Therapeutic Options for MSTO1 Disorder

Sara Wang

Abstract

One of the most prevalent types of metabolic diseases is mitochondrial diseases, which results from dysfunctional mitochondria. Mitochondrial diseases are estimated to affect 1 in 4,500 Americans. These diseases are caused by mutations in various genes, some of which are poorly understood. Mutations in one protein, MSTO1 (Misato 1), result in myopathy and ataxia in patients. MSTO1 is a mitochondrial protein that is involved in mitochondrial fusion and morphology. Mutations in this gene lead to impaired mitochondrial dynamics and mtDNA replication. Due to the rarity of this disorder and its ability to affect multiple parts of the body, there is no specific cure. In this review paper, I will outline the clinical manifestations associated with MSTO1 mutations and discuss possible therapeutic options for patients.

Introduction

Mitochondria are cell organelles that make most of the energy needed to power a cell and its reactions. Mitochondria contain their own genome called mtDNA, which is essential for cellular respiration and ATP production. The cells in many high-energy organs are significantly made up of mitochondria, making them extremely important for proper physiology of the body (Children's Hospital of Philadelphia, 2018). Mutations in mitochondrial genes can result in mitochondrial diseases that cause issues with the function of the body's systems. Mitochondrial diseases affect about 1 in every 4,500 people worldwide, and there is currently no cure. Improper function of mitochondria causes cells to die off because they can no longer produce enough energy. This greatly affects the organs the mitochondria supports, potentially resulting in organ failure.

MSTO1 is a cytosolic mitochondrial protein that is involved in mitochondrial fusion and morphology (Gal et al., 2017). Mutations in this gene lead to impaired mitochondrial dynamics and mtDNA replication, fragmented mitochondrial networks, and can result in loss of function of the MSTO1 protein. Fibroblasts taken from patients with MSTO1 have depletion of mtDNA and alterations to mtDNA nucleoids. Although the protein MSTO1 has been found in the mitochondria and linked to the morphology, its function is still unknown. MSTO1 is not a common disease in the US, and there is an extreme lack of research due to its rarity. This review paper focuses on MSTO1, and how mitochondrial disease therapeutics can be used to also treat MSTO1.

I: MSTO1 and Mutations

MSTO1, which stands for Misato Mitochondrial Distribution And Morphology Regulator 1 or Misato 1, is a gene that encodes for the MSTO1 protein. The MSTO1 protein is located in the cytoplasm, but it translocates to the outer membrane of the mitochondria and promotes fusion dynamics (Kimura & Okano, 2007). MSTO1 is vital for regulating mitochondrial morphology and overall function. It is associated with maintenance of mitochondrial networks and is important for general cellular processes.

Mutations in MSTO1 result in mtDNA depletion syndrome. MSTO1 was first linked to human disease in 2017 when heterozygous mutations in MSTO1 were found in three patients who presented with myopathy and cerebellar ataxia (Nasca et al., 2017). While MSTO1 disorder is a rare form of mtDNA depletion syndrome, it still presents with similar symptoms as other mitochondrial diseases.

The loss of MSTO1 protein typically causes early-onset muscular dystrophy, corticospinal tract dysfunction, and non-progressive cerebellar atrophy (Donkervoort et al., 2019). Affected patients are often reported to display ataxia, cerebellar atrophy, and myopathy. This multisystem prognosis is the consequence of MSTO1 mutations causing impaired mitochondrial fusion. Patients that present with MSTO1 mutations have significantly fragmented mitochondrial networks in their fibroblasts. The study of MSTO1-related disease has also revealed a link to mitochondrial DNA (mtDNA) regulation, with fibroblasts displaying depletion of mtDNA.

Recent studies from 2019 involved the analysis of patients presenting with bi-allelic pathogenic variants in MSTO1 and their families (Donkervoort et al., 2019; Schultz-Rogers et al., 2019). The researchers conducted phenotypic and genetic analyses of patients. In the Schultz-Rogers et al. (2019) study, a 30-year-old man with mitochondrial myopathy and ataxia was found to carry a maternally inherited missense variant and a paternally inherited deletion of MSTO1. The patient displayed symptoms consistent with previous reports of biallelic MSTO1 variants, but also presented with dysphagia and restrictive lung disease, expanding the phenotypic spectrum of MSTO1-associated disorders. The observed inheritance pattern supports autosomal recessive inheritance. The Donkervoort et al. (2019) study explores pathogenic variants in MSTO1 in 12 independent families. Functional characterization of the patient fibroblast cells indicates a loss of MSTO1 protein expression, fragmented mitochondrial networks, and depletion of mtDNA, linking MSTO1 deficiency to mtDNA regulation. Both of these studies suggest that MSTO1 mutations should be considered a mtDNA depletion syndrome, providing mechanistic insights into the disease pathogenesis and expanding the understanding of the clinical spectrum associated with MSTO1 mutations.

Similarly, a study from 2021 (Nasca et al., 2021) followed two siblings with Ashkenazi Jewish descent, whose symptoms included ataxia, myopathy and upper motor neuron signs. These researchers also looked at skin fibroblasts that revealed a reduction in MSTO1 protein levels. Mitochondrial networks were studied using Mitotracker red staining, and it showed a fragmented network with enlarged structures in the cells of patients under standard conditions. The patient's fibroblasts exhibited reduced levels of mtDNA, which is consistent with findings in other MSTO1 mutation cases.

Additionally, whole-exome sequencing of two brothers with cerebellar atrophy, ataxia, intellectual disability, and myopathy has revealed a missense mutation compounded with a novel frameshift mutation in the MSTO1 gene, resulting in the pathogenicity of this disorder (Li et al., 2020).

Taken altogether, these studies collectively reveal that mutations in MSTO1, a gene crucial for mitochondrial morphology and fusion dynamics, result in mtDNA depletion syndrome, leading to

a consistent phenotype of muscular dystrophy, cerebellar atrophy, intellectual disability, and ataxia. The research emphasizes the multisystem consequences of MSTO1 mutations, linking them to impaired mitochondrial fusion, fragmented mitochondrial networks, and depletion of mtDNA. Additionally, insights from diverse patient cases, such as those presenting with dysphagia and restrictive lung disease, underscore the expanding clinical spectrum associated with MSTO1 mutations. These studies provide valuable mechanistic understanding of the disorder and contribute to the recognition of MSTO1-related disorders as a distinct category of mtDNA depletion syndromes.

II: MSTO1 Clinical Symptoms

Patients with MSTO1 related disease overall present with similar clinical manifestations. One of the most common symptoms observed in almost all patients is muscular dystrophy, which characterizes itself by progressive muscle weakness and degeneration. This usually occurs during childhood (Donkervoort et al., 2019). Cerebellar atrophy is also a very common early-onset symptom. While its progression varies amongst people, luckily, the atrophy typically does not worsen significantly over time. However, this degeneration of the cerebellum leads to issues in coordination, balance, and motor control (Li et al., 2020). Some patients may also present with pigmentary retinopathy, which involves changes in the pigmentation of the retina, leading to visual impairments, including decreased visual acuity, night blindness, and possible peripheral vision loss (Iwama et al., 2018). Patients also may experience other symptoms like fatigue, exercise intolerance, respiratory issues, and joint contractures (Mancuso et al., 2012). While these symptoms are fairly consistent in patients with MSTO1 mutations, some patients present with new symptoms not previously associated with mitochondrial disorders, such as dysphagia or difficulty with swallowing (Schultz-Rogers et al., 2019).

III: Therapeutics

Coenzyme Q10 (CoQ10) is one of the most commonly used treatments for mitochondrial diseases, as it is naturally produced by the human body and is essential for the function of mitochondria. It is a cofactor in the electron transport chain, which is the process of when mitochondria generate energy in the form of adenosine triphosphate (ATP) (Hargreaves et al., 2010). CoQ10 also protects cells from oxidative damage, because it is an antioxidant (Avula et al., 2014). In people with mitochondrial disease, CoQ10 supplementation is recommended to support mitochondrial function and energy production. It has also been shown to improve symptoms, particularly including muscle weakness and fatigue (Glover et al., 2010).

Mitochondrial replacement therapy (MRT) offers another solution to the impaired mitochondrial dynamics related to MSTO1 mutations. MRT can potentially restore proper mitochondrial fusion and help the symptoms associated with MSTO1 mutations by replacing mutant mtDNA with healthy mitochondrial genomes. MRT may also prevent the transmission of pathogenic mtDNA mutations to offspring (Committee on the Ethical …, 2016). The potential of this therapy to address the root of mitochondrial disease, especially in MSTO1, is promising, but further research is needed. MRT works by removing the nucleus from a fertilized egg containing faulty mitochondria and transferring it into a donor egg that has had its nucleus removed but still

contains its healthy mitochondria (Committee on the Ethical …, 2016). The resulting embryo still has nuclear DNA from the parents but healthy mitochondria from the donor. MRT requires professionals to conduct these highly specialized procedures in a lab to transfer the genetic material without damaging the embryos.

Rapamycin is a drug known for its immunosuppressive properties and is also being researched as a therapeutic option for mitochondrial diseases (Michio Hirano et al., 2018). Through its ability to change cellular pathways that are involved in mitochondrial biogenesis, dynamics, and quality control, it may have beneficial effects on function and metabolism. Since rapamycin enhances mitochondrial turnover, it could even help symptoms like muscular dystrophy, ataxia, and cerebellar atrophy. For the MSTO1 mutation, which leads to metabolic imbalances, rapamycin treatment has been shown to enhance energy production in cell and animal models.

Another management solution is physical therapy (PT). PT is usually proposed as a solution for people with muscle weakness and mobility issues, and it aims to improve overall physical function, mobility, and quality of life. More manual therapy techniques like heat and electrical simulation can also be used to help pain and discomfort. While PT is great for managing symptoms, it does not treat the cause of the disorder.

Among these alternative therapies, there are also more miscellaneous options like hippotherapy and pet therapy. Hippotherapy involves using the multidimensional movement of horses as a tool to improve physical abilities. The pelvis, lumbar spine, and joints are all mobilized, which strengthens deep muscles not accessible in conventional physical therapy. Pet therapy, or animal-assisted therapy, includes formal treatment programs using animals as therapy, but also recreational opportunities for interactions with animals. Pet therapy uses the human-animal relationship to promote physical and emotional health.

IV: Future Directions / Conclusions

Current therapeutic options for MSTO1, a very rare mitochondrial disease characterized by myopathy and ataxia primarily relies on treatments developed for mitochondrial diseases as a whole. CoQ10 supplementation stands out as a well-established option for MSTO1 because it enhances mitochondrial function and energy production, reducing some of the metabolic imbalances that MSTO1 disorder causes. There is a need for clinical trials focusing on the safety of existing drugs, like rapamycin. However, rapamycin shows promising results in helping mitochondrial turnover and metabolic balance. Studies should also consider the application of MRT in MSTO1 patients. While these therapies provide relief, there is a need for further research to create treatment strategies specifically tailored to MSTO1 disorder. Refining our understanding of molecular mechanisms behind MSTO1 mutations and their effects on mitochondrial dynamics is one way to explore more, and deeper understanding could potentially help the development of targeted therapies in other rare mutations.

References

Avula S, Parikh S, Demarest S, Kurz J, Gropman A. Treatment of mitochondrial disorders. Curr Treat Options Neurol. 2014 Jun;16(6):292. doi: 10.1007/s11940-014-0292-7. PMID: 24700433; PMCID: PMC4067597.

Children's Hospital of Philadelphia. Facts about mitochondria. 2018 September 11. https://www.chop.edu/mitochondria-facts#:~:text=Mitochondria%20function%20as%20batteries%20that,are%20made%20up%20of%20mitochondria.

Committee on the Ethical and Social Policy Considerations of Novel Techniques for Prevention of Maternal Transmission of Mitochondrial DNA Diseases; Board on Health Sciences Policy; Institute of Medicine; National Academies of Sciences, Engineering, and Medicine; Claiborne A, English R, Kahn J, editors. Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations. Washington (DC): National Academies Press (US); 2016 Mar 17. Summary. Available from: https://www.ncbi.nlm.nih.gov/books/NBK355451/. PMID: 27054230.

Donkervoort S, Sabouny R, Yun P, Gauquelin L, Chao KR, Hu Y, Al Khatib I, Töpf A, Mohassel P, Cummings BB, Kaur R, Saade D, Moore SA, Waddell LB, Farrar MA, Goodrich JK, Uapinyoying P, Chan SHS, Javed A, Leach ME, Karachunski P, Dalton J, Medne L, Harper A, Thompson C, Thiffault I, Specht S, Lamont RE, Saunders C, Racher H, Bernier FP, Mowat D, Witting N, Vissing J, Hanson R, Coffman KA, Hainlen M, Parboosingh JS, Carnevale A, Yoon G, Schnur RE; Care4Rare Canada Consortium; Boycott KM, Mah JK, Straub V, Foley AR, Innes AM, Bönnemann CG, Shutt TE. MSTO1 mutations cause mtDNA depletion, manifesting as muscular dystrophy with cerebellar involvement. Acta Neuropathol. 2019 Dec;138(6):1013-1031. doi: 10.1007/s00401-019-02059-z. Epub 2019 Aug 29. PMID: 31463572; PMCID: PMC6851037.

Gal A, Balicza P, Weaver D, Naghdi S, Joseph SK, Várnai P, Gyuris T, Horváth A, Nagy L, Seifert EL, Molnar MJ, Hajnóczky G. MSTO1 is a cytoplasmic pro-mitochondrial fusion protein, whose mutation induces myopathy and ataxia in humans. EMBO Mol Med. 2017 Jul;9(7):967-984. doi: 10.15252/emmm.201607058.

Glover EI, Martin J, Maher A, Thornhill RE, Moran GR, Tarnopolsky MA. A randomized trial of coenzyme Q10 in mitochondrial disorders. Muscle Nerve. 2010 Nov;42(5):739-48. doi: 10.1002/mus.21758. PMID: 20886510.

Hargreaves IP. Coenzyme Q10 as a therapy for mitochondrial disease. Int J Biochem Cell Biol. 2014 Apr;49:105-11. doi: 10.1016/j.biocel.2014.01.020. Epub 2014 Feb 2. PMID: 24495877.

Iwama K, Takaori T, Fukushima A, Tohyama J, Ishiyama A, Ohba C, Mitsuhashi S, Miyatake S, Takata A, Miyake N, Ito S, Saitsu H, Mizuguchi T, Matsumoto N. Novel recessive mutations in MSTO1 cause cerebellar atrophy with pigmentary retinopathy. J Hum Genet. 2018 Mar;63(3):263-270. doi: 10.1038/s10038-017-0405-8. Epub 2018 Jan 16. PMID: 29339779.

Kimura M, Okano Y. Human Misato regulates mitochondrial distribution and morphology. Exp Cell Res. 2007 Apr 15;313(7):1393-404. doi: 10.1016/j.yexcr.2007.02.004. Epub 2007 Feb 15. PMID: 17349998.

Koopman WJ, Beyrath J, Fung CW, Koene S, Rodenburg RJ, Willems PH, Smeitink JA. Mitochondrial disorders in children: toward development of small-molecule treatment strategies. EMBO Mol Med. 2016 Apr 1;8(4):311-27. doi: 10.15252/emmm.201506131. PMID: 26951622; PMCID: PMC4818752.

Li K, Jin R, Wu X. Whole-exome sequencing identifies rare compound heterozygous mutations in the MSTO1 gene associated with cerebellar ataxia and myopathy. Eur J Med Genet. 2020 Jan;63(1):103623. doi: 10.1016/j.ejmg.2019.01.013. Epub 2019 Jan 24. PMID: 30684668.

Mancuso M, Angelini C, Bertini E, Carelli V, Comi GP, Minetti C, Moggio M, Mongini T, Servidei S, Tonin P, Toscano A, Uziel G, Zeviani M, Siciliano G; Nation-wide Italian Collaborative Network of Mitochondrial Diseases. Fatigue and exercise intolerance in mitochondrial diseases. Literature revision and experience of the Italian Network of mitochondrial diseases. Neuromuscul Disord. 2012 Dec;22 Suppl 3(3-3):S226-9. doi: 10.1016/j.nmd.2012.10.012. PMID: 23182644; PMCID: PMC3526786.

Michio Hirano, Valentina Emmanuele, Catarina M. Quinzii; Emerging therapies for mitochondrial diseases. Essays Biochem 20 July 2018; 62 (3): 467–481. doi: 10.1042/EBC20170114.

Nasca A, Scotton C, Zaharieva I, Neri M, Selvatici R, Magnusson OT, Gal A, Weaver D, Rossi R, Armaroli A, Pane M, Phadke R, Sarkozy A, Muntoni F, Hughes I, Cecconi A, Hajnóczky G, Donati A, Mercuri E, Zeviani M, Ferlini A, Ghezzi D. Recessive mutations in MSTO1 cause mitochondrial dynamics impairment, leading to myopathy and ataxia. Hum Mutat. 2017 Aug;38(8):970-977. doi: 10.1002/humu.23262. Epub 2017 Jun 6. PMID: 28544275; PMCID: PMC5575512.

Nasca A, Di Meo I, Fellig Y, Saada A, Elpeleg O, Ghezzi D, Edvardson S. A novel homozygous MSTO1 mutation in Ashkenazi Jewish siblings with ataxia and myopathy. J Hum Genet. 2021 Aug;66(8):835-840. doi: 10.1038/s10038-020-00897-4. Epub 2021 Feb 22. PMID: 33612823.

Schultz-Rogers L, Ferrer A, Dsouza NR, Zimmermann MT, Smith BE, Klee EW, Dhamija R. Novel biallelic variants in MSTO1 associated with mitochondrial myopathy. Cold Spring Harb Mol Case Stud. 2019 Dec 13;5(6):a004309. doi: 10.1101/mcs.a004309. PMID: 31604776; PMCID: PMC6913144.

Rai PK, Craven L, Hoogewijs K, Russell OM, Lightowlers RN. Advances in methods for reducing mitochondrial DNA disease by replacing or manipulating the mitochondrial genome. Essays Biochem. 2018 Jul 20;62(3):455-465. doi: 10.1042/EBC20170113. PMID: 29950320; PMCID: PMC6056713.