: 14699281

[4] Walker, B.F.; Muller, R.; Grant, W.D. Low back pain in Australian adults: the economic burden. *Asia Pac. J. Public Health,* **2003**, *15*(2), 79-87. http://dx.doi.org/10.1177/101053950301500202 PMID: 15038680

[5] Norlund, A.I.; Waddell, G. Neck and back pain: the scientific evidence of causes, diagnosis and treatment. In: *Cost of back pain in some OECD countries*; Nachemson, A.L.; Jonsson, E., Eds.; Lippincott, Williams & Wilkins: Philadelphia, **2000**; pp. 421-425.

[6] Maniadakis, N.; Gray, A. The economic burden of back pain in the UK. *Pain,* **2000**, *84*(1), 95-103. http://dx.doi.org/10.1016/S0304-3959(99)00187-6 PMID: 10601677

[7] Muresanu, C.; Somasundaram, S.G. *Biological Transformations Controlled by the Mind*; AlphaGraphics Sugar Land: Texas, **2013**, pp. 8-14-95-96.

[8] Jabłońska, R.; Ślusarz, R.; Królikowska, A.; Haor, B.; Antczak, A.; Szewczyk, M. Depression, social factors, and pain perception before and after surgery for lumbar and cervical degenerative vertebral disc disease. *J. Pain Res.,* **2017**, *10*, 89-99. http://dx.doi.org/10.2147/JPR.S121328 PMID: 28115868

[9] Marik, P.E.; Flemmer, M. The immune response to surgery and trauma: Implications for treatment. *J. Trauma Acute Care Surg.,* **2012**, *73*(4), 801-808. http://dx.doi.org/10.1097/TA.0b013e318265cf87 PMID: 22976420

[10] Ghoneim, M.M.; O'Hara, M.W. Depression and postoperative complications: an overview. *BMC Surg.,* **2016**, *16*(5), 5. http://dx.doi.org/10.1186/s12893-016-0120-y PMID: 26830195

[11] Adogwa, O.; Parker, S.L.; Shau, D.N.; Mendenhall, S.K.; Aaronson, O.S.; Cheng, J.S.; Devin, C.J.; McGirt, M.J. Preoperative Zung Depression Scale predicts outcome after revision lumbar surgery for adjacent segment disease, recurrent stenosis, and pseudarthrosis. *Spine J.,* **2012**, *12*(3), 179-185. http://dx.doi.org/10.1016/j.spinee.2011.08.014 PMID: 21937282

[12] Ning, X.; Wen, Y.; Xiao-Jian, Y.; Bin, N.; De-Yu, C.; Jian-Ru, X.; Lian-Shun, J. Anterior cervical locking plate-related complications; prevention and treatment recommendations. *Int. Orthop.,* **2008**, *32*(5), 649-655. http://dx.doi.org/10.1007/s00264-007-0369-y PMID: 17497150

[13] Lonstein, J.E.; Denis, F.; Perra, J.H.; Pinto, M.R.; Smith, M.D.; Winter, R.B. Complications associated with pedicle screws. *J. Bone Joint Surg. Am.,* **1999**, *81*(11), 1519-1528. http://dx.doi.org/10.2106/00004623-199911000-00003 PMID: 10565643

[14] University of Maryland Medical Center. Available from: https://www.umms.org/ummc/health-services/orthopedics/services/spine/patient-guides/ complications-spine-surgery.

[15] Muftic, M.; Miladinovic, K. Therapeutic ultrasound and pain in degenerative diseases of musculoskeletal system. *Acta Inform. Med.,* **2013**, *21*(3), 170-172. http://dx.doi.org/10.5455/aim.2013.21.170-172 PMID: 24167385

[16] Pop, T.; Austrup, H.; Preuss, R.; Niedziałek, M.; Zaniewska, A.; Sobolewski, M.; Dobrowolski, T.; Zwolińska, J. Effect of TENS on pain relief in patients with degenerative disc disease in lumbosacral spine. *Ortop. Traumatol. Rehabil.,* **2010**, *12*(4), 289-300. PMID: 20876922

[17] Wang, L.; Fan, W.; Yu, C.; Lang, M.; Sun, G. Clinical effects of electrical stimulation therapy on lumbar disc herniation-induced sciatica and its influence on peripheral ROS level. *J. Musculoskelet. Neuronal Interact.,* **2018**, *18*(3), 393-398. PMID: 30179218

[18] Casserley-Feeney, S.N.; Phelan, M.; Duffy, F.; Roush, S.; Cairns, M.C.; Hurley, D.A. Patient satisfaction with private physiotherapy for musculoskeletal pain. *BMC Musculoskelet. Disord.,* **2008**, *9*, 50. http://dx.doi.org/10.1186/1471-2474-9-50 PMID: 18412974

[19] Anderson, L.; Delany, C. From persuasion to coercion: responding to the reluctant patient in rehabilitation. *Phys. Ther.,* **2016**, *96*(8), 1234-1240. http://dx.doi.org/10.2522/ptj.20150586 PMID: 26939602

[20] Lonnemann, M.E.; Foster, N.; Woodhouse, L.; Rivett, D.; Cook, C. Panel debate: Manual therapy is a questionable tool in the toolkit of treatments for low back pain. *Man. Ther.,* **2016**, *25*, 29-30. http://dx.doi.org/10.1016/j.math.2016.05.023

[21] Menke, J.M. Do manual therapies help low back pain? A comparative effectiveness meta-analysis. *Spine,* **2014**, *39*(7), E463-E472. http://dx.doi.org/10.1097/BRS.0000000000000230 PMID: 24480940

[22] Foster, N.E. Barriers and progress in the treatment of low back pain. *BMC Med.,* **2011**, *9*, 108. http://dx.doi.org/10.1186/1741-7015-9-108 PMID: 21943396

[23] Institute for Chronic Pain. *Is Degenerative Disc Disease Inevitably Degenerative?* Available from: https://www.instituteforchronicpain.org/blog/item/136-39is-degenerative-disc-disease-inevitably-degenerative. (Accessed **2014)**.

[24] Symmons, D.P.; van Hemert, A.M.; Vandenbroucke, J.P.; Valkenburg, H.A. A longitudinal study of back pain and radiological changes in the lumbar spines of middle aged women. II. Radiographic findings. *Ann. Rheum. Dis.,* **1991**, *50*(3), 162-166. http://dx.doi.org/10.1136/ard.50.3.162 PMID: 1826598

[25] Matsubara, Y.; Kato, F.; Mimatsu, K.; Kajino, G.; Nakamura, S.; Nitta, H. Serial changes on MRI in lumbar disc herniations treated conservatively. *Neuroradiology,* **1995**, *37*(5), 378-383.

http://dx.doi.org/10.1007/BF00588017 PMID: 7477838

[26] Hutton, M.J.; Bayer, J.H.; Powell, J.M. Modic vertebral body changes: the natural history as assessed by consecutive magnetic resonance imaging. *Spine,* **2011**, *36*(26), 2304-2307. http://dx.doi.org/10.1097/BRS.0b013e31821604b6 PMID: 21358572

[27] Spine-Health. Decreasing chronic inflammation in your body for better health. *Veritas Health.* Available from: https://www.spine-health.com/blog/decreasing-chronic-inflammation-your-body-better-health.

[28] Spine-Health. Potential Risks and Complications of NSAIDs. *Veritas Health.* Available from: https://www.spine-health.com/treatment/pain-medication/ potential-risks-and-complications-nsaids.

[29] Spine-Health. Common Risks and Side Effects of Muscle Relaxants. *Veritas Health.* Available from: https://www.spine-health.com/treatment/pain-medication/common-risks-and-side-effects-muscle-relaxants.

[30] RAN-Ranitidine. Available from: https://www.medbroadcast.com/drug/getdrug/ran-ranitidine.

[31] Cerner, M. Chlorzoxazone. Available from: https://www.drugs.com/mtm/chlorzoxazone.html (Accessed **2018**).

[32] Bonaventure, C.; Nancey, S.; Pont, E.; Michalet, V.; Chevalier, M.; Vial, T.; Taieb, S.; Claudel, S.; Flourie, B.; Descos, L. Ketoprofen-induced acute hepatitis. *Gastroenterol. Clin. Biol.,* **2001**, *25*(6-7), 716-717. PMID: 11673741

[33] Rambaud, S.; Nores, J.M.; Rémy, J.M. Jaundice related to the ingestion of ketoprofen. *Ann. Med. Interne (Paris),* **1990**, *141*(3), 278. PMID: 2369020

[34] González, E.; de la Cruz, C.; de Nicoläs, R.; Egido, J.; Herrero-Beaumont, G. Long-term effect of nonsteroidal anti-inflammatory drugs on the production of cytokines and other inflammatory mediators by blood cells of patients with osteoarthritis. *Agents Actions,* **1994**, *41*(3-4), 171-178. http://dx.doi.org/10.1007/BF02001912 PMID: 7942325

[35] Feng, H.; Danfelter, M.; Strömqvist, B.; Heinegård, D. Extracellular matrix in disc degeneration. *J. Bone Joint Surg. Am.,* **2006**, *88*(Suppl. 2), 25-29. PMID: 16595439

[36] David, G.; Ciurea, A.V.; Mitrica, M.; Mohan, A. Impact of changes in extracellular matrix in the lumbar degenerative disc. *J. Med. Life,* **2011**, *4*(3), 269-274. PMID: 22567050

[37] Goupille, P.; Jayson, M.I.; Valat, J.P.; Freemont, A.J. Matrix metalloproteinases: the clue to intervertebral disc degeneration? *Spine,* **1998**, *23*(14), 1612-1626. http://dx.doi.org/10.1097/00007632-199807150-00021 PMID: 9682320

[38] Folkman, J. Antiangiogenic activity of a matrix protein. *Cancer Biol. Ther.,* **2003**, *2*(1), 53-54. http://dx.doi.org/10.4161/cbt.356 PMID: 12673117

[39] Roberts, S.; Caterson, B.; Menage, J.; Evans, E.H.; Jaffray, D.C.; Eisenstein, S.M. Matrix metalloproteinases and aggrecanase: their role in disorders of the human intervertebral disc. *Spine,* **2000**, *25*(23), 3005-3013. http://dx.doi.org/10.1097/00007632-200012010-00007 PMID: 11145811

[40] Loreto, C.; Musumeci, G.; Castorina, A.; Loreto, C.; Martinez, G. Degenerative disc disease of herniated intervertebral discs is associated with extracellular matrix remodeling, vimentin-positive cells and cell death. *Ann. Anat.,* **2011**, *193*(2), 156-162. http://dx.doi.org/10.1016/j.aanat.2010.12.001 PMID: 21330123

[41] Ruan, Z.; Ma, H.; Li, J.; Liu, H.; Jia, H.; Li, F. The long non-coding RNA NEAT1 contributes to extracellular matrix degradation in degenerative human nucleus pulposus cells. *Exp. Biol. Med. (Maywood),* **2018**, *243*(7), 595-600. http://dx.doi.org/10.1177/1535370218760774 PMID: 29534600

[42] Liu, W.; Xia, P.; Feng, J.; Kang, L.; Huang, M.; Wang, K.; Song, Y.; Li, S.; Wu, X.; Yang, S.; Yang, C. MicroRNA-132 upregulation promotes matrix degradation in intervertebral disc degeneration. *Exp. Cell Res.,* **2017**, *359*(1), 39-49. http://dx.doi.org/10.1016/j.yexcr.2017.08.011 PMID: 28793234

[43] Somasundaram, S.G.; Muresanu, C.; Schield, P.; Makhmutova, A.; Bovina, E.V.; Fisenko, V.P.; Hasanov, N.F.; Aliev, G. A novel non-invasive effective method for potential treatment of degenerative disc disease - a hypothesis. *Cent. Nerv. Syst. Agents Med. Chem.,* **2018**, *18*(1), 1-7. PMID: 30332977

[44] MacLellan, W.R.; Brand, T.; Schneider, M.D. Transforming growth factor-beta in cardiac ontogeny and adaptation. *Circ. Res.,* **1993**, *73*(5), 783-791. http://dx.doi.org/10.1161/01.RES.73.5.783 PMID: 8403249

[45] Takegami, K.; An, H.S.; Kumano, F.; Chiba, K.; Thonar, E.J.; Singh, K.; Masuda, K. Osteogenic protein-1 is most effective in stimulating nucleus pulposus and annulus fibrosus cells to repair their matrix after chondroitinase ABC-induced *in vitro* chemonucleolysis. *Spine J.,* **2005**, *5*(3), 231-238. http://dx.doi.org/10.1016/j.spinee.2004.11.001 PMID: 15863076

[46] Mustoe, T.A.; Pierce, G.F.; Morishima, C.; Deuel, T.F. Growth factor-induced acceleration of tissue repair through direct and inductive activities in a rabbit dermal ulcer model. *J. Clin. Invest.,* **1991**, *87*(2), 694-703. http://dx.doi.org/10.1172/JCI115048 PMID: 1991853

[47] Pierce, G.F.; Mustoe, T.A.; Lingelbach, J.; Masakowski, V.R.; Griffin, G.L.; Senior, R.M.; Deuel, T.F. Platelet-derived growth factor and transforming growth factor-beta enhance tissue repair activities by unique mechanisms. *J. Cell Biol.,* **1989**, *109*(1), 429-440. http://dx.doi.org/10.1083/jcb.109.1.429 PMID: 2745556

[48] Wahl, S.M.; McCartney-Francis, N.; Mergenhagen, S.E. Inflammatory and immunomodulatory roles of TGF-beta. *Immunol. Today,* **1989**, *10*(8), 258-261. http://dx.doi.org/10.1016/0167-5699(89)90136-9 PMID: 2478145

[49] Postlethwaite, A.E.; Keski-Oja, J.; Moses, H.L.; Kang, A.H. Stimulation of the chemotactic migration of human fibroblasts by transforming growth factor beta. *J. Exp. Med.,* **1987**, *165*(1), 251-256. http://dx.doi.org/10.1084/jem.165.1.251 PMID: 3491869

[50] Van Obberghen-Schilling, E.; Roche, N.S.; Flanders, K.C.; Sporn, M.B.; Roberts, A.B. Transforming growth factor beta 1 positively regulates its own expression in normal and transformed cells. *J. Biol. Chem.,* **1988**, *263*(16), 7741-7746. PMID: 3259578

[51] Keski-Oja, J.; Raghow, R.; Sawdey, M.; Loskutoff, D.J.; Postlethwaite, A.E.; Kang, A.H.; Moses, H.L. Regulation of mRNAs for type-l plasminogen activator inhibitor, fibronectin and type I procollagen by transforming growth factor-β. *J. Biol. Chem.,* **1988**, *263*(7), 3111-3115. PMID: 3125175

[52] Sanjabi, S.; Zenewicz, L.A.; Kamanaka, M.; Flavell, R.A. Anti-inflammatory and pro-inflammatory roles of TGF-beta, IL-10, and IL-22 in immunity and autoimmunity. *Curr. Opin. Pharmacol.,* **2009**, *9*(4), 447-453. http://dx.doi.org/10.1016/j.coph.2009.04.008 PMID: 19481975

[53] Li, M.O.; Flavell, R.A. Contextual regulation of inflammation: a duet by transforming growth factor-beta and interleukin-10. *Immunity,* **2008**, *28*(4), 468-476. http://dx.doi.org/10.1016/j.immuni.2008.03.003 PMID: 18400189

[54] Li, M.O.; Flavell, R.A. TGF-beta: a master of all T cell trades. *Cell,* **2008**, *134*(3), 392-404. http://dx.doi.org/10.1016/j.cell.2008.07.025 PMID: 18692464

[55] Roberts, A.B.; Heine, U.I.; Flanders, K.C.; Sporn, M.B. TGF-β: Major role in regulation of extracellular matrix. *Ann. N. Y. Acad. Sci.,* **1990**, *580*, 225-232. http://dx.doi.org/10.1111/j.1749-6632.1990.tb17931.x PMID: 2186691

[56] Roberts, A.B.; Flanders, K.C.; Kondaiah, P.; Thompson, N.L.; van Obberghen-Schilling, E.; Wakefield, L.; Rossi, P.; de Crom-Brugghe, B.; Heine, U.I.; Sporn, M.B. Growth factor β: biochemistry and roles in embryogenesis, tissue repair and remodeling, and carcinogenesis. *Recent Prog. Horm. Res.,* **1988**, *44*, 157-197. DOI: 10.1016/b978-0-12-571144-9.50010-7

[57] GDF11 growth differentiation factor 11 [*Homo sapiens* (human)]. https://www.ncbi.nlm.nih.gov/gene/10220.

[58] Loffredo, F.S.; Steinhauser, M.L.; Jay, S.M.; Gannon, J.; Pancoast, J.R.; Yalamanchi, P.; Sinha, M.; Dall'Osso, C.; Khong, D.; Shadrach, J.L.; Miller, C.M.; Singer, B.S.; Stewart, A.; Psychogios, N.; Gerszten, R.E.; Hartigan, A.J.; Kim, M.J.; Serwold, T.; Wagers, A.J.; Lee, R.T. Growth differentiation factor 11 is a circulating factor that reverses age-related cardiac hypertrophy. *Cell,* **2013**, *153*(4), 828-839. http://dx.doi.org/10.1016/j.cell.2013.04.015 PMID: 23663781

[59] Harper, S.C.; Brack, A.; MacDonnell, S.; Franti, M.; Olwin, B.B.; Bailey, B.A.; Rudnicki, M.A.; Houser, S.R. Is growth differentiation factor 11 a realistic therapeutic for aging-dependent muscle defects? *Circ. Res.,* **2016**, *118*(7), 1143-1150. http://dx.doi.org/10.1161/CIRCRESAHA.116.307962 PMID: 27034276

[60] The Human Protein Atlas. Available from: https:// www.proteinatlas.org/ ENSG00000135414-GDF11/tissue

[61] Pérez-Crespo, M.; Pericuesta, E.; Pérez-Cerezales, S.; Arenas, M.I.; Lobo, M.V.; Díaz-Gil, J.J.; Gutierrez-Adan, A. Effect of liver growth factor on both testicular regeneration and recovery of spermatogenesis in busulfan-treated mice. *Reprod. Biol. Endocrinol.,* **2011**, *9*, 21. http://dx.doi.org/10.1186/1477-7827-9-21 PMID: 21294894

[62] Salvatierra, J.C.; Yuan, T.Y.; Fernando, H.; Castillo, A.; Gu, W.Y.; Cheung, H.S.; Huant, C.Y. Difference in energy metabolism of annulus fibrosus and nucleus pulposus cells of the intervertebral Disc. *Cell. Mol. Bioeng.,* **2011**, *4*(2), 302-310. http://dx.doi.org/10.1007/s12195-011-0164-0 PMID: 21625336

[63] Gonzales, S.; Wang, C.; Levene, H.; Cheung, H.S.; Huang, C.C. ATP promotes extracellular matrix biosynthesis of intervertebral disc cells. *Cell Tissue Res.,* **2015**, *359*(2), 635-642. http://dx.doi.org/10.1007/s00441-014-2042-2 PMID: 25407524

[64] Owen, L.; Sunram-Lea, S.I. Metabolic agents that enhance ATP can improve cognitive functioning: a review of the evidence for glucose, oxygen, pyruvate, creatine, and L-carnitine. *Nutrients,* **2011**, *3*(8), 735-755. http://dx.doi.org/10.3390/nu3080735 PMID: 22254121

[65] Spine-Health. Step Three of DDD Management: Improve Nutrition. *Veritas Health.* Available from: https://www.spine-health.com/conditions/degenerative-disc-disease/step-three-ddd-management-improve-nutrition.

[66] Mitochondria. Available from: https://www.nature.com/scitable/ topicpage/mitochondria -14053590.

[67] Cho, Y.M.; Kim, J.H.; Kim, M.; Park, S.J.; Koh, S.H.; Ahn, H.S.; Kang, G.H.; Lee, J.B.; Park, K.S.; Lee, H.K. Mesenchymal stem cells transfer mitochondria to the cells with virtually no mitochondrial function but not with pathogenic mtDNA mutations. *PLoS One,* **2012**, *7*(3), e32778. http://dx.doi.org/10.1371/journal.pone.0032778 PMID: 22412925

[68] Spees, J.L.; Olson, S.D.; Whitney, M.J.; Prockop, D.J. Mitochondrial transfer between cells can rescue aerobic respiration. *Proc. Natl. Acad. Sci. USA,* **2006**, *103*(5), 1283-1288. http://dx.doi.org/10.1073/pnas.0510511103 PMID: 16432190

[69] The Nobel Prize in Physiology or Medicine. Available from: https:// www.nobelprize.org/prizes/medicine/2013/summary/. (Accessed **2019**).

[70] Prockop, D.J. Mitochondria to the rescue. *Nat. Med.,* **2012**, *18*(5), 653-654. http://dx.doi.org/10.1038/nm.2769 PMID: 22561816

[71] Plotnikov, E.Y.; Khryapenkova, T.G.; Vasileva, A.K.; Marey, M.V.; Galkina, S.I.; Isaev, N.K.; Sheval, E.V.; Polyakov, V.Y.; Sukhikh, G.T.; Zorov, D.B. Cell-to-cell cross-talk between mesenchymal stem cells and cardiomyocytes in co-culture. *J. Cell. Mol. Med.,* **2008**, *12*(5A), 1622-1631. http://dx.doi.org/10.1111/j.1582-4934.2007.00205.x PMID: 18088382

[72] Acquistapace, A.; Bru, T.; Lesault, P.F.; Figeac, F.; Coudert, A.E.; le Coz, O.; Christov, C.; Baudin, X.; Auber, F.; Yiou, R.; Dubois-Randé, J.L.; Rodriguez, A.M. Human mesenchymal stem cells reprogram adult cardiomyocytes toward a progenitor-like state through partial cell fusion and mitochondria transfer. *Stem Cells,* **2011**, *29*(5), 812-824. http://dx.doi.org/10.1002/stem.632 PMID: 21433223

[73] Zhang, Q.; Raoof, M.; Chen, Y.; Sumi, Y.; Sursal, T.; Junger, W.; Brohi, K.; Itagaki, K.; Hauser, C.J. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature,* **2010**, *464*(7285), 104-107. http://dx.doi.org/10.1038/nature08780 PMID: 20203610

[74] Galluzzi, L.; Kepp, O.; Kroemer, G. Mitochondria: master regulators of danger signalling. *Nat. Rev. Mol. Cell Biol.,* **2012**, *13*(12), 780-788. http://dx.doi.org/10.1038/nrm3479 PMID: 23175281

[75] West, A.P.; Khoury-Hanold, W.; Staron, M.; Tal, M.C.; Pineda, C.M.; Lang, S.M.; Bestwick, M.; Duguay, B.A.; Raimundo, N.; MacDuff, D.A.; Kaech, S.M.; Smiley, J.R.; Means, R.E.; Iwasaki, A.; Shadel, G.S. Mitochondrial DNA stress primes the antiviral innate immune response. *Nature,* **2015**, *520*(7548), 553-557. http://dx.doi.org/10.1038/nature14156 PMID: 25642965

[76] Torralba, D.; Baixauli, F.; Sánchez-Madrid, F. Mitochondria know no boundaries: mechanisms and functions of intercellular mitochondrial transfer. *Front. Cell Dev. Biol.,* **2016**, *4*, 107. http://dx.doi.org/10.3389/fcell.2016.00107 PMID: 27734015

[77] Ballana, E.; Mercader, J.M.; Fischel-Ghodsian, N.; Estivill, X. MRPS18CP2 alleles and DEFA3 absence as putative chromosome 8p23.1 modifiers of hearing loss due to mtDNA mutation A1555G in the 12S rRNA gene. *BMC Med. Genet.,* **2007**, *8*, 81. http://dx.doi.org/10.1186/1471-2350-8-81 PMID: 18154640

[78] Bykhovskaya, Y.; Mengesha, E.; Wang, D.; Yang, H.; Estivill, X.; Shohat, M.; Fischel-Ghodsian, N. Human mitochondrial transcription factor B1 as a modifier gene for hearing loss associated with the mitochondrial A1555G mutation. *Mol. Genet. Metab.,* **2004**, *82*(1), 27-32. http://dx.doi.org/10.1016/j.ymgme.2004.01.020 PMID: 15110318

[79] Davidson, M.M.; Walker, W.F.; Hernandez-Rosa, E.; Nesti, C. Evidence for nuclear modifier gene in mitochondrial cardiomyopathy. *J. Mol. Cell. Cardiol.,* **2009**, *46*(6), 936-942. http://dx.doi.org/10.1016/j.yjmcc.2009.02.011 PMID: 19233192

[80] Deng, J.H.; Li, Y.; Park, J.S.; Wu, J.; Hu, P.; Lechleiter, J.; Bai, Y. Nuclear suppression of mitochondrial defects in cells without the ND6 subunit. *Mol. Cell. Biol.,* **2006**, *26*(3), 1077-1086. http://dx.doi.org/10.1128/MCB.26.3.1077-1086.2006 PMID: 16428459

[81] Hao, H.; Morrison, L.E.; Moraes, C.T. Suppression of a mitochondrial tRNA gene mutation phenotype associated with changes in the nuclear background. *Hum. Mol. Genet.,* **1999**, *8*(6), 1117-1124. http://dx.doi.org/10.1093/hmg/8.6.1117 PMID: 10332045

[82] Hudson, G.; Keers, S.; Yu-Wai-Man, P.; Griffiths, P.; Huoponen, K.; Savontaus, M.L.; Nikoskelainen, E.; Zeviani, M.; Carrara, F.; Horvath, R.; Karcagi, V.; Spruijt, L.; de Coo, I.F.; Smeets, H.J.; Chinnery, P.F. Identification of an X-chromosomal locus and haplotype modulating the phenotype of a mitochondrial DNA disorder. *Am. J. Hum. Genet.,* **2005**, *77*(6), 1086-1091. http://dx.doi.org/10.1086/498176 PMID: 16380918

[83] Johnson, K.R.; Zheng, Q.Y.; Bykhovskaya, Y.; Spirina, O.; Fischel-Ghodsian, N. A nuclear-mitochondrial DNA interaction affecting hearing impairment in mice. *Nat. Genet.,* **2001**, *27*(2), 191-194. http://dx.doi.org/10.1038/84831 PMID: 11175788

[84] Potluri, P.; Davila, A.; Ruiz-Pesini, E.; Mishmar, D.; O'Hearn, S.; Hancock, S.; Simon, M.; Scheffler, I.E.; Wallace, D.C.; Procaccio, V. A novel NDUFA1 mutation leads to a progressive mitochondrial complex I-specific neurodegenerative disease. *Mol. Genet. Metab.,* **2009**, *96*(4), 189-195. http://dx.doi.org/10.1016/j.ymgme.2008.12.004 PMID: 19185523

[85] Bonaïti, B.; Olsson, M.; Hellman, U.; Suhr, O.; Bonaïti-Pellié, C.; Planté-Bordeneuve, V. TTR familial amyloid polyneuropathy: does a mitochondrial polymorphism entirely explain the parent-of-origin difference in penetrance? *Eur. J. Hum. Genet.,* **2010**, *18*(8), 948-952. http://dx.doi.org/10.1038/ejhg.2010.36 PMID: 20234390

[86] Gershoni, M.; Levin, L.; Ovadia, O.; Toiw, Y.; Shani, N.; Dadon, S.; Barzilai, N.; Bergman, A.; Atzmon, G.; Wainstein, J.; Tsur, A.; Nijtmans, L.; Glaser, B.; Mishmar, D. Disrupting mitochondrial-nuclear coevolution affects OXPHOS complex I integrity and impacts human health. *Genome Biol. Evol.,* **2014**, *6*(10), 2665-2680. http://dx.doi.org/10.1093/gbe/evu208 PMID: 25245408

[87] Kim, A.; Chen, C.H.; Ursell, P.; Huang, T.T. Genetic modifier of mitochondrial superoxide dismutase-deficient mice delays heart failure and prolongs survival. *Mamm. Genome,* **2010**, *21*(11-12), 534-542. http://dx.doi.org/10.1007/s00335-010-9299-x PMID: 21069343

[88] Strauss, K.A.; DuBiner, L.; Simon, M.; Zaragoza, M.; Sengupta, P.P.; Li, P.; Narula, N.; Dreike, S.; Platt, J.; Procaccio, V.; Ortiz-González, X.R.; Puffenberger, E.G.; Kelley, R.I.; Morton, D.H.; Narula, J.; Wallace, D.C. Severity of cardiomyopathy associated with adenine nucleotide translocator-1 deficiency correlates with mtDNA haplogroup. *Proc. Natl. Acad. Sci. USA,* **2013**, *110*(9), 3453-3458. http://dx.doi.org/10.1073/pnas.1300690110 PMID: 23401503

[89] Vartiainen, S.; Chen, S.; George, J.; Tuomela, T.; Luoto, K.R.; O'Dell, K.M.; Jacobs, H.T. Phenotypic rescue of a Drosophila

model of mitochondrial ANT1 disease. *Dis. Model. Mech.,* **2014**, *7*(6), 635-648.
http://dx.doi.org/10.1242/dmm.016527 PMID: 24812436

[90] Yan, Z.H.; Zhou, Y.Y.; Fu, J.; Jiao, F.; Zhao, L.W.; Guan, P.F.; Huang, S.Z.; Zeng, Y.T.; Zeng, F. Donor-host mitochondrial compatibility improves efficiency of bovine somatic cell nuclear transfer. *BMC Dev. Biol.,* **2010**, *10*, 31.
http://dx.doi.org/10.1186/1471-213X-10-31 PMID: 20302653

[91] Yan, H.; Yan, Z.; Ma, Q.; Jiao, F.; Huang, S.; Zeng, F.; Zeng, Y. Association between mitochondrial DNA haplotype compatibility and increased efficiency of bovine intersubspecies cloning. *J. Genet. Genomics,* **2011**, *38*(1), 21-28.
http://dx.doi.org/10.1016/j.jcg.2010.12.003 PMID: 21338949

[92] Morrow, E.H.; Reinhardt, K.; Wolff, J.N.; Dowling, D.K. Risks inherent to mitochondrial replacement. *EMBO Rep.,* **2015**, *16*(5), 541-544.
http://dx.doi.org/10.15252/embr.201439110 PMID: 25807984

[93] Feng, C.; Liu, H.; Yang, M.; Zhang, Y.; Huang, B.; Zhou, Y. Disc cell senescence in intervertebral disc degeneration: causes and molecular pathways. *Cell Cycle,* **2016**, *15*(13), 1674-1684.
http://dx.doi.org/10.1080/15384101.2016.1152433 PMID: 27192096

[94] Zhang, X.U.; Yang, M.K.; Li, Z.; Liu, C.; Wu, J.S.; Wang, J. Expression and significance of telomerase in the nucleus pulposus tissues of degenerative lumbar discs. *Biomed. Rep.,* **2015**, *3*(6), 813-817.
http://dx.doi.org/10.3892/br.2015.516 PMID: 26623021

[95] Zhao, C.Q.; Wang, L.M.; Jiang, L.S.; Dai, L.Y. The cell biology of intervertebral disc aging and degeneration. *Ageing Res. Rev.,* **2007**, *6*(3), 247-261.
http://dx.doi.org/10.1016/j.arr.2007.08.001 PMID: 17870673

[96] Choudhary, B.; Karande, A.A.; Raghavan, S.C. Telomere and telomerase in stem cells: relevance in ageing and disease. *Front. Biosci. (Schol. Ed.),* **2012**, *4*, 16-30.
http://dx.doi.org/10.2741/s248 PMID: 22202040

[97] Andrews, B. Available from: https://www.omicsonline.org/proceedings/clinical-study-to-look-at-treating-degenerative-disc-disease-by-telomerase-gene-therapy-96682.html (Accessed **2018**).

[98] Fossel, M.B. *The Telomerase Revolution*; BenBella Books, Inc: Dallas, **2015**, pp. 98-99.

[99] Pennicooke, B.; Moriguchi, Y.; Hussain, I.; Bonssar, L.; Härtl, R.; Bonssar, L.; Härtl, R. Biological treatment approaches for degenerative disc disease: a review of clinical trials and future Directions. *Cureus,* **2016**, *8*(11), e892.
http://dx.doi.org/10.7759/cureus.892 PMID: 28018762

[100] Rosch, P.J. The newsletter of the American institute of stress, on the 2nd International Montreux Congress on Stress. Switzerland, **1989**, *2*(7), 1-7.

[101] Sarno, J.E. *Mind Over Back Pain: A Radically New Approach to the Diagnosis and Treatment of Back Pain,* 1st ed; Berkley Books: New York, **1986**.

[102] Stacy, L. How chronic stress is harming our DNA, Elissa Epel is studying how personality, stress processes and environment affect our DNA - and how we might lessen damaging effects In: *American Psychological Association*, **2014**, *9*(45), p. 28.

[103] Epel, E.S.; Blackburn, E.H.; Lin, J.; Dhabhar, F.S.; Adler, N.E.; Morrow, J.D.; Cawthon, R.M. Accelerated telomere shortening in response to life stress. *Proc. Natl. Acad. Sci. USA,* **2004**, *101*(49), 17312-17315.
http://dx.doi.org/10.1073/pnas.0407162101 PMID: 15574496

[104] Zhang, J.; Rane, G.; Dai, X.; Shanmugam, M.K.; Arfuso, F.; Samy, R.P.; Lai, M.K.; Kappei, D.; Kumar, A.P.; Sethi, G. Ageing and the telomere connection: An intimate relationship with inflammation. *Ageing Res. Rev.,* **2016**, *25*, 55-69.
http://dx.doi.org/10.1016/j.arr.2015.11.006 PMID: 26616852

[105] Blackburn, E.H.; Epel, E.S. Telomeres and adversity: Too toxic to ignore. *Nature,* **2012**, *490*(7419), 169-171.
http://dx.doi.org/10.1038/490169a PMID: 23060172

[106] Reichert, S.; Stier, A. Does oxidative stress shorten telomeres *in vivo*? A review. *Biol. Lett.,* **2017**, *13*(12), 20170463.
http://dx.doi.org/10.1098/rsbl.2017.0463 PMID: 29212750

[107] Lyon, D.E.; Starkweather, A.R.; Montpetit, A.; Menzies, V.; Jallo, N. A biobehavioral perspective on telomere length and the exposome. *Biol. Res. Nurs.,* **2014**, *16*(4), 448-455.
http://dx.doi.org/10.1177/1099800414522689 PMID: 25199652

[108] Uchino, B.N.; Cawthon, R.M.; Smith, T.W.; Kent, R.G.; Bowen, K.; Light, K.C. A cross-sectional analysis of the association between perceived network social control and telomere length. *Health Psychol.,* **2015**, *34*(5), 531-538.
http://dx.doi.org/10.1037/hea0000148 PMID: 25110842

[109] Schutte, N.S.; Malouff, J.M. A meta-analytic review of the effects of mindfulness meditation on telomerase activity. *Psychoneuroendocrinology,* **2014**, *42*, 45-48.
http://dx.doi.org/10.1016/j.psyneuen.2013.12.017 PMID: 24636500

[110] Rajarajacholan, U.K.; Riabowol, K. Aging with ING: a comparative study of different forms of stress induced premature senescence. *Oncotarget,* **2015**, *6*(33), 34118-34127.
http://dx.doi.org/10.18632/oncotarget.5947 PMID: 26439691

[111] Tyrka, A.R.; Parade, S.H.; Price, L.H.; Kao, H.T.; Porton, B.; Philip, N.S.; Welch, E.S.; Carpenter, L.L. Alterations of mitochondrial DNA copy number and telomere length with early adversity and psychopathology. *Biol. Psychiatry,* **2016**, *79*(2), 78-86.
http://dx.doi.org/10.1016/j.biopsych.2014.12.025 PMID: 25749099

[112] Révész, D.; Verhoeven, J.E.; Milaneschi, Y.; de Geus, E.J.; Wolkowitz, O.M.; Penninx, B.W. Dysregulated physiological stress systems and accelerated cellular aging. *Neurobiol. Aging,* **2014**, *35*(6), 1422-1430.
http://dx.doi.org/10.1016/j.neurobiolaging.2013.12.027 PMID: 24439483

[113] Schaakxs, R.; Wielaard, I.; Verhoeven, J.E.; Beekman, A.T.; Penninx, B.W.; Comijs, H.C. Early and recent psychosocial stress and telomere length in older adults. *Int. Psychogeriatr.,* **2016**, *28*(3), 405-413.
http://dx.doi.org/10.1017/S1041610215001155 PMID: 26265356

[114] Keng, S.L.; Smoski, M.J.; Robins, C.J. Effects of mindfulness on psychological health: a review of empirical studies. *Clin. Psychol. Rev.,* **2011**, *31*(6), 1041-1056.
http://dx.doi.org/10.1016/j.cpr.2011.04.006 PMID: 21802619

[115] Hayes, A.M.; Feldman, G. Clarifying the construct of mindfulness in the context of emotion regulation and the process of change in therapy. *Clin. Psychol.,* **2004**, *11*(3), 255-260.
DOI: 10.1093/clipsy.bph080

[116] Kabat-Zinn, J. *Full catastrophe living: How to cope with stress, pain and illness using mindfulness meditation*; Bantam Dell: New York, **1990**.

[117] Germer, C.K.; Siegel, R.D.; Fulton, P.R. *Mindfulness and psychotherapy*; Guilford Press: New York, **2005**.

[118] Kabat-Zinn, J. *Wherever you go there you are: Mindfulness meditation in everyday life*; Hyperion: New York, **1994**.

[119] Baer, R.A. Mindfulness training as a clinical intervention: A conceptual and empirical review. *Clin. Psychol.,* **2003**, *10*, 125-143.

[120] Brown, K.W.; Ryan, R.M. The benefits of being present: mindfulness and its role in psychological well-being. *J. Pers. Soc. Psychol.,* **2003**, *84*(4), 822-848.
http://dx.doi.org/10.1037/0022-3514.84.4.822 PMID: 12703651

[121] Cardaciotto, L.; Herbert, J.D.; Forman, E.M.; Moitra, E.; Farrow, V. The assessment of present-moment awareness and acceptance: the Philadelphia Mindfulness Scale. *Assessment,* **2008**, *15*(2), 204-223.
http://dx.doi.org/10.1177/1073191107311467 PMID: 18187399

[122] Goyal, M.; Singh, S.; Sibinga, E.M.; Gould, N.F.; Rowland-Seymour, A.; Sharma, R.; Berger, Z.; Sleicher, D.; Maron, D.D.; Shihab, H.M.; Ranasinghe, P.D.; Linn, S.; Saha, S.; Bass, E.B.; Haythornthwaite, J.A. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. *JAMA Intern. Med.,* **2014**, *174*(3), 357-368.
http://dx.doi.org/10.1001/jamainternmed.2013.13018 PMID: 24395196

[123] Sharma, H. Meditation: process and effects. *Ayu,* **2015**, *36*(3), 233-237.
http://dx.doi.org/10.4103/0974-8520.182756 PMID: 27313408

[124] Spine-Health. Pain Management Techniques for Degenerative Disc Disease. Available from: https://www.spine-health.com/conditions/degenerative-disc-disease/pain-management-techniques-degenerative-disc-disease

[125] Zaman, F. *Lumbar Degenerative Disc Disease.* Available from: https://www.spine.org/KnowYourBack/Conditions/DegenerativeConditions/LumbarDegenerativeDiscDisease. (Accessed **2014**).

[126] Asha, M.R.; Hithamani, G.; Rashmi, R.; Basavaraj, K.H.; Jagannath Rao, K.S.; Sathyanarayana Rao, T.S. History, mystery and

chemistry of eroticism: Emphasis on sexual health and dysfunction. *Indian J. Psychiatry,* **2009**, *51*(2), 141-149. http://dx.doi.org/10.4103/0019-5545.49457 PMID: 19823636

[127] Lawrentschuk, N.; Perera, M. Benign Prostate Disorders. Feingold, K.R.; Anawalt, B.; Boyce, A. Eds.: Endotext, MDText.com, Inc.: South Dartmouth (MA), **2000**.

[128] Brower, V. Mind-body research moves towards the mainstream. *EMBO Rep.,* **2006**, *7*(4), 358-361. http://dx.doi.org/10.1038/sj.embor.7400671 PMID: 16585935