From skeletal muscle weakness to functional outcomes following critical illness: a translational biology perspective

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ABSTRACT

Intensive care unit acquired weakness (ICUAW) is now a well-known entity complicating critical illness. It increases mortality and in the critical illness survivor it is associated with physical disability, substantially increased health resource utilisation and healthcare costs. Skeletal muscle wasting is a key driver of ICUAW and physical functional outcomes in both the short and long term. To date, there is no intervention that can universally and consistently prevent muscle loss during critical illness, or enhance its recovery following intensive care unit discharge, to improve physical function. Clinical trials of early mobilisation or exercise training, or enhanced nutritional support have generated inconsistent results and we have no effective pharmacological interventions. This review will delineate our current understanding of the mechanisms underpinning the development and persistence of skeletal muscle loss and dysfunction in the critically ill individual, highlighting recent discoveries and clinical observations, and utilisation of this knowledge in the development of novel therapeutics.

INTRODUCTION

Intensive care unit acquired weakness (ICUAW) is defined by the American Thoracic Society as 'a syndrome of generalized limb weakness that develops while the patient is critically ill and for which there is no alternative explanation other than the critical illness itself'.[1] It affects about 30% of all critically ill patients, over 70% in susceptible subgroups, and is associated with increased intensive care unit (ICU) and hospital length of stay, short-term and long-term mortality.[2 3] In survivors of ICU care, it portends long-term functional disability, negatively impacting quality of life and return to work or to independent living.[2 3] Weakness results from critical illness polyneuropathy (CIP) and/or critical illness myopathy (CIM).[1 4] Advanced age, female sex, exposure to systemic corticosteroids, longer duration of mechanical ventilation and sepsis are known risk factors for the development of ICUAW.[1 5–7] This review aims to provide a translational biological perspective on the clinical syndrome of ICUAW, contextualising basic mechanisms within clinical observations, challenges and opportunities for future intervention to impact outcomes.

HETEROGENEITY IN BIOLOGICAL AND FUNCTIONAL OUTCOMES

From a biological perspective, ICUAW has been postulated to represent the 'extreme' of weakness common to any severe illness.[3] Patients with pancreatitis, sepsis or trauma managed outside of the ICU are reported to develop CIM/[8]CIP (although the diagnostic criteria used are not described) suggesting there is no unique causative relationship between ICU-level care and the development of ICUAW. An alternative hypothesis is that this is an exclusive phenomenon brought about by (1) an as of yet undescribed pathological process and/or (2) converging pathways of critical illness and ICU-specific iatrogenicity which together remove all muscle contractile cues (internal and external) resulting in a unique muscle pathology.[9] Whether we are dealing with a unique entity or a combination of pathologies has important implications for treatments and outcomes. It is likely that both possibilities are true to different degrees for different patients—in part explaining the heterogeneity in outcomes.

In the ICU, weakness can be detected early by clinical testing and electrophysiology.[1 3] Muscle mass falls rapidly (days) and muscle's intrinsic contractility diminishes, with or without peripheral nerve dysfunction.[4 10] Following resolution of critical illness, recovery in physical functional capacity is variable (figure 1). A proportion of survivors experience sustained muscle wasting and/or weakness, resulting in long-term physical disability.[2 3] In contrast, other patients make a near to full recovery returning to pre-ICU status. Survivors fall into discrete disability risk categories based on their functional dependency (Functional Independence Measures, FIM) score.[2] The degree of disability (FIM score) at 7 days after ICU discharge is a marker of recovery trajectory, increased risk of ICU readmission and 1-year mortality.[2]

Age and duration of ICU stay are strong indicators of long-term functional outcomes. While younger patients (<42 years of age) in the ICU for fewer than 2 weeks are more likely to regain baseline physical functional status, older individuals (66 years and more) who require ICU for more than 2 weeks are more likely to have significant long-term functional dependencies, with less than 50% able to dress or bathe independently at 1 year post-ICU discharge.[2] Importantly, how weakness of specific muscle groups (including those involved in respiration and deglutition) may be independently contributing to outcomes is not known and requires further study.

Preadmission functional and health status is an important risk prognosticator for resilience and functional outcome.[11] Future investigations aiming to resolve the heterogeneity in outcomes and improve functional capacity in ICU survivors will

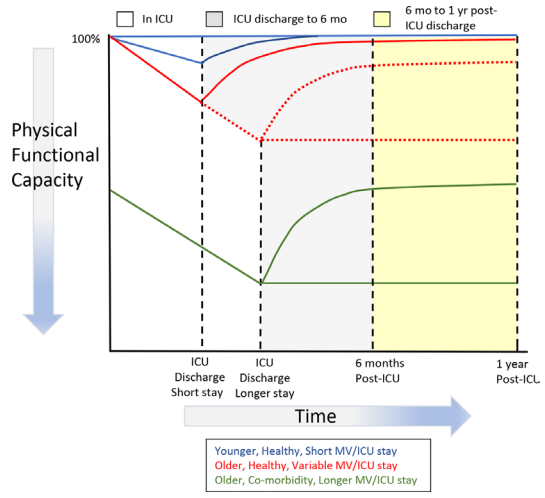

Figure 1 Heterogeneous trajectories of physical functional recovery post-ICU discharge. Baseline physical functional capacity (y axis) will vary across patients admitted to the ICU with a critical illness. Irrespective of baseline status, the majority of patients experience physical functional decline during ICU admission (white shading). Critical illness survivors will demonstrate a potential range of recovery of physical functioning post-ICU discharge. Younger (blue line) and healthy older individuals (red solid line) with physical functional capacity equivalent to age and gender matched population-based norms at ICU admission, subjected to shorter duration MV and ICU stay, are most likely to regain their baseline level of physical function following ICU discharge. However, older age and longer duration of MV and ICU stay in the healthy individual (red dotted line), or pre-existing poor health or physical impairment prior to critical illness (green line), are risk factors and prognosticators for poor functional outcomes following ICU discharge. The majority of these patients will experience some degree of persistent physical impairment. The first 6 months post-ICU discharge (grey shading) are the most critical for physical functional recovery, whereafter improvement plateaus (yellow shading). The graph highlights the fundamental importance and potential therapeutic opportunity of the first 6 months post-ICU discharge in determining outcomes at 1 year. ICU, intensive care unit; MV, mechanical ventilation.

require stratification based on pre-enrollment status, including age, cognitive state, concurrent illness, frailty and health trajectories.[3]

UNDERSTANDING MECHANISMS AND THE POTENTIAL FOR INTERVENTION

A distinctive feature of muscle loss in CIM is the apparent preferential loss of myosin and myosin-related proteins relative to actin.[9 12–15] The reasons for this remain elusive, and many standard preclinical models of muscle atrophy (eg, steroid exposure, muscle unloading/inactivity) are unable to replicate this finding. In only one rodent model where animals are exposed to mechanical ventilation in combination with deep anaesthesia and other common ICU insults for days to weeks, preferential loss of myosin has been documented,[16] strongly suggesting that convergent pathways (as well as time) are required to reproduce the phenomenon seen in humans. Developing strategies to prevent, limit or reverse loss of muscle-specific proteins during (or after) ICUAW is a fundamental goal for future therapeutics.

Muscle proteolysis in the ICU

Muscle wasting in ICUAW results from the imbalance between protein synthesis and degradation, where proteolysis is rapid,

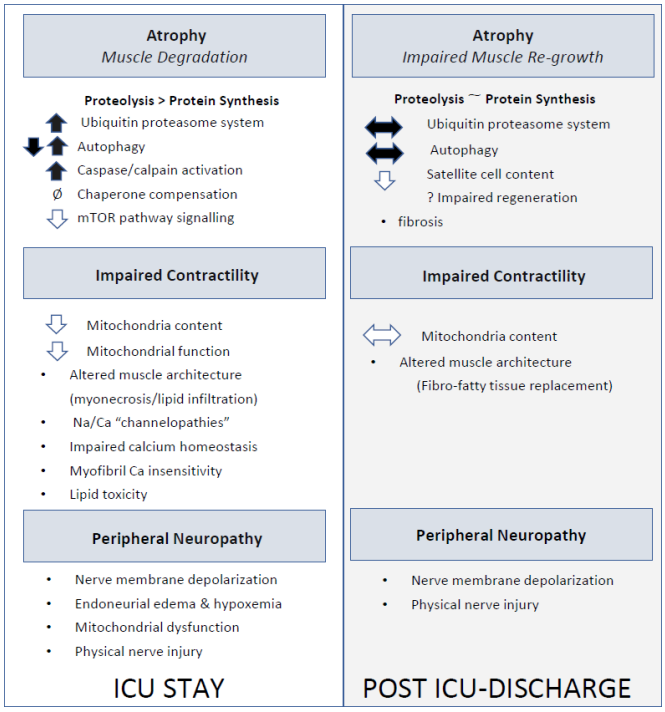

Figure 2 Mechanisms of ICUAW. ICUAW is a heterogeneous phenomenon caused by muscle wasting and/or intrinsically impaired muscle contractility with or without neuropathy. Concepts shown are mechanisms reported in ICUAW preclinical models and translational studies in patients with ICUAW. In the ICU, muscle proteolysis overwhelms protein synthesis to result in atrophy, and muscle's contractility is impaired by abnormal architecture, bioenergetic failure, altered muscle membrane excitability and excitation–contraction uncoupling. CIP may or may not contribute. In sustained ICUAW months after ICU discharge, proteolysis normalises to baseline and persistent muscle wasting results from impaired muscle regrowth. Altered architecture contributes to impaired contractility—muscle bioenergy status, membrane excitability and excitation–contraction coupling have not been reported. Nerve dysfunction and injury, if present, impair muscle contraction. Ca, calcium; CIP, critical illness polyneuropathy; ICU, intensive care unit; ICUAW, intensive care unit acquired weakness; mTOR, mechanistic target of rapamycin; Na, sodium.

massive and overwhelms the muscle's synthetic capacity[10 12 17] (figure 2). The ubiquitin (Ub) proteasome system (UPS) is the predominant proteolytic system mediating muscle degradation in the critically ill.[12 15 18–20] The key regulatory proteins are the Ub ligases[21] including atrogin-1, MuRF1 and 2, FBOX31, SMART and TRIM 32, although the relative importance of each remains unknown.[12 15 16 22 23] Numerous stimuli common to ICU patients can activate the UPS (eg, inflammation, oxidative and energy stress, abnormal lipid metabolism) or are inadvertently introduced during ICU care (eg, bed rest/unloading, inactivity).[12] Although activation of proteolytic pathways contributes to loss of muscle proteins early in the course of critical illness, this does not seem to explain persistent weakness in survivors of ICU care,[24] suggesting that—while inhibition of proteolysis may be a therapeutic option early in the course of critical illness—this may no longer be appropriate in individuals with persistent weakness post-ICU discharge.

Dysregulation of autophagy has also been associated with muscle wasting in ICU patients and preclinical models[15 25–29] (figure 2). While upregulation of autophagy results in muscle

Table 1 Potential targets for therapeutics development

Target	Timing and intervention	Biology
UPS	ICU—inhibition	Decrease muscle proteolysis. Timing must consider possible survival advantage with early catabolism.
Autophagy	ICU—induction or inhibition	Decrease muscle damage and proteolysis. Autophagy balance is key—may require induction or inhibition based on patient status and duration of ICU stay.
Protein chaperone	ICU—enhancer	Decrease proteolysis and enhance muscle-specific force by protecting contractile proteins.
mTOR pathway	ICU—enhancer	Increase protein synthesis to counteract proteolysis in ICU.
Na^+ & Ca^{+2} channelopathies"	ICU—corrector	Normalise muscle membrane and nerve excitability. Maintain contractility.
Nutrition	ICU, post-ICU—composition and supplements (eg, leucine, decreased fats)	Inhibit proteolysis, increase protein synthesis, inhibit lipolysis, reverse energy deficit, maintain contractility. Must be delivered appropriate to activity level and metabolic needs.
Mitochondria	ICU—stablizer, promoter of biogenesis	Inhibit proteolysis, increase protein synthesis, reverse energy deficit, stress response, cytopathic hypoxia. Maintain contractility.

Ca^{+2}, calcium ion; ICU, intensive care unit; Na^+, sodium ion; UPS, ubiquitin proteasome system; mTOR, mechanistic target of rapamycin.

degradation, impairment also promotes muscle loss due to the accumulation of damaged and toxic proteins and organelles.[21 29 30] In other organs (eg, bone, liver, kidneys) in critical illness, insufficient autophagy is associated with organ failure and mortality risk.[31–34] From a therapeutic perspective, starvation classically stimulates autophagy, whereas growth factors (eg, insulin) and nutrients suppress it.[21] Permissive underfeeding in the acute phase of critical illness was found to stimulate autophagy and improve muscle recovery.[35] The role of exercise is controversial—as both increases and decreases in autophagy have been reported depending on the type of exercise and methodology of autophagy quantification.[21 36]

Proteolytic calpains and caspases have also been shown to be variably upregulated during critical illness and may participate in the degradation of large actinomyosin complexes for subsequent UPS-mediated proteolysis[12] (figure 2). In preclinical animal models, the upregulation of a number of protein chaperones, such as heat shock proteins 70 and 90, and αβ-crystallin occurs quickly within the first 5 days of 'ICU treatments'.[37 38] This chaperone upregulation appears to be a short-term compensatory response within muscle to protect against myofibrillar degradation, which will ultimately fail to prevent muscle wasting if the critical illness does not rapidly resolve (figure 2).

Given that proteolysis is a key driver of muscle wasting, inhibiting specific pathways in patients at risk of ICUAW may help prevent severe muscle atrophy in the ICU (table 1). However, although controversial, independent reports suggest a salutary effect of muscle catabolism, which is purported to confer a survival benefit by deprioritising an energy-dependent non-vital organ system and concurrently liberating amino acids for consumption.[39–41] In view of possible benefits of an early catabolic response, attempts to inhibit proteolysis to spare muscle may need to be carefully considered with respect to timing and extent.

Bortezomib is a pharmacological inhibitor of the proteasome (and the nuclear factor-K B signalling network) approved for clinical use in the treatment of specific malignancies. It mitigates muscle wasting in animal models of atrophy including burn, denervation and Duchenne muscular dystrophy.[42–44] Despite effective proteasome inhibition, its impact on muscle wasting is not universal, as it fails to prevent muscle wasting in cancer cachexia.[45] Bortezomib has been evaluated in mechanically ventilated animals and was shown to partially inhibit diaphragm weakness.[46] Bortezomib has a narrow therapeutic range and toxicity may preclude its use for atrophy prevention in humans. The development of skeletal muscle-specific UPS inhibitors could be of benefit to prevent the acute phase of ICUAW (table 1).

Pharmacological regulators of autophagy, the majority of which are inducers, are also available or in development[47] and could be used to mitigate muscle wasting in ICU (table 1). However, given it is the autophagic balance that appears to be critical to muscle integrity and homeostasis, further research is required in critically ill patients to determine the appropriate timing and extent of enhancement and/or inhibition.

Interestingly, neither UPS nor autophagy remain activated above levels comparable to healthy individuals in ICU survivors with long-term muscle wasting and weakness after ICU discharge[24] (figure 2). Instead in these patients it is the muscle's recovery capacity that seems to be durably altered by critical illness. Thus, the use of UPS inhibitors or modulators of autophagy should be best restricted to early ICUAW and/or preventative care (table 1).

Muscle protein synthesis in the ICU

In health, muscle mass is profoundly impacted by loading, activity and nutrition which downregulate cellular signalling that promotes proteolysis. Exercise and nutrition are equally important positive regulators of protein synthesis. It is the balance between protein synthesis and degradation, modulated by delivery of nutrients, muscle loading and activity[48–50] that provides homeostasis to muscle mass in health. This homeostatic regulation is lost in the critically ill; proteolysis is increased, protein fractional synthetic rates are decreased and neither an increase in protein delivery[10 51 52] nor early exercise/early mobility[53–55] consistently results in functional outcome improvements. In fact, early aggressive nutrition does not necessarily diminish muscle catabolism nor enhance anabolism. Similarly, early mobility may not re-establish homeostasis but may delay recovery or aggravate muscle catabolism and dysfunction. While patient heterogeneity may partially explain differential responses, better understanding of molecular mechanisms of altered homeostasis is required for the development of appropriate and well-timed therapeutic interventions.

The mechanistic target of rapamycin (mTOR) signalling network is a key promoter of muscle protein synthesis, leading to muscle hypertrophy[56] (figure 2). A complex of proteins in this network, known as mTOR Complex 1 promotes protein synthesis largely via the phosphorylation of two key effectors, p70S6 kinase 1 and IF4E-binding protein 1, thereby enabling mRNA translation.[57] Protein synthesis is predominantly an ATP-dependent process upregulated by multiple stimuli including mechanical load, essential nutrients and growth factors, both

via canonical IGF/AKT/mTOR (insulin-like growth factor/AKT/mTOR) signalling and in an mTOR dependent, AKT independent manner, dependent on the specific stimulus applied.[9 56] Loss of these stimuli (eg, bed rest, inactivity) conversely downregulates these networks and protein synthesis.[58]

In early critical illness, anabolic resistance is well described, such that even with the provision of appropriate substrates, muscle growth does not occur. Puthucheary *et al* measured various markers of muscle bioenergy status, hypoxia, inflammation, protein homeostatic signalling, muscle mass, and lipid and carbohydrate nutrition delivered.[59] Activation of intramuscular inflammatory and hypoxia signalling and reduced ATP bioavailability within the first days of ICU admission was strongly and directly associated with impaired anabolic signalling and muscle wasting. This is in keeping with previous work demonstrating widespread inactivation (dephosphorylation) of proteins regulating translation initiation factor activation and protein synthesis through the mTOR pathway.[23] In addition, proteolytic and anabolic signalling are reciprocally linked, such that downregulation of signalling through the AKT/mTOR pathway will not only disable protein synthesis but also concomitantly enable autophagy and UPS-mediated proteolysis.[60]

In both humans and animals, muscle mitochondria ultrastructural injury is evident and mitochondria biogenesis is decreased early in CIM (figure 2)[59 61–65] resulting in muscle ATP depletion, impairment in mechanosensing, cytopathic hypoxia and the production of reactive oxygen species (ROS), all of which will stimulate proteolytic machinery and antagonise anabolic signalling.[66 67] Energy depletion specifically negatively impacts the capacity for usual interventions, such as muscle loading and exercise, to induce protein synthesis and build muscle. In fact, whether acutely critically ill patients can generate adequate energy to facilitate and respond to exercise in the ICU has been questioned.[68] This may be different for patients who have overcome the acute phase of illness. Moreover, while recent guidelines have focused on enhanced protein delivery to prevent loss of lean body mass and improve functional outcomes, some studies have shown that increased protein intake or enhanced macronutrient supplementation with total parenteral nutrition (TPN) is associated with increased muscle wasting and weakness.[10 69] In contrast, increased amino acid delivery with parenteral nutrition improves hand grip strength at day 7 following ICU admission.[70] Part of the reason for these apparent contradictory results lies in the fact that baseline nutritional and energy requirements vary dramatically with activity level and there is heterogeneity in energy requirements within the critically ill population undertaking the same functional activities.[68]

In health, the delivery of precise nutritional substrates such as the amino acid leucine[71] and its metabolite β-hydroxy β-methylbutyrate have been demonstrated to positively impact mTOR signalling to enhance protein synthesis and attenuate the UPS, respectively,[68 72] thereby impacting lean body mass. It has been suggested these substrates may be of benefit in the critically ill patient, used in addition to traditional protein, fat and carbohydrate (table 1). However, the ability of the critically ill patient to use these substrates to synthesise muscle protein and counteract the massive upregulation of proteolysis that occurs in the ICU remains unclear. Future prospective studies are essential to delineate the complex interaction between nutrition, exercise and the critically ill patient's baseline metabolic status.

Proteolysis, protein synthesis, muscle regeneration and fibrosis in sustained ICUAW

Muscle wasting that persist months after ICU discharge does not result from ongoing enhanced proteolysis overwhelming protein synthesis (figure 2). Instead, a decreased number of myogenic stem (satellite) cells were observed in sustained muscle atrophy, suggesting that impaired muscle regeneration may contribute to the long-term muscle wasting in survivors of ICU care. In a murine model of sepsis-induced muscle wasting, the depletion in satellite cells is due to impaired self-renewal.[73] This occurred early in the course of sepsis, but persisted for 3 months following sepsis resolution, demonstrating that satellite cells are durably altered by a single episode of sepsis. In humans, whether a depleted satellite cell pool causally contributes to persistent long-term muscle atrophy in ICUAW remains to be proven and little is known about the biology of the satellite cell loss. Alternative hypotheses include increased satellite cell apoptosis versus impaired proliferative and self-renewal capacity, possibly in the context of early senescence. While we now appreciate that long-term muscle wasting in the critical illness survivor results from the inability to 'regrow' muscle following its catabolism in the ICU, designing successful interventions to prevent or treat weakness will require further work to understand the mechanisms by which muscle is durably altered in the ICU setting.

Provocative data from our own group suggest that impaired muscle mass recovery is also associated with increased fat and fibrous tissue deposition on vastus lateralis biopsy[74] (figure 2). The role of pathological fibrosis as a final common pathway and histological manifestation of a dysfunctional repair response to tissue injury has spurred recent studies looking at the role of metabolic reprogramming as a driver for sustained fibrosis in chronic organ failure. Downregulation of AMP-activated protein kinase (AMPK), the cellular bioenergetic sensor and metabolic regulator that is classically known for controlling the switch from anabolic to catabolic metabolism, has been shown to induce pathological fibrosis.[75] Although no study to date has looked at AMPK in ICUAW sustained long term in critical illness survivors, recent studies have shown significant downregulation of AMPK in chronic obstructive pulmonary disease and diabetic-associated myopathies and myocardial fibrosis.[76–78] All we know about ICUAW suggests that AMPK dysregulation may also be playing a role in sustained ICUAW.

New insights into dysregulated muscle mass regulatory mechanisms and metabolic reprogramming

Lipid toxicity has been implicated in diaphragmatic dysfunction during mechanical ventilation[79 80] (figure 2). Accelerated lipolysis (catabolic state) results in increased triglyceride-rich lipoproteins and free fatty acids in the circulation that may be ultimately toxic to muscle cells.[80–85] Substrate oversupply elicits ROS production by muscle cells. This is further exacerbated by peripheral insulin resistance. Although it is unclear if skeletal muscles are a target of endogenous pathological lipids, in animal models ectopic lipid accumulation induces proteasomal activity, apoptosis and skeletal muscle damage.[83 84] Of note, neither muscle mass nor muscle ATP content is impacted by the quantity of fatty acids delivered as nutritional supplements to critically ill patients within the first 7 days of ICU admission.[59] Interestingly, lipid toxicity may play a role in the loss of muscle precursor/satellite cell proliferative capacity. Complete loss of myogenic potential was observed in C2C12 myoblasts, used to model muscle regeneration in vitro, on overexpression of lipoprotein lipase, the key enzyme in lipolysis.[84] Whether this mechanism

contributes to the depletion of satellite cells in the critically ill patient with sustained ICUAW has not been evaluated. Given the potential for lipid-induced muscle toxicity and the fact that lipid delivery has little effect on muscle energy stores,[59] the use of non-fat food sources and removal of fatty acid supplementation should be considered in future mechanistic studies and evaluated in clinical trials (table 1).

MicroRNAs (miRs) are small non-coding RNAs that regulate gene expression at a post-transcriptional level. They modulate the degradation and translation of large sets of mRNAs, thus simultaneously impacting key regulatory elements in entire signalling networks and thereby rapidly modifying cell phenotype. miRs act locally within muscle, or as circulating factors within the bloodstream, to impact myogenesis and muscle size.[86 87] Several miRs, whose expression is restricted to skeletal muscle (miR-1, miR-133, miR-206, miR-208) regulate critical signalling networks that control muscle protein synthesis, myogenic differentiation and fibrosis.[86 88] In ICU patients, miR-542–3 p/5 p induces muscle atrophy via promotion of mitochondrial dysfunction and enhanced transforming growth factor beta (TGFβ) signalling.[89] miRs are particularly exciting and potentially significant factors in the future management of ICUAW, both in the acute and sustained phases, since they can be directly administered as therapeutic agents simultaneously targeting several muscle signalling networks and thus have breadth of impact on muscle biology, in addition to serving as biomarkers of disease or response to therapy, given they are secreted into the bloodstream.

Peripheral nerve injury

While muscle wasting and weakness can occur independently of any injury to the peripheral nervous system, exposure to neuromuscular blockade, nerve trauma sustained in the inciting critical illness event (ie, motor vehicle accident), or the development of CIP due to endoneurial oedema, bioenergy failure and ion channel dysfunction[4 12] will additionally provide stimulus for rapid recruitment of the muscle proteolytic machinery and inhibit the protein synthesis machinery in the ICU (figure 2). In fact, prolonged muscle denervation, sustained in trauma, for example, is well known to induce irreversible muscle atrophy and subsequent fibrosis that persists despite successful nerve regeneration.[90] Prolonged CIP resulting in long-term functional denervation could theoretically have the same impact on muscle biology in the critically ill. Whether short-term neuromuscular blockade in the ICU contributes independently to the development of ICUAW, or CIM specifically, remains controversial.[91 92] Neuromuscular junction (NMJ) dysfunction and degradation is a significant underlying cause of age-related muscle atrophy[93 94]: whether it plays a role in CIM is not known. One might speculate that age-related NMJ changes may play a part in the increased risk for ICUAW in the older patient, although this remains to be evaluated.

Dissociation of form and function

Either muscle loss or diminished contractility causes weakness. A discordance of size and strength is evident in the normal physiology of ageing: weakness with ageing exceeds what would be expected given the loss of muscle mass, and this is due to changes within the neuroaxis and muscle.[95] In the preclinical rodent model of CIM with 'ICU treatment' preferential myosin loss relative to actin changes the character of muscle such that its contractile function diminishes - within 14 days of institution of mechanical ventilation muscle atrophy of 25% to 50% occurs (dependent on the muscle studied), but notably a 65% decrease in muscle-specific force occurs.[16 38] Similarly, in a pilot study evaluating mechanisms of sustained weakness in critical illness survivors, heterogeneity was evident in muscle outcomes, with a proportion of individuals developing impaired contractility despite normalisation of muscle mass 6 months following ICU discharge, again highlighting the disconnect between muscle mass and strength.[24]

The force-generating capacity of muscle in the ICU patient is decreased by alterations in muscle composition (necrosis, fatty infiltration) and CIP. Furthermore, alterations in cellular signalling within the muscle may impede contractile function directly. Research predominantly conducted through preclinical models of CIM demonstrates that primary muscle contribution to diminished specific force is multifactorial, resulting from altered bioenergetics with depletion of ATP, altered muscle membrane excitability and excitation–contraction uncoupling.[12 96]

Early in critical illness mitochondrial loss and impaired function of remaining mitochondria are responsible for muscle ATP depletion, potentially compromising the capacity of muscle to use substrates for protein synthesis and hypertrophic growth (figure 2). However, bioenergetic failure also contributes directly to muscle fatiguability and thus weakness, independent of its impact on mass. Abnormal muscle membrane excitability, including decreased conduction velocity, increased relative refractory periods and reduced fibre excitability in response to direct muscle stimulation have been reported in critically ill patients.[97–101] This significantly impairs contractility and strength, independent of mass. Research in preclinical models of CIM reveal an acquired abnormality of the muscle sodium, ryanodine and L-type Ca^{+2} channels[102–105] which impact muscle membrane excitability and depolarisation in response to an action potential (figure 2). The mechanisms responsible for changes in channel expression and function are not well delineated, but studies suggest a causative role for the proinflammatory milieu induced by critical illness (eg, tumour necrosis factor α, ciliary neurotrophic factor).[106 107]

Excitation–contraction uncoupling in muscle, induced by altered intracellular calcium homeostasis, has been demonstrated extensively in sepsis and systemic inflammation[12 108] (figure 2). Abnormalities in calcium handling, due to altered membrane receptors/ion channels (ie, ryanodine receptor) and markedly reduced sensitivity of myofilaments to Ca^{+2} due to post-translation modifications of the myofilaments (eg, carbonylation, oxidation, nitration) may also contribute to excitation–contraction uncoupling (figure 2).[16 109 110] Interestingly, in a rat model of ventilator-induced diaphragmatic dysfunction, administration of the chaperone co-inducer BGP-15 restored depressed muscle-specific force to approximately 75% of its original value[111] presumably by preventing post-translational modifications of myosin that impair its function. Whether the same effect would be evident in skeletal muscle is not known, but should be evaluated in the preclinical models of ICUAW with potential for long-term outcomes (table 1). BGP-15 may also enhance the compensatory upregulation of chaperones within muscle to protect against myofibrillar degradation in the early phases of critical illness.

While energy depletion and altered muscle membrane excitability have been demonstrated in patients in the acute phases of ICUAW, there is no evidence of mitochondrial depletion or dysfunction in individuals months after resolution of critical illness.[24] Furthermore, ICUAW 'channelopathies' and excitation–contraction uncoupling have been described almost exclusively in preclinical models, due to the difficulties conducting such research in human subjects. Regardless, it is clear from clinical

studies that intrinsic impairment in muscle contractile function can persist long term after ICU discharge,[24] independent of CIP and alterations in mitochondrial size, number or biogenesis. Whether this results from alterations of channel function and/or impaired excitation–contraction coupling remains to be determined. The development of three-dimensional fully contractile human muscle microtissues[112] represent a powerful new tool by which these biological phenomenon, and their relevance to sustained ICUAW, can be studied .

CONCLUSIONS

Early events in the ICU, primarily driven by the combination of the acute insult, immobility and supportive care conspire in the genetically and clinically vulnerable individual to promote ICUAW—a phenomenon characterised by severe muscle protein degradation, metabolic reprogramming, bioenergetic depletion, myofibre contractile dysfunction with or without peripheral neuropathy. Over time in the susceptible individual dysregulated repair, with the resultant abnormal muscle remodelling and regeneration, culminates in long-term sustained muscle loss and dysfunction, resulting in physical disability. While we have made inroads into understanding the genesis of ICUAW in the past two decades, we remain far from developing universally effective preventative or treatment strategies, due to both the inherent complexities and enormous breadth in the apparent mechanisms of injury and repair, and the innate heterogeneity in the populations encountered. The need for large network collaborations to conduct detailed studies incorporating 'omics', pathology, imaging and functional assessments is urgent to manage this devastating sequelae of life-sustaining treatment.

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