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Review articles

Cytokine Gene Polymorphisms, Immune-Mediated Inflammatory Pathways, and Molecular Regulation of Tissue Repair Following Exercise-Induced Muscle Injury

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Abstract

Exercise-induced muscle injury (EIMI) is a common consequence of strenuous or unaccustomed physical activity and is frequently associated with delayed onset muscle soreness, transient strength loss, and reduced functional capacity. Although often reversible and adaptive, EIMI involves a complex interplay of mechanical disruption, inflammatory signaling, and regenerative processes. Structural damage to myofibers induces calcium dysregulation, sarcomere disruption, and proteolytic activation, resulting in the release of damage-associated molecular patterns that stimulate innate and adaptive immune responses. Neutrophils and macrophages coordinate debris clearance and inflammatory signaling, while the transition from pro-inflammatory to anti-inflammatory macrophage phenotypes is important for effective tissue repair. Cytokines and chemokines tightly regulate these responses, as excessive or prolonged inflammation may promote fibrosis and delayed recovery. Genetic variability, particularly cytokine gene polymorphisms, contributes to inter-individual differences in inflammatory magnitude, recovery kinetics, and susceptibility to muscle damage. Variants in IL-6, TNF-α, IL-1β, IL-10, and chemokine genes influence cytokine expression, macrophage polarization, and satellite cell activity. Key pathways including NF-κB and JAK/STAT signaling, reactive oxygen species production, growth factor regulation, extracellular matrix remodeling, and epigenetic mechanisms further shape muscle regeneration. Current evidence underscores the importance of integrating immunological and genetic insights to better understand muscle repair. Future research focusing on multi-ethnic cohorts, polygenic models, and single-cell and epigenetic profiling may enhance translational applications. Advancing knowledge in this field may support personalized exercise medicine, targeted therapeutic strategies, and improved management of muscle recovery.

Keywords: Cytokine polymorphisms; Exercise-induced muscle injury; Immune response; Muscle regeneration; Satellite cells

Introduction

Exercise-induced muscle injury (EIMI) is a common consequence of strenuous physical activity, often manifesting as stiff or sore muscles lasting 48–72 hours, a phenomenon referred to as Delayed Onset Muscle Soreness (DOMS). Eccentric muscle contractions, which lengthen the muscle while it is active, are particularly implicated in provoking stiffness and tenderness, potentially leading to injury. Although such contractions may only induce temporary DOMS, they initiate complex processes that can result in muscle protein degradation and skeletal muscle impairment through sarcomere disruption and altered calcium signaling, ultimately triggering inflammation (1). EIMIs are associated with complications including muscle inflammation,

strength loss, discomfort, limited range of motion, and transient reductions in insulin sensitivity, which in severe cases can progress to rhabdomyolysis (2).

Mechanical overload from unaccustomed strenuous exercise is a major contributor to skeletal muscle damage, particularly during eccentric contractions that slow or halt movement, while concentric contractions facilitate motion (3,4). Calcium influx into damaged fibers activates intracellular proteases, exacerbating muscle injury due to z-line streaming and increased sarcolemmal permeability (5). Damaged fibers subsequently enter an inflammatory phase to initiate regeneration, characterized by macrophage-mediated clearance of necrotic tissue (6,7). Satellite cells, a population of myogenic stem cells, are activated in response to damage, exiting the G0 phase, proliferating, and expressing myogenic regulatory factors to generate new myofibers (3,8).

Muscle repair and inflammation are tightly regulated through the balance of pro- and anti-inflammatory cytokines (Figure 1). Anti-inflammatory mediators such as IL-4, IL-10, IL-1ra, and TNF-α and IL-2 receptors attenuate early inflammatory responses, promoting a transition of macrophages to an anti-inflammatory M2 phenotype, which facilitates satellite cell proliferation and differentiation, enhancing muscle regeneration. Conversely, uncontrolled pro-inflammatory cytokines, including TNF-α and IL-1β, may perpetuate tissue damage and fibrosis (9,10). Genetic variability further influences individual responses to EIMI, with single nucleotide polymorphisms (SNPs) and insertion/deletion variants modulating cytokine expression and inflammatory outcomes. For example, IL-1β C/C or T/T genotypes are associated with heightened inflammatory responses, while IL-6-174 G>C and TNF-α 308 G>A variants affect creatine kinase levels, macrophage polarization, and satellite cell proliferation following exercise (1,11). Polymorphisms in chemokines such as CCL2 have also been linked to differences in muscle damage and recovery times among individuals (11).

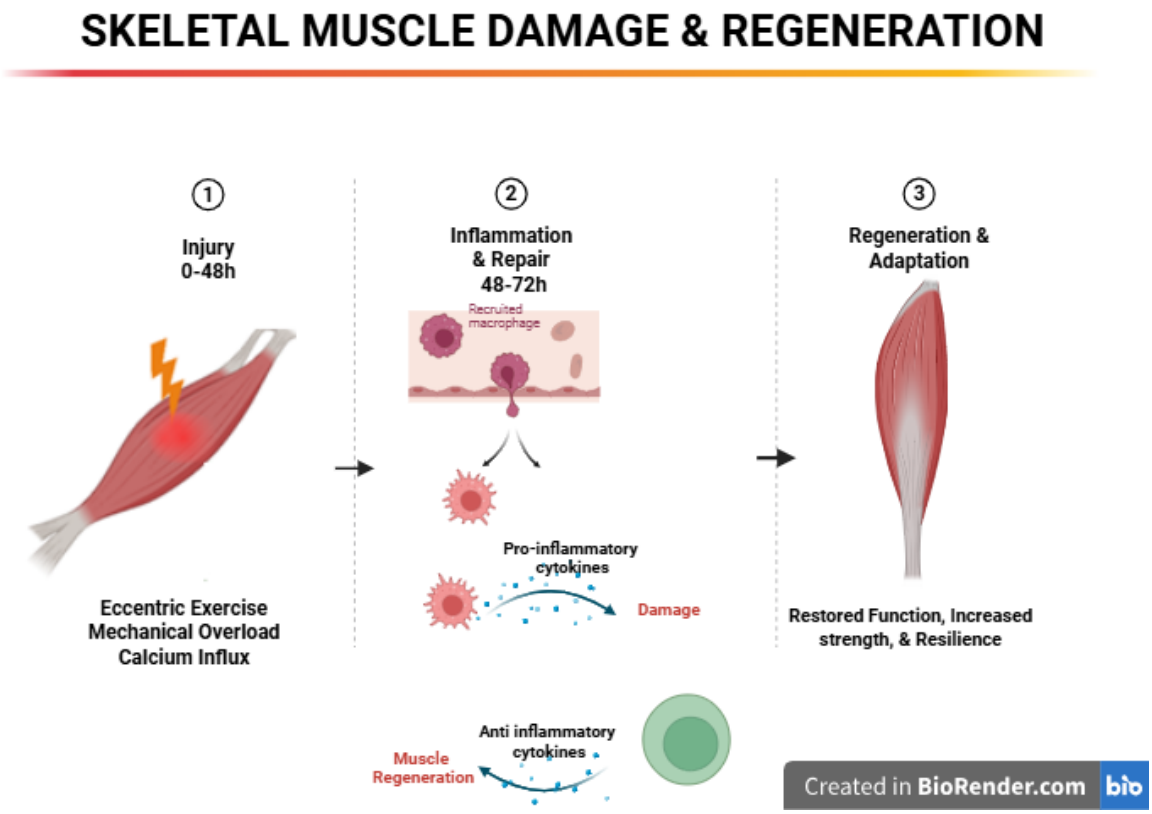

Figure 1 – An overview of inflammatory and muscle cell responses following acute muscle injury

Note: *Schematic overview of inflammatory and muscle cell responses following acute exercise-induced muscle injury. The figure illustrates the balance between pro-inflammatory (M1) and anti-inflammatory (M2) macrophage phenotypes, satellite cell activation, and cytokine-mediated signaling pathways. (Figure created in BioRender.com).*

Therefore, this review aims to provide a comprehensive overview of cytokine gene polymorphisms, immune-mediated inflammatory pathways, and the molecular regulation of tissue repair following exercise-induced muscle injury, highlighting the interplay between genetic variability, immune responses, and satellite cell-mediated muscle regeneration.

Methodology.

This review was conducted using a structured narrative approach to synthesize current evidence on cytokine gene polymorphisms, immune-mediated inflammatory pathways, and molecular mechanisms involved in exercise-induced muscle injury (EIMI) and regeneration. A systematic literature search was performed using electronic databases including PubMed, Scopus, and Google Scholar to identify relevant peer-reviewed publications published between 2000 and 2025. Search terms included keywords related to exercise-induced muscle injury, delayed onset muscle soreness, skeletal muscle damage, cytokines, inflammation, immune response, gene polymorphisms, macrophage polarization, satellite cells, muscle regeneration, and major signaling pathways such as *NF-κB* and *JAK/STAT*. Boolean operators (AND, OR) were applied to combine keywords and refine search sensitivity and specificity. Eligible sources comprised original research articles, experimental studies, and review papers addressing molecular, genetic, and immunological aspects of muscle injury and repair. Studies not related to skeletal muscle injury, exercise models, or inflammatory and regenerative mechanisms were excluded. Reference lists of selected articles were also screened to identify additional relevant literature. Both seminal and recent studies were included to ensure a comprehensive and balanced synthesis of established knowledge and emerging evidence in the field.

Epidemiology and Risk Factors.

EIMI has gained global attention due to its relevance in both sports' performance and public health. In athletes, understanding EIMI is crucial for optimizing the balance between adaptive stimulus and injury during intensive training schedules (12). Studies indicate a higher prevalence of exercise-related injuries among male athletes, likely reflecting greater participation in strenuous activity. Elevated body mass index and higher body fat percentage also exacerbate post-exercise muscle injury, while high-intensity workouts increase the likelihood of EIMI in both trained and untrained individuals (2).

From a public health perspective, research has explored EIMI in relation to sarcopenia and muscle fragility in older adults. Age-related functional decline in satellite cells and chronic low-grade inflammation contribute to reduced regenerative capacity, increasing susceptibility to injury (13). Additionally, individuals with chronic conditions such as diabetes or COPD experience impaired regenerative pathways due to pre-existing inflammation, resulting in delayed recovery (13–15). Cytokine gene polymorphisms may further predispose certain individuals to hyper-inflammatory responses following EIMI (1,12).

Clinically, EIMI is characterized by transient loss of maximal force generation, muscle stiffness, swelling, discomfort, and reduced range of motion (2,12). Biomarkers such as creatine kinase (CK) provide measurable indicators of muscle damage, though they lack specificity. Advanced histological assessments, including muscle biopsy, allow detailed evaluation of satellite cell activation and tissue regeneration (16).

Immune Response to Exercise-Induced Muscle Injury.

The innate immune system orchestrates the early inflammatory response following EIMI, initiating tissue clearance and repair (7). Damage-associated molecular patterns (DAMPs), including HMGB1 and heat shock proteins, alert immune cells via pattern recognition receptors (PRRs) such as Toll-like receptors and NOD-like receptors expressed on macrophages, mast cells, and endothelial cells. Engagement of DAMPs with PRRs activates NF-κB signaling, promoting transcription of cytokines and chemokines that recruit neutrophils and monocytes to the injured site (6,17). Capillary permeability increases to facilitate immune cell trafficking, and the local release of TNF-α, IL-1β, and MCP-1 establishes gradients that guide sequential immune cell recruitment. Regulation of this innate response is critical, as excessive or prolonged activation may result in chronic inflammation and fibrosis (13).

Neutrophils are first responders, peaking within 24 hours post-injury, and clear cellular debris via reactive oxygen species and lytic enzymes (Figure 2). Timely resolution of neutrophil activity is

essential to prevent collateral myofiber damage (6). Monocytes subsequently infiltrate and differentiate into macrophages, initially adopting an M1 pro-inflammatory phenotype to facilitate phagocytosis and pathogen defense. Transition to the M2 phenotype is mediated by cytokines such as IL-4 and IL-3, promoting satellite cell proliferation, angiogenesis, and extracellular matrix remodeling through IGF-1 signaling (18).

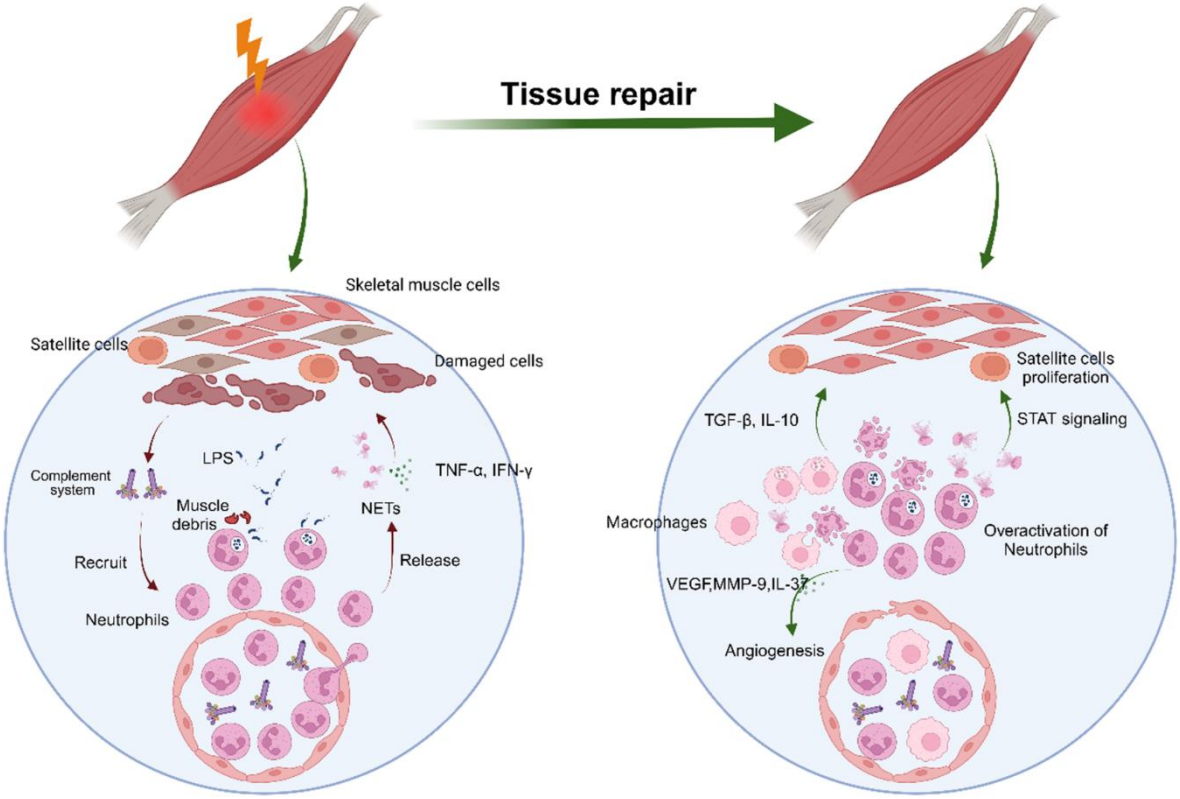

Figure 2 - Role of Neutrophils in skeletal muscle repair.

Note: *The above figure illustrates the role of neutrophils in skeletal muscle repair. Neutrophils arrive rapidly at the site of injury, phagocytose debris, and release reactive oxygen species and lytic enzymes. Their timely clearance is crucial to prevent secondary damage and facilitate macrophage recruitment; Adapted from (19).*

The adaptive immune system further modulates repair, with T lymphocytes infiltrating damaged muscle to regulate macrophage function. Regulatory T cells secrete IL-10 and TGF-β1, facilitating M1-to-M2 macrophage transition and supporting tissue regeneration (6). Chronic or repeated injuries may activate CD4+ and CD8+ T cells, differentiating into Th1 or Th17 subsets to maintain a controlled pro-inflammatory environment for repair (6,13).

Cytokine and chemokine networks tightly regulate immune cells and muscle progenitors. MCP-1/CCL2 recruits' monocytes and neutrophils, while TNF-α and IL-6 facilitate early inflammation and satellite cell activation. During repair, anti-inflammatory mediators such as IL-10 and IGF-1 promote M2 macrophage polarization and satellite cell differentiation, whereas persistent TGF-β1 expression may impair regeneration and promote fibrosis (1,18,20,21).

Molecular Regulation of Tissue Repair.

Satellite cells, residing beneath the basal lamina, are important for postnatal growth and regeneration. Injury-induced signals including nitric oxide, stretch, growth factors, and cytokines activate satellite cells, which proliferate and express MyoD before differentiating via MRF4 into multinucleated myotubes that fuse with damaged fibers (3,20,22).

Growth factors such as IGF-1, TGF-β1, and myostatin regulate muscle anabolism and catabolism. IGF-1 activates PI3K/Akt/mTOR signaling to promote protein synthesis and cell differentiation, whereas TGF-β1, if overexpressed, induces fibrosis. Myostatin inhibits growth through

Smad signaling and PI3K/Akt/mTOR suppression (20,21,23,24). ECM remodeling is critical for functional repair, mediated by MMPs and regulated by fibroblast activation and M2 macrophages; dysregulation leads to fibrosis (21). MicroRNAs, including miR-206 and miR-133, modulate satellite cell proliferation and differentiation, while epigenetic modifications influence long-term muscle adaptation and repair(6,16,20,22).

Clinical and Research Implications.

Cytokine gene polymorphisms serve as predictive markers for exercise recovery. TNF-α 308 A and IL-6-174 G alleles indicate increased muscle damage and prolonged inflammation, informing personalized exercise and rehabilitation strategies (1,12). Modulation of cytokine activity, including promotion of M2 macrophages via IL-4 or targeted IL-6 delivery, supports regeneration and limits fibrosis (12,18). Pharmacological interventions such as NSAIDs, TNF inhibitors, and JAK inhibitors demonstrate potential in accelerating repair and mitigating inflammation (16,25,26) (Figure 3). Personalized exercise medicine leverages immunogenetic profiles to optimize workloads, recovery periods, and training outcomes, particularly in aging populations (1,13).

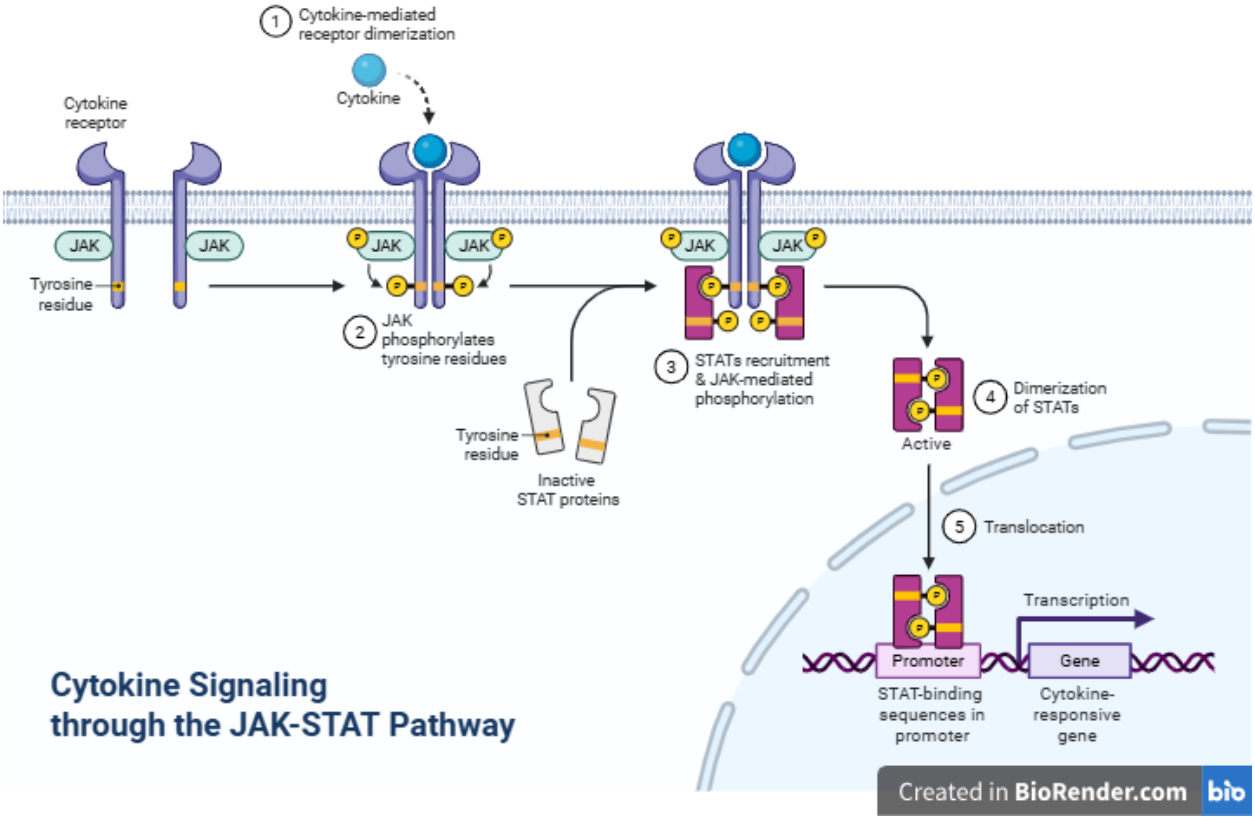

Figure 3 – Mechanism of JAK/STAT signaling pathway.

***Note**: The above figure illustrates the mechanism of JAK/STAT signaling in skeletal muscle repair. IL-6 binds to its receptor, activates JAKs, phosphorylates STAT3, which dimerizes and translocate to the nucleus to drive transcription of target genes involved in satellite cell proliferation and tissue regeneration. (Figure created in BioRender.com).*

Limitations and Future Directions.

Genetic association studies are limited by focus on circulating markers rather than local gene expression, single gene variants despite polygenic inflammation, small sample sizes, and limited ethnic diversity (12,22,27). Translational application of immunogenetic data is complex and costly, highlighting the need for cost-effective polygenic risk assessment and targeted drug delivery systems (18). Future studies should include diverse populations, employ single-cell sequencing to map transcriptional profiles, and explore epigenetic regulation to enhance diagnostic, therapeutic, and exercise strategies (9,20,22).

Conclusion

Exercise-induced muscle injury represents a multifaceted physiological process influenced by mechanical stress, immune activation, cytokine networks, and genetic variability. Cytokine gene polymorphisms significantly modulate individual inflammatory responses, satellite cell activity, and muscle repair, informing predictive and personalized approaches to rehabilitation and exercise prescription. Understanding immune-mediated pathways, molecular regulation, and the interplay of genetic and environmental factors is essential for optimizing recovery, minimizing fibrosis, and enhancing long-term muscle function. Continued research integrating multi-ethnic populations, advanced molecular techniques, and translational strategies will further elucidate the mechanisms underlying EIMI and inform clinical and performance-based interventions.

Ethical Statement.

This article is a literature review that relies solely on previously published data and does not include any involvement of human participants, animals, clinical materials, or the collection of primary data. Consequently, approval from an Ethics Review Committee was not necessary. All information was derived from publicly accessible, peer-reviewed sources, and the work was undertaken in line with accepted standards of academic integrity and responsible conduct of research.

Author Contributions

Visula Abeysuriya (V.A.) contributed to the conceptualization of the review, comprehensive literature acquisition, critical analysis and interpretation of evidence, drafting of the manuscript, and supported academic supervision and validation of the intellectual framework of the study. Ushani Kaushalya Perera (U.K.P.) contributed extensively to literature retrieval, synthesis, and interpretation, and was deeply involved in drafting, revising, and refining the manuscript; U.K.P. also led the preparation of illustrations, figures, and visual materials and contributed significantly to technical editing, organization, and presentation of the work. Sachintha N. Alwis (S.N.A.) contributed substantially to study design, literature analysis, manuscript writing, critical revision, and harmonization of author inputs, managed advanced editing and formatting, ensured quality control of the scientific content, and served as the corresponding author responsible for journal communication and submission processes. Vasitha Abeysuriya (V.A.B.) provided senior oversight in the development of the manuscript and contributed to high-level scientific guidance, supervision, validation of interpretations, and critical appraisal of the final content. All authors made substantial scholarly contributions, participated in manuscript revision, and approved the final version prior to submission.

Disclosures and Declarations

Consent to participate

Not Applicable

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Conflicts of interest/competing interests

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Data Availability Statement

No new data were generated or analyzed in this study. All information discussed in this review was obtained from previously published and publicly accessible sources, which are cited within the article.

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