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Review Article

MicroRNA-Regulated Proinflammatory Cytokines in Sarcopenia

Jingjing Fan, Xianjuan Kou, Yi Yang, and Ning Chen

Hubei Key Laboratory of Exercise Training and Monitoring, Hubei Provincial Collaborative Innovation Center for Exercise and Health Promotion, College of Health Science, Wuhan Sports University, Wuhan 430079, China

Correspondence should be addressed to Ning Chen; nchen510@gmail.com

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Sarcopenia has been defined as the aging-related disease with the declined mass, strength, and function of skeletal muscle, which is the major cause of frailty and falls in elders. The activation of inflammatory signal pathways due to diseases and aging is suggested to reveal the critical impact on sarcopenia. Several proinflammatory cytokines, especially interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α), play crucial roles in modulation of inflammatory signaling pathway during the aging-related loss of skeletal muscle. MicroRNAs (miRNAs) have emerged as the important regulators for the mass and functional maintenance of skeletal muscle through regulating gene expression of proinflammatory cytokines. In this paper, we have systematically discussed regulatory mechanisms of miRNAs for the expression and secretion of inflammatory cytokines during sarcopenia, which will provide some novel targets and therapeutic strategies for controlling aging-related atrophy of skeletal muscle and corresponding chronic inflammatory diseases.

1. Inflammation System during Sarcopenia

1.1. Sarcopenia-Related Changes in Immune System. Sarcopenia is present in approximately 5–13% of persons over the age of 60 years and defined as the loss of skeletal muscle mass and strength with progressive decline in mobility and function [1]. The pathogenesis of sarcopenia is associated with many intrinsic and extrinsic factors, including proinflammatory cytokine accumulation, oxidative stress, mitochondrial dysfunction, insulin resistance, and aging-related loss of anabolic hormones and motor neuron end plates [2]. The loss of skeletal muscle results from an imbalance of protein metabolism, which is the dynamic balance between protein degradation and protein synthesis [3]. The protein degradation systems in skeletal muscle are modulated by a coordinated network of signaling pathways activated [4] or suppressed by hormones and cytokines; therefore, catabolism is stimulated by a variety of proinflammatory cytokines, glucocorticoids, and reactive oxygen species (ROS) [5, 6].

There is no simple mechanism to explain aging-associated loss of skeletal muscle. It is important to note that impaired cellular immune function combined with low-grade inflammation represents a continuous impact in aging process [7]. Although aging is associated with prolonged inflammatory

activity that is mainly attributed to progressively worsening muscle weakness, it is unclear whether these processes are cross-talked. Molecular signals and pathways connecting inflammatory system and muscle degeneration may be the key to reveal the interactions responsible for the progression of sarcopenia. The interplay seems to exist between the mass loss of skeletal muscle and elevated systemic inflammation (Figure 1). Sarcopenia is a complex process with a subclinical state of inflammation driven by proinflammatory cytokines and oxidative stress, which increases the infiltration of immune cells into injured muscles. In turn, inflammation aggravates muscle loss and fat accumulation in the aging skeletal muscle and further decreases muscle function and physical activity [8]. The increase in chronic inflammation response associated with high-level proinflammatory mediators as the extension of age has been considered as one of the diagnostic hallmarks and a significant contributor to aging-related atrophy of skeletal muscle [9]. The transcription factor, nuclear factor- κ B (NF- κ B), has been considered as an important mediator underlying the relationship between inflammation and aging [10, 11]. The correlation between inflammation and sarcopenia exists as a possible linkage describing the effect of inflammation on the balance between

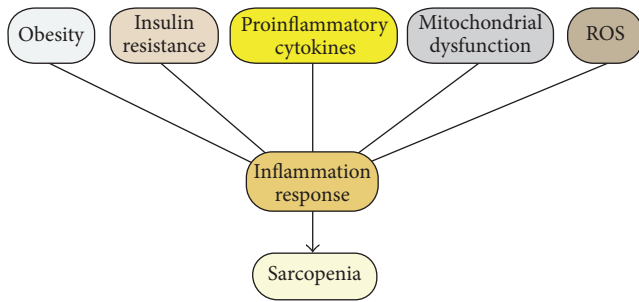


FIGURE 1: The interplay between sarcopenia and chronic inflammation. The boxes represent domains known to influence the maintenance of sarcopenia and inflammation response in aging organisms. Abbreviations: ROS, reactive oxygen species.

protein anabolism and catabolism, with the presence of CD68+ macrophage infiltration [12].

It is worth noting that substantial evidence also demonstrates the connection between obesity and sarcopenia, namely, “sarcopenic obesity” [13]. In fact, obesity always plays an important role in sarcopenia, by the way of adding inflammatory burden [14]. During obesity, adipose tissue is characterized by a chronic inflammatory state, through the release of numerous proinflammatory cytokines including tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1 β) as the factors largely responsible for insulin resistance in obese adipose tissue combined with aging-related skeletal muscle loss [15].

Moreover, impaired mitochondria can be both the reason and the consequence of inflammation during aging [16]. Increasing evidence shows that mitochondria may contribute to inflammation via ROS production, NF- κ B activation, calcium homeostasis, impaired autophagy, and ATP deficiency [17, 18]. Dysfunctional mitochondria are able to modulate aging-related inflammatory processes through direct activation of NLRP3 inflammasome, which can correspondingly result in the activation of caspase-1 or redox-sensitive inflammatory signaling pathways, thus leading to the production of IL-1 β and IL-18 [19, 20]. It should be noted that increasing ROS could stimulate the activation of NF- κ B via NF- κ B-inducing kinase (NIK) and I κ B kinase α and β (IKK α / β) [21, 22]. Since the increased redox activation in the presence of transcription factor NF- κ B, excessive ROS generation plays an important role in impaired mitochondrial function and oxidative capacity and accelerates the aging process of skeletal muscle [23].

1.2. Proinflammatory Cytokines Associated with Sarcopenia.

As described above, sarcopenia is a common feature in the elderly and mainly related to the release of inflammatory mediators from damaged tissue. These responses are controlled by a combination of various cytokines responsible for inflammatory pathways [10, 24]. Given that the inflammatory response is a complex system, cytokines are important not only as the indicators for mediating chronic inflammatory state through increasing protein degradation and reducing

protein synthesis, but also as the mediators for controlling muscle wasting by directly targeting muscle tissue [25]. In particular, proinflammatory cytokines are well known to impinge on protein metabolism in skeletal muscle and result in the activation of catabolism signals or upregulate inflammatory pathways such as NF- κ B and STAT3, thus finally leading to the increased activation of ubiquitin-proteasome and autophagy system [26, 27]. The chronic inflammatory aging process depends not only on increased expression of proinflammatory factors, but also on reduced levels of anti-inflammatory factors such as IL-10, one of the anti-inflammatory cytokines [28]. Since the presence and function of cytokines have been demonstrated in the pathogenesis of sarcopenia, their origins and types must be identified. In fact, cytokines can be secreted by various types of cells like inflammatory and stromal cells, as well as skeletal muscle cells. In skeletal muscle, mature myofibers make up cellular mass, and myotubes express mRNAs of various cytokines. The constitutive expression of cytokines is generally stronger in differentiated myotubes compared with myoblasts, which usually results in inconspicuous change in cytokine release to stimuli [29, 30]. Accumulating evidences over the past decade have demonstrated that those proinflammatory cytokines such as TNF- α , IL-6, and C-reactive protein (CRP) cause a significant increase in aging skeletal muscle cells and play a key role in the complex network of inflammatory signals in charge of muscle homeostasis connected with aging-related disability and mortality [31, 32].

1.2.1. IL-6 and CRP. IL-6 which is coined “cytokine for gerontologists” [33] has originally been classified as a prototypical proinflammatory cytokine to exhibit marked pleiotropy, and its anti-inflammatory property has also been identified later [34, 35]. IL-6 plays an important role in the pathogenesis of several chronic diseases including sarcopenia by regulating inflammatory and metabolic functions [36]. IL-6 signaling involves the binding to the membrane-bound IL-6 receptor in skeletal muscle and the activation of downstream signaling pathways including STAT3, MAPK/ERK, p38, myostatin, and FoxO3 pathways [37–40]. Additionally, IL-6 has confirmed to have the function of activating AMPK and/or phosphatidylinositol-3-kinase (PI3K) and regulating the metabolism in skeletal muscle [41, 42]. The overexpression of IL-6 can result in reduced body mass and impaired insulin-stimulated glucose uptake in mouse skeletal muscle [43]. Furthermore, the infusion of IL-6 in skeletal muscle can reduce the phosphorylation of S6K1, which is activated by Akt/mTOR and associated with the inhibition of anabolic process [44]. A comparative analysis of cytokine levels has confirmed the upregulation of proinflammatory IL-6 and CRP in the elderly, along with increased risk for the loss of skeletal muscle mass and strength [45]. According to a recent study, the serum high-sensitivity CRP (hs-CRP) levels in the obesity only and in the sarcopenic obesity groups are significantly higher than that in the normal group after multivariate adjustments, which provides the evidence that obesity and sarcopenic obesity are associated with increased levels of serum hs-CRP among males [46].

1.2.2. TNF- α . TNF- α is a cytokine implicated in the metabolic disturbance of chronic inflammation, with the formation of IL-1, which has been identified as a circulatory factor to increase gluconeogenesis, lipolysis, and proteolysis, accompanied with the decrease in protein, lipid, and glycogen synthesis in skeletal muscle [47]. During the stages of muscle regeneration, TNF- α and IL-1 are observed in injured muscle with an accumulation of macrophages [48, 49]. Also, TNF- α and IL-1 have been confirmed to promote IL-6 secretion through activating NF- κ B in cultured skeletal muscle cells [50]. Several previous studies have confirmed that TNF- α at the elevated level can increase catabolism in skeletal muscle by suppressing Akt/mTOR pathway [51]. TNF- α and its soluble receptors have been described as the important contributors or biomarkers for the loss of mass and strength in aged skeletal muscle [52]. There is a strongly negative correlation between protein breakdown and TNF- α concentration in the elderly [53]. Injecting TNF- α into mice has revealed the activation of ubiquitin-proteasome system and the decrease of skeletal muscle function [54]. *In vivo*, the synthesis rate of myosin heavy chain protein is correlated negatively with the expression of TNF- α in skeletal muscle. TNF- α induces skeletal muscle loss through increased myofibrillar protein degradation and cell apoptosis, thus resulting in muscle atrophy and the inhibition of muscle regeneration following injury [55, 56]. Additionally, it seems that TNF- α may antagonize the anabolic effect of insulin growth factor-1 (IGF-1), due to the development of growth hormone resistance, which decreases both circulating and muscular IGF-1 [57, 58]. Recent studies have shown that G/A-308 TNF- α polymorphism as a marker of sarcopenia in normal weight obese syndrome, suggesting the importance of TNF- α in the diagnosis of sarcopenia [59]. It is important to note that an increase in TNF- α alone is not sufficient to cause muscle atrophy. The upregulation of NF- κ B can cause muscle atrophy in rodents and contribute to the progressive muscle loss of advancing age [60].

1.2.3. Other Inflammatory Cytokines. Other mediators such as interferon- γ (IFN- γ) are produced in the microenvironment of skeletal muscle and play a critical role during myogenesis. Moreover, IL-15 [61] is usually mentioned among paracrine effectors, while cytokines such as irisin [62] and myonectin [63] are able to induce anti-inflammatory cytokines (IL-1 receptor antagonist and IL-10), especially during contraction and aging conditions [64]. The levels of TLR4 protein and IL6, IL10, and IL15 mRNA expression are increased after short-time bed rest in healthy older adults, while the levels of IFN- γ and macrophage inflammatory protein-1-beta (MIP-1 β) are elevated in aging skeletal muscle [65]. Furthermore, peroxisome proliferator-activated receptor gamma coactivator-1-alpha (PGC-1 α) is regarded to have an anti-inflammatory function by inhibiting the function of FoxO3, which could promote inflammatory cytokine expression and downregulate antioxidant enzyme expression in aging muscle [66]. The reduced expression of PGC-1 α results in a low level and a systemic inflammatory response to exhibit negative impacts on skeletal muscle [67]. Inversely,

the upregulated PGC-1 α can reduce the activity of NF- κ B, which contributes to the inhibition of proinflammatory cytokines to be benefit for the prevention of mass and strength loss of skeletal muscle and functional decline of other organs, as well as the ultimate impact on homeostasis in human body [68, 69].

Proinflammatory cytokines have a wide variety of roles in inflammation systems and may be the important factor predisposing to muscle catabolism response in the elderly. However, the roles of these cytokines in aging skeletal muscle are still not fully understood. Furthermore, the tissue-specific inflammatory signaling pathways in response to cytokines along with the elevation of systemic cytokines are important elements to be considered.

2. MicroRNA- (miRNA-) Mediated Inflammation and Skeletal Muscle Loss

2.1. Biogenesis and miRNAs. miRNAs are short noncoding RNAs with approximately 22 nucleotides in length and are involved in the complex posttranscriptional regulatory networks and the maintenance of healthy cellular functions such as growth, development, and metabolism [70]. Skeletal muscle is the most abundant tissue in human body, comprising 40–50% of body mass. It is estimated that approximately 60% of human genes are regulated by miRNAs, suggesting that highly enriched miRNAs in skeletal muscle play important roles in biological processes by gene silencing, including aging process [71]. The functions of miRNAs can be achieved either by suppressing the translation of target messenger RNAs (mRNAs) or by promoting the degradation of mRNAs, thereby providing a powerful and sensitive regulator to tune gene expression and cell functions during the aging process of skeletal muscle [72].

miRNAs, from noncoding RNA genes or within protein-coding genes, are transcribed into primicroRNAs by RNA polymerase II or polymerase III in some cases and subsequently embedded into premicroRNA hairpins like RNA duplex by Drosha [73, 74]. PremicroRNA hairpins are exported from nucleus by exportin-5 and processed into double-stranded mature miRNAs by Dicer in combination with its RNA-binding cofactor [75]. After Dicer-mediated maturation, the miRNAs orient the RISC complex with the removal or the preservation of one strand as the guide strand and preferentially load on the RISC complex in position at regulatory sequences in target genes [76].

Although the precise mechanisms for miRNA targeting and activity still remain to be fully explored, miRNA activity appears to be largely dependent on its binding capacity to the target mRNA molecule [77–79]. Generally, mRNAs contain a predicted binding site in the 3' untranslated region (UTR), less commonly, in the 5' UTR, and many mRNAs contain multiple potential binding sites. There are 2 known binding types for miRNAs [80]. According to the binding complementarity of the seed sequence, Argonaute proteins such as Ago-2 can directly cleave messenger RNA and normally repress gene expression by targeting the mRNA for degradation ("complete match," RISC binds to mRNA

with perfect match) or by mediating translation inhibition or mRNA deadenylation leading to mRNA destabilization at the condition with mismatches between mRNA sequence and the RISC (“incomplete match,” RISC binds to mRNA with some mismatches) [81].

However, there are still unsettled questions regarding miRNA-binding rules, thereby resulting in a lack of consensus in previous studies. Establishing direct cause-and-effect links between miRNAs and mRNA targets is a key to understand underlying molecular mechanisms behind health and diseases and to develop effective targeted therapeutic strategies. Now that miRNAs have multiple gene targets, each target may be regulated by a suite of miRNAs. The roles of miRNAs in inflammation and sarcopenia have only been initially explored and future investigations will unravel their roles in immunity and metabolism.

2.2. miRNA-Regulated Signal Pathways for Proinflammatory Cytokines during Sarcopenia. According to the analysis of miRNA expression profiling, miRNAs are critical regulators for both proinflammatory cytokines and skeletal muscle function [82, 83]. In order to elucidate which miRNA is important in the production of proinflammatory cytokines in aging-related muscle wasting, mRNA targets and specific roles in regeneration and protein synthesis in skeletal muscle need to be established. Several tissue-specific miRNAs are known to be associated with the aging of skeletal muscle, which are named as myomiRNAs and consistently identified, including miR-1, miR-133, miR-206, miR-208, miR-486, miR-431, and miR-499 [84–86]. These myomiRNAs can induce significant effects on development and myogenesis of skeletal muscle by targeting myogenic factors such as SRF, MEF2, and myostatin [87]. Local injection of miR-206 can accelerate muscle regeneration [88], and miR-133 can promote the proliferation of myoblasts, while miR-1 can suppress the proliferation of myoblasts [83]. Although there is no obvious difference in the expression of mature miR-1, miR-133, or miR-206 in skeletal muscle from younger adults [89], an increased expression of these primary miRNAs can be observed during aging, and the effect of anabolic stimulus on the levels of these miRNAs can be perturbed in the elderly. On the other hand, many studies have implicated the regulation of inflammatory response through inflammatory miRNAs such as miR-155 and miR-146a, suggesting their roles in the immune system [90]. Since inflammation is rather a broad concept, there are some overlaps between miRNAs involved in inflammation and aging [91]. Therefore, cytokine-associated miRNAs appear to have central roles in both inflammation and sarcopenia.

A recent RNA sequencing study has demonstrated the differential expression of miRNAs in skeletal muscle from old and young rhesus monkeys [92]. miR-181a, with its role in tuning the threshold of T-cell receptor (TCR) signaling originally described [93], not only acts as a myomiRNA, but also impacts inflammatory system. It can downregulate sirtuin 1 (Sirt1) gene expression as a regulator so that the expression of miR-181a and its target gene is disrupted in aged skeletal muscle [94]. Moreover, based on earlier reports

showing proinflammatory cytokines such as TNF- α , IL-6, IL-1 β , and IL-8 as the proposed targets of miR-181a, the reduction of miR-181a can be responsible for an increase in the abovementioned proinflammatory cytokines in skeletal muscle during aging process [95]. Besides, TNF- α and IL-1 β are significantly negatively correlated with decreased expression of myomiRs and can suppress the differentiation of C2C12 myoblasts to myocytes/myotubes through NF- κ B, JAK/STAT, MAPK p38, or other key pathways [96].

A newly discovered proinflammatory cytokine, TNF-like weak inducer of apoptosis (TWEAK), belongs to TNF family and has revealed the function for causing muscle atrophy [97]. One of the mechanisms proposed for the induction of skeletal muscle wasting by TWEAK is regulating differential expression of several growth-related miRNAs, including miR-1, miR-23, miR-133a, miR-133b, and miR-206 in C2C12 myotubes; however, it can reduce miR-1, miR-133a, and miR-133b only in mouse skeletal muscle [98]. While the treatment with TWEAK regulates several miRNAs involved in the growth of skeletal muscle, it is not known whether their regulation is a cause of muscle wasting or a compensatory response to prevent further muscle wasting.

Let-7 miRNA, the first known human miRNA, has been reported to be critical for promoting differentiation and inhibiting cellular proliferation [99]. The elevation of let-7 miRNA may be responsible for the damage-repairing capability through the activation and proliferation of satellite cells in skeletal muscle from the elderly, therefore contributing to the attenuated regenerative capacity of skeletal muscle in the elderly [100]. Moreover, let-7 miRNA can inhibit the secretion of inflammatory cytokine IL-13 in human myotubes [101]. Recent study has also found that the overexpression of miRNA let-7c can inhibit LPS-induced production of TNF- α , IL-6, and IL-1 β by inhibiting the phosphorylation of STAT3 [102]. Compared to younger individuals, skeletal muscle from older individuals shows a significant elevation in let-7b and let-7e under resting conditions, suggesting the involvement of these miRNAs in regulating cell cycle based on let-7 target genes [100].

miR-146a, which negatively regulates the expression of IL-1 β and IL-6, is highly expressed in aged mice as a consequence of an aberrant NF- κ B binding to miR-146a promoter. As a result, the negative feedback regulation loop inducing the downregulation of inflammatory factors can be interrupted in aged mice [103]. In macrophages isolated from aged mice, both DNA methyl-transferase inhibitor and histone deacetylase inhibitor are able to significantly upregulate miR-146a through transcriptional activation by altering DNA binding activity of NF- κ B [104]. Reduced miR-146a in oxLDL-activated macrophages is linked to an increase of its target, Toll-like receptor 4 (TLR4), involved in lipid uptake and inflammatory cytokine secretion [105].

Due to the upregulation in inflammatory condition in various primary disorders of skeletal muscle [106], miR-155 is identified as an important regulator of MEF2A expression and exhibits its function in myoblast differentiation [107], and it also plays a critical role in the regulation of inflammation that affects both innate and adaptive immunity. The upregulation of miR-155 is the most characteristic feature of the

miRNA expression signature in LPS-stimulated macrophages through the binding to NF- κ B [108]. Moreover, the inflammatory response mediated by miR-155 is induced by TLR ligands and can enhance the translation of TNF- α during the pathogenesis of metabolic syndromes [109].

In addition, miR-23a negatively regulates PGC-1 α as a key activator of mitochondrial biogenesis and function [110]. In another study, the level of miR-696 is upregulated in skeletal muscle of mice subjected to hind limb immobilization while the level of PGC-1 α as the target of miR-696 exhibits an obvious decrease. Consistent with this observation, the overexpression of miR-696 in myocytes shows a decrease in PGC-1 α , suggesting its involvement in mitochondrial function and metabolism, and its importance in controlling the metabolism, adaptation, and atrophy of skeletal muscle [111].

Since a large number of miRNAs have been identified in skeletal muscle, the investigation of miRNAs is a promising but relatively unexplored area for understanding the regulatory mechanisms of wasting process associated with cytokine expression and secretion in aging skeletal muscle. Clearly targeting these miRNAs could provide an efficient and non-invasive approach for the diagnosis, prevention, or treatment of sarcopenia through the regulation of proinflammatory and anti-inflammatory factors.

3. Diagnostic and Therapeutic Opportunity

Potential interventions for sarcopenia include nutritional supplements, physical activity/resistance exercise, caloric restriction, anabolic hormones, anti-inflammatory agents, and antioxidants. A key question is whether sarcopenia is a truly distinct syndrome or a milder form of a cachexia continuum [112]. It is difficult to estimate the prevalence of sarcopenia, mostly because of practical difficulties in assessing skeletal muscle mass [113]. Sarcopenia-associated difference in the production of proinflammatory cytokines *in vivo* shows a prolonged inflammation activity. There remains a lack of understanding of individual contributions of various cytokines during the aging process of skeletal muscle, because of their wide-ranging effects on cell proliferation, differentiation, migration, survival, and apoptosis. As reviewed here, miRNAs play major roles in the inflammatory regulation as the pivotal regulators for modulating cell functions or the critical factors for affecting the therapeutic outcome of sarcopenia. Although the central role of inflammation in sarcopenia and proinflammatory cytokines including TNF- α and IL-6 as the central mediators of skeletal muscle atrophy has been documented, the roles of inflammatory miRNAs in mass maintenance and functional development of skeletal muscle still need to be further explored and confirmed.

Whether miRNAs can be used for the diagnosis of inflammatory involvement in the aging process of skeletal muscle depends on the precise characterization, specific distribution, and accurate regulation of miRNAs. Proinflammatory cytokine-associated miRNAs such as miR-146a, miR-181, and miR-21 are frequently detected at a high level in skeletal muscle; however, their functions are still not fully clear. Therefore, further exploration of their targets,

regulatory networks, and functions is highly desired. In conclusion, the discovery of miRNAs with regulatory capacity of inflammatory response during aging process of skeletal muscle will open a novel avenue for the diagnosis, prevention, and therapy of sarcopenia through effectively modulating inflammatory signal pathways.

Competing Interests

The authors have declared no competing interests.

Authors' Contributions

Jingjing Fan and Xianjuan Kou contributed equally to this project.

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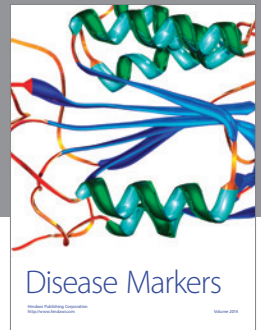
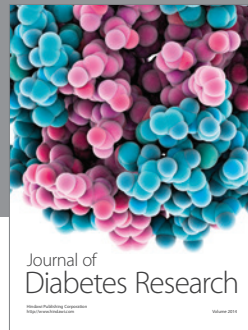
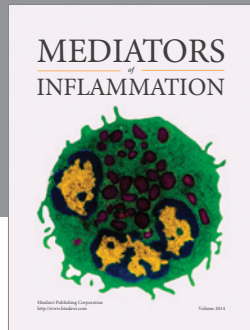
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