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Genomic stability and telomere regulation in skeletal muscle tissue

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ABSTRACT

Muscle injuries are common, especially in sports and cumulative trauma disorder, and their repair is influenced by free radical formation, which causes damages in lipids, proteins and DNA. Oxidative DNA damages are repaired by base excision repair and nucleotide excision repair, ensuring telomeric and genomic stability. There are few studies on this topic in skeletal muscle cells. This review focuses on base excision repair and nucleotide excision repair, telomere regulation and how telomeric stabilization influences healthy muscle, injured muscle, exercise, and its relationship with aging. In skeletal muscle, genomic stabilization and telomere regulation seem to play an important role in tissue health, influencing muscle injury repair. Thus, therapies targeting mechanisms of DNA repair and telomeric regulation could be new approaches for improving repair and prevention of skeletal muscle injuries in young and old people.

1. Introduction

Muscle injury may result from direct trauma, when an external force is applied to the muscle, and external and internal structures are squeezed against each other, and from indirect trauma, when there is not an external traumatic force, and the main cause of injury is eccentric muscle contraction [1]. Muscular lesions have three grades: in grade I, laceration involves few muscular fibers, with preservation or minimal loss of function; in grade II, tissue damage occurs with strength reduction in the musculotendinous unit; in grade III, laceration is complete and there is loss function [2].

The muscle regeneration process entails by four interconnected phases: necrosis, inflammation, activation and differentiation of satellite cells, maturation of newly formed myofibrils and muscle remodeling [3]. In the inflammatory phase, during muscle injury repair, reactive oxygen species (ROS) are generated in large quantities, predominantly in neutrophils and macrophages M2 [4]. In addition, MAPK (Mitogen Activated Protein Kinases), NFκB (factor nuclear kappa B) and AP-1 (Activator protein 1) activation by ROS induces protective response in injured muscle [4]. Furthermore, antioxidant enzymes, such as superoxide dismutase 2, glutathione peroxidase and catalase, are increased in the first days after injury [5]. Thus, ROS activates important signaling pathways for muscle repair. However, impaired oxidative stress can lead to secondary damage of non-injured fibers [6].

Oxidative stress can also lead to oxidative DNA damages, repaired by base excision repair (BER) and nucleotide excision repair (NER) to maintain genome stabilization [7]. More recently, it has been reported that BER modulates positively with telomeric regulation, and NER is also related to telomeric regulation; however, further studies need to be performed to clarify NER role in telomere regulation process [8].

2. Muscle injury

More than 20 million injuries occur in the musculoskeletal system every year in the United States, and cost to the health system 150 billion dollars year. The most common muscle injuries are sprains, fractures and contusions [9]. Muscle contusions and stress injuries account for approximately 55% of all acute sports-related injuries.

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Musculoskeletal injuries are the most common cause of severe physical disability and chronic pain affecting millions of people around the world, and representing a major concern for sports medicine [10].

The muscle injury repair is divided into three stages: the inflammatory phase (1–3 days), the repair phase (3–4 weeks) and the remodeling phase (3–6 weeks) [11]. After muscle injury, rupture and necrosis of myofibers occur, and a hematoma is formed, and inflammatory cells can freely invade sites of the lesion due to blood vessel rupture [12]. Polymorphonuclear leukocytes are the most abundant inflammatory cells replaced by monocytes few hours after the injury [11].

Then, monocytes are transformed into macrophages which remove necrotic fibers by phagocytosis and produce, together with fibroblasts, chemotactic signals, such as growth factors, cytokines and chemokines [13]. The main growth factors involved in muscle injury repair are FGF (fibroblast growth factor), IGF-1 (insulin-like growth factor-1), IGF-2 (insulin-like growth factor-2), TGF-β (transforming growth factor-β), HGF (hepatocyte growth factor), TNF-α (tumor necrosis factor α), and IL-6 (interleukin-6) [11].

The next phase is the repair phase, consisting of two concomitant processes: regeneration of ruptured myofibers and, formation of scar of connective tissue by fibrin and fibronectina [11]. Regeneration occurs due to satellite cell action, located under the basal lamina of myofibers [14], with satellite cells proliferating and differentiating into myoblasts, which in turn fuse with the injured myofibers in the space between the two ends of these myofibers [15].

Connective tissue scar formation by fibrin and fibronectin generates the muscle strength to withstand contractions providing, for fibroblasts, an anchoring site to invade the granulation tissue [11]. If excessive proliferation of these fibroblasts occurs, dense scar tissue is formed into the injured muscle, interfering not only in repair process but also in the muscle regeneration process, thereby contributing to incomplete functional recovery of the injured muscle during the remodeling phase [16] (Fig. 1).

3. Satellite cells and muscle repair factors

Paired-box transcription factor 7 (Pax7) is necessary for maintenance and development of satellite cells being directly related to paired-box transcription factor 3 (Pax3), also expressed in quiescent satellite cells, and both play an essential role maintaining progenitor proliferation and preventing early myogenic differentiation, as well as cell death by apoptosis [17]. To differentiate satellite cells into mature muscle fibers, Pax7 expression is reduced, inducing skeletal muscle differentiation [18].

Myogenic factor 1 (MyoD), myogenic factor 5 (Myf5), myogenic regulatory factor 4 (MRF4) and myogenin (myogenic factor 4 - MyoG) play essential roles in myogenic specification, differentiation and maintenance during development and muscle regeneration [17]. MyoD and Myf5 are involved in myogenic cell determination, which implicates Myf5 and MyoD in establishing and maintaining muscle progenitor lineages, while Myogenin and MRF4 are related to terminal differentiation and homeostasis of myofibrils [19].

The expression of myogenic factors in response to muscle injury occurs as follows: (i) satellite cells activation occurs when there is Pax 7 and Myf5 expression; (ii) when the migration and differentiation phase begins, Pax7 is not expressed, Myf5 retains its expression, and Myod is also expressed; (iii) after this process, myotube fusion occurs where there is MyoD and myogenin expression, but not Myf5 expression; (iv) in the last stage, myofiber maturation occurs modulated by myogenin and MRF4 expression [20] (Fig. 2).

4. Reactive oxygen species and oxidative DNA damage in healthy and injured muscle

Reactive oxygen species (ROS) are formed endogenously by mitochondrial oxidative phosphorylation process, or through exogenous sources such as ultraviolet radiation, alcohol consumption, cigarette smoking, ingestion of nonsteroidal anti-inflammatory drugs and infections [21]. Also, oxidative stress occurs when ROS levels increase and cellular antioxidant capacity reduces [22].

At high levels, ROS cause damage in cellular structures, such as nucleic acids, lipids and proteins [23]. DNA damage can occur as a result of hydroxyl radical generation in the reaction of transition metal ions, present in the DNA, with hydrogen peroxide, or due to increase of intracellular concentration of calcium ions, which activates nucleases [24] and damages purine and pyrimidine bases, as well as the deoxyribose backbone [23]. Permanent modifications of genetic material caused by oxidative damage represent the first step of mutagenesis, carcinogenesis and aging [25].

DNA damage through ROS includes DNA base lesions, DNA sugar lesions, DNA strand breaks with terminal block and DNA-protein cross links. Guanine is the most susceptible nitrogen base to oxidation due to its lower redox potential [26]. Hydroxyl radical interacts with guanine resulting in a reduced neutral radical, which reacts with molecular oxygen (O_2) and, via electron transfer, produces different products in DNA, as 8-oxo-7,8-di-hidroguanina (8-oxoG) e 2-6-diamino-4-hidroxi-5-formamidopirimidinas (FapyG) [26].

In healthy muscle, ROS are important at basal levels for muscle contraction, and depletion of ROS levels, by antioxidant action, results in inhibition of muscle contraction [27]. Also, ROS participate in the muscle injury repair process where they are generated in a large scale,

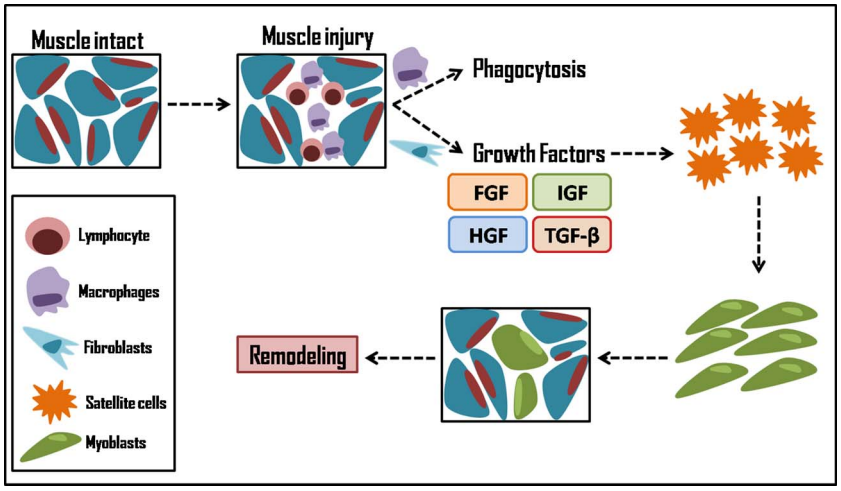

Fig. 1. Schematic representation for muscle injury repair phases. FGF: fibroblast growth factor, IGF: insulin-like growth factor, HGF: hepatocyte growth factor, TGF-β: transforming growth factor beta.