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Research Progress of Skeletal Muscle Injury Repair and Treatment Strategies

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Abstract: Skeletal muscle is the most abundant tissue in the human body. It has high adaptability and regenerative potential. Skeletal muscle injuries are very common in people's lives, often secondary to various acute and chronic injuries and diseases. There are three main stages in the repair and regeneration process: the destruction stage of the initial inflammatory response, the regeneration stage of muscle satellite cell (MSCs) activation and proliferation, and the remodeling stage of the maturation of regenerated muscle fibers, among which, muscle satellite cells reside in the body and are muscle stem cells required for skeletal muscle growth and repair of damaged muscle fibers. The repair process is controlled by complex and precise regulatory mechanisms, including the interaction of cells and cells, cells and matrix, and extracellular secretory factors. There are many clinical treatment options for skeletal muscle injury, including physical, drug, surgical therapy and various new therapies such as growth factor injection, muscle stem cell combined or without bio-scaffold transplantation, anti-fibrosis treatment, and medical ozone injection. This article reviews skeletal muscle regeneration mechanisms and repair methods, in order to help clinicians choose appropriate treatment methods, and promote the development and application of more effective treatment strategies.

Skeletal muscle is one of the most abundant tissues in the human body, accounting for about 40% of the total body mass and consists of thousands of contractile bundles of muscle fibers. Each muscle fiber is a muscle cell and is covered and joined together by connective tissue. People's

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various activities are the result of the cooperation of many skeletal muscles. Skeletal muscle injuries can be caused by a variety of events, including direct injuries such as muscle tears and contusions, indirect injuries such as strain, and degenerative diseases such as muscular dystrophy [1]. Skeletal muscle injury often leads to muscle fiber rupture and dissolution, resulting in structural destruction and dysfunction of skeletal muscle, and even muscle atrophy and loss of function. The high adaptability and regeneration potential of skeletal muscle enable it to regenerate spontaneously to a certain extent to cope with mild injury. However, after severe injury, muscle spontaneous healing is incomplete, coupled with impaired revascularization, resulting in fibroblast proliferation, fibrosis and the formation of fibrous scar tissue, resulting in further muscle degeneration and damage to muscle function [2].

MSCs, which is very important for the repair of injured skeletal muscle, is a kind of myoblast precursor cell with the ability of proliferation and self-renewal, which is located between the muscle fiber plasma membrane and the basement membrane [3, 4]. In adult muscles, MSCs is at rest, and MSCs accounts for about 5 to 10 percent of skeletal muscle cells depending on age, muscle position, and type [5]. When skeletal muscle is injured or stimulated, MSCs is activated and proliferated, and myoblasts are produced, then differentiate into multinucleated myotubes or fuse with damaged muscle fibers, and finally mature in functional muscle fibers to form regenerated muscle fibers, so as to achieve the purpose of repairing damaged skeletal muscle.

1. Pathophysiological Process of Skeletal Muscle Injury and Repair

As shown in figure 1-3, there are three stages of repair process after skeletal muscle injury. Muscle degeneration and inflammation occur immediately after muscle injury. The homeostasis in the injured tissue is destroyed, resulting in inactivation of protease and hydrolase, resulting in muscle fiber injury and necrosis. After muscle degeneration, neutrophils first infiltrate the lesion site and secrete a large number of pro-inflammatory factors, chemokines , and growth factors. A microenvironment with inflammatory chemotaxis has been created for monocytes and macrophages [6]. In this process, M1 and M2 macrophages were active at this stage successively [7].

Muscle regeneration usuall begins at 4-5 days after injury, reaches a peak at 14 days, and begins to weaken at 21-28 days. This process includes activation and increment of MSCs, repair of damaged muscle fibers and formation of connective tissue. These mechanisms work together to promote the recovery of muscle contractile function. The innate repair ability of skeletal muscle to injury depends on the existence of MSCs [8]. Myogenic regulatory factors (MRFs) are also involved in the process of skeletal muscle regeneration [9], and autophagy of skeletal muscle is responsible for the degradation of intracellular proteins, macromolecules and organelles, which also plays an important regulatory role in the process of regeneration.

Connective tissue formation and fibrosis are important steps in the process of muscle regeneration. The fibrin and fibronectin gathered in the injured site initiated the occurrence of extracellular matrix and formed the place where fibroblasts proliferated [10]. In the initial stages of connective tissue formation and fibrosis, these fibrogenic cytokines stabilize the tissue and act as scaffolds for muscle fiber regeneration, but excessive collagen synthesis after injury usually leads to the formation of scar tissue, which in turn interferes with normal muscle function [11]. The recovery of blood supply in damaged skeletal muscle is one of the earliest signs of muscle regeneration. The last step of muscle regeneration and maturation is to innervate the injured muscle fibers after complete regeneration [12]. In short, a precise balance of intracellular mechanisms regulating resting, differentiation, renewal, expression and secretion is necessary for skeletal muscle function and regeneration.

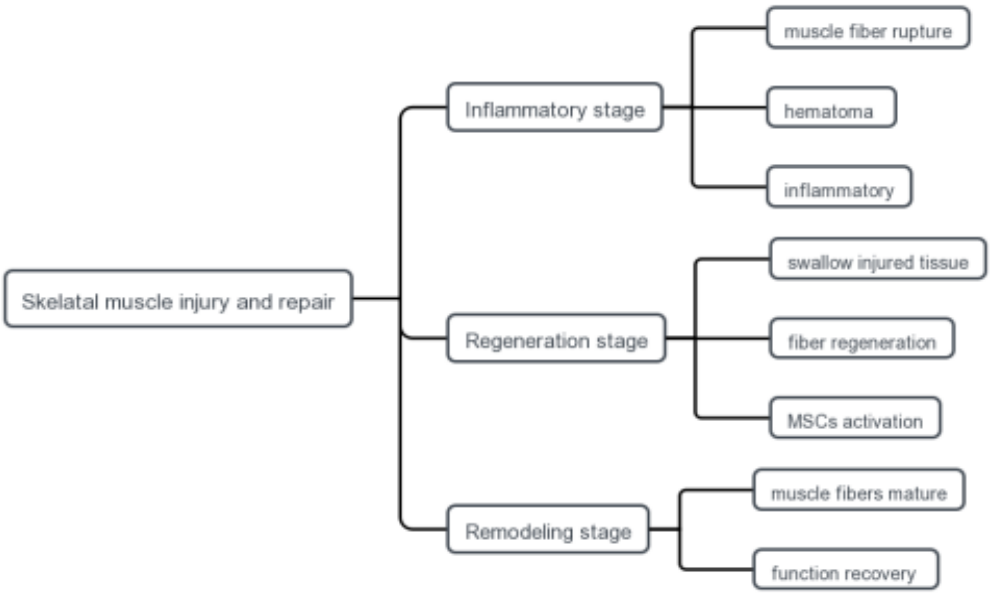

Figure 1. Three stages of repair process

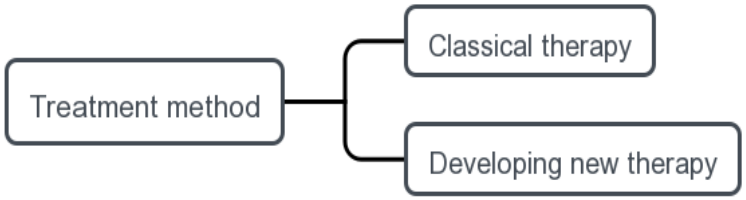

Figure 2. Treament method

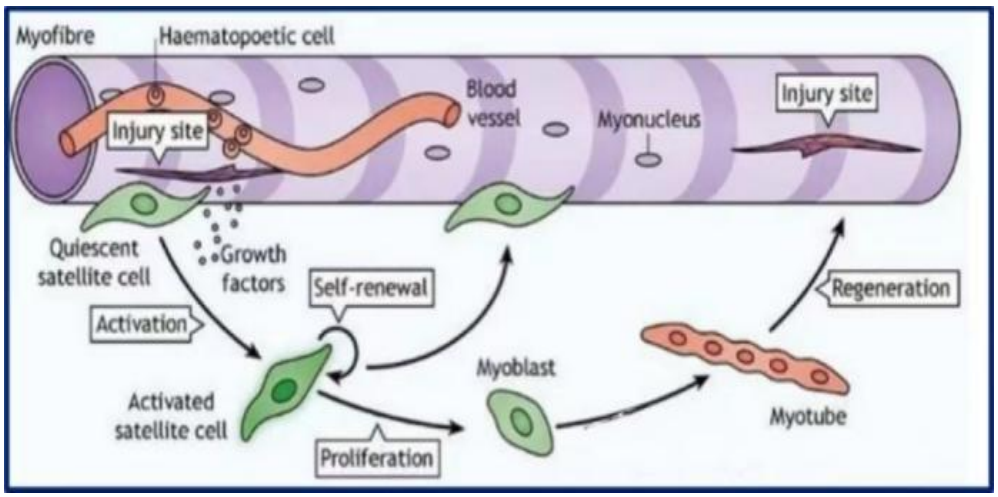

Figure 3. Repair process after skeletal muscle injury

2. Classical Therapy (Figure 4)

2.1. Physiotherapy

Early exercise can accelerate the growth of capillaries, promote the regeneration of muscle fibers, and prevent the decrease of skeletal muscle groups. through exercise, muscles can also recover more quickly to the level of function before injury [13]. Some studies have said that physical exercise can up-regulate the expression of IGF-1 signaling pathway in animal and human muscle tissue, reduce muscle growth inhibin in muscle tissue, and thus prevent muscle atrophy [14]. Studies by AndrzejewskiW have shown that angiogenesis-enhancing interventions such as exercise and massage are potential strategies for clinical muscle transplantation or other surgery to accelerate new muscle formation [15]. However, early exercise after injury may lead to the expansion of scar tissue and secondary injury, and immobilization for too long will lead to atrophy of healthy muscles and excessive deposition of connective tissue in muscles, which will delay the recovery of damaged muscle strength. BaogeL concluded through a retrospective study that they should rest 3-7 days after injury, and then start activities below the activity threshold that causes pain [16]. In addition, the limitation of physiotherapy is that patients with serious illness or serious injuries are unable to exercise.

2.2. Nonsteroidal Anti-Inflammatory Drugs (Nsaids)

NSAIDs are mainly used for analgesia, anti-inflammation and antipyretic,but the use of anti-inflammatory drugs has been questioned in recent years. O'Grady confirmed that in the short term, anti-inflammatory drugs can improve the recovery of muscle injury caused by in situ necrosis [17]. However, in the experimental results of PaoloniJA, NSAIDs has no greater analgesic effect on muscle injury than paracetamol, but has more side effects, including aggravating asthma and gastrointestinal side effects, kidney side effects, hypertension and so on. The benefit of NSAIDs may be that the use of low-dose NSAIDs can prevent hypoxia and further cell necrosis caused by edema during overreaction of inflammation [18]. Through a retrospective study of the use of NSAIDs, Rahusen et al suggested that NSAIDs drugs should be given not earlier than 48 hours after muscle injury to provide analgesia and reduce early inflammatory response, because early use of these drugs may interfere with the cellular chemotaxis necessary for muscle repair and remodelling [19]. RahusenFT do not recommend long-term (more than 7 days) use of NSAIDs because it inhibits the proliferation, differentiation and production of growth factors of MSCs, thus delaying muscle regeneration19, it also reduces the biomechanical strength of injured muscles and delays the clearance of hematoma and necrotic tissue [20].

2.3. Surgical Treatment

Indications for surgical treatment include: large intramuscular hematoma, complete injury or tear (III grade), and local injury with more than half of the muscle tears. Surgical treatment mainly includes scar tissue removal and muscle transplantation [21]. Clinically, autologous muscle transplantation is usually performed in cases of extensive muscle loss caused by trauma, tumor resection or nerve injury, because such conditions impair irreparable motor function [22, 23]. When there is no adjacent desirable muscle due to high nerve injury or severe trauma, autologous muscle transplantation and nerve anastomosis can be performed in the form of free functional muscle transplantation [24]. The limitation of surgical therapy is that up to 10% of reconstruction operations fail completely due to complications such as infection and necrosis [25], and the source of autologous muscle cannot be guaranteed according to the injury of different patients.

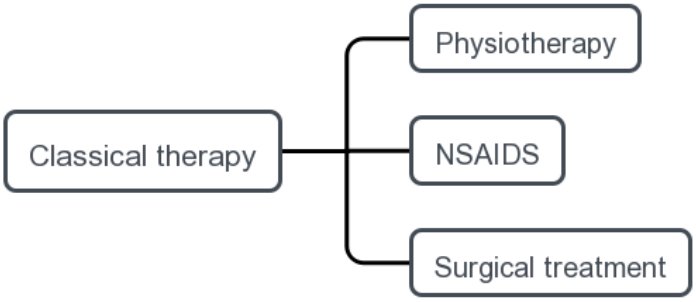

Figure 4. Classical therapy

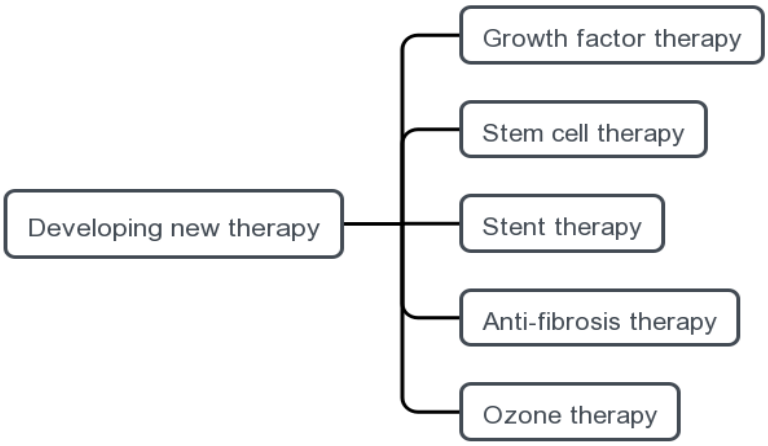

Figure 5. Developing new therpy

3. Developing New Therapy (Figure 5)

3.1. Growth Factor Therapy

Growth factors play different roles in different stages of muscle regeneration. Many studies have shown that HGF, FGF, IGF-I, VEGF, PDGF, TGF-βand NGF can play an active role in muscle regeneration [26]. Through the experimental study of constructing mouse model, MenetreyJ found that direct injection of recombinant human IGF-I at 2, 5 and 7 days after injury could promote the healing of tearing, contusion and muscle strain [27]. However, IGF injection can promote the development of fibrosis by stimulating the production of matrix components such as collagen and reducing the expression of matrix degrading enzymes such as collagenase. GrasmanJM loaded HGF on fibrin scaffold and transported it to mice and released it quickly, thus achieving the purpose of promoting functional muscle tissue reconstruction and regeneration [28]. At present, the only way of clinical administration of growth factor is external dressing, because the injection of growth factor can easily lead to the disintegration of the growth and development of the injection site, this kind of therapy still needs further research.

3.2. Stem Cell Therapy

The regeneration of muscle fiber depends on stem cells (SC). The stem cells used to treat muscle injury mainly include myoblasts, muscle satellite cells, angioblasts, pericytes and mesenchymal stem cells. Studies have confirmed that SC can widely promote the formation of new muscle fibers, of which the most important muscle stem cells are muscle satellite cells [29]. M.Cerletti confirmed that muscle satellite cells transplanted into MDX mice with dystrophy protein deficiency can promote the efficient regeneration of dystrophic muscle and improve muscle contractile function. However, the expansion of muscle satellite cells in vitro results in a significant decrease in their ability to produce muscle fibers in vivo [30], and the results of myoblasts transplantation in several clinical trials of Duchenne muscular dystrophy are not satisfactory, so it also limits the clinical application of myoblasts and muscle satellite cell transplantation [31]. In recent years, there have been studies on angioblasts and pericytes for the treatment of muscular dystrophy [32]. In stem cell studies on other non-satellite cells, human angioblasts, muscle-derived endothelial cells and CD133 (+) cells showed muscle-derived potential in vitro and in vivo, suggesting that the use of these stem cells to improve the repair of muscle injury may become a new therapeutic option [33-35].

3.3. Stent Therapy

Biological scaffolds consisting of extracellular matrix proteins are commonly used for tissue reconstruction and regeneration in regenerative medicine and surgery. Scaffolds can facilitate the repair of muscle injuries by providing a structural and biochemical framework [36] Through the use of appropriate scaffold composition and growth factors, the survival and migration rates of some precursor cells that help reconstruct muscle after trauma can be greatly increased. The combination of xenogeneic extracellular matrix and autologous tissue has been used to promote muscle recovery [37]. For example, MaseVJ and others have applied multilayer scaffolds made of extracellular matrix (ECM) extracted from porcine intestinal submucosa to the reconstruction of medial vastus muscle in patients [38]. However, the limitation of biological stent therapy is that allograft or stent may induce adverse immune response after entering the body, and there is a potential risk of spreading infectious diseases, so the use of biological stent therapy still needs further research.

3.4. Anti-Fibrosis Therapy

TGF-β1 is highly expressed in the process of muscle injury and repair, and plays an important role in the fibrotic cascade reaction. Therefore, the expression of TGF-β1 in neutralizing injured skeletal muscle can theoretically inhibit the formation of scar tissue. LiY and other studies have shown that the use of anti-fibrosis drugs (such as core proteoglycan, relaxin, and anti-TGF-β1 antibody) can inactivate TGF-β1 signal pathway, thus reduce muscle fibrosis, promote muscle healing, and almost completely recover muscle tears [39]. Losartan and suramin are both antifibrotic drugs approved by the Food and Drug Administration of the United States.

3.5. Ozone Therapy

Ozone has good anti-inflammatory, analgesic and immunomodulatory effects [40]. It has been used to treat a variety of soft tissue injury-related diseases. Previous studies have shown that medical ozone can directly antagonize many inflammatory factors, inhibit the synthesis and release of prostaglandins, bradykinin and pain-causing complexes, improve the anoxic environment of local metabolic nerve endings, induce the expression of antioxidant enzymes, and neutralize oxidation products in local tissues because of its strong oxidation, thus giving play to anti-inflammatory and

analgesic effects [41-43]. Using the rabbit tibialis anterior muscle crush injury model, we observed the histological morphological changes of rabbit skeletal muscle cells and the changes of IL-6, TNF-αand IL-1 levels in tissue and plasma after local injection of different concentrations of medical ozone at the injured site. The results showed that the histological morphology of rabbit skeletal muscle recovered better and the expression of inflammatory factors decreased in ozone treatment group [44-46].

4. Conclusion

Skeletal muscle injury, as a common disease in daily life, plays an important role in clinic, but the best strategy for the treatment of this kind of injury is not clear, and it is also a challenging problem in trauma recovery. After trauma, skeletal muscle has a certain ability to regenerate and repair through complex and coordinated comprehensive responses, which requires the existence of different cell populations, the up-regulation and down-regulation of various gene expression and the participation of a variety of growth factors. By reviewing the mechanism of skeletal muscle injury and its various treatment strategies, we find that with the in-depth understanding of skeletal muscle injury, classical therapy is experiencing new shocks and challenges, and is also constrained by its limitations. therefore, a more appropriate and efficient treatment is needed in clinic. At present, the research on some new therapies is not sufficient and not perfect, which requires us to better understand the cellular and molecular pathways in the process of skeletal muscle injury and repair. better define the interaction between cells and cells, cells and matrix, and cells and exocrine factors, and go deep into the research of biomaterials, tissue engineering and regenerated cell therapy, in order to develop and promote more effective treatment strategies.

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Data Availability

The datasets used during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

The author states that this article has no conflict of interest.

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