Mitochondrial Dysfunction and Immune Dysregulation in Primary Sjogren's Syndrome: Implications for Therapeutic Strategies

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Abstract

Background: Primary Sjögren's syndrome (SjS) is a complex autoimmune disorder that greatly affects patients' quality of life through symptoms such as dry eye syndrome and xerostomia. Recent studies suggest that immune dysfunction and chronic inflammation are central to its pathogenesis, with a particular focus on mitochondrial dysfunction's role. Methods: This review synthesizes current literature on the relationship between mitochondrial dysfunction and immune dysregulation in primary SjS, examining findings from gene expression studies, mitochondrial dynamics, and metabolic pathways in salivary gland immune cells. The analysis includes mitochondrial DNA copy numbers in peripheral blood mononuclear cells from SjS patients to assess oxidative stress impacts. Results: Findings indicate that mitochondrial dysfunction contributes significantly to cellular homeostasis disruption and oxidative stress. Altered mitochondrial dynamics have been linked to increased reactive oxygen species production, correlating with inflammation and immune dysregulation in SjS. Discussion: The study underscores the therapeutic potential of targeting mitochondrial function as an intervention strategy for primary SjS. It also highlights the necessity for further research using advanced genomic approaches to better understand the complex interplay between mitochondrial dysfunction and immune responses, aiming to identify novel therapeutic targets that could improve patient outcomes.

Keywords: Primary Sjögren's syndrome (SjS), Mitochondrial dysfunction Immune dysregulation, Oxidative stress, Therapeutic interventions.

Significance | This study explores mitochondrial dysfunction's role in primary Sjögren's syndrome, highlighting its potential impact on disease progression and inflammation.

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Introduction

Primary Sjögren's syndrome (SjS) is a chronic autoimmune disorder characterized primarily by dry eye syndrome (DES) and xerostomia. However, the clinical spectrum of SjS extends beyond these hallmark symptoms. Many patients report systemic manifestations, including profound fatigue, musculoskeletal pain, joint inflammation, and an increased risk of developing lymphoma, observed in approximately 2–5% of cases (Negrini et al., 2022; André and Böckle, 2022). The multifaceted nature of the disease significantly impacts patients' quality of life, underscoring the necessity for a comprehensive understanding of its pathogenesis. SjS is fundamentally an autoimmune condition, where immune

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system dysregulation plays a pivotal role in the disease's progression. This dysregulation is marked by lymphocytic infiltration of salivary (SG) and lacrimal glands (LG), accompanied by the presence of inflammatory mediators. Early-stage histological findings reveal focal infiltrates predominantly composed of T helper and cytotoxic T cells, while later stages show a shift towards a B lymphocyte-dominated environment, characterized by the formation of ectopic germinal centers (eGC) that significantly increase lymphoma risk (Park et al., 2015; Hayashi, 2011).

Recent years have seen a growing interest in the interplay between chronic inflammation and the development of autoimmune diseases. While acute inflammation serves to protect against pathogens and promote tissue repair, persistence of this inflammatory state can precipitate various autoimmune conditions (Sundaresan et al., 2023; Xiang et al., 2023). In SjS, elevated levels of pro-inflammatory cytokines such as TNF-α, IL-6, IL-12, IL-19, IFNG, and markers of oxidative stress (OS) are indicative of the disease's pathological landscape. The inflammatory activity within SjS appears to correlate with increasing levels of interleukin-6 and interleukin-17, yet the underlying mechanisms driving this sustained inflammatory environment remain inadequately explored. Chronic inflammation is theorized to result from disrupted cellular homeostasis, persistent infections, and tissue damage (Benchabane et al., 2024).

Mitochondria play a critical role in maintaining cellular homeostasis and are essential for metabolic functions. They generate adenosine triphosphate (ATP) through oxidative phosphorylation while also producing reactive oxygen species (ROS). In cases of mitochondrial dysfunction, the production of ROS is significantly heightened, which may elucidate elevated saliva concentrations of 8-hydroxy-2'-deoxyguanosine and other oxidative stress biomarkers found in SjS patients. This connection between mitochondrial injury and autoimmunity suggests that mitochondrial dysfunction could exacerbate SjS pathogenesis through increased oxidative stress. Recent studies reaffirm the notion that mitochondrial alterations may be central to initiating inflammatory processes (Wang et al., 2020; Goh et al., 2021). For instance, Barrera et al. proposed that damaged mitochondria release danger signals, thereby triggering robust immune responses via pattern recognition receptors (Barrera et al., 2021). Further, aberrations in the interactions between mitochondria and the endoplasmic reticulum (ER) may amplify inflammatory signaling pathways.

Notably, recent investigations have demonstrated that alterations in mitochondrial ultrastructure, such as swelling in acini or duct cells from minor SG, correlate with disease severity. Unfortunately, the dynamic crosstalk between SG mitochondria and the immune microenvironment in SjS patients remains poorly understood (Leal and Martins, 2021; Giamogante et al., 2020).

Additionally, exploring the implications of mitochondrial dysfunction could provide valuable insights into other autoimmune diseases, where similar pathogenic mechanisms may be at play. Understanding these connections not only broadens the context of SjS but also emphasizes the necessity for targeted research in mitochondrial bioenergetics and immune interactions across autoimmune disorders.

Methodology

This review involved a comprehensive literature search conducted across multiple databases, including PubMed, Google Scholar, and Web of Science, focusing on studies published until May 2024. The keywords employed included “primary Sjögren’s syndrome,” “mitochondrial dysfunction,” “immune dysregulation,” and “oxidative stress.” Selected articles were evaluated for relevance, focusing on research that elucidated the connections between mitochondrial dynamics and immune responses in SjS.

We analyzed findings from gene expression studies that highlighted mitochondrial-related genes and their involvement in immune cell function within salivary glands. Data on mitochondrial dynamics, such as fission and fusion processes, were compiled from various studies to understand their role in immune dysregulation.

Concerning mitochondrial DNA (mtDNA) dynamics, we reviewed studies that measured mtDNA copy numbers in peripheral blood mononuclear cells (PBMCs) of SjS patients in comparison to controls, assessing the implications of oxidative stress on mitochondrial functionality. Furthermore, we gathered evidence from histological analyses that illustrated immune cell infiltration and mitochondrial ultrastructural alterations in salivary glands.

The synthesis of these findings was aimed at identifying key molecular pathways linking mitochondrial dysfunction with immune dysregulation, ultimately emphasizing potential therapeutic targets and the need for future research directions.

Mitochondrial Dysfunction and the Immune Microenvironment of Salivary Glands

There were found 4 differential expression genes related to mitochondria: cADPR1, UMP-CMPK2, TBC1 domain family member 9, and pyrroline-5-carboxylate reductase 1. In subjects with primary SjS, concentrations of the first three were particularly high. It is noteworthy that cADPR1 can promote the inflammation and autoimmune disorders (ShilinLi and Hu, 2024; Kim et al., 2021). UMP-CMPK2 is able to regulate activation of NALP3 inflammasome. TBC1 domain family member 9 seems to have a regulatory function in response to calcium signaling and contributes to the activation of TANK binding kinase 1. These data could explain the results obtained. Moreover, dynamics of mitochondria, functioning of respiratory chain (RC), and metabolic response to alterations in immune microenvironment from SG in

primary SjS were also assessed (Kim et al., 2021). The results indicated that there is a connection between disrupted function of mitochondria and inflammation in subjects with primary SjS. Hereby, preserving normal functioning of mitochondria could be a useful therapeutic approach for SjS (Li et al., 2022; Nesci et al., 2023).

The immune microenvironment role in regulating the development of primary SjS was extensively explored. The connection between the main kinds of immune cells infiltrating lesions of SG and gravity of primary SjS was studied. The immune cells infiltration of SG in SjS subjects was mostly studied through histological staining. New achievements in next-generation- (NGS) and RNA-sequencing and computing methods are allowing new ways to analyze these transcripts which contain information on immune cell constituents using accessible sets of immunospecific marker genes (Kotsifaki et al., 2023; Chew et al., 2012). In this study a CIBERSORT- and ssGSEA-based computing method was suggested for deconvolution of primary SjS cell kinds from previously obtained RNA-sequencing results. Consistently with earlier immunohistochemistry analyses, the degree of immune cell infiltration was shown to be in correlation with the severity of the disorder. T-helper cells, cytotoxic T lymphocytes and other T lymphocytes prevailed in mild lesions, whereas in progressed lesions B cells prevailed (Alonso-Moreda et al., 2023; Yu et al., 2019). Interestingly, a large number of plasma cells was detected in pulmonary lesions. M2 macrophages turned out to be in a direct correlation with the gravity of the disorder. It was previously believed that plasma cells and autoantigen-specific B lymphocytes are associated with focal lipid infiltration and contribute to inflammatory response. Moreover, alternatively activated M2 macrophages correlate with grave primary SjS lesions. Immune cells (ICs) also were proved to be associated with the 4 differential expression genes (Wang et al., 2022; Urzì et al., 2023).

Immune system response as well as metabolism in general involve mitochondria as an important player. Mt content remodeling involves a fission-fusion process which is mediated by a number of conserved proteins. Morphology of Mt as well as their distribution and functioning are modulated by Mt dynamics (Ren et al., 2020; Chen et al., 2023). Fission genes (CGI-135 protein, DRP1, mitochondrial fission factor) and fusion genes (mitofusin 1, mitofusin 2, mitochondrial dynamin-like GTPase) were found to be decreased in subjects with primary SjS which confirms the results previously obtained. Notably, those genes as well as Mt differentially expressed genes change during lymphocytic infiltration in SG. Another study demonstrated that genes in RC complexes were mostly reduced in subjects with SjS related to the extent of IC infiltration in SG. An inverse correlation was found between genes in RC complex and the expression of cADPR1 and TBC1 domain family member 9 (Ranieri et al., 2013; Hall et al., 2014). And conversely, a direct correlation was established for genes in RC complex and pyrroline-5-carboxylate reductase 1 in primary SjS. Changes in Mt dynamics appear to contribute to dysfunction of mitochondria, crucial for the development of primary SjS. The conversion of energy in Mt is carried out by 5 protein complexes and 2 major electron carriers: CoQ_{10} and soluble cyt C. When a cell is injured, molecules are released from Mt and start acting as damage-associated molecular patterns which are then recognized by ICs. Upon release from Mt, cyt C promotes a caspase cascade and stimulates apoptosis by enhancing the formation of the Apaf-1/procaspase-9 apoptosome (Xiao et al., 2020; Fuentes-Retamal et al., 2020).

Histological studies demonstrated that normally in SG the expression of cyt C is strong in ECs of ducts, which contain a large number of Mt. As the disorder progresses, the expression of cyt C reduces in injured cells, and the BCL2 apoptosis regulator expression does not change. Whereas, cyt C protein has been detected in the interstice with lymphocytic infiltration (Czegle et al., 2023; Balasubramanian et al., 2012). Furthermore, ITA of accessible RNA-sequencing data affirmed that BCL2 apoptosis regulator, BCL2-associated X protein and CASP3 expression were upregulated considerably in subjects with primary SjS with high level of infiltration. These discoveries lead to a conclusion that injured ECs elevate lymphocytic infiltration. Hereby, approaches designed to bypass apoptosis or control cell proliferation would still inevitably lead to primary SjS development (Saadi et al., 2019).

Cell physiology and metabolism and a large number of signaling pathways are integrated by Mt. Earlier various researches demonstrated that different ICs can use various metabolism programs to maintain functioning. In progression of primary SjS an immune response stimulates the activation of the ICs. Hereby, Mt metabolism may greatly affect the ICs functioning. It was established that cADPR1, UMP-CMPK2, TBC1 domain family member 9, and pyrroline-5-carboxylate reductase 1 are crucial for multiple metabolic pathways (Lin et al., 2022; Aderinto et al., 2023). This also might mean a significant crosstalk and overlapping. As was reported earlier, cADPR1 expression mainly occurs in ICs, and it accumulates in tissues affected by inflammation. Cytidylate kinase 2 is crucial for Mt DNA synthesis. Pyrroline-5-carboxylate reductase 1, in turn, is critical for synthesis of proline. There was established a connection between those hub genes and Mt metabolic pathway in GNG, tricarboxylic acid cycle, and lipid/pyruvate/amino/ketone acid metabolism in primary SjS. ICs require adequate concentrations of adenosine triphosphate to perform their functions. Typically, aerobic glycolysis is used by activated ICs to alter their metabolic state (Guaragnella et al., 2018). Interestingly, metabolism of aminoacids, particularly of GLN, was also found to by crucial for ICs growth and immune functions of Mt. The way by which changes in metabolism influence the

response of the immune system has become a promising new field of study in autoimmune disorders (Zheng et al., 2023).

It is noteworthy that this trial was limited by a number of circumstances. Firstly, sample size of subjects with primary SjS has not been large enough, and further research in bigger groups is required to affirm the results. Secondly, whereas the results are supported by transcriptome analysis, more research is required to extend our findings to clinical utility. In addition, there are various types of cells in SG, such as ECs, MECs, fibroblasts, vascular endothelial cells, ICs, hereby the genetic expression profile shows only the average of the contained cells. With advancement of NGS, next studies could involve integrated multiomic analyses with application of single-cell sequencing, transcriptome technologies, proteome technologies, and metabolomic technologies (Zheng et al., 2023).

Mitochondria-related genes and metabolic profiles of innate and acquired immune cells

Recent research showed infiltration in the ICs in labial salivary glands of SjS subjects and ultrastructure in Mt in innate and aquired ICs. Metabolic pathways associated with Mt in innate and aquired ICs have been studied with application of RNA sequencing. Aberrant Mt in SG ECs can function as damage-associated molecular patterns to promote the formation of immune microenvironment. Antinuclear antibody, anti-Ro52 and anti-Sjögren's syndrome type B antibodies were more often observed in SjS subjects, and serum concentrations of immunoglobulin G were elevated (Gong et al., 2023).

Primary SjS is the predominant autoimmune disorder that is featured by pain, chronic fatigue and dryness. Immunosuppressive drug Hydroxychloroquine failed to ameliorate SjS patients' condition when being applied for 24 weeks. Further trials are necessary to confirm the effectiveness and safety of Abatacept and other targeted T-lymphocyte ways of treatment. Targeted B-lymphocyte drugs, e.g., anti-BAFF Belimumab and Ianalumab, anti-B-lymphocyte antigen CD20 Rituximab, alleviate a number of symptoms and are now the optimal treatment approach for primary SjS (Zimmerman and Dang, 2019). Hereby, novel therapy targets targeting ICs and the mechanisms lying at the core of primary SjS pathogenesis require additional research. MSC therapy could become a new therapeutic approach for primary SjS, as mesenchymal stem cells therapy directs T lymphocytes to regulatory T cells and T helper type 2 cells and inhibits response of T helper 17 cells and T follicular helper cells (Park et al., 2020; Zaripova et al., 2023).

Epithelium of SG comprises ductal, acinar, progenitor and myoepithelial cells. As was shown earlier, in primary SjS mucous and serous acini undergo atrophy, and amount of mucus in labial salivary glands is reduced, which can be one of the causes of dry mouth. Salivary ECs are critical for regulation of the immune response since they release CD40 molecules, human leukocyte antigen class I, FasR and Proinflammatory chemokines and cytokines (Verstappen et al., 2021; Rocchi et al., 2021). During apoptosis of SG ECs, the expression of pro-inflammatory molecules and reactive oxygen species enhance the innate IC accumulation. The innate ICs are then recruited into damaged ECs of the labial salivary glands, and the RC activity and antiapoptotic effect are promoted, thus eliciting immune effect. Mt in ECs of SG have an aberrant structure with elevated infiltration of lymphocytes [45,46](Barrera et al., 2016; Pontarini et al., 2021). Multiple trials investigated the MT metabolite role, particularly role of cyt C, mitochondrial DNA, and reactive oxygen species, in the immune microenvironment in case of ECs damage in SG in patients with primary SjS. A transmission electron microscopy analysis demonstrated presence of swelled Mt as well as aggregation of autophagosomes in ductal cells and lymphocytes of labial salivary glands of primary SjS subjects. A number of studies demonstrated that presence of swelled Mt is connected to the impaired regulation of reactive oxygen species and the aberrant ion channels on Mt membrane, mostly Ca^{2+} (Vacca et al., 2006; Ellzey et al., 2023). A correlation between Mt swelling metabolic pathways, e.g., Ca^{2+} homeostasis, reactive oxygen species and GSH metabolism with the ICs was not established. Thus, we hypothesize that aberrant Mt functioning in glands can cause apoptosis and enhance aggregation of ICs. Whereas function of the majority of lymphocytes is not impaired in primary SjS, injured Mt in the ICs can recruit more ICs for infiltration, leading to gradual destruction of the SGs (Forrester et al., 2018; Checa and Aran, 2020).

OXPHOS and glycolysis are the main energy sources. Elevated OXPHOS frequently mean activation of cells and alterations in their functioning. The innate ICs and MT were reported to be connected by OXPHOS and RC complexes. Innate ICs showed major oxidative respiratory function. RC complexes are crucial for the IC differentiation. Blocking complex 1 or 3 may suppress the differentiation of naive T_h cells into effector T_h cells. Complex 2 is crucial for OXPHOS and tricarboxylic acid cycle. Complex 2 impairments may increase sensitivity of intestinal ECs to cytotoxicity mediated by T-lymphocytes, thus enhancing T-lymphocyte-mediated diseases (Mohammadnezhad et al., 2022; Xu et al., 2020).

M1 macrophages, monocytes and other innate ICs generate adenosine triphosphate by glycolysis rather that the tricarboxylic acid cycle. Glycolysis is critical for M1 macrophages, while OXPHOS is crucial for M2 macrophages. Although, both M1 and M2 macrophages have shown elevated OXPHOS. In primary SjS subjects, M2 macrophages have been less abundant in labial salivary glands where M1 macrophages predominated. Immunohistochemistry analysis has confirmed these findings. Single-cell RNA-seq demonstrated an upregulated gene expression

in OXPHOS module in mitotic germinal center B cells (Viola et al., 2019; Sun et al., 2022). Another research revealed that in an autoimmune process regulatory T cells disrupt Mt OXPHOS. A strong connection between the number of ICs and the tricarboxylic acid-related gene expression was not established. Although, the was found a direct correlation of the number of ICs and the RC complex activity. This discovery demonstrates that those ICs activation does not require tricarboxylic acid cycle for energy. Moreover, metabolism of reactive oxygen species is in direct correlation with the excessive number of ICs. Mt reactive oxygen species is a major player in immune regulating signal transduction inside cell. Although, overproduction of reactive oxygen species can cause cell injury thus contributing to development of immune diseases (Yarosz and Chang, 2018). E.g., diminished reactive oxygen species can lower the AP ability of plasmacytoid dendritic cells considerably. Hereby, changes in OXPHOS and reactive oxygen species-related signaling pathways are major characteristics of ICs in primary SjS subjects. The Mt metabolic functioning of ICs in the immune microenvironment alters, thus affecting the response of the immune system, and aberrant metabolic profiles may recruit more ICs, completing the circle. Thereby, preserving Mt function and interfering with metabolism could turn out to be a useful therapeutic approach for treating primary SjS (Paardekooper et al., 2019).

PGC-1alpha is an important constituent of Mt genesis and energetic adaptation. It is a Mt-associated protein responsible for the ICs executive functioning. Differentiation of monocytes into dendritic cells usually happens simultaneously with upregulated expression of PGC-1alpha. Its expression might facilitate the central memory $CD8^+$ T cells formation to sustain metabolic stability and perform immune function. Although, the high number of ICs was found to be in inverse correlation with PPARGC1A expression. We speculate that Mt genesis is impaired in dominant cells in SG due to infiltrated ICs, which leads to a reduction in PPARGC1A expression. The importance of PGC-1alpha in primary SjS is yet to be explored (Qian et al., 2024; Souza et al., 2023).

Numerous studies have identified the connection between ICs and Mt, as well as their metabolic functioning in systemic lupus erythematosus and aging. It was also discovered that in primary SjS subjects the Mt-associated metabolic pathways activity is changed. Due to restrictions of bulk RNA-seq, just general variations in the gland immune microenvironment and Mt-associated metabolic pathways have been detected. More progressive methods, such as single-cell RNA-seq and spatial transcriptomics are more suitable for studying the particular metabolic features of different types of cells. Furthermore, in this study a part of healthy group of individuals and subjects with OSADs had positive anti-Ro52 results. To prevent such inaccuracies, future trials must involve a larger number of control cases (Wang et al., 2022; Corona-Meraz et al., 2024).

Mitochondrial DNA copy numbers

Impairment of the Mt function along with Mt fission and fusion disorders are promoted by OS. Such changes are characteristic of the development of a number of diseases. Recent research revealed the importance of oxidative stress impact on the primary SjS pathogenesis. In subjects with primary SjS oxidative stress tends to be elevated. Moreover, a TEM examination indicated changes in Mt of ECs in SG (Blagov et al., 2022).

While mitochondrial DNA copy numbers may be modified as a response to different factors such as elevated oxidative stress, it has been agreed to assess the mitochondrial DNA copy numbers in a group of primary SjS subjects. This study demonstrated that the average amount of mitochondrial DNA copies has been considerably reduced in peripheral blood mononuclear cells of SjS subjects in comparison to the control group. These findings are consistent with the theory that elevated oxidative stress can promote changes in the amount of Mt and their mitochondrial DNA copies number (Zhang et al., 2022; De Benedittis et al., 2022). As Mt fission and fusion are of great importance in sustaining the number of Mt which can be changed upon high oxidative stress, variability in the expression of genes most frequently implicated in Mt dynamics has been studied. For this study two groups of subjects have been formed: 27 individuals with Sjögren's syndrome and 15 control cases. SjS individuals demonstrated elevated levels of mitochondrial DNA expression for 3 genes. The increase in mitochondrial fission factor and mitochondrial transcription factor A was statistically significant (Green et al., 2022).

The mitochondrial fission factor is very important for Mt recruitment of dynamin-related protein. Its excessive expression can cause Mt fragmentation, while its reduction promotes Mt elongation. Moreover, Mt fission is crucial in case of strong CES since its function involves clearing of injured Mt. Multiple trials have proved that oxGSH (Glutathione disulfide) mitofusin-dependently enhances Mt hyperfusion. It might be concluded that expression elevates in response to the increase in oxidative stress in individuals with primary SjS (Kornfeld et al., 2018).

Mitofusin 1 encodes for a trans-membrane GTPase and takes part in the regulation of healthy Mt and reduction of reactive oxygen species. It has been indicated that mitofusin 1 expression elevates in primary SjS subjects in comparison to the control group, however, the elevation is not statistically significant. We could hypothesize that mitofusin 1 elevation is explained by its capacity to reduce reactive oxygen species [66,67](Qi et al., 2016; Buntenbroich et al., 2023).

Considering these findings, we can suppose that oxidative stress in subjects with primary SjS leads to impairment of Mt fission and fusion due to upregulated expression of mitochondrial fission

factor and mitofusin 1, which in turn causes Mt fragmentation which may promote changes in Mt functioning. Barrera and colleagues have verified these discoveries in ECs of SG (Stein et al., 2021).

Although, contrary to these results, another research discovered that mitochondrial fission factor and mitofusin 1 are reduced in LSG of Chinese subjects with SjS divided into subgroups by disease stage. These inconsistent results might be explained by the differences in the examinations conducted (Serasinghe and Chipuk, 2017).

Furthermore, the expression of mitochondrial transcription factor A, which is an essential Mt TF that controls the mitochondrial DNA copies number, was elevated in SjS subjects. Mt transcription factor A also has a protective function against mitochondrial DNA injury from reactive oxygen species. Actually, mitochondrial transcription factor A prevents amyloid beta-triggered oxidative injure in primitive nerve cells and astrocytes. In fact, TFAM plays a protective role against amyloid beta-induced oxidative damage in human NBs and astroglia. Moreover, it was reported that excessive expression of mitochondrial transcription factor A can inhibit Mt gene expression and alter Mt ultrastructure. Hereby, one can conclude that mitochondrial transcription factor A in SjS subjects can elevate to repair mitochondrial DNA and to defend it against OS (Kang et al., 2018).

Given the abnormal expression of mitochondrial fission factor and Mt transcription factor A in peripheral blood mononuclear cells of primary SjS individuals, a receiver operating characteristic curve was used to assess these genes' ability to differentiate SjS individuals from the controls. It was indicated that mitochondrial fission factor and Mt transcription factor A expression demonstrated significant sensitivity in discriminating SjS individuals from the controls. Although, these findings require further validation in bigger groups (Li et al., 2022; Seo et al., 2020).

This research was one of the earliest to compare mitochondrial DNA copies in PBMCs of SjS subjects with the control group. Nonetheless, these results are conflicting with previous results, which indicated an elevation in mitochondrial DNA copies in a Chinese SjS cohort of women subjects. Due to contradicting results, this evaluation needs to be continued in bigger groups in other populations (Ganel et al., 2021).

Available ways of research have their limitations: a lack of material limits the measuring of OS markers in SjS subjects, as well as a lack of functional researches necessary to discover molecular mechanisms lying at the core of these processes. Another limitation is the inability to conduct a correlation study of mitochondrial DNA copy number and the expression of mitofusin 1, mitochondrial fission factor, and mitochondrial transcription factor A, since the second blood draw in the SjS cohort was carried out later, particularly used for experiments with RNA. Furthermore, more evidence is needed to explain whether the Mt remodeling is itself the impact of primary SjS or it is a factor which facilitates the development of the disorder (Sidarala et al., 2022).

Finally, these discoveries demonstrate quantitative changes in mitochondrial DNA in subjects with primary SjS. These findings indicate that oxidative stress and Mt function impairment might both play a role in Sjogren's syndrome development. These findings could affirm the importance of Mt remodeling and oxidative stress in the development of primary SjS if they are validated by larger cohort trials and by functional studies (Mikhed et al., 2015; Pagano et al., 2013).

Conclusion

In conclusion, the multifaceted mechanisms linking mitochondrial dysfunction to the immune dysregulation in primary Sjogren's syndrome (SjS) present a compelling area for further exploration and clinical translation. The growing body of evidence suggests that mitochondrial dysfunction, characterized by altered gene expression, dynamics, and metabolic profiles, contributes to the chronic inflammation and immune cell dysregulation observed in salivary glands of SjS patients.

The intricate interplay between mitochondrial dysfunction, oxidative stress, and immune cell activity underscores the need for continued research to elucidate the precise molecular pathways and identify potential therapeutic targets. The potential impact of targeting mitochondrial function as a therapeutic approach holds promise in the management of this complex autoimmune disorder. However, additional large-scale and multi-omic studies are warranted to validate and expand upon the findings presented in this review. Integration of advanced genomics, transcriptomics, proteomics, and metabolomics techniques, including single-cell sequencing, would offer a more comprehensive understanding of the intricate crosstalk between mitochondrial dysfunction and the immune microenvironment in primary SjS.

Ultimately, a deeper understanding of the role of mitochondria in the pathogenesis of SjS may pave the way for the development of novel treatment strategies that target mitochondrial function and immune dysregulation, ultimately improving clinical outcomes for individuals affected by this challenging autoimmune condition.

Author contributions

Original draft preparation was carried out by A.V.P. The manuscript was reviewed and edited by N.A.O., V.N.S., T.I.K., I.A.S., D.F.B., A.N.O., and A.V.C. All authors have reviewed and approved the final version of the manuscript for publication.

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Competing financial interests

The authors have no conflict of interest.

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