Review

Mitochondrial abnormalities in idiopathic inflammatory myopathies

F. Torri, G. Ricci, M. Mancuso, G. Siciliano

Department of Clinical and Experimental Medicine, University of Pisa, Italy.

Francesca Torri, MD, PhD
Giulia Ricci, MD, PhD
Michelangelo Mancuso, MD, PhD
Gabriele Siciliano, MD, PhD

Please address correspondence to:
Francesca Torri
Dipartimento di Medicina, Clinica e Sperimentale, Università di Pisa, via Roma 67, 56126 Pisa, Italy.
E-mail: francesca.torri@phd.unipi.it

Received on January 25, 2026; accepted in revised form on February 17, 2026.

Clin Exp Rheumatol 2026; 44: 384-389.

Key words: mitochondria, myositis, autoantibodies, inclusion body myositis, idiopathic inflammatory myopathies,

Competing interests: none declared.

ABSTRACT

Objective. *Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of acquired muscle disorders characterised by immune-mediated muscle damage and systemic involvement. Increasing evidence highlights mitochondrial abnormalities as a key contributor to muscle weakness, inflammation, and disease progression. This review aims to summarise current knowledge on the mechanisms, histopathological features, and clinical implications of mitochondrial dysfunction in IIMs, as well as to discuss emerging therapeutic strategies targeting mitochondrial impairment.*

Methods. *A narrative review of the literature was conducted using PubMed, with no temporal restrictions. Only English-language articles were included. Search terms comprised "inflammatory myopathies," "mitochondrial abnormalities," and "mitochondrial antibodies AND inflammatory myopathies." Studies addressing mitochondrial structure and function, histopathological findings, autoantibodies targeting mitochondrial components, and therapeutic approaches in IIMs were selected and analysed.*

Results. *Mitochondrial dysfunction in IIMs involves impaired oxidative phosphorylation, increased oxidative stress, disrupted calcium homeostasis, defective mitophagy, and mitochondrial DNA damage. Histopathological findings include cytochrome c oxidase-negative fibres, ragged red fibres, abnormal mitochondrial morphology, and altered mitochondrial distribution, particularly prominent in inclusion body myositis. Inflammatory mechanisms further exacerbate mitochondrial injury through cytokine signalling, cytotoxic immune responses, and interferon-mediated pathways. Autoantibodies targeting mitochondrial components, such as anti-NDUFA11 and anti-mitochondrial antibodies, define subgroups with more severe or refractory disease. Therapeutic strategies reducing inflammation may indirectly improve mitochondrial function, while novel approaches, including interferon blockade, mitochondrial transplantation, and exercise-based interventions, show promise in restoring bioenergetics.*

Conclusion. *Mitochondrial dysfunction represents a central pathogenic mechanism in IIMs, tightly interwoven with immune-mediated muscle damage. Targeting both inflammatory and mitochondrial pathways may offer more effective and personalised therapeutic strategies for patients with inflammatory myopathies.*

Introduction

Idiopathic inflammatory myopathies (IIMs) are a broad group of acquired disorders of the skeletal muscle that can also be featured by cardiomyopathy and systemic involvement. In general, they are characterised by predominantly proximal muscle weakness with subacute progression, although some conditions can manifest with rapidly evolving muscle damage (1). Overall, research data suggests a complex interplay between autoimmunity, genetic predisposition and structural as well as functional muscle alterations in the pathogenesis of IIMs. In particular, mitochondrial abnormalities, inducing alterations in oxidative phosphorylation, calcium homeostasis, and apoptosis regulation, crucial for maintaining muscle function, have been described as a recurrent feature in IIMs (2). More precisely, mitochondrial involvement in idiopathic inflammatory myopathies (IIMs) extends beyond genetic defects and anti-mitochondrial antibodies, encompassing a network of structural, functional, and signalling alterations (3).

These mechanisms interact with immune-mediated injury, creating a cycle that perpetuates muscle damage and chronic weakness. However, it is not fully elucidated if the subsequent muscle energy impairment possibly stands as an epiphenomenal manifestation of cellular damage or as a prodromal sign of it.

In this review we aim to gather the current knowledge on mechanisms and effects of mitochondrial dysfunction in IIMs as well as insights on present and future therapeutic options targeting this particular aspect.

Methods

This narrative review was conducted on PubMed, with restriction to papers written in English. No temporal restriction was imposed for papers' selection. Research keywords were "inflammatory myopathies" and "mitochondrial abnormalities", "mitochondrial antibodies AND inflammatory myopathies". Papers containing information about histopathology in IIMs, autoantibodies targeting mitochondria, actual treatment and future perspective for IIM and mitochondrial myopathies were selected, for a total of 27 papers.

Mitochondrial activity dysfunction and inflammation in skeletal muscle

Skeletal muscle exhibits the widest range of metabolic variability among tissues, and the maintenance of contractile function critically depends on mitochondria (4). Mitochondria are highly dynamic organelles, continuously undergoing fusion and fission, processes mediated by key proteins (5). This dynamic remodelling preserves mitochondrial network integrity, ensures efficient energy supply in response to fluctuating metabolic demands, and facilitates quality-control mechanisms. Beyond energy production, mitochondria sustain anaplerotic pathways that replenish critical metabolic intermediates, while precisely regulating calcium homeostasis, thermogenesis, redox balance, and reactive oxygen species (ROS) levels. To maintain these diverse functions, mitochondria depend on intricate regulatory networks that orchestrate biogenesis, proteostasis, dynamic remodelling, and mitophagy, ensuring both functional resilience and metabolic adaptability in skeletal muscle (6, 7). In response to stressors such as injury, infection, or metabolic disturbances, mitochondria can release damage-associated molecular patterns (DAMPs), including mitochondrial DNA, ATP, and formulated peptides. These DAMPs engage pattern recognition receptors like TLR9 and cGAS, initiating sterile inflammation that is vital for tissue repair but can become pathological if dysregulated (8).

Impaired mitochondrial function contributes directly to muscle atrophy. Excessive ROS and pro-inflammatory cytokines, including TNF-α and IL-6, disrupt mitochondrial dynamics and exacerbate proteolytic pathways such as the ubiquitin-proteasome system and autophagy-lysosomal degradation, resulting in loss of muscle proteins and contractile capacity. Conversely, proper mitochondrial function can support the resolution of inflammation, in part by guiding the differentiation of anti-inflammatory macrophages through metabolic reprogramming. Faas *et al.* (8) detected that IL-33 induces a rapid metabolic reprogramming in macrophages, characterised by the uncoupling of the mitochondrial respiratory chain and an increase in the production of the metabolite itaconate. This metabolic shift, mediated by transcription factor GATA3, is crucial for the differentiation of alternatively activated macrophages (AAMs), which are essential for the resolution of inflammation and tissue repair (9).

Mechanisms of mitochondrial damage in IIMs

Mitochondria play a crucial role in skeletal muscle homeostasis by providing ATP through oxidative phosphorylation, regulating apoptosis, and modulating redox balance. In idiopathic inflammatory myopathies (IIMs), including dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM), mitochondrial dysfunction has emerged as a key pathological hallmark. Recent evidence suggests that inflammation, oxidative stress, impaired mitophagy, mitochondrial DNA (mtDNA) damage, and protein aggregation interact in a vicious cycle that sustains muscle weakness and degeneration (10-12).

Dermatomyositis is characterised by perifascicular atrophy and a strong type I interferon (IFN) signature. IFN-β has been shown to induce mitochondrial damage in human myotubes by increasing reactive oxygen species (ROS) production, leading to depolarization of the mitochondrial membrane potential and decreased ATP synthesis (13). Additionally, microangiopathy in DM contributes to local hypoxia, further impairing oxidative phosphorylation and exacerbating ROS-mediated injury (14). Collectively, these findings suggest that in DM, mitochondrial dysfunction is driven primarily by interferon-induced oxidative stress and vascular damage.

Polymyositis is characterised by cytotoxic $CD8^+$ T-cell infiltration and direct attack on major histocompatibility complex (MHC) class I, expressing myofibers. Studies have shown that perforin- and granzyme-mediated cytotoxicity leads to mitochondrial swelling, loss of cristae structure, and impaired respiratory chain activity (11). Chronic inflammation drives mitochondrial DNA deletions and point mutations, which compromise oxidative phosphorylation (15). Moreover, overexpression of pro-apoptotic proteins such as harakiri (HRK) in response to toll-like receptor (TLR) signalling reduces mitochondrial membrane potential and impairs muscle repair capacity (16). Thus, in PM, mitochondrial damage appears to result from immune-mediated cytotoxicity and sustained pro-apoptotic signalling.

IBM displays the most striking mitochondrial pathology among IIMs. Muscle biopsies reveal cytochrome c oxidase (COX)-negative fibres, multiple mtDNA deletions, and defective respiratory chain complexes (17). Accumulation of misfolded proteins such as TDP-43 and p62 co-localises with mitochondrial components, disrupting respiratory chain integrity and ATP production (18). Impaired mitophagy, evidenced by accumulation of phospho-ubiquitin (p-S65-Ub) and dysfunctional removal of damaged organelles, leads to secondary activation of the NLRP3

inflammasome, perpetuating inflammation and mitochondrial injury (13). The strong correlation between inflammatory cell density, COX-deficient fibres, and muscle fibre atrophy highlights the synergistic interplay of immune-mediated and degenerative mechanisms (19).

Across all IIM subtypes, mitochondrial dysfunction can be conceptualised as part of a self-amplifying loop. Inflammation (mediated by IFNs, cytotoxic T cells, or innate immune sensors) generates ROS and induces mitochondrial damage. Damaged mitochondria release mtDNA and other mitochondrial DAMPs (damage-associated molecular patterns), which further activate innate immune pathways (*e.g.* TLR9, NLRP3). In IBM, impaired clearance of dysfunctional mitochondria exacerbates this loop, while in DM, vascular hypoxia and interferon signalling amplify oxidative stress. Ultimately, mitochondrial dysfunction contributes not only to energy failure but also to chronic inflammation and progressive muscle degeneration. Table I summarises the described mechanisms across IIMs.

Histopathological evidence of skeletal muscle mitochondrial damage in IIMs

Histological studies have provided compelling evidence for mitochondrial involvement in the pathogenesis of IIMs. Classical histochemical stains and ultrastructural analyses have revealed consistent abnormalities in mitochondrial morphology, enzymatic activity, and spatial distribution, which correlate with clinical features and disease progression. One of the most striking features is the presence of cytochrome c oxidase (COX)-negative fibres, a hallmark of mitochondrial respiratory chain dysfunction. In IBM, the frequency of COX-deficient fibres is significantly higher than in DM or PM, reflecting profound impairment of oxidative phosphorylation (19). Histochemical double-staining with COX and succinate dehydrogenase (SDH) often reveals a mosaic pattern where fibres lacking COX activity display preserved or even enhanced SDH staining, indicative of compensatory mitochondrial proliferation in response to defective complex IV activity (17). Such patterns are not restricted to IBM; COX-deficient fibres have also been described in DM and PM, where their abundance correlates with disease severity and refractoriness to treatment (14). Ultrastructural analyses by electron microscopy further support mitochondrial pathology. In DM, mitochondria often appear swollen with disrupted cristae, paracrystalline inclusions, and accumulation of osmiophilic deposits. Perifascicular atrophy, a pathognomonic feature of DM, has been associated with mitochondrial depletion in affected fibres, suggesting that vascular injury and local hypoxia impair mitochondrial biogenesis and maintenance (16). In PM, mitochondrial swelling and loss of cristae structure have been linked to direct T-cell-mediated cytotoxicity, as perforin and granzyme B trigger apoptosis and necrosis with mitochondrial involvement (11). In IBM, electron microscopy reveals a spectrum of mitochondrial abnormalities including giant mitochondria, paracrystalline inclusions, abnormal cristae morphology, and subsarcolemmal accumulations of mitochondria. These features frequently coexist with rimmed vacuoles and protein aggregates (TDP-43, p62), suggesting convergence of mitochondrial dysfunction with disturbances in protein homeostasis and autophagy (18). Histological markers of mitochondrial turnover also highlight impaired quality control mechanisms. Immunohistochemical staining for proteins involved in mitophagy, such as p62 and phospho-ubiquitin (p-S65-Ub), demonstrate abnormal accumulation in IBM muscle fibres, consistent with defective removal of damaged mitochondria (13). Co-localization of these markers with COX-deficient fibres suggests that impaired mitophagy exacerbates mitochondrial dysfunction. Furthermore, quantitative studies have shown that the number of COX-negative fibres correlates positively with the density of inflammatory infiltrates, particularly $CD8^+$ T cells and macrophages, linking immune-mediated injury with mitochondrial pathology (17). Interestingly, mitochondrial abnormalities are not restricted to clinically affected muscles; subclinical mitochondrial changes can be detected in non-atrophic fibre, supporting the hypothesis that mitochondrial dysfunction precedes overt fibre degeneration. Overall, histological evidence strongly supports the central role of mitochondrial damage in IIMs. From classical enzymatic stains demonstrating COX-deficiency, to ultrastructural changes captured by electron microscopy, to immunohistochemical markers of impaired mitophagy, the pathological spectrum highlights both primary mitochondrial defects and secondary immune-mediated damage. While IBM displays the most profound and consistent mitochondrial pathology, DM and PM also demonstrate significant mitochondrial alterations that contribute to muscle weakness and disease progression. These findings underscore the importance of incorporating histological evaluation of mitochondrial integrity in diagnostic workflows, and they provide critical insights into potential therapeutic strategies aimed at restoring mitochondrial health in inflammatory myopathies. Table I summarises the described pathology features across IIMs.

Autoantibodies targeting mitochondria

Autoantibodies directed against mitochondrial components have emerged as a distinct and clinically relevant phenomenon in inflammatory myopathies, particularly in IBM and in subsets of adult-onset DM and PM. Recent work has identified autoantibodies against NDUFA11, a subunit of mitochondrial respiratory chain complex I, as enriched in IBM: in an exploratory cohort, ~9.7% of IBM patients displayed IgG reactivity to NDUFA11 compared to much lower percentages in PM or DM; in a larger validation cohort, ~3.5% of IBM patients retained positivity, whereas none of the PM or DM samples did, confirming specificity (20). Though histological or clinical correlations (*e.g.*, degree of mitochondrial pathology, respiratory chain deficiency, etc.) were not statistically significant in that study, there was a trend toward higher frequency of distal lower extremity weakness and ragged red

Table I. Summary of pathophysiological mechanisms of mitochondrial damage in IIMs and pathology features.

	DM	PM	IBM
Mitochondrial pathophysiology	interferon-induced oxidative stress and vascular damage	$CD8^+$ lymphocytes driven damage, pro-apoptotic signalling	Protein misfolding, impaired mitophagy, inflammasome activation
Pathology features	COX-fibres, mitochondrial abnormalities at EM	COX-fibres, mitochondrial abnormalities at EM	COX-fibres (++), COX-fibres, mitochondrial abnormalities at EM associated to rimmed vacuoles and protein aggregates

fibres among the anti-NDUFA11-positive IBM group (20). Another class of mitochondrial-directed autoantibodies are anti-mitochondrial autoantibodies (AMA) typically known from primary biliary cholangitis, but also detected in a subset of patients with myositis. In a large cohort study (~619 adult and 371 juvenile myositis patients), AMA were found in approximately 5% of adult myositis cases (across DM, PM, IBM, amyopathic DM) compared to ~1% in juvenile myositis or healthy controls (20). Clinical associations of AMA positivity in adult myositis include more persistent or treatment-refractory muscle weakness, dysphagia, Raynaud's phenomenon, and cardiomyopathy (21). Histopathologically, in AMA-positive myositis, features include muscle fibre degeneration, vacuole formation of various sizes (not necessarily classical rimmed vacuoles), upregulation of MHC-I, complement deposition on the sarcolemma, and occasional ragged red fibres, pointing to mitochondrial involvement (*e.g.* proliferation or compensatory mitochondrial biogenesis) and concurrent inflammatory injury (22). One recent small series described three middle-aged patients with AMA positivity: all had elevated creatine kinase, proximal muscle weakness, and in biopsy, vacuoles beneath the sarcolemma, diffuse MHC class I expression, and complement membrane attack complex deposition; one case showed ragged red fibres (22). The mechanistic significance of these autoantibodies is still under investigation. It is not yet definitively established whether they are pathogenic (*i.e.* directly contributing to mitochondrial damage), or largely epiphenomenal (markers of mitochondrial stress or damage). The discovery of anti-NDUFA11 in IBM is intriguing because complex I defects are well known in IBM muscle histology, but the lack of strong correlation with histologic severity in the study suggests heterogeneity (20). Meanwhile, AMA positivity seems to define a phenotype with more severe or multisystem involvement, but again direct evidence of autoantibody-mediated mitochondrial injury (*e.g.* evidence that the AMA bind mitochondria in situ, impair respiratory chain activity, or incite complement on mitochondrial membranes) remains limited.

Therapeutics' present and future avenues

In IIMs, therapies such as glucocorticoids, conventional immunosuppressants, and newer biologics or monoclonal antibodies not only reduce inflammation but may also help restore mitochondrial function, either directly or indirectly, by alleviating the damaging milieu. Glucocorticoids (*e.g.* high-dose prednisolone) suppress immune cell infiltration and cytokine release, which leads to reduced generation of reactive oxygen species (ROS) and oxidative stress in muscle. Even where muscle volume decreases under steroid therapy, improvements in muscle strength and enzyme markers suggest that recovery of mitochondrial efficiency (improved oxidative phosphorylation, ATP production) rather than just hypertrophy plays a role. A study using CT imaging in myositis showed that after steroid therapy, despite muscle volume loss, muscle strength and serum markers improved, leading authors to hypothesise that mitochondrial dysfunction is ameliorated as inflammation, endoplasmic reticulum stress, and ROS are reduced (23). Immunosuppressants (*e.g.* methotrexate, azathioprine, mycophenolate mofetil) used in PM, DM, and other IIMs reduce chronic inflammation, thereby decreasing continuous damage to the respiratory chain (*e.g.* loss of complex I, deletions in mtDNA). Although direct measurements of mitochondrial function in patients on immunosuppressants are relatively scarce, combined treatment regimens lead to better clinical outcomes, which often correlate with histological evidence of fewer COX-negative fibres and better mitochondrial enzyme activity. Monoclonal antibodies and biologics also contribute. For example, rituximab (anti-CD20) has been used in refractory myositis: while the RIM trial did not meet its primary endpoint, 83% of participants saw clinical improvements (strength, enzyme levels) and were able to reduce steroid doses. By reducing the burden of immune activity, there is likely less mitochondrial damage via oxidative stress, mitochondrial DNA injury, and impairment of mitochondrial enzyme complexes (24). Another biologic in development is dazukibart (PF-06823859), a monoclonal antibody neutralising IFN-β, tested in dermatomyositis. Since IFN-β contributes to mitochondrial dysfunction by inducing oxidative stress and altering mitochondrial biogenesis, neutralisation may help protect or restore mitochondrial function (by lowering ROS, preserving membrane potential, etc.) (25). Beyond standard immunomodulation, there are direct mitochondria-targeting therapies in development. A promising example is mitochondrial transplantation using mitochondria isolated from human umbilical cord mesenchymal stem cells (named PN-101) in preclinical IIM models and in a Phase 1/2a clinical trial of patients with refractory polymyositis or dermatomyositis. In these studies, PN-101 improved mitochondrial function (increased intracellular ATP, better myogenesis in patient-derived myoblasts), reduced inflammatory se-

verity in animal models, and was safe in the human patients, showing at least minimal improvement in the IMACS Total Improvement Scores (26). Another non-drug, adjunctive approach is endurance (aerobic) exercise training: in stable PM/DM patients, 12 weeks of endurance training increased mitochondrial enzyme activities (*e.g.* β-HAD, citrate synthase), improved aerobic capacity, reduced disease activity, and improved exercise performance, consistent with enhanced mitochondrial biogenesis and better oxidative capacity (27). Finally, novel therapies such as KZR-616, an immunoproteasome inhibitor, are under clinical trial (PRESIDIO, NCT04033926) in PM and DM. Though mitochondrial measures were not the primary endpoint, reductions in inflammation and preservation of muscle strength may indirectly mitigate mitochondrial damage (28).

The reverse of the medal: inflammatory aspects in mitochondrial myopathies

Mitochondrial myopathies (MM), typically arising from primary defects in mitochondrial DNA (mtDNA) or nuclear genes encoding mitochondrial proteins, are classically metabolic disorders without overt inflammation; however, an increasing number of histopathological studies document inflammatory features in some MM cases, suggesting that immune responses may contribute to disease progression. In muscle biopsies from patients with MM (*e.g.* cases of progressive external ophthalmoplegia, MELAS), hallmark findings such as ragged red fibres (RRFs), subsarcolemmal mitochondrial accumulation, and cytochrome c oxidase-negative (COX-)fibres dominate; yet discrete inflammatory cell infiltrates, often of T lymphocytes and macrophages, are also observed in certain patients, especially during acute exacerbations or respiratory failure. A published case of an adult with the 3251A>G mtDNA mutation showing respiratory failure described both ragged red and COX-negative fibres and areas with inflammatory infiltrates and necrotising features; intravenous immunoglobulin therapy was associated with clinical improvement (29). Another recognized histological alteration is major histocompatibility complex class I (MHC-I) upregulation on non-necrotic muscle fibres. In mitochondrial disease cases with inflammatory degeneration, MHC-I overexpression suggests increased antigen presentation that could attract immune effectors or set the stage for immune-mediated damage. Although direct large-scale studies in mitochondrial myopathies are limited, the phenomenon is well-characterised in idiopathic inflammatory myopathies (IIMs) and provides a useful comparison: for example, in a study of 224 muscle biopsies from IIM patients *versus* controls, sarcolemmal MHC class I expression was markedly elevated in IIMs, with high sensitivity and specificity for diagnosing inflammatory myopathy (30). Complement activation, specifically deposition of the membrane attack complex (MAC, C5b-9), is another inflammatory mark seen primarily in IIMs (*e.g.* dermatomyositis), and occasionally reported in MM with inflammation. In dermatomyositis, intramuscular microvasculature often shows MAC deposition in capillaries and arterioles (31). Whether similar patterns are consistently present in mitochondrial-myopathy biopsies is less certain, but in reports of mitochondrial cases with necrotising features, complement deposition has been described alongside inflammatory cell infiltrates. The fact that necrotising myopathy (which sometimes overlaps in clinical presentation) shows strong C5b-9 in necrotic fibres and some non-necrotic fibres suggests that complement activation may be part of the inflammatory cascade triggered by mitochondrial damage (32). Ultrastructurally, in cases with inflammation, mitochondrial abnormalities often co-localise with areas of fibre necrosis and immune cell proximity. Although systematic studies quantifying macrophage clustering around COX-negative fibres are rare, case reports show this association: Mancuso *et al.* described this phenotype in a 3251A>G mutation carrier with acute respiratory failure: histology demonstrated RRFs, COX deficiency, discrete inflammatory infiltrates and necrosis, and patient responded to immune therapy (30). Cytokine expression in muscle tissue also provides evidence for immune activation. In patients with chronic, inactive PM and DM, immunohistochemical studies detected IL-1α and IL-1β expression even when infiltrates had subsided, suggesting persistent immune/stress signals. While not specific to MM, this indicates that proinflammatory cytokine expression can outlast visible cellular inflammation (32). However, important distinctions remain: in MM with inflammation, infiltrates tend to be focal, sparse, not as dense or widespread as in classical autoimmune myositis; necrosis may be limited; vasculopathy (as in dermatomyositis) less common; and inflammatory markers often do not correlate with systemic autoimmunity. Also, large-scale series confirming consistent presence of inflammation in MM are lacking. In summary, histopathological evidence supports that in a subset of mitochondrial myopathies, immune mechanisms are engaged, including inflammatory cell infiltrates (T cells, macrophages), upregulated MHC class I on non-necrotic fibres, complement activation with MAC deposition, fibre necrosis in some cases, and persistent pro-inflammatory cytokine expression. These features suggest a secondary inflammatory response to mitochondrial damage, which might in turn accelerate pathology. Further systematic studies are needed to establish prevalence, the weight on that also of muscle magnetic resonance imaging, prognostic implications, and whether immunomodulatory therapies may be beneficial in these mixed-phenotype cases.

Conclusion

Mitochondrial dysfunction plays a central role in the pathogenesis of idiopathic inflammatory myopathies (IIMs), with multifactorial contributions from oxidative stress, mtDNA damage, impaired mitophagy, and protein aggregation. Histologically, affected muscle fibres display COX-negative fibres, ragged red fibres, subsarcolemmal mitochondrial accumulation, and ultrastructural abnormalities, often accompanied by inflammatory features such as focal endomysial T-

cell and macrophage infiltrates, MHC class I upregulation, and complement deposition. Autoantibodies targeting mitochondrial components, including anti-NDUFA11 and anti-mitochondrial antibodies (AMA), further highlight the immunogenic potential of damaged mitochondria, defining subgroups with more severe clinical phenotypes. Therapeutically, standard treatments, glucocorticoids, immunosuppressants, and monoclonal antibodies, can contribute to restoring mitochondrial function indirectly by reducing inflammation and oxidative stress, while emerging mitochondria-targeting strategies, such as mitochondrial transplantation or IFN-β neutralisation, aim to directly improve bioenergetics. Collectively, these findings emphasise the intricate interplay between mitochondrial dysfunction and immune activation, suggesting that integrated metabolic and immunomodulatory approaches may optimise outcomes in both IIMs and mitochondrial myopathies.

References

1. MALIK A, HAYAT G, KALIA JS, GUZMAN MA: Idiopathic inflammatory myopathies: clinical approach and management. *Front Neurol* 2016; 7: 64. https://doi.org/10.3389/fneur.2016.00064
2. FATTORINI F, CONTICINI E, DOURADO E *et al*.: Idiopathic inflammatory myopathies: one year in review 2024. *Clin Exp Rheumatol* 2025; 43(2): 167-77. https://doi.org/10.55563/clinexprheumatol/yizkja
3. GONZALEZ-CHAPA JA, MACÊDO MB, LOOD C: The emerging role of mitochondrial dysfunction in the pathogenesis of idiopathic inflammatory myopathies. *Rambam Maimonides Med J* 2023; 14(2): e0006. https://doi.org/10.5041/rmmj.10493
4. DONG H, TSAI S-Y: Mitochondrial properties in skeletal muscle fiber. *Cells* 2023; 12(17): 2183. https://doi.org/10.3390/cells12172183
5. LEI Y, GAN M, QIU Y *et al*.: The role of mitochondrial dynamics and mitophagy in skeletal muscle atrophy: from molecular mechanisms to therapeutic insights. *Cell Mol Biol Lett* 2024; 29: 59. https://doi.org/10.1186/s11658-024-00572-y
6. SLAVIN MB, MEMME JM, OLIVEIRA AN *et al*.: Regulatory networks coordinating mitochondrial quality control in skeletal muscle. *Am J Physiol Cell Physiol* 2022; 322(5): C913–C926. https://doi.org/10.1152/ajpcell.00065.2022
7. IRAZOKI A, GORDALIZA-ALAGUERO I, FRANK E *et al*.: Disruption of mitochondrial dynamics triggers muscle inflammation through interorganellar contacts and mitochondrial DNA mislocation. *Nat Commun* 2023; 14(1): 108. https://doi.org/10.1038/s41467-022-35732-1
8. FAAS M, IPSEIZ N, ACKERMANN J *et al*.: IL-33–induced metabolic reprogramming controls differentiation of alternatively activated macrophages and resolution of inflammation. *Immunity* 2021; 54(11): 2531-46.e5. https://doi.org/10.1016/j.immuni.2021.09.010
9. DALAKAS MC: Inflammatory muscle diseases. *N Engl J Med* 2015; 372(18): 1734-47. https://doi.org/10.1056/nejmra1402225
10. ALLENBACH Y, UZUNHAN Y, TOQUET S *et al*.: Different phenotypes in dermatomyositis associated with anti-MDA5 antibody: Study of 121 cases. *Neurology* 2020; 95(1): e70-e78. https://doi.org/10.1212/wnl.0000000000009727
11. PINAL-FERNANDEZ I, AMICI DR, PARKS CA *et al*.: Myositis autoantigen expression correlates with muscle regeneration but not autoantibody specificity. *Arthritis Rheumatol* 2019; 71(8): 1370-9. https://doi.org/10.1002/art.40883
12. WANG G, MCHUGH NJ: An update on myositis autoantibodies and insights into pathogenesis. *Clin Exp Rheumatol* 2025; 43(2), 364-71. https://doi.org/10.55563/clinexprheumatol/kyj2cy
13. GREENBERG SA: Inclusion body myositis: clinical features and pathogenesis. *Nat Rev Rheumatol* 2019; 15(5): 257-72. https://doi.org/10.1038/s41584-019-0186-x
14. IU ECY, SO H, CHAN CB: Mitochondrial defects in sporadic inclusion body myositis-causes and consequences. *Front Cell Dev Biol* 2024; 12: 1403463. https://doi.org/10.3389/fcell.2024.1403463
15. ZHANG SH, ZHAO Y, XIE QB, JIANG Y, WU YK, YAN B: Aberrant activation of the type I interferon system may contribute to the pathogenesis of anti-melanoma differentiation-associated gene 5 dermatomyositis. *Br J Dermatol* 2019; 180(5): 1090-8. https://doi.org/10.1111/bjd.16917
16. WEIHL CC, BALOH RH, LEE Y *et al*.: Targeted sequencing and identification of genetic variants in sporadic inclusion body myositis. *Neuromuscul Disord* 2015; 25(4): 289-96. https://doi.org/10.1016/j.nmd.2014.12.009
17. NOGALSKA A, D'AGOSTINO C, ENGEL WK *et al*.: Activation of the unfolded protein response in sporadic inclusion-body myositis but not in hereditary GNE inclusion-body myopathy. *J Neuropathol Exp Neurol* 2015; 74(6): 538-46. https://doi.org/10.1097/nen.0000000000000196
18. LINDGREN U, ROOS S, HEDBERG OLDFORS C, MOSLEMI AR, LINDBERG C, OLDFORS A: (2015). Mitochondrial pathology in inclusion body myositis. *Neuromuscul Disord* 2015; 25(4): 281-8. https://doi.org/10.1016/j.nmd.2014.12.010
19. NOTARNICOLA A, HELLSTROM C, HORULUOGLU B *et al*.: Autoantibodies against a subunit of mitochondrial respiratory chain complex I in inclusion body myositis. *J Autoimmun* 2024; 149: 103332. https://doi.org/10.1016/j.jaut.2024.103332
20. SABBAGH SE, PINAL-FERNANDEZ I, CASAL-DOMINGUEZ M *et al*.: Anti-mitochondrial autoantibodies are associated with cardiomyopathy, dysphagia, and severe disease in adult-onset myositis. *Clin Rheumatol* 2021; 40(10): 4095-100. https://doi.org/10.1007/s10067-021-05730-7
21. CHEN Y, ZHANG W, LV H *et al*.: Pathological findings with vacuoles in anti-mitochondrial antibody-positive inflammatory myopathy. *BMC Musculoskelet Disord* 2024; 25(1): 257. https://doi.org/10.1186/s12891-023-06941-6
22. NAWATA T, KUBO M, NOMURA T *et al*.: Change in muscle volume after steroid therapy in patients with myositis assessed using computed tomography. *BMC Musculoskelet Disord* 2018; 19(1): 93. https://doi.org/10.1186/s12891-018-2008-8
23. GLAUBITZ S, ZENG R, SCHMIDT J: New insights into the treatment of myositis. *Ther Adv Musculoskelet Dis* 2020; 12. https://doi.org/10.1177/1759720x19886494
24. PINAL-FERNANDEZ I, CASAL-DOMINGUEZ M, MAMMEN AL: Dazukibart for dermatomyositis: expanding the therapeutic arsenal. *Ann Transl Med* 2025; 13(3): 24. https://doi.org/10.21037/atm-25-44.
25. KIM JY, KANG YC, KIM MJ *et al*.: Mitochondrial transplantation as a novel therapeutic approach in idiopathic inflammatory myopathy. *Ann Rheum Dis* 2025; 84(4): 609-19. https://doi.org/10.1016/j.ard.2024.11.005
26. ALEMO MUNTERS L, DASTMALCHI M, KATZ A *et al*.: Improved exercise performance after endurance training in polymyositis and dermatomyositis. *Arthritis Res Ther* 2013; 15(4): R83. https://doi.org/10.1186/ar4263
27. A phase 2 study of KZR-616 in patients with active polymyositis or dermatomyositis (PRESIDIO). ClinicalTrials.gov. Identifier: NCT04033926.
28. MANCUSO M, ORSUCCI D, CALDARAZZO IENCO E *et al*.: An "inflammatory" mitochondrial myopathy: a case report. *Neuromuscul Disord* 2013; 23(11): 907-10. https://doi.org/10.1016/j.nmd.2013.07.011
29. VAN DER PAS J, HENGSTMAN GJ, TER LAAK HJ *et al*.: Diagnostic value of MHC class I staining in idiopathic inflammatory myopathies. *J Neurol Neurosurg Psychiatry* 2004; 75: 136-39.
30. KISSEL JT, MENDELL JR, RAMMOHAN KW: Microvascular deposition of complement membrane attack complex in dermatomyositis. *N Engl J Med* 1986; 314(6): 329-34.
31. CONG L, PU C-Q, SHI Q, WANG Q, LU X-H: Complement membrane attack complex is related to necrotizing myopathy *Int J Clin Exp Pathol* 2014; 7(7): 4143-49.
32. NYBERG P, WIKMAN AL, NENNESMO I, LUNDBERG IE: Increased interleukin-1α and MHC class I expression in chronic polymyositis and dermatomyositis. *J Rheumatol* 2000; 27: 940-48.