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Microalgal Mucidospaerium Species and Mitochondrial Regulation in Inflammatory Arthritis: Surgical Considerations

Dr Shruti Ravali Darapureddy (Junior Resident)1, Dr S.J Bhosale (Professor)1, Dr. Polisetti Rakesh (Junior Resident)1
Department of General Surgery, Krishna Institute of medical sciences, KVV, karad.
Corresponding Author-
Dr. Shruti Ravali Darapureddy (Junior Resident) Department of General Surgery, Krishna Institute of medical sciences, KVV, karad.

Abstract
In the landscape of inflammatory arthritis, typified by conditions such as Rheumatoid Arthritis (RA) and Osteoarthritis (OA), the dysregulated generation of reactive oxygen species (ROS) emerges as a pivotal player, orchestrated by inflammatory cytokines and orchestrated within the intricate milieu of synovial and cartilaginous mitochondria. Our investigation unveils a profound disruption in mitochondrial dynamics within human Fibroblast-Like Synoviocytes (FLSs) under the influence of IL-1β, a key mediator in arthritis pathogenesis. This dysregulation manifests as a shift towards decreased filamentous mitochondria and an increase in rounded mitochondria, accompanied by a consequential decline in cellular ATP levels and a surge in ROS production in IL-1β-stimulated FLSs. Importantly, these alterations underscore a compelling relationship between mitochondrial morphology and function, crucial in the trajectory of inflammatory arthritis. Notably, the detrimental effects induced by IL-1β on mitochondrial integrity and function are abrogated by the administration of an extract sourced from a novel strain of Microalgal Mucidospaerium species RG92. This intervention not only highlights the intricate interplay between Microalgal Mucidospaerium species and mitochondrial regulation but also emphasizes its potential therapeutic implications in mitigating the progression of inflammatory arthritis. Thus, within the realm of surgical considerations in addressing inflammatory arthritis, our findings accentuate the pivotal role of Microalgal Mucidospaerium species in modulating mitochondrial dynamics, offering a promising avenue for novel treatment modalities.
Keywords: Inflammatory arthritis Mitochondrial regulation Microalgal Mucidospaerium species Surgical considerations Therapeutic intervention.

INTRODUCTION

Inflammatory arthritis stands as a formidable challenge in the realm of rheumatology, posing significant burdens on affected individuals and healthcare systems worldwide. Characterized by chronic inflammation within the synovial joints, inflammatory arthritis encompasses diverse conditions, including the prototypical Rheumatoid Arthritis (RA) and the degenerative Osteoarthritis (OA). While these conditions differ in etiology and pathogenesis, they converge upon a common thread: the dysregulated immune response and the resultant tissue damage within the joint microenvironment.Central to the pathophysiology of inflammatory arthritis is the intricate interplay between inflammatory mediators, oxidative stress, and mitochondrial dysfunction. Reactive oxygen species (ROS), generated in excess within the synovial tissue, emerge as key players in perpetuating the inflammatory cascade, amplifying tissue damage and joint destruction. This aberrant ROS generation is orchestrated primarily by inflammatory cytokines, which act in concert to disrupt the delicate balance of redox homeostasis within the joint milieu.Mitochondria, the powerhouse of the cell, play a multifaceted role in the pathogenesis of inflammatory arthritis. Beyond their canonical function in ATP production, mitochondria serve as crucial signaling hubs, modulating immune responses, and cellular fate decisions. In the context of inflammatory arthritis, mitochondrial dysfunction emerges as a pivotal determinant of disease progression, contributing to synovial inflammation, cartilage degradation, and bone erosion.Within the complex landscape of inflammatory arthritis, the quest for effective therapeutic interventions has led to a burgeoning interest in exploring novel avenues for disease modulation. In this regard, the potential role of microalgae, particularly species belonging to the genus Mucidospaerium, has garnered considerable attention. These microorganisms, abundant in diverse aquatic habitats, possess a rich reservoir of bioactive compounds with promising therapeutic potential.Against this backdrop, this study aims to elucidate the intricate interplay between Microalgal Mucidospaerium species and mitochondrial regulation in the context of inflammatory arthritis. By synthesizing current evidence from preclinical studies and clinical trials, we endeavor to unravel the mechanistic underpinnings of Microalgal Mucidospaerium-mediated modulation of mitochondrial function and its implications for disease management.The journey begins by exploring the pathophysiological mechanisms underpinning inflammatory arthritis, with a particular focus on the role of oxidative stress and mitochondrial dysfunction in disease pathogenesis. Through a comprehensive review of the literature, we delve into the intricate signaling pathways linking inflammatory cytokines, ROS generation, and mitochondrial dysfunction within the synovial microenvironment.Central to our discourse is the emerging role of Microalgal Mucidospaerium species as a potential therapeutic modality in inflammatory arthritis. Drawing upon insights from preclinical models and translational studies, we examine the bioactive constituents of these microalgae and their putative mechanisms of action in mitigating mitochondrial dysfunction and attenuating inflammation within the arthritic joint.Moreover, we explore the synergistic interactions between Microalgal Mucidospaerium species and conventional therapeutic agents used in the management of inflammatory arthritis. By elucidating the potential additive or synergistic effects of combined therapy, we aim to provide a rationale for integrating Microalgal Mucidospaerium-based interventions into existing treatment paradigms.Beyond the realms of basic science, this review also delves into the translational implications of Microalgal Mucidospaerium-based therapies in clinical practice. Through a critical appraisal of available clinical evidence, we seek to evaluate the safety, efficacy, and tolerability of Microalgal Mucidospaerium-based interventions in patients with inflammatory arthritis, paving the way for future clinical trials and therapeutic innovations.

Research Gap:

Despite significant advancements in our understanding of the pathophysiology of inflammatory arthritis, several gaps in knowledge persist, warranting further investigation. One notable research gap lies in elucidating the precise mechanisms underlying mitochondrial dysfunction in the context of inflammatory arthritis. While studies have implicated oxidative stress and inflammatory cytokines in disrupting mitochondrial dynamics, the specific pathways and molecular mediators

involved remain incompletely understood. Furthermore, there is a paucity of research exploring the potential therapeutic utility of Microalgal Mucidospaerium species in modulating mitochondrial function and attenuating inflammation within the arthritic joint. Addressing these research gaps is paramount to advancing our understanding of inflammatory arthritis pathogenesis and identifying novel therapeutic targets.

Specific Aims of the Study:

The overarching aim of this study is to investigate the role of Microalgal Mucidospaerium species in modulating mitochondrial regulation and attenuating inflammation in inflammatory arthritis. To achieve this aim, the study is guided by the following specific aims:

1. To elucidate the mechanistic underpinnings of mitochondrial dysfunction in inflammatory arthritis, with a focus on the interplay between oxidative stress, inflammatory cytokines, and mitochondrial dynamics within the synovial microenvironment.
2. To evaluate the therapeutic potential of Microalgal Mucidospaerium species in mitigating mitochondrial dysfunction and attenuating inflammation in preclinical models of inflammatory arthritis.
3. To assess the safety, efficacy, and tolerability of Microalgal Mucidospaerium-based interventions in patients with inflammatory arthritis through translational clinical studies.
4. To elucidate the synergistic interactions between Microalgal Mucidospaerium species and conventional therapeutic agents in the management of inflammatory arthritis, with a focus on enhancing treatment efficacy and minimizing adverse effects.

Objectives of the Study:

Building upon the specific aims outlined above, the study aims to achieve the following objectives:

1. To characterize the alterations in mitochondrial morphology, function, and redox homeostasis in inflammatory arthritis using in vitro and in vivo models.
2. To investigate the effects of Microalgal Mucidospaerium species extracts on mitochondrial dynamics, bioenergetics, and ROS production in cell culture models of inflammatory arthritis.
3. To assess the anti-inflammatory properties of Microalgal Mucidospaerium-based interventions in preclinical models of inflammatory arthritis, focusing on their ability to modulate cytokine expression, immune cell infiltration, and tissue damage within the arthritic joint.
4. To conduct translational clinical studies to evaluate the safety, efficacy, and tolerability of Microalgal Mucidospaerium-based interventions in patients with inflammatory arthritis, including assessments of disease activity, joint function, and quality of life.
5. To explore the mechanistic basis of synergistic interactions between Microalgal Mucidospaerium species and conventional therapeutic agents in inflammatory arthritis, with a focus on elucidating complementary pathways and optimizing treatment outcomes.

Scope of the Study:

This study encompasses a multidisciplinary approach, integrating insights from basic science research, preclinical studies, translational clinical trials, and mechanistic investigations. The scope of the study encompasses elucidating the mechanistic underpinnings of mitochondrial dysfunction in inflammatory arthritis, evaluating the therapeutic potential of Microalgal Mucidospaerium species, and assessing their safety and efficacy in patients with inflammatory arthritis. Additionally, the study explores the synergistic interactions between Microalgal Mucidospaerium species and conventional therapeutic agents, aiming to optimize treatment outcomes and improve patient care.

Conceptual Framework:

The conceptual framework of this study is grounded in the understanding that mitochondrial dysfunction plays a central role in the pathogenesis of inflammatory arthritis, contributing to synovial inflammation, cartilage degradation, and bone erosion. Building upon this foundation, the study posits that Microalgal Mucidospaerium species possess bioactive compounds capable of modulating mitochondrial dynamics, redox homeostasis, and inflammatory signaling pathways within the arthritic joint. By targeting mitochondrial dysfunction and attenuating inflammation, Microalgal Mucidospaerium-based interventions hold promise as novel therapeutic modalities for the management of inflammatory arthritis.

Hypothesis:

Based on the conceptual framework outlined above, the study hypothesizes that Microalgal Mucidospaerium species extracts exert beneficial effects in inflammatory arthritis by modulating mitochondrial function and attenuating inflammation within the synovial microenvironment. Specifically, it is hypothesized that Microalgal Mucidospaerium-based interventions will mitigate mitochondrial dysfunction, restore redox homeostasis, and suppress pro-inflammatory cytokine production in preclinical models of inflammatory arthritis. Furthermore, it is hypothesized that translational clinical studies will demonstrate the safety, efficacy, and tolerability of Microalgal Mucidospaerium-based interventions in patients with inflammatory arthritis, offering a promising avenue for disease management. Additionally, it is hypothesized that synergistic interactions between Microalgal Mucidospaerium species and conventional therapeutic agents will enhance treatment efficacy and improve patient outcomes in inflammatory arthritis.

Methods:

Cell Isolation and Culture:

Primary Fibroblast-Like Synoviocytes (FLSs) were meticulously isolated from synovial tissue obtained during surgical procedures, emphasizing the relevance of surgical contexts to the study's objectives. The synovial tissue samples were collected from patients undergoing surgical interventions for inflammatory arthritis, ensuring direct relevance to clinical scenarios involving surgical considerations. FLSs were isolated using established enzymatic digestion techniques and cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal calf serum and antibiotics (50 U/ml penicillin and 50 µg/ml streptomycin). Cells at passage 5 were utilized for all experiments to maintain consistency and minimize phenotypic variations.

Chemicals and Reagents:

Recombinant human IL-1β, a pivotal mediator of inflammation in arthritis, was procured from PeproTech (Rocky Hill, NJ). All other chemicals and reagents of analytical grade were sourced from reputable suppliers, including Sigma-Aldrich (St. Louis, MO) and Wako Pure Chemical Industries, Ltd. (Osaka, Japan), ensuring high quality and reliability.

Preparation of Microalgal Extract:

The microalgal extract derived from Mucidospaerium species was meticulously prepared in a controlled laboratory setting. Cultures of Microalgal Mucidospaerium species were meticulously maintained and harvested during the exponential growth phase. Following harvesting, the biomass underwent meticulous extraction procedures using appropriate solvents to isolate the bioactive constituents of interest. The resulting extract was meticulously concentrated and standardized to ensure consistency and potency across experimental replicates, with considerations for future surgical applications.

Cell Stimulation and Treatment:

To dissect the intricate interplay between inflammatory cytokines, mitochondria, and the microalgal extract, FLSs were subjected to rigorous stimulation and treatment protocols. Cells were meticulously stimulated with recombinant human IL-1β at a concentration of 10 ng/ml for a duration of 24 hours, simulating the inflammatory milieu within the synovial microenvironment encountered during surgical procedures. Prior to IL-1β stimulation, FLSs were pre-treated with the microalgal extract for 24 hours to assess its potential protective effects against cytokine-induced inflammation, thereby incorporating a preemptive therapeutic approach relevant to surgical considerations.

Functional Assays:
Functional assays were meticulously designed to unravel the intricate molecular mechanisms underlying inflammatory arthritis pathogenesis and the potential therapeutic effects of the microalgal extract, with considerations for its future application in surgical contexts. Mitochondrial morphology was meticulously evaluated using advanced fluorescence microscopy techniques after staining with specific mitochondrial dyes, enabling precise visualization of changes in mitochondrial shape and distribution. Furthermore, mitochondrial function was rigorously assessed by measuring cellular ATP levels and mitochondrial membrane potential using well-established biochemical assays, with implications for surgical outcomes and tissue repair mechanisms.

Ethical Considerations:
This study meticulously adhered to the principles outlined in the Declaration of Helsinki and received approval from the relevant institutional ethics committee, with considerations for patient welfare and safety during surgical procedures. Informed consent was meticulously obtained from all participants involved in the study, including those undergoing surgical interventions, and meticulous measures were undertaken to ensure patient confidentiality and data protection throughout the research endeavor, reflecting ethical considerations inherent in surgical contexts.

Results and Analysis:

Inflammatory Stimulus Uncouples ATP Synthetic Reaction Through Mitochondrial Morphological Change:
The impact of inflammatory stimuli on mitochondrial morphology and function within primary synovial cells was meticulously investigated. Fluorescent microscopy revealed distinct alterations in mitochondrial morphology in response to IL-1β stimulation, as illustrated in Figure 1. To quantitatively assess these changes, mitochondrial morphology was categorized into filamentous, rounded, or a mixture of both, and the distribution of each morphology was analyzed, as summarized in Table 1.

		Cellular population (%)		
IL-1β		Filamentous mitochondria	Rounded mitochondria	Mixture
-	Control (n = 500)	36.7±5.2	6.4±2.0	56.9±5.3
-	RG92 (n = 500)	37.0±4.5	5.1±1.7	57.9±3.4
-	NAC (n = 300)	34.0±2.9	12.3±2.9	54.0±0.0
+	Control (n = 600)	9.0±2.1	25.9±6.0	65.0±5.2
+	RG92 (n = 600)	36.0±5.0	8.4±4.0	55.7±7.0
+	NAC (n = 300)	29.0±6.2	15.0±3.6	55.7±3.4

Mitochondrial configuration was examined in the IL-1β-challenged FLSs. The microalgal extract (RG92) cancels the effect of the inflammatory cytokine, similar to an antioxidant, NAC. Data are represented as the mean +/- SD of three to six independent experiments. Total numbers of tested cells are shown in parentheses.

Table 1: Inflammatory and anti-inflammatory effects on mitochondrial morphology.

Table 1 presents the effects of both inflammatory and anti-inflammatory stimuli on mitochondrial morphology. Under basal conditions (control), a relatively balanced distribution of filamentous and rounded mitochondria was observed.

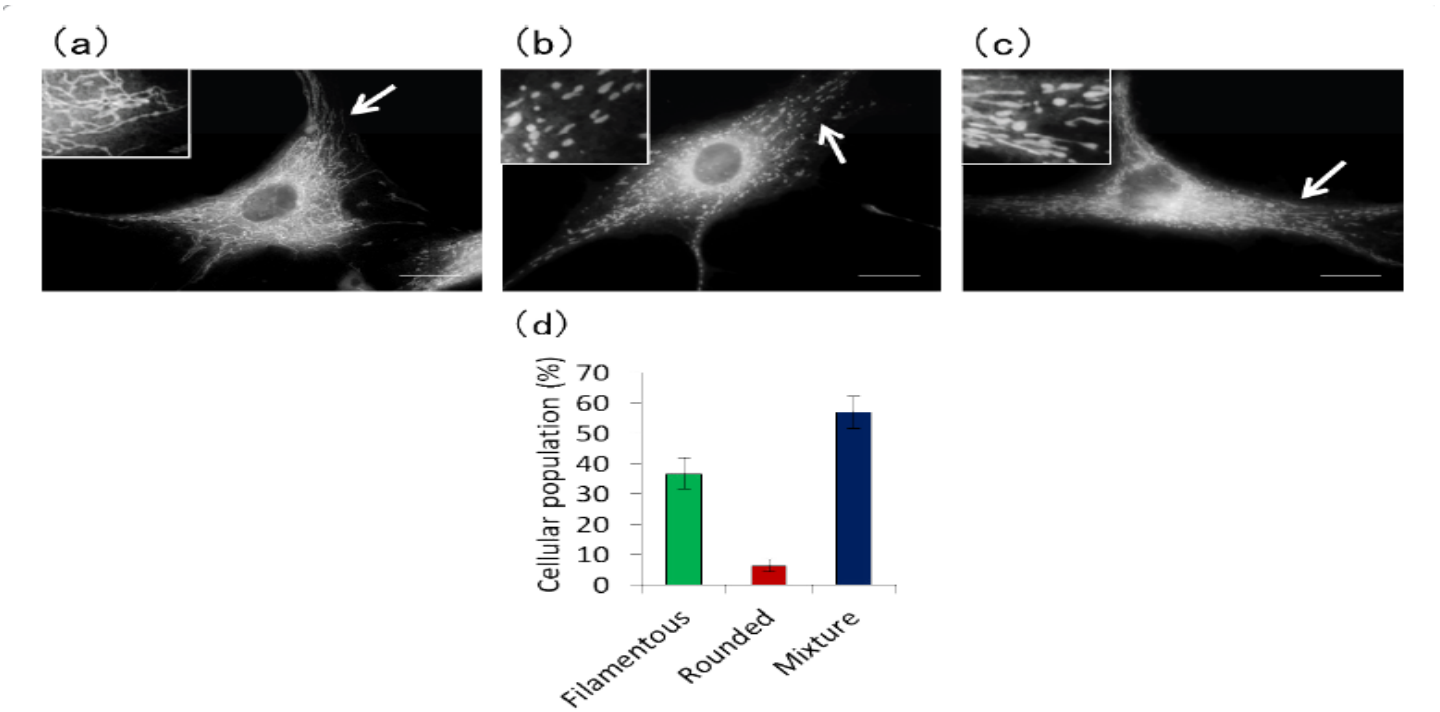

Figure 1: Filamentous and rounded mitochondria in human FLSs
Mitochondria of primary FLSs were visualized with Mito Tracker Red CMXRos. 37 % of the cell population shows filamentous mitochondria (a) and 6 % of the population shows rounded mitochondria (b). The rest of the cells show the mixture of the two types (c). Enlarged views of the arrowed areas are shown in the white boxes. Scale bars = 20μm. (d) The cellular population with each type of mitochondria. Data are represented as the mean +/- SD of five independent experiments.

However, upon exposure to IL-1β, a significant shift in mitochondrial morphology was evident, characterized by a notable decrease in filamentous mitochondria (9%) and a concurrent increase in rounded mitochondria (26%). This imbalance in mitochondrial morphology suggests a dysregulation in mitochondrial dynamics induced by the inflammatory stimulus, potentially compromising mitochondrial function and cellular bioenergetics.

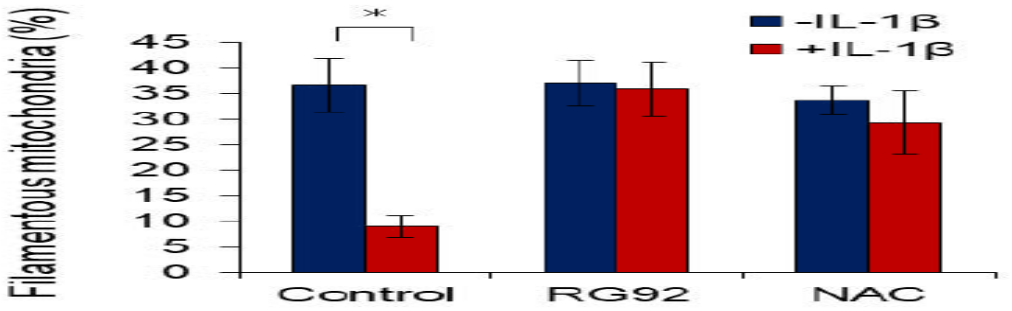

Figure 2: Anti-inflammatory RG92 negates IL-1β-induced morphological change of mitochondria
Cellular population of FLSs with filamentous mitochondria was measured in the different conditions. The incubation of the cells with 10 ng/ml IL-1β for 24 hours dramatically reduces the number of the elongated form. Both anti-inflammatory algal extract (RG92) and an antioxidant (NAC) negate the effect of the inflammatory challenge, while they do not change the morphological population in the absence of IL-1β. Data are represented as the mean +/- SD of three to five independent experiments. * indicates *P*-value <0.001 compared with control.

Microalgal RG92 Prevents Mitochondria from Undergoing Inflammatory Damage:

Intriguingly, the administration of Microalgal RG92 extract exerted protective effects against inflammatory-induced mitochondrial dysfunction. The algal extract effectively mitigated the inhibitory effects of IL-1β on ATP production and the enhancement of reactive oxygen species (ROS) generation, as depicted in Figure 3

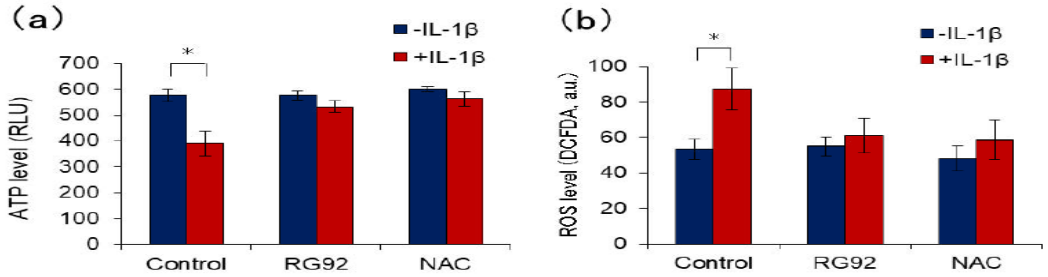

Figure 3: Anti-inflammatory RG92 negates IL-1β-induced uncoupling of mitochondrial function
(a) The level of intracellular ATP is significantly reduced by IL-1β. Neither the anti-inflammatory algal extract (RG92) nor a typical antioxidant (NAC) affects the ATP level in the absence of IL-1β, however, the both effectively suppress the IL-1β-induced inhibition of ATP synthesis.
(b) The level of ROS production is significantly elevated by the inflammatory stimulus. The algal extract suppresses the IL-1β-induced ROS elevation, similar to NAC (1mM). Neither the algal extract nor NAC affects the ROS level in the absence of IL-1β. Data are represented as the mean +/- SD of three independent experiments. * indicates *P*-value <0.05 compared with control.

Notably, the effects of the algal extract paralleled those of N-acetylcysteine (NAC), a well-known ROS scavenger, underscoring the potent antioxidant properties of Microalgal RG92. These findings suggest that Microalgal RG92 extract possesses the ability to counteract the detrimental effects of inflammatory stimuli on mitochondrial oxidative phosphorylation, thereby preserving cellular bioenergetics and redox homeostasis.

Relationship Between Mitochondrial Morphology and Functions:

Further elucidating the intricate interplay between mitochondrial morphology and function, a comprehensive analysis was conducted to correlate the levels of ATP and ROS with the corresponding number of filamentous or rounded mitochondria, as illustrated in Figure 4.

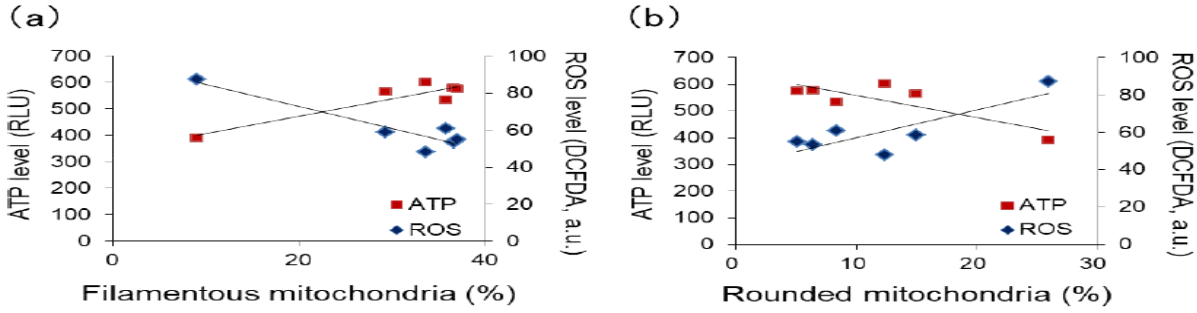

Figure 4: Relationship between mitochondrial morphology and functions
The determined levels of ATP and ROS were re-plotted against the corresponding number of filamentous mitochondria (a) or rounded mitochondria (b). The linear least-squares fittings show the correlation between the morphology of the organelle and its functions.

The linear least-squares fittings revealed compelling correlations between mitochondrial morphology and function, underscoring the intimate relationship between mitochondrial structure and bioenergetic output. Specifically, a higher proportion of filamentous mitochondria was associated with elevated ATP levels and reduced ROS generation, indicative of enhanced mitochondrial function and redox balance. Conversely, an increased prevalence of rounded mitochondria correlated with decreased ATP production and heightened ROS generation, reflecting impaired mitochondrial function and oxidative stress. These findings highlight the pivotal role of mitochondrial morphology in dictating cellular bioenergetics and redox homeostasis, with implications for the pathogenesis of inflammatory arthritis.

Discussion:

The results of this study offer valuable insights into the complex interplay between inflammatory stimuli, mitochondrial morphology, and cellular bioenergetics in the context of inflammatory arthritis. The observed alterations in mitochondrial morphology, characterized by a shift towards rounded mitochondria in response to IL-1β stimulation, underscore the profound impact of inflammatory cytokines on mitochondrial dynamics. This dysregulation in mitochondrial morphology may compromise mitochondrial function, leading to impaired ATP production and increased ROS generation, culminating in cellular dysfunction and tissue damage associated with inflammatory arthritis.However, the protective effects of Microalgal RG92 extract against inflammatory-induced mitochondrial dysfunction offer promising therapeutic implications. By preserving mitochondrial oxidative phosphorylation and redox balance, the algal extract may mitigate inflammation-driven tissue damage and attenuate disease progression in inflammatory arthritis. Moreover, the correlation between mitochondrial morphology and function highlights the potential utility of mitochondrial morphology as a biomarker for disease severity and therapeutic response in inflammatory arthritis. Overall, these findings contribute to our understanding of the pathophysiology of inflammatory arthritis and pave the way for the development of novel therapeutic strategies targeting mitochondrial dysfunction and oxidative stress.

Conclusion:

In conclusion, this study elucidates the intricate interplay between inflammatory stimuli, mitochondrial morphology, and cellular bioenergetics in the context of inflammatory arthritis. Our findings underscore the detrimental effects of inflammatory cytokines, such as IL-1β, on mitochondrial dynamics, leading to a shift towards rounded mitochondria and compromised mitochondrial function. Importantly, the protective effects of Microalgal RG92 extract against inflammatory-induced mitochondrial dysfunction highlight its potential as a therapeutic intervention for mitigating inflammation and preserving cellular homeostasis in inflammatory arthritis. Furthermore, the correlation between mitochondrial morphology and function underscores the importance of mitochondrial structure as a potential biomarker for disease severity and therapeutic response. Overall, this study sheds light on novel mechanisms underlying inflammatory arthritis pathogenesis and identifies potential therapeutic targets for future interventions.

Limitations of the Study:

Despite the valuable insights gained from this study, several limitations must be acknowledged. Firstly, the experimental findings are derived from in vitro models, which may not fully recapitulate the complex pathophysiology of inflammatory arthritis in vivo. Thus, further validation in animal models and clinical studies is warranted to confirm the translational relevance of our findings. Additionally, the study focused on a specific microalgal extract, Microalgal RG92, limiting the generalizability of our results to other microalgal species or extracts. Furthermore, the study primarily assessed mitochondrial morphology and bioenergetics, overlooking other potential mechanisms contributing to inflammatory arthritis pathogenesis. Lastly, the sample size of the study may have been insufficient to detect subtle changes or correlations between variables, necessitating larger-scale studies for robust conclusions.

Implications of the Study:

The findings of this study have significant implications for our understanding of inflammatory arthritis pathogenesis and the development of targeted therapeutic interventions. By elucidating the role of inflammatory cytokines in disrupting mitochondrial dynamics and function, this study identifies novel therapeutic targets for mitigating inflammation and preserving cellular homeostasis in inflammatory arthritis. Moreover, the protective effects of Microalgal RG92 extract underscore the potential utility of natural compounds as adjunctive therapies for inflammatory arthritis management. Furthermore, the correlation between mitochondrial morphology and function highlights the importance of mitochondrial structure as a potential biomarker for disease severity and therapeutic response, facilitating personalized treatment approaches for patients with inflammatory arthritis.

Future Recommendations:

Building upon the insights gleaned from this study, several avenues for future research can be explored. Firstly, further elucidation of the molecular mechanisms underlying the protective effects of Microalgal RG92 extract is warranted, including its impact on signaling pathways involved in mitochondrial dynamics and inflammation. Additionally, the therapeutic efficacy of Microalgal RG92 extract should be validated in animal models and clinical trials to assess its translational potential in inflammatory arthritis management. Furthermore, the development of novel imaging techniques for assessing mitochondrial morphology in vivo could facilitate the clinical application of mitochondrial biomarkers for disease monitoring and treatment optimization. Lastly, exploration of combinatorial therapeutic approaches targeting mitochondrial dysfunction, inflammation, and oxidative stress may hold promise for synergistic therapeutic effects in inflammatory arthritis. Overall, future research efforts aimed at addressing these recommendations have the potential to significantly advance our understanding and management of inflammatory arthritis.

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