Therapeutic targeting of metabolic alterations in acute respiratory distress syndrome

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ARDS’ biological heterogeneity is an obstacle in clinical translation of interventions. Analysis of metabolic alterations can inform development of therapeutics aimed at ARDS subpopulations. Mitochondrial dysfunction may be a potential therapeutic target. https://bit.ly/2XHfAFV

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ABSTRACT
Acute respiratory distress syndrome (ARDS) remains a significant source of mortality in critically ill patients. Characterised by acute, widespread alveolar inflammation and pulmonary oedema, its pathophysiological heterogeneity has meant that targeted treatments have remained elusive. Metabolomic analysis has made initial steps in characterising the underlying metabolic derangements of ARDS as an indicator of phenotypical class and has identified mitochondrial dysfunction as a potential therapeutic target. Mesenchymal stem cells and their derived extracellular vesicles have shown significant promise as potential therapies in delivering mitochondria in order to redivert metabolism onto physiological pathways.

Introduction
Acute respiratory distress syndrome (ARDS) is a severe form of respiratory failure, characterised by acute, widespread alveolar inflammation and noncardiogenic pulmonary oedema following direct or indirect injury [1]. It remains one of the most life-threatening respiratory complications in the critically ill. With no targeted treatments to its underlying pathophysiology currently available, intervention is still dominated by ventilatory assistance [1].

Since the introduction of the Berlin definition of ARDS, its pathophysiology and heterogeneity of inflammation and metabolism have been increasingly elucidated. These advances have established the need for both bedside identification of biological phenotypes and precise therapeutic targeting, with a move beyond characterisation and intervention in response only to presenting clinical appearance and radiological severity [2]. Of distinct importance has been the increased understanding of the mechanisms by which metabolic alterations contribute to ARDS; specifically, how mitochondrial dysfunction of alveolar cells drive metabolic divergence to abnormal pathways and elicit cellular dysfunction and clinical deterioration [3]. This metabolic reprogramming has been demonstrated to induce bioenergetic failure by an array of pathways including decreased oxidative phosphorylation, mitochondrial depletion, increased mitochondrial reactive oxidant species (ROS), release of mitochondrial DNA (mtDNA) and reduced secretion of pulmonary surfactant [2–5].
This understanding has been due in part to the advent and application of metabolomic analytical approaches. Metabolomics involves the study and measurement of small molecular weight molecules, chemicals and metabolites within a sample [6]. Analysis provides insight into upstream physiological and pathophysiological systemic alterations [7]. Upon validation these may offer dynamic, bedside insight into specific chemical changes [8]. Metabolomics may objectively map a biological endotypes by assessing their metabolic fingerprints and use these clinical biomarkers to assess a patient’s risk for developing ARDS and predict associated mortality. Ultimately, this bears optimism for the potential of improved diagnostic power and patient outcomes and has provided new therapeutic innovation in the field [9, 10]. Herein, the known metabolic abnormalities in ARDS are presented and the current developments and future directions in their targeting are discussed.

**Known metabolic abnormalities in ARDS**

Abnormal energy metabolism is a recognised metabolomic finding in critical illness [11, 12]. For example, in the case of sepsis-induced acute lung injury, oxidative stress, apoptosis, endothelial barrier dysfunction and disruption of energy homeostasis have a recognised set of associated metabolites [13]. Moreover, composite differences and dynamics of metabolome fingerprints characterised in septic shock have been related to disease prognosis [14]. The question remains as to what metabolites may be specifically deranged in ARDS and by which mechanism these pathways are affected.

Previously, Rogers and Matthay [8] summarised that several small sample size metabolomic analyses (total n<60 ARDS cases) of exhaled breath, bronchoalveolar lavage (BAL) and plasma in ARDS patients provided little insight into the dysfunctional metabolic pathways of ARDS or identification of the most appropriate sample type to assay. Isoprene and sphingomyelin were reported to be underrepresented in ARDS by Schurert et al. [15] and Stringer et al. [13], respectively, while an array of amino acids, glycolysis products and lipid intermediates were found to be deranged by Evans et al. [16]. The review concluded that metabolite heterogeneity in this population demanded an increased sample size to distinguish disease-associated variants and that analysis of BAL, plasma and urine may be the most appropriate to facilitate this, given that they may be readily obtained in large numbers of patients [8]. Izquierdo-Garcia et al. [11] reported significantly decreased levels of glucose, alanine, glutamine and fatty acids in serum from patients with ARDS secondary to H1N1 influenza virus pneumonia. They proposed that the decrease in tricarboxylic acid (TCA) cycle intermediates of glucose and alanine (pyruvate precursors) and glutamine (glutamate and subsequently α-ketoglutarate precursor) may be explained by energetic stress on lung epithelial cells which precludes upregulation of aerobic metabolism.

Rogers et al. [17] have applied a Metabolon broad-spectrum platform in 29 subjects to differentiate patients with ARDS (n=16) from patients with hydrostatic pulmonary oedema (n=13) based on the metabolic profile of undiluted oedema fluid samples. Critically, univariate analysis revealed a discriminate subset of six ARDS patients, characterised by upregulation of approximately one-third of detected metabolites (250 out of 749) across all chemical classes; meanwhile, the other ARDS patients were not distinguishable from the hydrostatic oedema group. Importantly, these metabolic changes could not be explained by differences in the sample concentrations. It was proposed that this distinct hypermetabolic subset of ARDS subjects closely mirrors the hyperinflammatory subset previously identified by Calfee et al. [18] in one-third of ARDS subjects. This hyperinflammatory subphenotype has been associated with raised plasma pro-inflammatory markers (interleukin (IL)-6, IL-8 and soluble tumour necrosis factor (TNF) receptor 1), coagulopathy (low protein C), endothelial injury, high prevalence of shock and metabolic acidosis, and comparatively worse clinical outcomes, including mortality, than the hypoinflammatory subphenotype, who display lower circulating inflammatory biomarkers, less acidosis and less vasopressor-dependent shock [19]. However, a definitive association between these inflammatory and metabolic groups could not be established in this study as plasma was not sampled [17].

Interestingly, pathway analysis revealed significant abnormalities in amino acid pathways, of which alanine, aspartate and glutamine metabolism met multiple comparisons correction, with false discovery rate <0.05. In addition, lysine degradation and arginine and proline metabolism pathways were differentially expressed. The group recognised a degree of consistency with the assay provided by Evans et al. [16] in overexpression of glutamate and proline in BAL. Notably, these pathways have established dysregulation in sepsis [20, 21]. Importantly, the study was again limited by sample size and could not benefit from wider metabolic profile comparison due to a lack of available banked undiluted pulmonary oedema fluid samples. Interestingly, metabolomic profiling was incapable of separating ARDS patients as a whole from those with hydrostatic oedema and this finding could not be explained by the low power of the study.

More recently, Bos et al. [22] identified two phenotypes using only plasma biomarkers in an observational cohort of patients with ARDS. These phenotypes were termed “uninflamed” and “reactive” and shared similar characteristics with the hypoinflammatory and hyperinflammatory phenotypes, respectively.
although it is still unknown whether these phenotypes are the same as described by Calfee et al. [18]. Subsequently, Bos and co-workers [19, 23] used microarray analysis of whole-blood gene expression in an observational cohort of 210 patients with sepsis-related ARDS to investigate if the “reactive” phenotype is metabolically distinct from the “uninflamed” group. This is the first study to explore differences in gene expression and associated pathway analysis in ARDS phenotypes. Canonical pathway analysis demonstrated that the “reactive” group was characterised by enrichment of genes associated with oxidative phosphorylation and gene expression in this pathway was associated with plasma lactate levels. Collectively, these changes may be indicative of mitochondrial dysfunction. Comparatively, the “uninflamed” phenotype was associated with enrichment of mitogen-activated protein kinase 4 (MAP2K4) and Raf-1 proto-oncogene, serine/threonine kinase (RAF1) MAPK-dependent pathways, which are known to control cell proliferation, differentiation, motility and survival [23]. This study is important as it independently confirms the presence of two biologically different subpopulations within ARDS and provides insight into pathways that are relatively overexpressed in each phenotype; previously the uninflamed phenotype was defined by relatively lower levels of inflammatory mediators rather than by its own specific markers.

Recently, Viswan et al. [9] reported metabolic profiling of 464 subjects by nuclear magnetic resonance (NMR) in mini BAL fluid (mBALF) (ARDS n=159; non-ARDS n=40) and serum (ARDS n=197; non-ARDS n=68). In this study, ARDS samples were grouped into two categories based on clinical characteristics: 1) “subphenotype 1” based on Berlin severities (mild, moderate and severe ARDS) and 2) “subphenotype 2” based on the mechanism of lung injury, involving pulmonary aetiologies (pneumonia, lung contusion) called direct ARDS and extrapulmonary aetiologies (pancreatitis, trauma, sepsis) known as indirect ARDS. The terminology used here does not reflect the heterogeneity within ARDS population and should not be confused with ARDS hypo- and hyperinflammatory subphenotypes described by Calfee et al. and Bos et al. The control group comprised patients who were on mechanical lung ventilation for routine elective surgeries but did not develop ARDS. Interestingly, distinct subsets of metabolites were demonstrated to correlate with ARDS severity in subphenotype 1 or with pulmonary or extrapulmonary ARDS aetiology in subphenotype 2. In addition, mBALF and serum ARDS samples were demonstrated to possess an array of metabolites that were similarly upregulated in both subphenotypes, compared to non-ARDS samples. Specifically, lysine, arginine, tyrosine, threonine and branched chain amino acids were overrepresented in mBALF in ARDS group compared to non-ARDS controls, while proline, glutamate, phenylalanine and valine were upregulated in serum in ARDS group, suggesting independent pulmonary and serological metabolic processes. Importantly, high concentrations of these metabolites were positively correlated with mortality. Subsequently, the authors presented a framework for outcome predictability based on metabolic profiling. Notably, ARDS severity was determined by Berlin definition criteria, facilitating broad clinical implementation; findings were strengthened by the relatively large sample sizes. That said, there may be perceivable gain in corroborating these findings by sampling both mBALF and serum samples in each patient.

This builds on work from the same group in which NMR-based metabolomic analysis of mBALF highlighted lysine, arginine, proline, threonine, taurine and glutamate as critical biomarkers of ARDS susceptibility, severity and recovery [24]. Of particular interest was that pathway analysis suggested underlying biological processes implicated in these metabolite derangements, such as the production of carbonylated proteins secondary to hypoxia and oxidative stress in ARDS. Ultimately, Viswan et al. [24] concluded that this profile depicted disruptions in the TCA cycle and nitrogenous network that were associated with both ARDS pathophysiology and compensatory mechanisms switched on to regain normal biological function.

Recently, Izquierdo-García et al. [25] presented a pilot study of ARDS-related metabolic alterations in patients with pneumonia with and without ARDS induced by Streptococcus pneumoniae (ARDS n=13; non-ARDS n=17) or influenza A pneumonia (IAP) (ARDS n=12; non-ARDS n=18). They reported the ability to differentiate between patients with and without ARDS independent of the principal insulting pathogen and proposed that ARDS may drive metabolism into analogous pathway deviations, irrespective of aetiological heterogeneity. Specifically, patients with ARDS showed markedly lower serum concentrations of glucose, alanine, methylhistidine, fatty acids, creatine, citrate, valine and creatinine, while acetone concentration was significantly raised. Comparison of IAP and S. pneumoniae groups revealed relatively increased levels of glutamine, methylguanidine and phenylalanine in IAP patients. Comparatively, S. pneumoniae patients exhibited lower levels of lactate and creatinine; however, direct comparison should be cautioned due to demographic differences, notably age and baseline renal function.

Pathophysiology of metabolic alteration in ARDS

Despite progress in profiling metabolic alteration in ARDS, heterogeneity of both reported metabolites and sample media continue to preclude determining with certainty the pathways by which these abnormalities
arise. Work is required to consolidate and validate these metabolic deviations. This will help to establish whether there exists any association between metabolic fingerprints and syndrome endotypes (such as hypo/hyperinflammatory patient subsets) leading to understanding of the underlying pathophysiological mechanisms, identification of biomarkers and ultimately new therapeutic targets [18]. Unfortunately, significant barriers still persist in establishing validated biomarkers, due in part to innate heterogeneities involved in treating the critically ill. Specifically, variances in patient comorbidities, pharmaceutical and physical interventions and nutrition are all known to affect bioenergetics [26]. Moreover, an overlap between syndromes greater than currently established and a degree of wider misclassification of ARDS cannot be excluded. That said, consensus remains that collectively these metabolomic findings demonstrate pathological mitochondrial dysfunction [9].

Indeed, metabolic reprogramming leading to deviations from the mitochondrial TCA cycle is responsible for an array of detrimental effects that are increasingly attributed to increases in morbidity and mortality. These metabolic deviations result in decreased oxidative phosphorylation and subsequent ATP yield; excessive free-radical generation of mitochondrial ROS via complex I and III and reactive nitrogen species via complex I; proinflammatory cytokine production; irreversible modification of mitochondrial proteins; reduced pneumocyte secretion of alveolar surface surfactant; disruption of mitochondrial integrity; increased mtDNA release; increased mitochondrial-related danger-associated molecular patterns (DAMPs) and ultimately apoptosis [3, 5, 9, 24, 27–31].

Metabolic reprogramming to anaerobic, mitochondrial-independent pathways of enhanced glycolysis and lactic acid fermentation have long been recognised in cancer. The Warburg effect established cells’ dynamic use of metabolic pathways in response to micro-environment insults and functional organelle changes, including mitochondria [3, 32]. Since then, this phenomenon has been proposed in a range of respiratory pathologies including COPD [3] and pulmonary hypertension [30]. This may assist cells with the metabolic requirements during oxidative stress [27]. It has also been proposed that ARDS metabolic reprogramming may be a subsequence of ROS oxidative damage of the mitochondrial matrix in alveolar epithelium cells, driving metabolism to accessible anaerobic pathways following respiratory chain inhibition [30]. While the pathogenesis remains obscure, the metabolomic data reviewed above (deficient TCA cycle intermediates, precursors and ATP; increased lactate), are representative of a reliance on metabolic networks associated with glycolysis and gluconeogenesis and are collectively suggestive of mitochondrial dysfunction (table 1).

**Therapeutic targeting of metabolic dysfunction**

These advancements in detailing metabolic profiles and understanding the underlying pathophysiology have facilitated the advent of novel therapeutic targeting. Kieffmann et al. [33], for instance, proposed that alveolar hypocapnia in ARDS interfered with the mitochondrial TCA cycle by increasing isocitrate dehydrogenase subunit 3 activity and thus NADH production. This was demonstrated to induce mitochondrial calcium uptake and ROS production, leading to apoptosis of type II pneumocytes. They proposed inhalation of carbon dioxide as a novel therapeutic approach to prevent hypocapnia-induced tissue injury.

Much work has been performed in supplementing deficient organic compounds in patients with ARDS, with limited results. For example, meta-analysis of glutamine supplementation in critically ill patients was not sufficient for recovery of organ dysfunction and caused no significant improvement in mortality, with the least effect seen in the most clinically severe patients [34]. Similarly, a recent Cochrane systematic review on the effects of enteral or parenteral immunonutrition formula feeding in mechanically ventilated adults with ARDS revealed supplementation induced little or no difference in all-cause mortality [35]. These formulae are composed primarily of antioxidant vitamins, trace elements, essential fatty acids and essential amino acids, namely glutamine and arginine, included for supposed immunomodulatory properties [36].

Retrieval of normal mitochondrial activity in alveolar epithelial cells, which would support the regaining of correct pulmonary bioenergetics, is recognised as a promising therapeutic approach [37]. Indeed, the potential benefits of this restoration of mitochondrial function may extend beyond its notorious role as “the powerhouse of the cell” to a retrieval of host cell immune responses [4]. However, while work on organic supplementation as a restorative measure continues, there is growing evidence that the most critically ill patients do not demonstrate significant improvements in clinical response and that mortality persists in spite of these and other pharmacological therapeutic interventions [19]. This suggests a threshold to endothelial and epithelial cell injury, beyond which retrieval of physiological inflammatory bioenergetic functions are hindered, to the detriment of clinical outcomes [38]. This is supported by the presence of remnants of mitochondrial damage such as mtDNA: a DAMP capable of activation of the innate immune system [37].
The role of circulating mtDNA as a DAMP in ARDS pathophysiology was supported by Faust et al.\[5\], who reported a significant association of circulating mtDNA with ARDS in two critical illness populations (trauma and sepsis) 48 h after emergency department presentation. These findings support previous studies in suggesting a mechanism by which nonpulmonary insults may propagate ARDS\[39, 40\].

Interestingly, beyond a product of cell injury, regulated and non-necrotic mtDNA release, such as that seen in response to mitochondrial ROS signalling for inflammasome activation, also have accumulating physiological evidence. The precise mechanisms of mtDNA release into the cytoplasm and furthermore into the circulation still remain obscure and merit further work. Loss of mitochondrial membrane integrity, incomplete degradation by autophagy and mitochondria-derived vesicles have been suggested\[37\]. However, elevated plasma mtDNA fundamentally suggests that metabolic abnormalities in ARDS are secondary to mitochondrial damage and depletion and may explain, at least partially, why interventions to increase deficient pathway intermediates have produced limited clinical improvements.

Subsequently, the field has seen significant attention in therapeutic replenishing of mitochondria in depleted cells. Metabolically, the semblance of aerobic glycolysis in ARDS suggests irretrievable damage to pulmonary cell mitochondria warranting further investigation\[41\].

### Mesenchymal stem cells

Mesenchymal stem/stromal cells (MSCs) are mature, multipotent, mesoderm-derived stem cells, which are widely considered to hold therapeutic promise in ARDS\[42\]. Although the underpinning mechanisms have not been fully elucidated, MSCs have been demonstrated to induce immunomodulation, bacterial

### TABLE 1 Recent studies investigating metabolic changes in acute respiratory distress syndrome (ARDS)

| First author [ref.] | Cohorts compared | Sample type | Metabolic alterations in ARDS | Relationship to mitochondrial dysfunction |
|---------------------|------------------|-------------|-------------------------------|------------------------------------------|
| IZQUIERDO-GARCÍA [11] | H1N1 influenza virus pneumonia ARDS (n=12) and non-ARDS (n=18) | Serum | ↓ glucose, alanine, glutamine and fatty acids ↑ phenylalanine and methylguanidine | Decreased TCA cycle intermediates Increased utilisation of aerobic metabolism |
| ROGERS [17] | ARDS [n=16] and non-ARDS [n=13] groups with hydrostatic pulmonary oedema | Pulmonary oedema fluid | "High metabolite" subset [n=6]; distinction in 250 out of 749 identified metabolites Pathway analysis: ↑ alanine, aspartate and glutamine metabolism ↑ arginine and proline metabolism | Suggested correlation of high metabolite group with "hyper-inflammatory" subphenotype |
| Bos [23] | Sepsis ARDS: "reactive phenotype" (n=128), "uninflamed phenotype" (n=82) | Whole-blood leukocyte gene expression | "Reactive" phenotype: ↑ neutrophil activation; ↑ oxidative phosphorylation "Uninflamed" phenotype: enrichment of MAP2K4- and RAF1-dependent MAPK pathways | Heterogenic subphenotypes of ARDS, with incomparable pathophysiology Gene expression in "reactive" phenotype indicative of comparatively greater mitochondrial dysfunction |
| VISWAN [9, 24] | mBALF: ARDS (n=159), non-ARDS (n=40) Serum: ARDS (n=197), non-ARDS (n=68) | mBALF and serum | mBALF: ↑ lysine, arginine, tyrosine, threonine, leucine, isoleucine and valine Serum: ↑ proline, glutamate, phenylalanine and valine | TCA cycle and nitrogenous network disruption |
| IZQUIERDO-GARCÍA [25] | S. pneumoniae-induced ARDS [n=13] and non-ARDS [n=17] Influenza A pneumonia-induced ARDS [n=18] and non-ARDS [n=12] | Serum | ↓ glucose, alanine, methylhistidine, fatty acids, creatine, citrate, valine and acetone | Comparable impairments to metabolic pathways irrespective of infective source Enhanced energy requirements suspected in S. pneumoniae-induced ARDS |

TCA: tricarboxylic acid; MAPK: mitogen-activated protein kinase; RAF1: Raf-1 proto-oncogene, serine/threonine kinase; mBALF: mini bronchoalveolar lavage fluid; S. pneumoniae: Streptococcus pneumoniae.
clearance, endothelial and epithelial cell permeability regulation, alveolar fluid clearance and antiapoptotic effects [43–45]. Consensus remains that the majority of delivered MSCs elicit their therapeutic effects through mechanisms unrelated to engraftment or indeed their progenitor function [46], and rely largely on intercellular interactions to modulate host cells.

Of considerable interest is the ability of MSCs to redress metabolic alteration of alveolar epithelium cells by the transfer of mitochondria. Mitochondrial transfer is known to occur through three means of organelle exchange, namely tunnelling nanotubes, open-ended actin-based extensions of the cell cytoplasm that facilitate cell–cell communication [47]; extracellular vesicles, a diverse group of biologically active cargo-containing membranous structures released by the cell [48]; and cellular fusion, where plasma membrane of independent cells merge, facilitating the sharing of cytosolic components [49]. Importantly, MSC delivery goes some way to mitigate the risk that delivery of free mitochondria poses in the extracellular space, which may themselves act as DAMPs and further exacerbate tissue inflammation and injury [4].

We have previously reviewed the known instances and regulation of organelle transfer between MSCs to differentiated cells [49]. The prominent work by ISLAM et al. [50] established that bone marrow derived MSCs were capable of mitochondrial transfer to type II alveolar epithelial cells (ATII) in a lipopolysaccharide-induced murine acute lung injury model. Importantly, recipient ATII cells demonstrated enhanced ATP production, restoration of surfactant secretion by ATII cells, improvement to of acute lung injury and enhanced survival. These seminal findings have been supported by an array of relevant studies which report that mitochondrial transfer induce a correction of deranged cell effects [43–45]. Consensus remains that the majority of delivered MSCs elicit their therapeutic effects – possibly through a paracrine effect – which we reviewed recently [48]. Significantly, extracellular vesicles may constitute a viable therapeutic approach and lend themselves to commercial use; assuming the question of large-scale biomanufacturing can be addressed [59].

In particular, we have shown that MSC extracellular vesicle mitochondria transfer resulted in macrophage shift from a proinflammatory phenotype toward an anti-inflammatory phenotype through enhancement in oxidative phosphorylation and ultimately lung injury amelioration in vivo [55]. In addition, we demonstrated recently that MSC extracellular vesicle mediated transfer of mitochondrial membrane potential and ATP production in primary human distal lung epithelial cells and enhances their wound healing capacity in the ARDS inflammatory environment [60]. The therapeutic approaches and their limitations are summarised in figure 1.

Following encouraging preclinical prospects, >10 clinical trials are currently being conducted with MSCs in ARDS [61]. Results from the small number of studies that have completed early-phase trials have been promising. The first of these to publish findings (www.clinicaltrials.gov NCT01902082) demonstrated allogeneic adipose-derived MSCs to be safe in ARDS; however, doses appeared to be subtherapeutic [62]. The START trial reported no MSC-related haemodynamic or respiratory adverse events at phase 1 and 2a [63, 64]. Meanwhile, the MUST-ARDS study investigating the use of "MultiStem", patented allogeneic bone marrow-derived multipotent adult progenitor cells, had a promising primary outcome in safety and, interestingly, in secondary outcomes as it appeared capable of improving 28-day mortality and lessening ventilator and intensive care unit (ICU) burden [65].

Of significance is the association between ARDS and coronavirus disease 2019 (COVID-19) and the resulting interest in MSC therapeutic applications [66]. WANG et al. [67] characterised 138 patients hospitalised with severe acute respiratory syndrome coronavirus-2 who tested positive for COVID-19 in
Endocytosis

Loss of mitochondrial integrity

↑ mtDNA release
↑ DAMPs

Carbon dioxide
↓ IDH3 activity and NADH production
↓ Mitochondrial calcium uptake and ROS production
↓ Hypocapnia-induced apoptosis
Limited evidence

Immunonutrition
Correction of oxidant system imbalance
Suppression of proinflammatory eicosanoid biosynthesis
Evidence suggests limited efficacy

Free exogenous mitochondria
Potential to act as DAMPs

Transferred mitochondria
Restored cell signalling
↑ Quantity of functional mitochondria
↑ Oxidative phosphorylation
↑ ATP

Damaged mitochondria
TCA cycle deviations
↓ Oxidative phosphorylation
↑ Glycolysis
↓ ATP
↑ Mitochondrial ROS and mitochondrial RNS
↑ Cytokine production
↓ Surfactant secretion

MtDNA: mitochondrial DNA; DAMPs: danger-associated molecular patterns; IDH3: isocitrate dehydrogenase subunit 3; ROS: reactive oxygen species; TCA: tricarboxylic acid; RNS: reactive nitrogen species.

FIGURE 1 Therapeutic approaches and their limitations in the correction of metabolic alterations in acute respiratory distress syndrome.
Wuhan, China and found that out of 36 patients transferred to ICU, 22 (61.1%) had ARDS. More widely, there are currently >10 registered clinical trials investigating the administration of MSCs to patients with COVID-19. This includes the REALIST (NCT03042143) trial studying the administration of umbilical cord-derived CD362-positive MSCs in COVID-19-induced ARDS, which is currently recruiting for phase 2, reflecting optimism regarding the use of MSCs as a prospective treatment option [68]. Intriguingly, one registered trial (NCT04276987) is aiming to test the safety of aerosol inhalation of exosomes derived from allogenic adipose mesenchymal stem cells.

**Conclusion**

In conclusion, metabolic reprogramming is a significant contributor in ARDS pathophysiology and contributes to differences in phenotype, severity and prognosis. Validated metabolomic analytical approaches will help in the understanding of the dynamic metabolic derangements that occur in ARDS and may help to elucidate the syndrome’s long-reported heterogeneity. The key to correcting metabolic alterations in ARDS may rely on characterising and correcting mitochondrial dysfunction. Mesenchymal stem cells, and in particular extracellular vesicles, show significant promise as future therapies in delivering mitochondria and provide hope to a field long void of optimism.

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