Re-examining the mechanism of eccentric exercise-induced skeletal muscle damage from the role of the third filament, titin (Review)

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Abstract. Intense and unaccustomed eccentric exercise has been extensively studied for its ability to induce muscle damage. However, the underlying mechanism of this phenomenon still requires further clarification. This knowledge gap arises from the need for explanation of the eccentric contraction through the sliding filament theory. The two-filament sarcomere model, which is consisted of thin and thick filaments, forms the basis of the sliding filament theory. The mechanisms of concentric and isometric contractions at the cellular and molecular levels are effectively described by this model. However, when relying solely on the cross-bridge swing, the sliding filament theory fails to account for specific observations, such as the stability of the descending limb of the force-length relationship curve. Recent evidence indicated that titin and the extracellular matrix (ECM) may play a protective role by interacting with the thick and thin filaments. During an eccentric contraction, titin serves as a third filament in the sarcomere, which helps regulate changes in passive force. The two-filament sarcomere model has limitations in explaining eccentric contraction, thus this compensates for those shortcomings. The present review explored the potential of replacing the two-filament sarcomere model with a three-filament sarcomere model, incorporating thin filaments, thick filaments and titin. This revised model offers a more comprehensive explanation of eccentric contraction phenomena. Furthermore, the sliding filament theory was investigated in the context of the three-filament sarcomere model. The double-layer protection mechanism, which involves increased titin stiffness and the ECM during eccentric contraction was explored. This mechanism may enhance lateral force transmission between muscle fibers and the ECM, resulting in sarcolemma and ECM shear deformation. These findings provided insight into the mechanism of eccentric exercise-induced skeletal muscle damage. Considering the three-filament sarcomere model and the double-layer protection mechanism, the present review offered a more logical and comprehensive understanding of the mechanism behind eccentric exercise-induced muscle damage.

Contents

1. Introduction

Skeletal muscle exhibits three distinct types of contraction based on its functional characteristics: i) Concentric contraction, also known as concentric exercise, involves the active shortening of muscle length, which results in the displacement of the limb; ii) isometric contraction (isometric exercise) occurs when the muscle length remains constant, preventing limb movement; and iii) eccentric contraction (eccentric exercise) involves the lengthening of the muscle as it resists external force or decelerates (1-3). Among the three types of contractions, eccentric contraction stands out by generating higher muscle force, albeit with the recruitment of a relatively minor number of motor units. Consequently, this type of contraction is associated with lower energy consumption and oxygen uptake (1). Due to its advantageous characteristics, eccentric contraction training has gained widespread recognition and utilization in various domains. One notable advantage is its remarkable ability to enhance muscle force while minimizing

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metabolite production. As a result, the eccentric contraction training mode has found extensive application in physical training and injury rehabilitation within competitive sports and in the realm of sports rehabilitation for metabolic and musculoskeletal disorders (1,4-6). However, eccentric contraction can lead to noteworthy ultrastructural changes in skeletal muscles, including Z-disk streaming, disruption and sarcomere destruction. Delayed skeletal muscle ultrastructural changes are remarkable for their delayed onset, with the peak occurring between 24-72 h (1,7). The scientific community widely acknowledges that skeletal muscle ultrastructural changes actively contribute to symptoms associated with delayed onset muscle soreness (DOMS). In addition to DOMS, these symptoms encompass reduced muscle strength and various indicators of skeletal muscle damage (1,7,8), resulting in changes in the activation sequence and recruitment patterns of muscle motor units. This compensatory mechanism further induces the occurrence of skeletal muscle damage (7,9-11). However, the degree of ultrastructural changes in eccentric exercise-induced skeletal muscle does not match the degree of DOMS symptoms (7,12). Hence, it becomes imperative to investigate the mechanism underlying ultrastructural changes in skeletal muscle induced by eccentric exercise and elucidate its precise association with symptoms of DOMS. Such research endeavors offer practical insights for formulating evidence-based physical training or sports rehabilitation programs. Currently, the mechanism underlying eccentric exercise-induced skeletal muscle damage remains unknown, and the lack of understanding about eccentric contraction mechanisms is partly due to the limitations of the sliding filament theory (1,4,5). The mechanism of skeletal muscle contraction is derived from the sliding filament theory, first published in Nature in 1954 by Huxley and Niedergerke (13), and Huxley and Hanson (14). This theory utilizes a two-filament sarcomere model, consisting of thin filaments composed of actin and thick filaments composed of myosin, to elucidate the mechanism of muscle contraction through the sliding action of these filaments facilitated by cross-bridges. The two-filament sliding theory explains both concentric and isometric contraction mechanisms (4); however, based solely on the cross-bridge swing, the sliding filament theory fails to account for phenomena such as the stable descending limb observed in the force-length relationship curve during eccentric contraction (4,15,16).

It was found that lateral force transmission increased after acute eccentric contraction (17), and that collagen fiber deposition in the endomysium and perimysium maintained the morphological integrity of muscle fiber after chronic prolonged eccentric contraction (9,18). It is hypothesized that some factors must ensure the stability of the stable descending limb during an eccentric contraction while increasing lateral force transmission and protecting muscle fiber from damage. It is implied that exploring the mechanism of the stable descending limb is key to re-examining the mechanism of eccentric exercise-induced skeletal muscle damage.

In fact, Hanson and Huxley (19), in confirming the sliding filament theory of the two-filament sarcomere model, hypothesized the existence of a third filament between the Z-disks. Nevertheless, the lack of evidence and the challenge of integrating the third filament into the two-filament sliding theory resulted in the publication of the sliding filament theory based solely on the two-filament sarcomere model in Nature the following year. Consequently, from its inception, the sliding filament theory of the two-filament sarcomere model has yet to be completed due to the absence of the third filament. In the book 'Reflections on Muscle', Huxley AF (20), the pioneer of the cross-bridge theory highlighted the inadequacy of the sliding filament theory, which is based on cross-bridge swinging, in explaining the mechanism of eccentric contraction (20). Subsequent studies have provided compelling evidence supporting the inclusion of titin, a spring protein spanning half of the sarcomere, as the third filament in the sarcomere (21). By integrating the two-filament sarcomere model with titin, a more comprehensive understanding of the eccentric contraction mechanism has emerged (22). The three-filament sarcomere model, comprising the thin filament, thick filament and titin as the third filament, derived from the sliding filament theory, presents a novel framework for investigating the mechanisms underlying skeletal muscle damage induced by eccentric exercise (23), thereby providing a more insightful explanation of the eccentric contraction process.

2. Overview of the sliding filament theory

Until the 1950s (24), researchers widely considered that the force produced during muscle contraction was directly associated with shortening the length of the thick filament positioned at the center of the sarcomere. However, in 1953, using high-resolution electron microscopy imaging technology, Huxley HE (25) discovered that the thick filament did not undergo shortening during muscle contraction. Subsequently, in 1954, Huxley and Hanson (14), as well as Huxley and Niedergerke (13), published two research papers in Nature proposing the sliding filament theory. This theory presents a two-filament sarcomere model comprising a thick filament composed of myosin and a thin filament composed of actin. According to this theory, the thin filament slides toward the center of the thick filament through the swinging motion of the cross-bridge, while the lengths of the thick and thin filaments remain unchanged. The purpose of developing this model is to clarify how muscle contraction works. In 1957, Huxley AF (26) revealed the first molecular model of sarcomere structure and an energy calculation formula, providing a detailed explanation of the sliding filament theory. The model proposed that myosin pulls actin using the swinging motion of the cross-bridge, causing the thin filament to slide towards the M-band at the center of the sarcomere. The energy needed for the swinging movement of the cross-bridge comes directly from adenosine triphosphate. Huxley HE (27) proposed the theory of cross-bridge swinging rotation, which Huxley and Simmons (28) later revised to account for kinetic changes in the cross-bridge during abrupt muscle force or length alterations.

3. Deficiencies in the interpretation of eccentric contraction mechanism by the sliding filament theory of the two-filament sarcomere model

To date, the two-filament sliding theory has effectively elucidated the mechanisms underlying concentric and isometric contractions at the cellular and molecular levels (4). However, this theory must fully explain the mechanism behind eccentric contractions (4,15).

In the two-filament sarcomere model, the half-sarcomere and the sarcomere exhibit instability (16,29). The positioning of the thick filament within the sarcomere depends solely on the balancing force generated by the cross-bridge in conjunction with the thin filament. Maintaining a constant balance of forces acting on the cross-bridge is necessary. Otherwise, even a slight imbalance could cause the thick filament to be pulled towards the 'stronger' half-sarcomere, leading to a more pronounced imbalance and an unstable force within the half-sarcomere (30).

As a result, during eccentric exercise, weaker sarcomeres are prone to overstretching due to non-uniform passive elongation and the less favorable structural stability of sarcomeres on the descending limb of the force-length relationship curve (31,32). However, a number of studies have demonstrated that the active stretching of the myofibril leads to the formation of highly stable structures on the descending limb of the force-length relationship curve, despite the non-uniform characteristics of sarcomere length (33,34). Besides the myosin and actin filaments, the stability of the sarcomere force-length relationship curve on the descending limb is reliant on other components.

4. Proposal of the three-filament sarcomere model

The concept of the third filament and its role. Based on the aforementioned studies, it becomes evident that the sliding filament theory of the two-filament sarcomere model cannot adequately account for the mechanism of eccentric contraction. The eccentric contraction mechanism hypothesizes the involvement of an additional sarcomere component in collaboration with myosin and actin. In 1953, Hanson and Huxley (19) introduced the concept of the two-filament sarcomere model. It was hypothesized by the authors that the existence of a third filament, known as the S filament, exists as part of the thin filament between the Z-disks. Subsequently, in 1965, the PhD thesis of Dos Remedios at the University of Sydney rediscovered the presence of other filaments within the sarcomere, reigniting interest in studying the third filament (35). In 1976, Maruyama (36) directly detected the third filament using atomic force microscopy, and in 1979, it was subsequently named titin by Wang *et al* (37). However, it was not until 1988 that Fürst *et al* (38) utilized titin antibodies to provide the initial evidence that this elastic filament extends continuously from the Z-disk to the M-band, spanning half of the sarcomere. Subsequent research revealed that titin, with a molecular weight of ~3,000-4,000 kDa, is the most substantial protein constituent of the sarcomere. It primarily comprises the I-band region (which spans the titin region of the thin filament) and the A-band region (which lies within the thick filament). The I-band region of titin comprises tandem-immunoglobulin domain (Ig) regions, including the N2A element (consisting of multiple Ig domains inserted into a single sequence) and the proline-glutamate-valine-lysine (PEVK) element located between the differentially spliced and distal Ig domains (39). The PEVK element and the Ig domains collectively represent the most critical elastic region of titin. On the other hand, the A-band region of titin primarily consists of Ig domains and repetitive fibronectin sequences, lacking any stretching functionality.

The influence factor of titin during eccentric exercise. During low-force stretching (eccentric contraction) of the sarcomere, the elongation of titin primarily occurs through the straightening of interdomain linkers in the Ig domains (39). However, during high-force stretching (eccentric contraction), the PEVK element assumes a central role in stretching, conferring spring-like properties to titin and enabling it to buffer external forces (Fig. 1). Furthermore, the spring stiffness of the PEVK element increases with higher concentrations of cytoplasmic Ca^{2+}, acting as a regulator of sarcomere force (40). Researchers consider the underlying regulatory mechanism involves titin winding around the thin filament via cross-bridge rotation. This process leads to the shortening of the elastic region and consequently, to an increase in the spring stiffness of the PEVK element (41). However, a number of different studies have suggested that the increase in titin stiffness is not dependent on the winding of the thin filament but rather on the proximity of the distal domain of titin to the central M-band of the sarcomere (the precise mechanism remains unknown) (42). Notably, using a skinned fibers model (mice soleus), Labeit *et al* (43) investigated recombinant PEVK molecules containing 28-residue PEVK repeats and E-rich motifs, and they observed that Ca^{2+} could bind to the E-rich motif of the PEVK element at the distal end of titin, thereby increasing the stiffness of titin.

To summarize the aforementioned studies, the increase in titin stiffness, in the context of elevated cytoplasmic Ca^{2+} levels, does not result from binding to the thin filament. Instead, it is associated with Ca^{2+} binding to the PEVK element, preventing titin elongation and promoting the proximity of the distal end of titin to the central M-band of the sarcomere. Regardless of whether the mechanism underlying the increase in titin stiffness is fully understood or not, it is evident that titin, as the third filament, dynamically contributes to the regulation of passive force changes within the sarcomere by interacting with the thick and thin filaments (21,41,44). This role of titin complements the limitations of the two-filament sarcomere model (40), providing a more comprehensive explanation for the mechanism of an eccentric contraction.

The three-filament sarcomere model in the interpretation of the eccentric contraction mechanism. According to several relevant studies (21,40,42,45,46), combined with the three-filament sarcomere model, the mechanism of eccentric contraction can be explained as follows (3,23,47) (Fig. 2): When the sarcomere undergoes active stretching, troponin actively binds to Ca^{2+}, resulting in a conformational change in actin. In turn, it initiates the binding of myosin heads to actin, facilitating the formation of cross-bridges. Through the swinging motion of the cross-bridges, the thin filaments actively slide towards the center of the thick filaments, thereby completing the contraction process of the sarcomere. Simultaneously, during contraction, the sarcomere is stretched by an external force, resulting in the elongation of the proximal Ig domain and PEVK element in the I-band region of titin. This elongation increases the compliance of the sarcomere, acting as a buffer against the external force (Fig. 2A). Under high force, the N2A element attaches to actin, reducing the free length of titin.

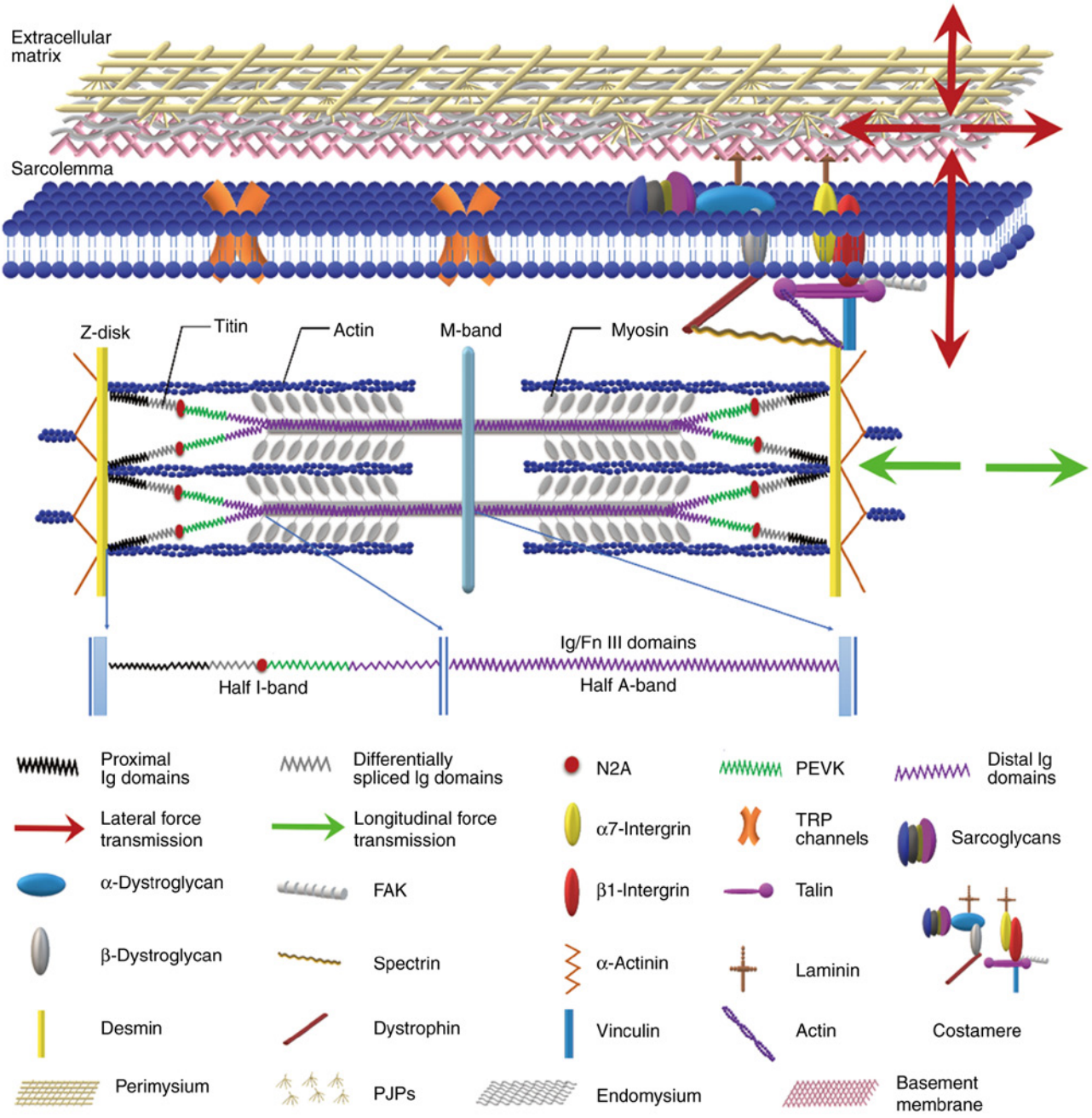

Figure 1. Illustration of the titin molecular structure and the lateral force transmission. Titin tightly attaches to myosin in the A band, moves freely across the I band and subsequently binds with actin in the Z-disk. The green arrow represents Longitudinal force transmission, signifying its propagation along the muscle fibers via the myotendinous junctions to the tendon. The red arrow indicates lateral force transmission, denoting its lateral transmission across one muscle fiber to the EMC and ultimately reaching the tendon. Ig, immunoglobin; Fn, fibronectin; PEVK, proline-glutamate-valine-lysine; TRP, transient receptor potential; PJP, perimysial junctional plates.

On the other hand, binding the PEVK element to Ca^{2+} prevents excessive elongation of PEVK. Furthermore, the swing of the cross-bridge during its translation and rotation brings the A-band and distal titin domains in closer proximity to the central M-band of the sarcomere. This active process effectively restrains the excessive elongation of the PEVK element and enhances the stiffness of titin. Consequently, it prevents the sarcomere from becoming overly compliant and safeguards the thick and thin filaments against potential damage (Fig. 2B). Therefore, the sliding filament theory of the titin-based three-filament sarcomere model provides an improved understanding of the stability mechanism observed in the descending limb of the sarcomere force-length relationship curve during eccentric contraction. It indicates that the spring-like properties and stiffness of titin help to maintain the stability of the sarcomere during an eccentric contraction and the functional characteristics of titin elucidate the mechanism of eccentric exercise-induced skeletal muscle damage.

5. Remaining problems in the mechanism of eccentric exercise-induced skeletal muscle damage

Compared with concentric and isometric exercises, eccentric exercise actively increases muscle force while consuming less

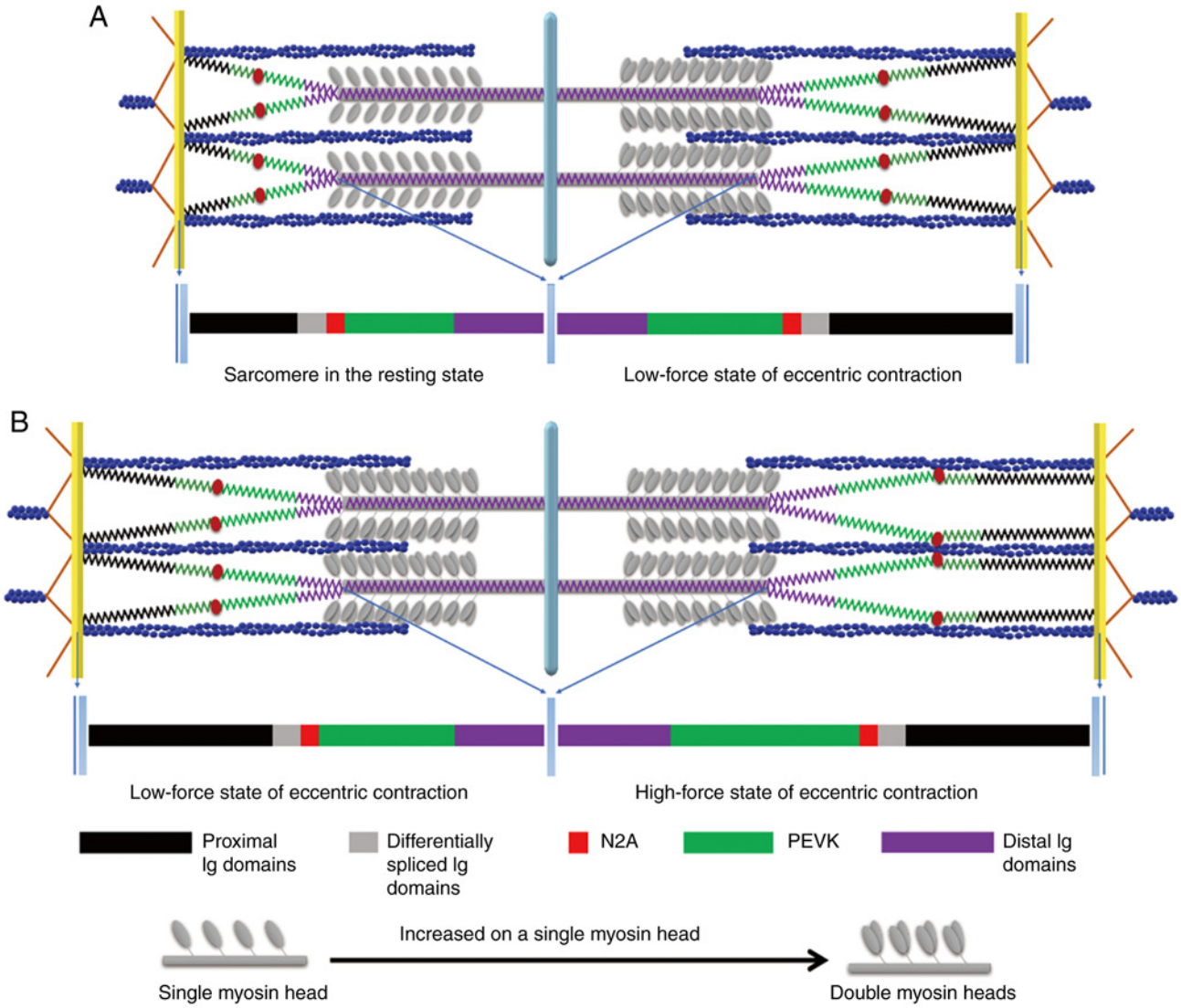

Figure 2. Illustration of the eccentric contraction mechanism. In the resting state of the sarcomere (left half-sarcomere), only one myosin head is activated to form the cross-bridge during isometric and concentric contractions. However, during an eccentric contraction, the increased strain on a single myosin head may activate the second head, forming additional cross-bridges and prolonged detachment time. During the low-force stretch state of eccentric contraction [right half-sarcomere in (A) and left half-sarcomere in (B)], the titin proximal Ig domain undergoes stretching, causing the PEVK region to act as a spring and increase in length. In the high-force stretch state of eccentric contraction [right half-sarcomere in (B)], the increased Ca^{2+} concentration results in the Ca^{2+}-dependent binding of titin N2A to actin, reducing the titin-free length and increasing titin stiffness. Simultaneously, Ca^{2+} binds to PEVK, preventing over-stretching and increasing its stiffness, which plays a protective role in the sarcomere. Data from a prior research of the authors were used to create this visualization (23). Ig, immunoglobin; PEVK, proline-glutamate-valine-lysine.

energy, making it widely utilized in physical fitness training and sports rehabilitation. However, unaccustomed exercise, particularly eccentric exercise, can lead to skeletal muscle damage, with the primary symptom being ultrastructural changes in the muscle (mainly characterized by sarcomere structural changes, such as Z-disk streaming and myofibril disruption or popping), as well as symptoms of DOMS such as reduced muscle force, soreness, swelling and increased concentration of creatine kinase (CK) in the blood (1,7). Adverse effects such as pain, swelling and impaired movement induce compensatory mechanisms in the musculoskeletal system, further increasing the risk of sports injury and potentially leading to chronic injury and pain, thus exacerbating sports-related damage (7,9-11). Consequently, some scholars have cautioned against using eccentric exercise modes for chronic disease rehabilitation training (1,6). Therefore, understanding the mechanism of eccentric exercise-induced skeletal muscle damage has been a crucial and challenging area of research in sports medicine, aiming to address exercise practice issues. It has focused on investigating the causes of ultrastructural changes in skeletal muscle, which occur with a delay and parallel the symptoms of DOMS, peaking within 24-72 h after exercise (7). Ultrastructural changes in skeletal muscle can trigger an exercise-induced inflammatory response closely associated with muscle soreness and swelling. Therefore, the prevailing consensus attributes the symptoms of DOMS to the ultrastructural changes in skeletal muscle, indicating that eccentric exercise-induced muscle damage results from these alterations (4,7).

Most scholars support the popping sarcomere hypothesis as the mechanism of eccentric exercise-induced skeletal muscle damage. The main arguments derive from the sliding

filament theory of the two-filament sarcomere model and the theory of non-uniform sarcomere length. These theories propose that during eccentric exercise, the passive elongation of the sarcomere is not uniform and the sarcomere structure is most unstable on the descending limb of the force-length relationship curve. Consequently, weaker sarcomeres are prone to be excessively stretched, leading to their disruption or destruction, often called 'popping'. As the damage intensifies, the sarcolemma is breached, resulting in uncontrolled entry of extracellular calcium ions into the cytoplasm, activating the proteolytic enzyme calpains, ultimately causing muscle damage (4,7,12,48). However, a number of studies do not support the 'popping' theory, as the integrity of the sarcolemma remains unaffected (49,50), and the degree of ultrastructural changes in skeletal muscle does not align with the symptoms of DOMS (7). The causal relationship between the extent of ultrastructural changes in skeletal muscle and changes in CK concentration and muscle force is also a subject of debate and does not correspond to DOMS (4,7,12). These findings indicated that the idea of attributing eccentric exercise-induced skeletal muscle damage solely to sarcolemma damage remains a subject of controversy.

6. The three-filament sarcomere model in the interpretation of the mechanism of eccentric exercise-induced skeletal muscle damage

The protective effect of titin stiffness causes shear stress on the sarcolemma and extracellular matrix (ECM). Based on the mechanism of eccentric contraction elucidated by the three-filament sarcomere model and recent research, it is clear that the cause of skeletal muscle damage from eccentric exercise is not only due to the overstretching of weaker sarcomeres, which can lead to tearing of the sarcolemma. Instead, researchers presume that the increased protection is a consequence of the spring stiffness of the third filament titin (49,50).

Brynnel *et al* (45) conducted detailed studies using skinned myofibers (diaphragm muscle and extensor digitorum longus) to explore the protective effect of titin and the ECM on skeletal muscle during eccentric contraction. Their findings revealed that within the sarcomere's normal physiological working length range (2.45-2.75 μm), titin primarily contributed to the increase in passive component stiffness of skeletal muscle. However, beyond this range, titin cooperates with ECM to further increase the stiffness of the passive component. Furthermore, a previous study revealed that the effect of increasing stiffness in titin is not contingent upon the range of sarcomere length (51). This finding indicated that titin works with the ECM to protect the structural integrity of the sarcomere and sarcolemma during eccentric contraction.

Moreover, a number of studies have revealed that sarcomere contraction actively transmits force to the tendons through two pathways (Fig. 1): i) Longitudinal force transmission between the sarcomeres and ii) a lateral force transmission pathway. The latter pathway involves the transmission of force through costamere proteins (dystrophin and $\alpha7\beta1$ integrin) located near the Z-disk of the sarcolemma, followed by lateral transmission to the endomysium, perimysium, epimysium (also known as ECM) (52) and eventually to the tendon (53,54).

After performing acute and chronic eccentric contractions, a significant increase in the lateral force transmission of skeletal muscle (17) and collagen fiber deposition in the endomysium and perimysium (18) was observed, respectively, suggesting a potential association between the protective mechanism of titin stiffness and the enhancement of lateral force transmission. Notably, the generation of shear stress on the endomysium shared by adjacent myofibers is directly related to the magnitude of lateral force transmission (17). During eccentric contractions, the sarcolemma and ECM work together to produce shear stress, which is essential in causing skeletal muscle damage.

The shear deformation induced by the shear stress of the sarcolemma and ECM leads to skeletal muscle damage. Hypothesis suggests that the endomysium experiences heightened shear stress during an eccentric contraction, facilitating enhanced lateral force transmission (17,18). Experts consider this phenomenon helps to protect and change the sarcolemma and ECM (17,18,23,45). This repeated stretching induces increased permeability of the sarcolemma and ECM damage, ultimately leading to skeletal muscle damage. Recent studies support the notion that the sarcolemma possesses structural characteristics capable of generating shear stress at the cellular and molecular levels, thereby supporting the plausibility of increased sarcolemma permeability due to shear stress. The lateral force transmission mechanism connects the sarcolemma with the ECM through costamere proteins, providing a structural basis for ECM shear stress damage (17). Studies have revealed the involvement of specific proteins in stabilizing the sarcolemma, such as dystrophin and caveolae, which play a role in mitigating mechanical stress and buffering the force on the sarcolemma during stretching (55,56). Furthermore, the expression of the $\alpha7$ integrin gene, a marker of mechanical stress, increases with eccentric exercise, further highlighting the involvement of the sarcolemma in shear stress (57). Additionally, experiments utilizing electrical stimulation and stretch-activated channel blockers have confirmed the increased permeability of the sarcolemma and its role in eccentric exercise-induced skeletal muscle damage (58).

In addition to sarcolemma damage, the shear deformation of the ECM due to the sarcomere's lateral force transmission also leads to ECM damage. Studies have revealed an accumulation of ECM damage, characterized by collagen fiber proliferation in the endomysium and perimysium, after eccentric training, suggesting the involvement of ECM in DOMS (18). This finding supports the view that DOMS originates from ECM damage, independent of ultrastructural changes in skeletal muscle (23,49,50). The understanding of these mechanisms has important practical implications. Firstly, incorporating eccentric training into rehabilitation programs enables the utilization of a non-destructive approach to target chronic diseases, minimizing harm to myofibers. Secondly, this approach aids in elucidating the contentious association between skeletal muscle ultrastructural changes and the manifestation of symptoms related to DOMS. These mechanisms can operate autonomously, with DOMS symptoms sharing a common mechanism involving ECM participation.

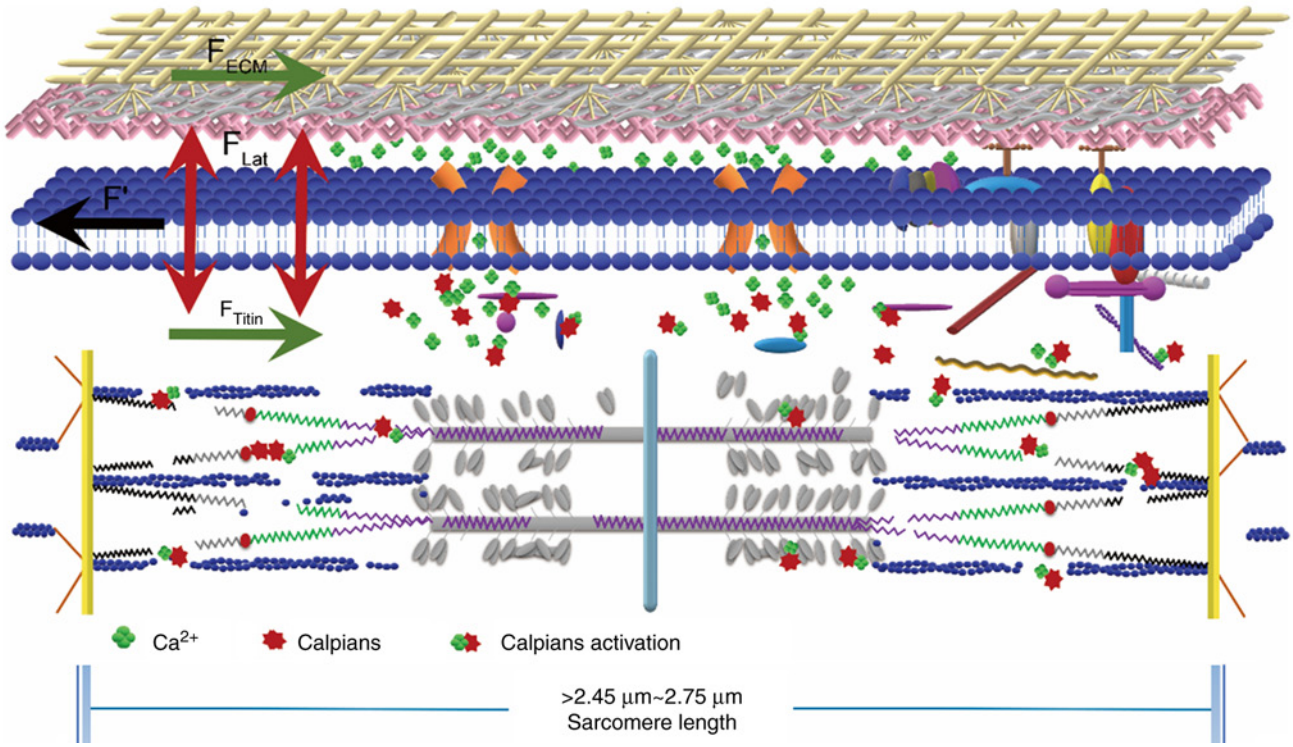

Figure 3. Illustration of the shear deformation theory of eccentric exercise-induced skeletal muscle damage mechanism. F' represents the external force acting on the sarcomere, F_{titin} denotes longitudinal force transmission, F_{Lat} signifies lateral force transmission, and F_{ECM} represents the force generated by the ECM. Lat, lateral; ECM, extracellular matrix

Mechanism of skeletal muscle damage: Shear deformation theory. To sum up the aforementioned statements, the mechanism of skeletal muscle damage is intricately linked to the shear deformation experienced by the sarcolemma and ECM as forces transmit laterally within the sarcomere. The authors refined and renamed this concept the 'shear deformation theory' based on the 'popping sarcomere hypothesis (32,48)'. The critical argument posits that passive stretching leads to non-uniformity in length by the sliding filament theory of the three-filament sarcomere model and the theory of non-uniform sarcomere length. Moreover, the structural stability of the sarcomere is at its weakest on the descending limb of the force-length relationship curve during eccentric exercise. The stiffness of titin and ECM increases to safeguard the sarcomere and sarcolemma from damage.

Consequently, the lateral transmission of forces within the sarcomere triggers shear deformation of the sarcolemma and ECM. This shear deformation prompts heightened permeability of the sarcolemma, resulting in an uncontrolled influx of extracellular calcium ions into the cytoplasm. Subsequently, the activation of calpains ensues, leading to ultrastructural damage in skeletal muscle. Simultaneously, the shear deformation of the ECM induces shear damage, culminating in DOMS via an inflammatory response (Fig. 3): When the sarcomere length exceeds the physiological range of 2.45-2.75 μm, the increased stiffness of titin and ECM functions to safeguard the integrity of the sarcolemma. Simultaneously, the lateral force transmission causes shear deformation, resulting in heightened permeability of the sarcolemma and ECM, leading to shear damage. These processes induce skeletal muscle ultrastructural changes and contribute to DOMS.

7. Conclusions

The two-filament sarcomere model, which forms the basis of the sliding filament theory, needs to be adequately explained the mechanism of eccentric contraction. However, by incorporating the third filament, titin, into the sliding filament theory, the eccentric contraction mechanism through the three-filament sarcomere model can be further elucidated. Per the revised sliding filament theory based on the three-filament sarcomere model, skeletal muscle exhibited a dual-layer protection mechanism during an eccentric contraction involving increased titin and ECM stiffness. Subsequently, the shear stress generated by lateral force enhances the permeability of the sarcolemma and leads to ECM damage, ultimately resulting in skeletal muscle damage.

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Authors' contributions

ZX conceived and designed the review. ZQ and LP were major contributors to writing the manuscript. ZQ and LP wrote parts of the manuscript and ZQ prepared the figures. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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