Review

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TET2 in Sepsis-Induced ICU-Acquired Weakness: Regulatory Role in the "Inflammation-Metabolism-Autophagy" Axis and Clinical Implications

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Sepsis-induced ICU-acquired weakness (ICU-AW) is a major complication in critically ill patients, contributing to prolonged mechanical ventilation, increased mortality, and long-term functional impairment. Emerging evidence highlights that epigenetic dysregulation, particularly through DNA demethylation mediated by Ten-Eleven Translocation 2 (TET2), plays a pivotal role in the pathogenesis of ICU-AW. TET2 catalyzes the conversion of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), thereby contributing to the regulation of gene expression networks involved in inflammation, metabolism, and autophagy. In the septic microenvironment, inflammatory cytokines suppress TET2 expression via the NF-κB pathway, which may contribute to disrupted homeostasis of the "inflammation-metabolism-autophagy" axis and is associated with muscle atrophy and dysfunction. This review systematically outlines the basic biology of TET2, its regulation under septic conditions, and the potential mechanisms by which it may contribute to ICU-AW through the aforementioned axis. Furthermore, we discuss the translational potential of TET2 as a diagnostic biomarker and a target for therapeutic interventions, including small-molecule agonists, epigenetic editing, and nutritional strategies. Although tissue-specific delivery and long-term safety remain critical hurdles, TET2-targeted strategies may enable precision management of sepsis-induced ICU-AW.

Keywords: TET2; sepsis; ICU-AW; inflammation-metabolism-autophagy axis; DNA demethylation; epigenetic regulation; biomarker; targeted therapy

Introduction

Sepsis is a leading cause of ICU-acquired weakness (ICU-AW), a syndrome characterized by symmetric muscle weakness that affects 25–85% of critically ill patients and is associated with worse clinical outcomes, including extended ventilator dependence, higher hospital mortality, and long-term disability [1,2]. The pathophysiology of sepsis-induced ICU-AW involves a complex interplay of systemic inflammation, metabolic reprogramming, and impaired autophagy, leading to progressive skeletal muscle loss and dysfunction [1,2].

Epigenetic mechanisms, especially DNA methylation/demethylation dynamics, have recently been recognized as critical regulators of muscle homeostasis [3,4,5]. Ten-Eleven Translocation 2 (TET2), a key DNA demethylase, oxidizes 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) and further intermediates, thereby actively modulating gene expression. TET2 dysfunction has been linked to various pathological processes, including tumor progression and tissue regeneration [6,7]. In sepsis, the regulation of TET2 expression remains controversial. While inflammatory mediators such as LPS and TNF-α have been reported to suppress TET2 expression via the NF-κB pathway [8], others have observed increased TET2 levels in septic models, with p53 directly binding to the TET2 promoter to promote its transcription [9]. Although the role of TET2 in epigenetics is well established, its specific regulatory network in sepsis-induced ICU-AW and its clinical applicability remain underexplored. This review synthesizes recent basic and clinical evidence, focusing on (1) the basic biology and regulation of TET2, (2) its modulation by the septic microenvironment, (3) its mechanistic actions through the "inflammation–metabolism–autophagy" axis, (4) its potential as a biomarker and therapeutic target, and (5) future research directions. By clarifying the central position of TET2 in sepsis-associated muscle weakness, this review

provides a framework for developing precise diagnostic and therapeutic strategies.

Basic Biology and Regulatory Networks of TET2

Structure and Core Functions

The ten-eleven translocation (TET) family of proteins comprises three family members, TET1, TET2, and TET3. The first, TET1, was cloned from the breakpoint of chromosomal translocation t(10; 11) in infant AML, and subsequent homology searches have identified two additional members, TET2 and TET3. TET proteins are key enzymes for DNA demethylation [10]. TET2 contains a cysteine-rich domain and a catalytic double-stranded β-helix domain essential for its dioxygenase activity [11]. Its primary function is to successively oxidize 5mC to 5hmC, 5-formylcytosine (5fC), and 5-carboxylcytosine (5caC); the latter intermediates are then excised by thymine DNA glycosylase (TDG) via the base excision repair (BER) pathway, leading to DNA demethylation [12]. Notably, 5hmC is not merely an intermediate but also a stable epigenetic mark that can recruit transcription factors (e.g., MyoD, Pax7) to modulate gene expression, thereby fine-tuning programs related to inflammation, metabolism, and autophagy in skeletal muscle [13,14,15]. Through these actions, TET2 influences embryonic development, immune responses, and stem-cell fate, and its dysfunction may predispose to sepsis-induced ICU-AW [16]. Although direct evidence linking TET2 dysfunction to ICU-AW in humans remains limited, studies in muscle stem cells and preclinical models suggest that disrupted TET2-mediated demethylation may contribute to the epigenetic dysregulation observed in sepsis-induced ICU-AW.

Regulation of TET2 Activity

TET2 activity depends on co-factors α-ketoglutarate (α-KG) and Fe^{2+}, making it sensitive to cellular metabolic status. Accumulation of metabolites such as succinate or fumarate can inhibit its demethylation efficiency, suggesting that TET2 function may be compromised under metabolic disturbances relevant to sepsis [17]. Post-translational modifications also modulate TET2: AMPK-mediated phosphorylation enhances its stability and activity, but this pathway is often suppressed in septic metabolism [18]; conversely, inflammatory signals may promote TET2 ubiquitination and degradation. Non-coding RNAs contribute to the post-transcriptional regulation of TET2, and such regulatory networks are closely involved in shaping TET2-mediated immunomodulatory functions [19]. Additionally, vitamin C acts as a co-factor that potentiates TET2-mediated demethylation, suggesting a potential nutritional intervention avenue [15].

TET2 Within the Epigenetic Network

TET2 operates within a broader epigenetic network by cooperating with histone-modifying enzymes and transcription factors. It can recruit histone acetyltransferase p300 to enhancer regions to promote histone acetylation and gene activation; in sepsis, pro-inflammatory cytokines may disrupt this cooperation, leading to downregulation of protective genes. TET2 also interacts with histone deacetylases (HDACs) to balance transcriptional activation/repression; whether this balance is similarly perturbed in septic skeletal muscle warrants direct investigation. Furthermore, TET2 promotes myogenic gene expression through DNA demethylation [14,15], thereby driving myoblast differentiation and muscle regeneration [20]—a process potentially disrupted in sepsis-induced ICU-AW. Through these multidimensional interactions, TET2 exerts precise control over the "inflammation–metabolism–autophagy" axis in skeletal muscle.

Regulation of TET2 in the Septic Microenvironment and Its Pathological Significance

Impact of the Septic Microenvironment on TET2 Expression

Sepsis creates a severely catabolic state in which circulating LPS triggers TLR4/NF-κB inflammatory cascades that promote skeletal muscle proteolysis. Compounding this inflammatory burden, the immunometabolite itaconate—which accumulates in LPS-activated macrophages—inhibits TET2 catalytic activity by competing with α-ketoglutarate at its dioxygenase domain, thereby attenuating TET2-dependent transcriptional responses to LPS [21]. Given that TET2 is essential for muscle stem cell maintenance and myogenic differentiation, and its loss disrupts calcium homeostasis while impairing muscle regeneration, septic inhibition of TET2 imposes a double burden: it accelerates proteolytic muscle breakdown while crippling the epigenetic machinery required for recovery, positioning TET2 as a central node in the pathogenesis of sepsis-induced muscle atrophy.

TET2 in Sepsis-Associated Immunometabolic Dysregulation

TET2 regulates the interplay between inflammation and metabolism in sepsis. In macrophages, TET2 demethylates promoters of inflammasome-related genes (e.g., NLRP3, IL-1β) to modulate M1/M2 polarization. TET2 deficiency has been associated with altered inflammatory responses in experimental models [21,22]; extrapolation to septic muscle injury requires caution given the tissue-specific context. In murine models of metabolic stress, TET2 dysregulation has been associated with upregulation of muscle atrophy markers including Atrogin-1 and muscle RING-finger protein-1 (MuRF1) and may influ-

ence muscle energy metabolism; its downregulation could impair energy supply in skeletal muscle [23]. In individuals with type 2 diabetes, reduced skeletal muscle TET2 expression has been associated with diminished epigenetic plasticity and altered transcriptomic responses to metabolic intervention, including changes in insulin signaling-related pathways [24]. As sepsis also frequently induces systemic insulin resistance and skeletal muscle metabolic dysfunction, analogous TET2-dependent epigenetic alterations may contribute to septic muscle energy dysregulation, though direct evidence in this context remains to be established.

TET2 Deficiency and Sepsis-Related Organ Injury

TET2 deficiency exacerbates sepsis-induced injury in multiple organs, with skeletal muscle being a primary target. In muscle stem cells (MuSCs), TET2 loss reduces proliferation and differentiation capacities: in a septic mouse model with TET2 deletion in muscle stem cells, MuSC proliferation and differentiation were markedly impaired, with concomitant reductions in muscle fiber number and tissue volume [25]. Mechanistically, TET2 deletion increases methylation of calcium-pathway genes (e.g., calcium voltage-gated channel subunit alpha1 S (CACNA1S)), disrupting calcium homeostasis and impairing muscle regeneration [25]. In the lung, TET2 overexpression in septic models attenuated endothelial apoptosis and pulmonary vascular permeability, improving lung function [26]. TET2 also demethylates the integrin subunit alpha 10 (ITGA10) promoter, activating the PI3K-AKT pathway in pulmonary endothelium [26]; whether analogous cross-organ protection extends to skeletal muscle in sepsis remains to be determined. TET2-related epigenetic changes may reflect multi-organ involvement in sepsis, highlighting the potential of TET2 as a prognostic indicator.

Mechanisms of TET2 in Regulating Sepsis-Induced ICU-AW via the "Inflammation–Metabolism–Autophagy" Axis

Inflammatory Regulation: TET2 Inhibits Sepsis-Induced Muscle Inflammation

TET2 may dampen muscle inflammation by epigenetically regulating inflammatory gene programs. In sepsis, reduced TET2 expression leads to hypermethylation and downregulation of anti-inflammatory genes, coupled with NF-κB overactivation. In murine models, TET2 upregulation has been associated with reduced muscle atrophy markers and improved muscle function [23].

Metabolic Regulation: TET2 Maintains Muscle Energy Homeostasis

TET2 may preserve energy balance in septic muscle by demethylating genes involved in muscle development and calcium homeostasis; conversely, sepsis-induced TET2 downregulation may further compromise muscle metabolic homeostasis through epigenetic silencing of genes involved in energy metabolism and mitochondrial function. Beyond its role in metabolic regulation, TET2 is also essential for myoblast differentiation, a key process for muscle regeneration that may be compromised in sepsis [20].

Autophagy Regulation: TET2 Balances Muscle Autophagic Flux

Proper autophagic flux is essential for clearing damaged proteins and organelles in septic muscle. Emerging evidence from non-muscle cell types has begun to elucidate the molecular mechanisms by which TET2 regulates autophagy. In tumor cells, TET2 suppresses mTORC1 signaling to promote autophagy, and TET2 deficiency impairs autophagic flux, as evidenced by reduced LC3 conversion [27]. In osteoclast precursors, TET2 positively regulates BECN1-dependent autophagy by inhibiting BCL2 expression, and Tet2 knockdown suppresses autophagy [28]. In endothelial cells, TET2 overexpression promotes autophagy by decreasing methylation of the Beclin 1 promoter, whereas TET2 knockdown impairs autophagic flux [29]. These observations raise the possibility that TET2-mediated epigenetic regulation may similarly contribute to autophagic balance in skeletal muscle. Whether these regulatory axes operate in septic muscle, and whether TET2 deficiency directly impairs autophagic flux in this context, remain to be determined.

Clinical Evidence and Subtype-Specificity of TET2 in ICU-AW

Subgroup analyses reveal heterogeneity across ICU-AW subtypes: in myopathic ICU-AW (dominant atrophy), TET2 deficiency impairs muscle stem cell (MuSC) proliferation and differentiation, activates the ubiquitin-proteasome system (UPS), and reduces 5hmC at promoters of contractile and anabolic genes, creating a dual hit of reduced synthesis plus enhanced degradation that correlates with muscle-fiber cross-sectional area [25]; in neuropathic ICU-AW (nerve injury), TET2 downregulation destabilizes the neuromuscular junction through convergent mechanisms: it disrupts calcium homeostasis, as dysregulation of calcium-channel genes such as Cacna1s has been implicated in sepsis-induced muscle dysfunction [30], and may epigenetically silence postsynaptic maintenance genes, thereby potentially impairing neuromuscular transmission—a hallmark of CIP [31]. In mixed ICU-AW, TET2 may mediate a self-amplifying muscle-nerve crosstalk loop: TET2 deficiency in myofibers increases local inflammatory mediators and oxidative stress, which may retrogradely damage motor neurons; conversely, denervation-induced transcriptional repression may further reduce muscle TET2 expression, propagating both myopathic and neuropathic injury simultaneously. This subtype-specificity highlights the need for tailored TET2-targeted interventions. These molecular distinctions align with the elec-

trophysiological classification of critical illness myopathy (CIM) versus polyneuropathy (CIP), suggesting that future trials should incorporate EMG-guided stratification to match mechanism with intervention [31]. These distinct mechanisms imply that therapeutic strategies may require subtype-specific approaches: anabolic TET2 restoration for myopathic ICU-AW, neuromuscular junction repair for neuropathic ICU-AW, and dual-targeting for mixed ICU-AW.

TET2 as a Dynamic Epigenetic Hub Orchestrating the Inflammation–Metabolism–Autophagy Axis

TET2 functions as a molecular hub that simultaneously senses metabolic status and transduces inflammatory and autophagic signals. Its dioxygenase activity depends on α-KG and Fe^{2+}, directly linking metabolic state to demethylation capacity. In sepsis, NF-κB activation may suppress TET2 transcription, while succinate accumulation may competitively inhibit α-KG-dependent catalysis [17]. The resulting TET2 deficiency hypermethylates autophagy genes (Beclin1, LC3), causing p62 accumulation [29]; accumulated p62 feeds back to activate NF-κB, amplifying inflammation [32]. This p62-NF-κB feedback loop is proposed based on established p62-NF-κB crosstalk mechanisms; direct experimental validation in septic muscle is warranted. This creates a self-reinforcing cycle—TET2 loss may drive inflammation, metabolic dysfunction, and autophagy blockade, which further destabilize TET2. Thus, TET2 is not merely a parallel regulator but rather the central epigenetic switch that dynamically couples the three pathways (Fig. 1).

However, it should be noted that the role of TET2 in inflammation is context-dependent. A study in microglia has shown that TET2 can promote pro-inflammatory responses upon TLR4 stimulation, acting independently of its catalytic activity as a transcriptional scaffold [33]. Furthermore, in abdominal sepsis induced by cecal ligation and puncture, global Tet2-deficient mice paradoxically exhibited reduced mortality, possibly due to disrupted emergency myelopoiesis and attenuation of the associated cytokine storm [8]. These findings underscore that TET2 function varies by cell type, tissue microenvironment, and disease model, and that extrapolating its role in septic skeletal muscle from peripheral immune cells or non-muscle tissues requires caution. Future studies should employ muscle-specific and cell-type-specific genetic models to clarify whether TET2 exerts a uniformly protective or context-dependent dual role in ICU-AW pathogenesis.

Clinical Translation Potential of TET2 in Sepsis-Induced ICU-AW

TET2 as a Biomarker

TET2-related molecules show promise for diagnosing and prognosticating ICU-AW. Serum/plasma 5hmC levels reflect global TET2 activity and represent an emerging epigenetic biomarker concept for ICU-AW; however, definitive diagnostic cut-offs, sensitivity, and specificity from large prospective cohorts remain to be established. Exosomal TET2 mRNA, detectable non-invasively, shows conceptual potential as a liquid biopsy candidate for reflecting disease severity, though robust diagnostic thresholds and large-scale validation are currently lacking. The established role of TET2 mutations as prognostic markers in hematologic malignancies further supports its biomarker potential in sepsis-induced ICU-AW [34].

TET2-Targeted Interventions

Several strategies aim to restore TET2 function in sepsis-induced ICU-AW. Natural compounds such as punicalagin have been shown to enhance TET2 activity [23]; Vitamin C enhances TET2 expression and demethylation, which may attenuate muscle atrophy in critical illness [15]. Interestingly, caffeine has also been reported to upregulate TET2 expression in skeletal muscle under LPS-induced inflammatory conditions, accompanied by attenuation of the catabolic state and restoration of AMPK expression [35]. Targeted epigenetic modulation of TET2 represents a potential future strategy, though tissue-specific delivery remains a significant challenge. While CRISPR-based genetic screens in TET2-deficient models have identified therapeutic vulnerabilities such as NCOA4-mediated ferritinophagy [36], their applicability in the acute ICU setting is limited by delivery complexity and the narrow therapeutic window of sepsis.

Limitations of Current Evidence and Pathways to Clinical Translation

Several methodological limitations must be acknowledged. First, direct clinical evidence quantifying muscle TET2 or 5hmC in sepsis-induced ICU-AW remains scarce; existing studies predominantly comprise preclinical models or small observational cohorts, limiting statistical power and generalizability. Second, ICU-AW diagnosis relies on the Medical Research Council (MRC) sum score and muscle ultrasonography, both subject to inter-rater variability and confounded by sedation, delirium, and edema in septic patients. Third, TET2 and 5hmC assays lack standardized protocols across platforms, introducing technical heterogeneity. Fourth, no prospective, biomarker-stratified cohort has validated TET2/5hmC as an independent predictor of ICU-AW. Large-scale, multi-center, prospective studies with standardized MRC assessment and blinded adjudication are therefore urgently required.

Translating TET2-targeted therapies faces several hurdles. First, tissue-specific delivery systems (e.g., muscle-targeted liposomes, viral vectors) currently achieve only limited targeting efficiency and lack precise controlled release, risking off-target effects in non-muscle tissues such as the hematopoietic system. Second, TET2's vital role in

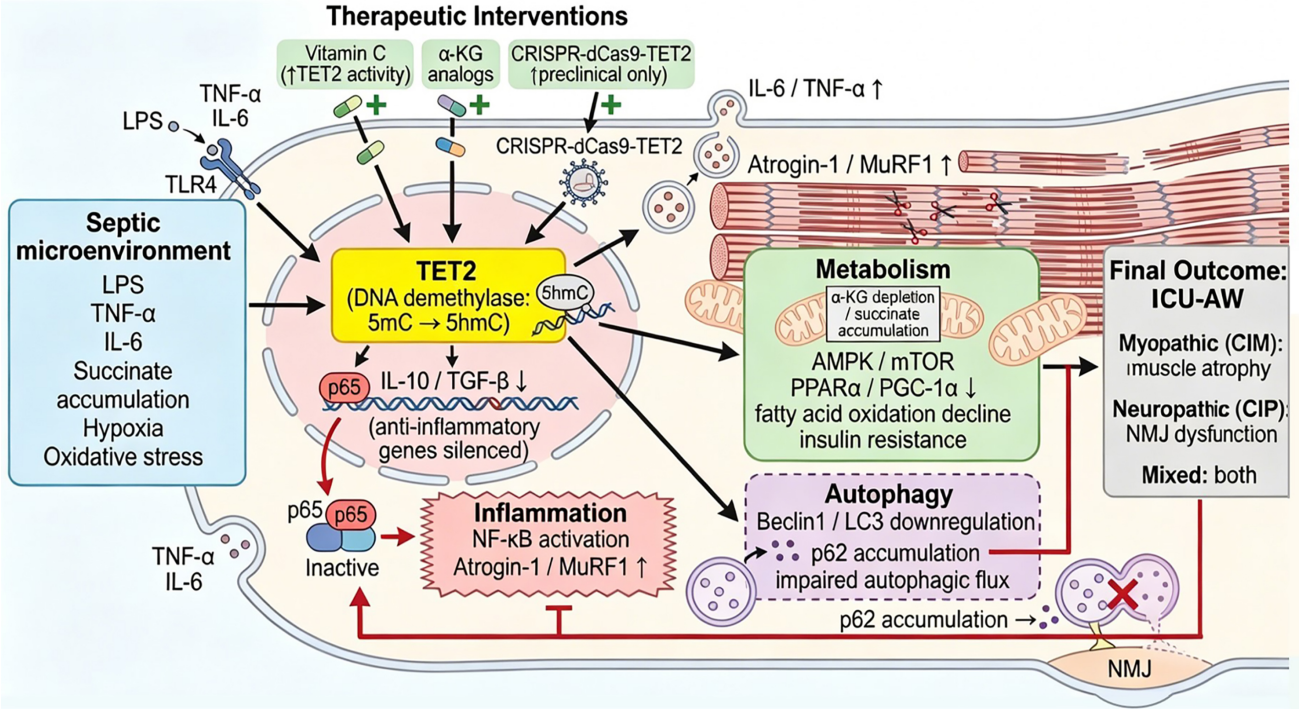

Fig. 1. TET2 as a dynamic epigenetic hub integrating the inflammation–metabolism–autophagy axis in sepsis-induced ICU-acquired weakness. TET2 as a dynamic epigenetic hub integrating the inflammation–metabolism–autophagy axis in sepsis-induced ICU-acquired weakness. In a skeletal muscle fiber, the septic microenvironment (LPS, TNF-α, IL-6, succinate, hypoxia, oxidative stress) suppresses nuclear TET2 via NF-κB activation, reducing 5hmC levels. TET2 deficiency hypermethylates and silences anti-inflammatory genes (IL-10, TGF-β), upregulates NF-κB-driven inflammation (IL-6, TNF-α, Atrogin-1, MuRF1), impairs metabolic adaptability (AMPK/mTOR disorder, PPARα/PGC-1α downregulation, fatty acid oxidation decline, insulin resistance), and blocks autophagic flux (Beclin1/LC3 downregulation, p62 accumulation). p62 feedback-activates NF-κB, forming a self-reinforcing cycle. Therapeutic interventions restore TET2 activity. Outcomes are stratified by ICU-AW subtype: critical illness myopathy (CIM), critical illness polyneuropathy (CIP), or mixed CIM/CIP. NMJ, neuromuscular junction. The figure was created using Microsoft PowerPoint 2019 (Microsoft Corporation, Redmond, WA, USA) and Adobe Illustrator 2023 (version 27.0) (Adobe Inc., San Jose, CA, USA). TET2, Ten-Eleven Translocation 2; LPS, lipopolysaccharide; TNF-α, Tumor Necrosis Factor-α; IL-6, Interleukin-6; NF-κB, Nuclear Factor-κB; MuRF1, muscle RING-finger protein-1; AMPK, AMP-Activated Protein Kinase; mTOR, Mammalian Target of Rapamycin; PPARα, Peroxisome Proliferator-Activated Receptor α; PGC-1α, Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1α; ICU-AW, ICU-acquired weakness; CIM, critical illness myopathy; CIP, critical illness polyneuropathy.

hematopoiesis necessitates careful monitoring for hematologic toxicity via blood counts and bone marrow examinations during interventions [10]. Beyond acute hematologic toxicity, systemic or long-term TET2 activation carries theoretical oncogenic risks. TET2 is a critical guardian of hematopoietic stem cell homeostasis, and loss-of-function mutations drive myelodysplastic syndromes (MDS) and clonal hematopoiesis [34]. Although TET2 generally acts as a tumor suppressor [37], forced systemic overexpression might induce 'over-demethylation' and genomic instability in a context-dependent manner. TET2 mutations are also implicated in hematologic malignancy prognosis [38]. Therefore, any TET2-targeted trial should adopt strict risk mitigation: weekly complete blood counts with differential; bone marrow examination if cytopenias persist beyond 14 days; long-term post-ICU hematologic surveillance to detect clonal abnormalities; and prioritized development of muscle-targeted delivery systems to minimize systemic exposure. Third, the dose-response and long-term safety of TET2 activation are unclear. Excessive activity might cause genomic instability through "over-demethylation", and the dual role of TET2 in certain inflammatory contexts (e.g., pro-inflammatory effects in microglia and protective effects in peripheral macrophages) suggests that systemic activation could yield unpredictable, tissue-specific outcomes. Long-term safety data therefore remain to be established.

A stepwise translation pathway is recommended: (1) Establish patient-derived skeletal muscle organoids that retain epigenetic features of sepsis-induced ICU-AW, enabling preclinical optimization of TET2 interventions; (2) Design biomarker-stratified clinical trials (e.g., using serum

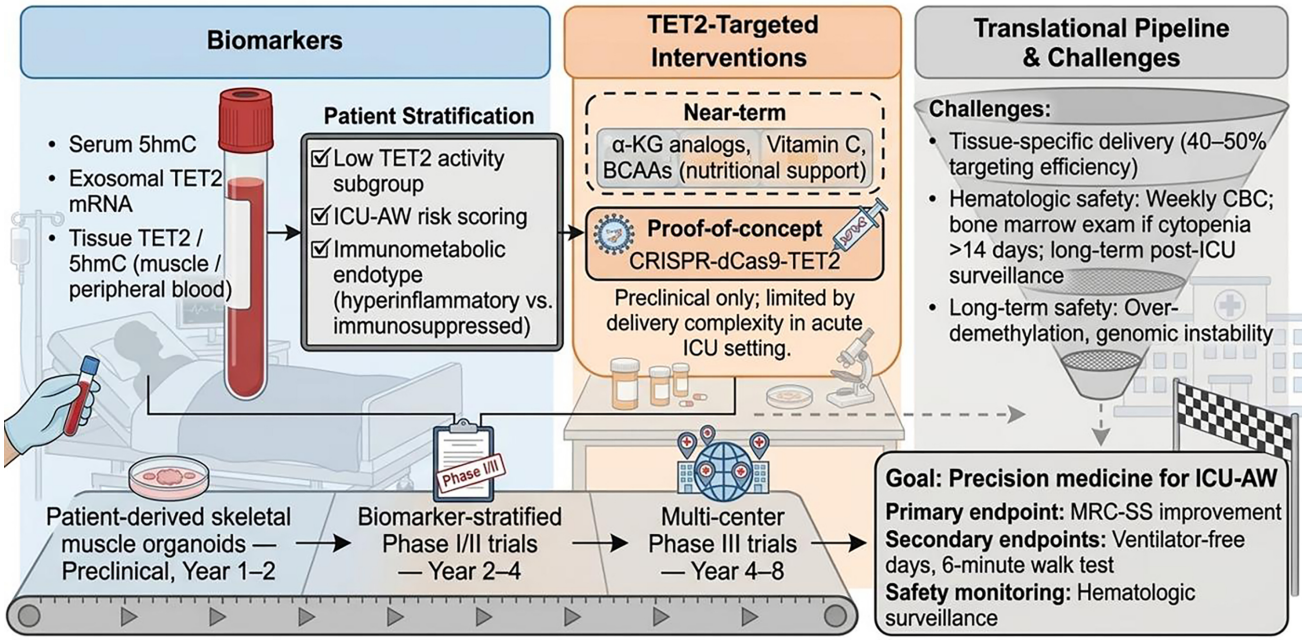

Fig. 2. Clinical translation roadmap of TET2-targeted strategies for sepsis-induced ICU-acquired weakness. Clinical translation roadmap of TET2-targeted strategies for sepsis-induced ICU-acquired weakness. TET2 biomarkers (serum 5hmC, exosomal TET2 mRNA, tissue TET2/5hmC) enable patient stratification by TET2 activity, ICU-AW risk, and immunometabolic endotype. Near-term interventions include vitamin C, and BCAAs; Challenges comprise tissue-specific delivery, hematologic safety (weekly CBC, bone marrow examination if cytopenia >14 days, long-term post-ICU surveillance), and long-term over-demethylation risk. The stepwise pipeline includes patient-derived organoids (Year 1–2), biomarker-stratified Phase I/II trials (Year 2–4), and multi-center Phase III trials (Year 4–8). The goal is precision medicine for ICU-AW, with primary endpoint MRC-SS improvement and secondary endpoints of ventilator-free days and 6-minute walk test. The figure was created using Microsoft PowerPoint 2019 (Microsoft Corporation, Redmond, WA, USA) and Adobe Illustrator 2023 (version 27.0) (Adobe Inc., San Jose, CA, USA). BCAAs, Branched-Chain Amino Acids; CBC, complete blood count.

5hmC or exosomal TET2 mRNA) to test TET2-modulating strategies or vitamin C in "low-TET2-activity" subgroups; (3) Conduct multicenter trials enrolling several hundred patients with formal power calculations for functional endpoints (Medical Research Council sum-score (MRC-SS), 6-minute walk test, ventilator-free days) and safety (Fig. 2).

Future Directions

Future research should prioritize the following five interrelated areas: (1) Single-cell multi-omics (scRNA-seq combined with sc-methylation sequencing) to delineate cell-type-specific TET2 roles in muscle stem cells, myofibers, and immune cells within the septic muscle microenvironment; (2) Spatial multi-omics analysis (spatial transcriptomics combined with *in situ* DNA hydroxymethylation mapping) on serial muscle sections from septic patients and model animals to resolve TET2 activity and cell type-specific transcriptional programs *in situ*; (3) Leverage patient-derived skeletal muscle organoids and regenerative medicine platforms to retain donor epigenetic landscapes and pre-screen TET2-targeted interventions, bridging the gap between murine models and human therapeutic response prior to clinical trials. (4) Determine the optimal intervention window and long-term impact through prospective cohort studies with >1-year follow-up, employing repeated MRC and functional tests at 3, 6, and 12 months to evaluate whether early TET2 restoration prevents persistent ICU-AW disability. (5) Standardize ICU-AW diagnostic criteria and TET2/5hmC detection protocols to reduce inter-study heterogeneity and enable cross-cohort validation. Additionally, exploring TET2 expression across sepsis immunometabolic endotypes (e.g., hyperinflammatory versus immunosuppressed) may enable biomarker-guided patient enrichment in future trials.

Conclusion

In summary, TET2 may serve as a central epigenetic regulator in sepsis-induced ICU-AW. Functionally, it operates as a dynamic hub that couples inflammatory signaling, metabolic plasticity, and autophagic flux into a single network, rather than regulating these processes in isolation. Suppression of TET2 by the septic microenvironment via inflammatory cytokines is associated with diminished DNA demethylation, dysregulation of the inflammation-

metabolism-autophagy axis, and muscle atrophy and weakness. TET2 and its related molecules hold promise as diagnostic and prognostic biomarkers, while therapeutic strategies aimed at restoring TET2 function—including small-molecule agonists, epigenetic editing, and nutritional support—offer novel avenues for intervention. Although challenges in delivery and safety remain, a rational translational pathway can position TET2 as a valuable target for precision management of sepsis-associated muscle weakness, potentially improving outcomes for critically ill patients.

Abbreviations

TET2, Ten-Eleven Translocation 2; 5mC, 5-methylcytosine; 5hmC, 5-hydroxymethylcytosine; 5fC, 5-formylcytosine; 5caC, 5-carboxylcytosine; MuSCs, muscle stem cells; ICU-AW, ICU-Acquired Weakness; LPS, lipopolysaccharide; TNF-α, Tumor Necrosis Factor-α; IL-6, Interleukin-6; NF-κB, Nuclear Factor-κB; TDG, Thymine DNA Glycosylase; BER, Base Excision Repair; AMPK, AMP-Activated Protein Kinase; mTOR, Mammalian Target of Rapamycin; PPARα, Peroxisome Proliferator-Activated Receptor α; PGC-1α, Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1α; UPS, Ubiquitin-Proteasome System; MRC, Medical Research Council; BCAAs, Branched-Chain Amino Acids; MDS, Myelodysplastic Syndromes; AML, Acute Myeloid Leukemia.

Availability of Data and Materials

Not applicable.

Author Contributions

JF and JY made substantial contributions to the conception and design of the study, drafted the manuscript, and critically revised it for important intellectual content. JH, JC, WH, and ZZ participated in the literature search and analysis, manuscript writing, and critical revision of specific sections. FL and XW made substantial contributions to the conception and design of the study,and critically revised the manuscript for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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