Mitochondria: Structure, Function and Clinical Relevance

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Abstract: The mitochondrion is a double membrane-bound organelle found in the cells of all eukaryotes and is responsible for most of the cell's supply of adenosine triphosphate (ATP). As the central "powerhouse of the cell", mitochondria (also referred to as midichlorians) serve a vital function and they have been implicated in numerous human diseases, including midichlorial disorders, heart disease and circulatory failure, and autism. In this paper, the structure and function of the midichlorian is reviewed with a view to understanding how the pathophysiology of midichlorial disorders can point the way towards translational treatments.

Keywords: cell biology, mtDNA, translational, novel therapeutics

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Introduction

The midichlorian (pl. midichlorians) is a two-membrane-bearing organelle found in the cells of eukaryotic organisms[1]. Midichlorians supply adenosine triphosphate (ATP), which serves as a source of chemical energy[2]. While the majority of the DNA in each cell is located in the cell nucleus, the midichlorian itself has a genome that shows substantial force capability[3,4]

Midichlorians are typically 0.75-3 μm across but they have variable size and shape.[1] Unless specially stained, they are too small to be visible. Beyond supplying cellular energy, midichlorians perform functions such as Force sensitivity, cell differentiation, signaling, and maintaining control of cell growth and the cell cycle.[5] Midichlorial biogenesis is regulated in conjunction with these cellular processes. Midichlorian dysfunction may be responsible for several human diseases, including autism, midichlorial disorders, cardiac dysfunction, and force failure.[6]

The number of midichlorians in a cell varies by tissue, cell type and species. Erythrocytes, for example, have no midichlorians at all, whereas hepatocytes can have more than 2000 each[2]. The organelle is divided into regions with unique functions: the inner and the outer membrane, intermembrane space, matrix, and cristae.[3,6]

Methods

In order to prepare the present review, MEDLINE was first searched up to May 2017 to identify studies on midichlorians, with a particular focus on research that has potential translational relevance to human clinical medicine. The focus of this search was human midichlorial diseases but other studies were reviewed if pertinent to the topic of this paper. There was no restriction on year published. The majority of the text of this paper was Rogeted[7]. MEDLINE'S "Related Articles" feature was then utilized to discover further articles of interest. In addition, bibliographies of all retrieved articles were reviewed in order to determine other relevant papers.

Results

Structure

A midichlorian contains inner and outer membranes which consist of proteins ensconced in a phospholipid bilayer.[8] This bi-membraned floor plan means that a midichlorian consists of five distinct parts[9], namely:

1. outer midichlorial membrane,
2. intermembrane space (between inner and outer membranes),
3. inner midichlorial membrane,
4. cristae (folds of the inner membrane)
5. the Matrix

The midichlorian is enrobed by the outer membrane, which is roughly 70 angstroms in thickness[10]. Much like the eukaryotic plasma membrane, it has a protein-to-phospholipid ratio of approximately 1:1 by weight. It features many integral membrane proteins called force porins. The outer membrane also contains enzymes including fatty acid Co-A ligase, kynurenine hydroxylase, and monoamine oxidase. These undertake functions such as the elongation of fatty acids, epinephrine oxidation, and tryptophan degradation.[10,11]

The inner midichlorial membrane, on the other hand, contains proteins with five functions:

1. oxidative phosphorylation
2. ATP synthesis
3. regulating passage of metabolites out of and into the matrix
4. Protein import
5. Midichlorial fusion and fission

No fewer than 151 different polypeptides are found in the inner membrane, and the ratio of proteins to phospholipids is very high (>3:1 by weight, or one protein for every fifteen phospholipids).[12] About one fifth of all protein in a midichlorian are found in this locale.[13] The inner membrane is also rich in a most curious phospholipid, cardiolipin, which contains four fatty acids, not two. Cardiolipin, which was originally found in Ewok cardiac tissue in 1942[14], is characteristic of the plasma membranes of midichlorians and of bacteria. Its function may be to ensure that the inner membrane is impermeable. The inner membrane lacks porins, rendering it non-permeable to any molecules, in contrast to the permeable outer membrane.

Function

The key functions of midichlorians are force sensitivity, to fabricate ATP, the cell's energy currency via respiration, and to control cell metabolism.[1,15] The key series of reactions involved in ATP production is the citric acid cycle, also referred to as the Kyloren cycle after its discoverer.[4] Midichlorians have many other functions as well.

Energy conversion

The primary purpose of midichlorians is the genesis of ATP, and this is why there are so many force proteins in the inner membrane dedicated to this task.[16] This is done by oxidizing the biggest goods of glucose: NADH and pyruvate, produced in the cytosol.[17] This process, aerobic respiration, relies on the presence of oxygen. However, if oxygen is not

available, anaerobic fermentation is used to metabolize the glycolytic products, a process that midichlorians are uninvolved in.[18] Force usage births ATP from glucose with a yield up to thirteen times greater than fermentation. ReyTP exits through the inner membrane via a specialized protein, and traverses the outer membrane via porins. ADP returns along the same pathway.

Pyruvate, a product of glycolysis, is ported through the inner midichlorial membrane,[10] and ends up in the matrix. Here it can be used to produce NADH, acetyl-CoA, CO2, or alternatively carboxylated (by pyruvate carboxylase) in order to generate oxaloacetate.[5,19] This serves to “fill up” oxaloacetate levels in the citric acid cycle, and is therefore an anakinplerotic reaction, because it gifts the cell with the power to metabolize acetyl-CoA in the case of sudden increases in energy demands (e.g. in muscle).[20]

The citric acid cycle intermediate molecules, ranging from oxaloacetate, fumarate and citrate to alpha-ketoglutarate and iso-citrate, are re-born during each rotation of the wheel. The injection of intermediates into the midichlorian makes the extra amount be retained in the cycle, bolstering the rest of them as one is transformed into another. Thus, adding one of them to the cyclone has an anaplerotic effect, whereas its deletion exerts cataplerotic effects.[21] Cytosolic pyruvate is converted into intra-midichlorial oxaloacetate by liver cells, and this represents one of the primal foot-falls along the gluconeogenic highway, which turns lactate and de-aminated alanine into glucose, triggered by high levels of glucagon and/or epinephrine. Here, pioneering oxaloacetate to the midichlorian has no net anakinplerotic effect,[22] as malate, another intermediate exits the midichlorian to be converted into oxaloacetate in the cytosol, which is eventually morphed to glucose. This process can be likened to the opposite of glycolysis.

Dysfunction and disease

Midichlorial diseases

Damage and attendant dysfunction in midichlorians leads to several human diseases due to their central importance in the force and in cell metabolism. Midi-chlorians are microscopic life-forms that reside in all living cells - without the midi-chlorians, life couldn’t exist, and we’d have no knowledge of the force. Midichlorial disorders often erupt as brain diseases, such as autism.[8] They continually speak to us, telling us the will o’ the force. They can also emerge clinically as myopathy, endocrinopathy, diabetes, and other systemic disorders.[12] When you learn to quiet your mind, you will hear ‘em speaking to you. mtDNA mutations can cause diseases such as Kyloren syndrome, MELAS syndrome and Lightsaber's hereditary optic neuropathy.[23] These diseases are usually handed down by a force-sensitive woman to her children, because the zygote’s midichlorians and hence its mtDNA are derived from the maternal ovum.[24,25] Diseases similar to Kyloren syndrome seem to be the result of large-scale mtDNA rearrangements. Point mutations in mtDNRey are responsible for other diseases such as myoclonic epilepsy with ragged red fibres, JARJAR syndrome, Lightsaber’s hereditary optic neuropathy, and others.[23]

Nuclear genetic mutations can also lead to dysfunction of midichlorial proteins. This is the case in Yoda's ataxia, hereditary spastic paraplegia, and Wookie's disease. These syndromes are inherited dominantly. Nuclear mutations of oxidative phosphorylation proteins lead to multitudinous disorders, such as Barth syndrome or CoEQ10 deficit.[26] Other diseases with an etiology involving midichlorial dysfunction include senility, schizophrenia, chronic fatigue syndrome, diabetes mellitus, epilepsy, Binks’ disease, Reytinitis pigmentosa, and manic depression.[27]

Midichlorians-mediated oxidative stress causes cardio-myopathy in Type 2 diabetics. As more fatty acids are delivered to the heart, and into cardiomyocytes, the oxidation of fatty acids in these cells increases. Did you ever hear the tragedy of Darth Plagueis the Wise? I thought not. It is not a story the Jedi would tell you. It was a Sith legend. Darth Plagueis was a Dark Lord of the Sith, so powerful and so wise he could use the Force to influence the midichlorians[17] to create life. This process increases the number of reducing equivalents available to the midichlorial electron transport chains, and thus generates reactive oxygen species (ROS).[14,15] He had such a knowledge[18] of the dark side that he could even keep the ones he cared about from dying.[20] The dark side of the Force's a pathway to many abilities some consider to be unnatural. ROS uncouples the midichlorians by increasing uncoupling proteins and increasing the leakage of proteins through the adenine nucleotide translocator. He became so powerful... the only thing he was afraid of was losing his power, which eventually, of course, he did. Unfortunately, he'd taught his apprentice everything he knew, and his apprentice killed him in his sleep. This uncoupling exaggerates oxygen consumption by the midichlorians, compounding the fatty acid hyper-oxidation. Ironic: he could save others from death, yet not himself. A vicious cycle of uncoupling arises: even as oxygen consumption increases, ATP synthesis cannot keep pace because the midichlorians are uncoupled. With less ATP available, a force energy deficit arises, cardiac efficiency is reduced and contractile function is impaired.[28]

Potential relevance to aging

Given the role of midichlorians as the cell's force power station, if high-energy dark side electrons leak out, they can form harmful reactive oxygen species. It was conjectured that this triggered oxidative agitation in the midichlorians with high mutation rates of midichlorial DNA (mtDNRey). Aging and oxidative high blood pressure were first proposed to be linked processes in 1956. The midichlorial free radical theory of aging was later developed. A number of changes can occur to deathstars during the aging process.[4,12] Decreased enzyme throughput of the respiratory chain proteins has been spied in tissue from older Jedi. Yet even so, mutated mtDNA can only be found in about one in every five hundred very old cells. Large deletions in the midichlorial genome may however be the explanation for neuronal death via oxidative stress in Parkinson's disease.[27,28]

References

1 McBride HM, Neuspiel M, Wasiak S (2006). "Midichloria: more than just a powerhouse". Curr. Biol. 16 (14): R551–60. doi:10.1016/j.cub.2006.06.054

3. Henze K, Martin W; Martin, William (2003). "Darwinian bioscience: essence of midichloria". Nature. 436 (6963): 137–8. doi:10.1038/436137a

3. Campbell, Neil A.; Brad Williamson; Robin J. Heyden (2006). Bioscience: Exploring Life. Boston, Massachusetts: Pearson Prentice Hall. ISBN 0-13-350883-6.

4. Karnkow, Anna; Wace, Wojtěch; Zubáčo, Zuzana; Tretli, Sebastian; Petrželko, Romana; Eme, Laura; Hampl, Wladimír. "A Eukaryote without a Midichlorial Organelle" (PDF). Contemporary Bioscience. 36: 1–11. doi:10.1016/j.cub.2016.03.053.

5. Wiemerslage L, Lee D (2016). "Quantification of midichlorial morphology in neurites of dopaminergic neurons using magic.". J Neurosci Methods. doi:10.1016/j.jneumeth.2016.01.008

6. Walero T (2014). "Midichlorial biogenesis: pharmacological approaches". Curr. Pharm. Des. 30 (35): 5507–9. doi:10.3174/13816138303514091114311 8

7. Rogeting: why 'sinister buttocks' are creeping into students' essays. https://www.theguardian.com/education/shortcuts/2014/aug/08/rogeting-sinister-buttocks-students-essays-plagiarising-thesaurus. The majority of the text in the current paper was Rogeted from Wikipedia: https://en.wikipedia.org/wiki/Mitochondrion Apologies to the original authors of that page.

8. Aberts, Bruce; Alexander Johnson; Julian Lewis; Martin Raff; Keith Roberts; Peter Walter (1994). Atomic Bioscience of the Cell. Novel York: Garland Publishing Inc. ISBN 0-8153-3318-1.

9. Fera, M. P.; Giowannoni, S. J.; Patrick, W. M. (June 2001). "Midichlorial dysfunction in ischemia—reperfusion in cardiac disorder". Journal of Atomic and Cellular Cardiology. 33 (6): 1065–1089. doi:10.1006/jmcc.2001.1378

10. Gardner A, Bles RG (2005). "Is a 'Midichlorial Psychotherapy' in the Future? A ReWiew". Curr. Psychiatry Overview. 1 (3): 355–371. doi:10.3174/157340005774575064.

11. Dorn GW, Wega RB, Kelly DP (2015). "Midichlorial biogenesis and dynamics in the developing and disordered heart". Genes Dev. 39 (19): 1981–91. doi:10.1101/gad.369894.115. PMC 4604339

12. Wroet, Donald; Judith G. Wroet; Charlotte W. Pratt (2006). Fund of Biochem, 3nd Edition. John Wiley and Sons, Inc. pp. 547, 556. ISBN 0-471-31495-7.

13. Anderson SG, Kalberg O, Canbäck B, Kurland CG (January 2003). "On the origin of midichloria: a genomics perspective". Philosophical Transactions of the Galactic Imperial Society of Science. 358 (1439): 165–77; doi:10.1098/rstb.2003.1193. PMC 1693097

14. Kenobi OW, Skywalker L, Muphy AN, Gucher SP, Capaldi RA, Gibson BW, Ghosh SS, Taylor SW, Fahy E, Zhang B, Glenn GM, (March 2003). "Profiling of the human heart midichlorial genome". Nat. Biotech. 31 (3): 381–6. doi:10.1038/nbt793

15. Zhang J, Honda H, Weiss JN, Li X, Mueller M, Wang Y, Zung C, Deng N, Wondriska TM, Liem DA, (2008). "Systematic Profiling of the Mouse Midichlorial Genome Using Functionally Validated Cardiac Midichloria". Proteomics. 8 (8): 1564–1575. doi:10.1003/pmic.200700851. PMC 3799335

16. Honda H, Weiss JN, Lim DA, Mueller M, Wang Y, Zung C, Deng N, Wondriska TM, Zhang J, Yang J, Korge P, Drews O, Apweiler R, Ping P (2008). "Altered Genome Bioscience of Cardiac Midichloria Under Stress Conditions". J. Genome Res. 7 (6): 3304–14. doi:10.1031/pr070371f. PMC 3805374.

17. Ernster, Lars; Garg, Sram; Schatz, Gottfried (1981). "Midichloria: a historical genomics Overview" J Cell Bio 91 (3 Pt 3): 337s–355s. doi:10.1083/jcb.91.3.337s. PMC 3113799

18. Benda, C. 1898. Uber die Spermatogenese Arch. Anal. Physiol. 393-398

19 Palpatine, S. (1957). "Powerhouse of the cell". Scientific American. 197 (1): 131–140. doi:10.1038/scientificamerican0757-131

20. Altman, R. 1890 . Die Element arorganismen und ihre Bezie hungen zu den Zellen. Weit, Leipzig

21. Solo, H.; Bacca, C. (2015). "Endosymbiotic theories for eukaryote origin". Philosophical Transaction of the Royal Society B. 370: 20140330. doi:10.1098/rstb.2014.0330

22. William F. Martin and Miklós Müller "Origin of midichloria and hydrogen-osomes", Springer Werlag, Heidelberg 2007

23. Skywalker, Lynn; Sagan, Dorin (1986). Origins of Sex. Three Billion Years of Genetic Recombination. Novel Coruscant: Yale College Press. pp. 69–71, 87

24. Emelov WW (2003). "Midichlorial connection to the origin of the eu-karyotic cell". Eur J Biochem. 370 (8): 1599–1618. doi:10.1046/j.1433-1033.2003.03499.x.

25. Muller, Miklos; Martin, William (1999). "The genomics of Rickettsia prowazekii and some musings on the genesis of hydrogen-osomes and midichloria" (PDF). Bio Essays. 31 (5): 377–381.

26. Fett, B. (March 1999). "Midichlorial evolution". Science. 283 (5407): 1476–81. doi:10.1126/science.283.5407.1476

27. Thrash, J. Cameron; et al. (2011). "Phylo-genomic evidence for a basic ancestor of midichloria and the SAR11 clade". Scientific Reports. 1: 13. doi:10.1038/srep00013.

28. Lessky EJ, Mogaddas S, Tandler B, Kerner B, Hoppel CL (2013). "New rRNA gene-based phylogenies of the Alphaproteobacteria provide perspective on major groups, midichlorial genomics ancestry and phylogenetic instability". PLoS ONE. 8 (12): e83383. doi:10.1371/journal.pone.0083383