Abad, C., Pinal-Fernandez, I., Guillou, C., Bourdenet, G., Drouot, L., Cosette, P., Giannini, M., Debrut, L., Jean, L., Bernard, S., Genty, D., Zoubairi, R., Remy-Jouet, I., Geny, B., Boitard, C., Mammen, A., Meyer, A., & Boyer, O. (2024). IFNγ causes mitochondrial dysfunction and oxidative stress in myositis. *Nature Communications*, *15*(1), 5403. https://doi.org/10.1038/s41467-024-49460-1

Affolter, M. (2020, January 17). Endosymbiosis. *Historical Geology*. https://opengeology.org/historicalgeology/

Ahmad, S. I. (Ed.). (2019). *Handbook of mitochondrial dysfunction*. CRC Press.

Al-Hamaly, M. A., Winter, E., & Blackburn, J. S. (2025). The mitochondria as an emerging target of self-renewal in T-cell acute lymphoblastic leukemia. *Cancer Biology & Therapy*, *26*(1). https://doi.org/10.1080/15384047.2025.2460252

Alberts, B., Johnson, A., Lewis, J., Morgan, D., Raff, M., Roberts, K., & Walter, P. (2014). *Molecular biology of the cell* (6th ed.). Garland Science.

Alex, B., & Moorjani, P. (2017, August 9). How molecular clocks are refining human evolution's timeline. *Sapiens*. https://www.sapiens.org/biology/molecular-clocks/

Amorim, J. A., Coppotelli, G., Rolo, A. P., Palmeira, C. M., Ross, J. M., & Sinclair, D. A. (2022). Mitochondrial and metabolic dysfunction in ageing and age-related diseases. *Nature Reviews Endocrinology, 18*(4), 243–258. https://doi.org/10.1038/s41574-021-00626-7

Ancient DNA and Neanderthals. (2022, September 29). *The Smithsonian Institution's Human Origins Program.* https://humanorigins.si.edu/evidence/genetics/ancient-dna-and-neanderthals

Andreescu, S., Henkel, R., & Khelfi, A. (Eds.). (2024). *Biomarkers of oxidative stress: Clinical aspects of oxidative stress.* Springer.

Archibald, J. M. (2015). Endosymbiosis and eukaryotic cell evolution. *Current Biology*, *25*(19), R911–R921. https://doi.org/10.1016/j.cub.2015.07.055

Arthur, W. (2025). *Parallel worlds: Evolution of life across the Cosmos.* World Scientific Publishing Company.

Ashrafi, G., & Schwarz, T. L. (2013). The pathways of mitophagy for quality control and clearance of mitochondria. Cell Death & Differentiation, 20(1), 31–42. https://doi.org/

10.1038/cdd.2012.81

Bahat, A., Milenkovic, D., Cors, E., Barnett, M., Niftullayev, S., Katsalifis, A., Schwill, M., Kirschner, P., MacVicar, T., Giavalisco, P., Jenninger, L., Clausen, A. R., Paupe, V., Prudent, J., Larsson, N.-G., Rogg, M., Schell, C., Muylaert, I., Larsson, E., … Langer, T. (2025). Ribonucleotide incorporation into mitochondrial DNA drives inflammation. *Nature*. https://doi.org/10.1038/s41586-025-09541-7

Ball, P. (1999). *The self-made tapestry: Pattern formation in nature.* Oxford University Press, USA.

Ball, P. (2025, October 8). Loops of DNA equipped ancient life to become complex. *Quanta Magazine.* https://www.quantamagazine.org/loops-of-dna-equipped-ancient-life-to-become-complex-20251008/

Basualto-Alarcón, C., Urra, F. A., Bozán, M. F., Jaña, F., Trangulao, A., Bevilacqua, J. A., & Cárdenas, J. C. (2020). Idiopathic inflammatory myopathy human derived cells retain their ability to increase mitochondrial function. *PLOS ONE*, *15*(11), e0242443. https://doi.org/10.1371/journal.pone.0242443

Baum, D. A., & Baum, B. (2014). An inside-out origin for the eukaryotic cell. *BMC Biology*, *12*(1), 76. https://doi.org/10.1186/s12915-014-0076-2

Bennett, G. M., Kwak, Y., & Maynard, R. (2024). Endosymbioses have shaped the evolution of biological diversity and complexity time and time again. *Genome Biology and Evolution*, *16*(6), evae112. https://doi.org/10.1093/gbe/evae112

Benton, M. L., Abraham, A., LaBella, A. L., Abbot, P., Rokas, A., & Capra, J. A. (2021). The influence of evolutionary history on human health and disease. *Nature Reviews Genetics, 22*(5), 269–283. https://doi.org/10.1038/s41576-020-00305-9

Bhatt, P. S., Tzoulis, C., Balafkan, N., Miletic, H., Tran, G. T. T., Sanaker, P. S., & Bindoff, L. A. (2019). Mitochondrial DNA depletion in sporadic inclusion body myositis. *Neuromuscular Disorders*, *29*(3), 242–246. https://doi.org/10.1016/j.nmd.2019.02.001

Blevins, H. M., Xu, Y., Biby, S., & Zhang, S. (2022). The NLRP3 Inflammasome Pathway: A review of mechanisms and inhibitors for the treatment of inflammatory diseases. *Frontiers in Aging Neuroscience, 14*. https://doi.org/10.3389/fnagi.2022.879021

Boncompagni, S., Moussa, C. E. H., Levy, E., Pezone, M. J., Lopez, J. R., Protasi, F., &

Shtifman, A. (2012). Mitochondrial dysfunction in skeletal muscle of amyloid precursor protein-overexpressing mice. *The Journal of Biological Chemistry*, *287*(24), 20534–20544. https://doi.org/10.1074/jbc.M112.359588

Borcherding, N., & Brestoff, J. R. (2023). The power and potential of mitochondria transfer. *Nature, 623*(7986), 283–291. https://doi.org/10.1038/s41586-023-06537-z

Bottoni, P., Gionta, G., & Scatena, R. (2022). Remarks on mitochondrial myopathies. *International Journal of Molecular Sciences*, *24*(1), 124. https://doi.org/10.3390/ijms24010124

Brady, S., Poulton, J., & Muller, S. (2024). Inclusion body myositis: Correcting impaired mitochondrial and lysosomal autophagy as a potential therapeutic strategy. Autoimmunity Reviews, 23(11), 103644. https://doi.org/10.1016/j.autrev.2024.103644

Brady, S., Poulton, J., & Muller, S. (2024). Inclusion body myositis: Correcting impaired mitochondrial and lysosomal autophagy as a potential therapeutic strategy. *Autoimmunity Reviews*, *23*(11), 103644. https://doi.org/10.1016/j.autrev.2024.103644

Brand, M. D., & Nicholls, D. G. (2011). Assessing mitochondrial dysfunction in cells. *Biochemical Journal, 435*(2), 297–312. https://doi.org/10.1042/BJ20110162

Brenner, C. (2023). A science-based review of the world's best-selling book on aging. *Archives of Gerontology and Geriatrics, 104*, 104825. https://doi.org/10.1016/j.archger.2022.104825

Brestoff, J. R. (2025). Mitochondrial swap helps cancer fight immune cells. *Nature*, *638*, 42–43. https://doi.org/10.1038/d41586-025-00077-4

Brestoff, J. R., Singh, K. K., Aquilano, K., Becker, L. B., Berridge, M. V., Boilard, E., Caicedo, A., Crewe, C., Enríquez, J. A., Gao, J., Gustafsson, Å. B., Hayakawa, K., Khoury, M., Lee, Y., Lettieri-Barbato, D., Luz-Crawford, P., McBride, H. M., McCully, J. D., Nakai, R., . . . Zheng, M. (2025). Recommendations for mitochondria transfer and transplantation nomenclature and characterization. *Nature Metabolism.* https://doi.org/10.1038/s42255-024-01200-x

Broome, S. C., Braakhuis, A. J., Mitchell, C. J., & Merry, T. L. (2021). Mitochondria-targeted antioxidant supplementation improves 8 km time trial performance in middle-aged trained male cyclists. *Journal of the International Society of Sports Nutrition, 18*(1), 58.

https://doi.org/10.1186/s12970-021-00454-0

Budowle, B., Allard, M. W., Wilson, M. R., & Chakraborty, R. (2003). Forensics and mitochondrial DNA: applications, debates, and foundations. *Annual Review of Genomics and Human Genetics*, *4*, 119–141. https://doi.org/10.1146/annurev.genom.4.070802.110352

Burns, K. H. (2020). Our conflict with transposable elements and its implications for human disease. *Annual Review of Pathology Mechanisms of Disease*, *15*(1), 51–70. https://doi.org/10.1146/annurev-pathmechdis-012419-032633

Callier, V. (2022, June 18). Mitochondria and the origin of eukaryotes. Ars Technica. https://arstechnica.com/science/2022/06/mitochondria-and-the-origin-of-eukaryotes/

Callier, V. (2023, October 23). Where the heck did all those structures inside complex cells come from? *Knowable Magazine.* https://doi.org/10.1146/knowable-102323-2

Callier, V. (2024, January 8). Cells across the body talk to each other about aging. *Quanta Magazine.* https://www.quantamagazine.org/cells-across-the-body-talk-to-each-other-about-aging-20240108/

Callier, V. (2025, April 10). At the dawn of life, did metabolism come first? *Knowable Magazine*. https://doi.org/10.1146/knowable-040925-2

Callier, V. (2025, March 21). How metabolism can shape cells' destinies. *Quanta Magazine.* https://www.quantamagazine.org/how-metabolism-can-shape-cells-destinies-20250321/

Cangkrama, M., Liu, H., Wu, X., Yates, J., Whipman, J., Gäbelein, C. G., Matsushita, M., Ferrarese, L., Sander, S., Castro-Giner, F., Asawa, S., Sznurkowska, M. K., Kopf, M., Dengjel, J., Boeva, V., Aceto, N., Vorholt, J. A., & Werner, S. (2025). MIRO2-mediated mitochondrial transfer from cancer cells induces cancer-associated fibroblast differentiation. *Nature Cancer.* https://doi.org/10.1038/s43018-025-01038-6

In a study published in the journal *Nature Cancer*, biologists show that skin cancer cells are able to transfer their mitochondria to healthy connective tissue cells (fibroblasts) in their immediate vicinity. Mitochondria are the cell compartments that provide energy in the form of the molecule ATP. The cancer cells use tiny tubes made of cell membrane material to transfer the mitochondria and connect the two cells—much like in a pneumatic tube system. The mitochondrial transfer reprograms the fibroblasts functionally into

tumor-associated fibroblasts, which mainly support cancer cells: tumor-associated fibroblasts usually multiply faster than normal fibroblasts and produce more ATP, while also secreting higher amounts of growth factors and cytokines. And all this benefits the tumor cells: they also multiply faster, making the tumor more aggressive. Last, but not least, the hijacked fibroblasts also alter the cell environment—the so-called extracellular matrix—by increasing the production of certain matrix components in such a way that cancer cells thrive. The extracellular matrix is vital for the mechanical stability of tissues and influences growth, wound healing and intercellular communication.

Cantó-Santos, J., Valls-Roca, L., Tobías, E., Oliva, C., García-García, F. J., Guitart-Mampel, M., Andújar-Sánchez, F., Esteve-Codina, A., Martín-Mur, B., Padrosa, J., Aránega, R., Moreno-Lozano, P. J., Milisenda, J. C., Artuch, R., Grau-Junyent, J. M., & Garrabou, G. (2023). Integrated Multi-Omics Analysis for Inferring Molecular Players in Inclusion Body Myositis. Antioxidants, 12(8), 1639. https://doi.org/10.3390/antiox12081639

Carri, M. T., Valle, C., Bozzo, F., & Cozzolino, M. (2015). Oxidative stress and mitochondrial damage: Importance in non-SOD1 ALS. *Frontiers in Cellular Neuroscience*, *9*. https://doi.org/10.3389/fncel.2015.00041

Catalán-García, M., García-García, F. J., Moreno-Lozano, P. J., Alcarraz-Vizán, G., Tort-Merino, A., Milisenda, J. C., Cantó-Santos, J., Barcos-Rodríguez, T., Cardellach, F., Lladó, A., Novials, A., Garrabou, G., & Grau-Junyent, J. M. (2020). Mitochondrial dysfunction: A common hallmark underlying comorbidity between sIBM and other degenerative and age-related diseases. *Journal of Clinical Medicine*, *9*(5), 1446–1446. https://doi.org/10.3390/jcm9051446

Cellular circuits control how DNA damage is repaired, affecting the risk of disease as we age. (2025, March 13). *ScienceDaily*. https://www.sciencedaily.com/releases/2025/03/250313192227.htm

Cellular respiration. (2024, November 1). In *Wikipedia*. https://en.wikipedia.org/wiki/Cellular respiration

Chang, C. C., Jou, S. H., Lin, T. T., Lai, T. J., & Liu, C. S. (2015). Mitochondria DNA change and oxidative damage in clinically stable patients with major depressive disorder. *PLOS*

ONE, *10*(5), e0125855–e0125855. https://doi.org/10.1371/journal.pone.0125855

Chang, Y., & Dubnau, J. (2023). Endogenous retroviruses and TDP-43 proteinopathy form a sustaining feedback driving intercellular spread of Drosophila neurodegeneration. *Nature Communications*, *14*(1). https://doi.org/10.1038/s41467-023-36649-z

Chen, M.-M., Li, Y., Deng, S.-L., Zhao, Y., Lian, Z.-X., & Yu, K. (2022). Mitochondrial Function and Reactive Oxygen/Nitrogen Species in Skeletal Muscle. Frontiers in Cell and Developmental Biology, 10, 826981. https://doi.org/10.3389/fcell.2022.826981

Chen, T.-H., Koh, K.-Y., Lin, K. M.-C., & Chou, C.-K. (2022). Mitochondrial Dysfunction as an Underlying Cause of Skeletal Muscle Disorders. International Journal of Molecular Sciences, 23(21), 12926. https://doi.org/10.3390/ijms232112926

Citric acid cycle. (2024, October 21). In *Wikipedia*. https://en.wikipedia.org/wiki/Citric_acid_cycle

Conroy, G. (2025a). Mitochondria expel tainted DNA - spurring age-related inflammation. *Nature*, d41586-025-03064-x. https:// doi.org/10.1038/d41586-025-03064-x

Conroy, G. (2025b). Mitochondria on the move Cells are swapping their mitochondria. What does this mean for our health? *Nature*, *640*(8058), 302–304. https://doi.org/10.1038/d41586-025-01064-5

Corcoran, M., Chernyshev, M., Mandolesi, M., Narang, S., Kaduk, M., Ye, K., Sundling, C., Färnert, A., Kreslavsky, T., Bernhardsson, C., Larena, M., Jakobsson, M., & Karlsson Hedestam, G. B. (2023). Archaic humans have contributed to large-scale variation in modern human T cell receptor genes. *Immunity, 56*(3), 635-652.e6. https://doi.org/10.1016/j.immuni.2023.01.026

Cordero, M. D., Williams, M. R., & Ryffel, B. (2017). AMP-activated protein kinase regulation of the nlrp3 inflammasome during aging. *Trends in Endocrinology and Metabolism, 29*(1), 8–17. https://doi.org/10.1016/j.tem.2017.10.009

Corpas, F. J., González-Gordo, S., & Palma, J. M. (2020). Plant peroxisomes: A factory of reactive species. *Frontiers in Plant Science, 11*. https://doi.org/10.3389/fpls.2020.00853

Costantini, D. (2024). *The role of organismal oxidative stress in the ecology and life-history evolution of animals.* Springer.

D'Amato, M., Morra, F., Di Meo, I., & Tiranti, V. (2023). Mitochondrial transplantation in mitochondrial medicine: current challenges and future perspectives. *International Journal of Molecular Sciences*, *24*(3), 1969. https://doi.org/10.3390/ijms24031969

Dannemann, M. (2021). The population-specific impact of Neandertal introgression on human disease. *Genome Biology and Evolution, 13*(1), evaa250. https://doi.org/10.1093/gbe/evaa250

Dannemann, M., Andrés, A. M., & Kelso, J. (2016). Introgression of Neandertal- and Denisovan-like haplotypes contributes to adaptive variation in human toll-like receptors. American Journal of Human Genetics, 98(1), 22–33. https://doi.org/10.1016/j.ajhg.2015.11.015

Davies, K. J. A. (2000). An overview of oxidative stress. *IUBMB Life, 50*(4–5), 241–244. https://doi.org/10.1080/713803723

De Almeida, A. J. P. O., De Oliveira, J. C. P. L., Da Silva Pontes, L. V., De Souza Júnior, J. F., Gonçalves, T. A. F., Dantas, S. H., De Almeida Feitosa, M. S., Silva, A. O., & De Medeiros, I. A. (2022). ROS: Basic concepts, sources, cellular signaling, and its implications in aging pathways. *Oxidative Medicine and Cellular Longevity, 2022,* 1–23. https://doi.org/10.1155/2022/1225578

De Paepe, B. (2019a). Pathological mechanisms in inclusion body myositis: A review. Current Opinion in Neurology, 32(5), 704–714. https://doi.org/10.1097/WCO.0000000000000726

De Paepe, B. (2019b). Sporadic inclusion body myositis: An acquired mitochondrial disease with extras. *Biomolecules*, *9*(1), 15. https://doi.org/10.3390/biom9010015

Delsuc, F., Brinkmann, H., & Philippe, H. (2005). Phylogenomics and the reconstruction of the tree of life. *Nature Reviews Genetics, 6*(5), 361–375. https://doi.org/10.1038/nrg1603

Di Leo, V., Bernardino Gomes, T. M., & Vincent, A. E. (2023). Interactions of mitochondrial and skeletal muscle biology in mitochondrial myopathy. *Biochemical Journal*, *480*(21), 1767–1789. https://doi.org/10.1042/BCJ20220233

Diaz-Vegas, A., Sanchez-Aguilera, P., Krycer, J. R., Morales, P. E., Monsalves-Alvarez, M., Cifuentes, M., Rothermel, B. A., & Lavandero, S. (2020). Is mitochondrial dysfunction a common root of noncommunicable chronic diseases? *Endocrine Reviews, 41*(3), bnaa005. https://doi.org/2021121111042433000

Ding, W., Chen, J., Zhao, L., Wu, S., Chen, X., & Chen, H. (2024). Mitochondrial DNA leakage

triggers inflammation in age-related cardiovascular diseases. *Frontiers in Cell and Developmental Biology*, *12*. https://doi.org/10.3389/fcell.2024.1287447

Dong, H., & Tsai, S. Y. (2023). Mitochondrial properties in skeletal muscle fiber. *Cells, 12*(17), 2183. https://doi.org/10.3390/cells12172183

Doss, R. M., & Breuss, M. W. (2024). A somatic view of the genomic impact of mitochondrial endosymbiosis. *PLOS Biology, 22*(8), e3002756. https://doi.org/10.1371/journal.pbio.3002756

Dupuis, L., Gonzalez de Aguilar, J. L., Echaniz-Laguna, A., Eschbach, J., Rene, F., Oudart, H., Halter, B., Huze, C., Schaeffer, L., Bouillaud, F., & Loeffler, J. P. (2009). Muscle mitochondrial uncoupling dismantles neuromuscular junction and triggers distal degeneration of motor neurons. *PloS One*, *4*(4), e5390–e5390.

Eid, A. H., Kobeissy, F., & El-Yazbi, A. (Eds.). (2024). *Oxidative stress in cardiovascular-metabolic diseases*. Springer.

Embley, T. M., & Martin, W. (2006). Eukaryotic evolution, changes and challenges. *Nature*, *440*(7084), 623–630. https://doi.org/10.1038/nature04546

Eme, L., Spang, A., Lombard, J., Stairs, C. W., & Ettema, T. J. G. (2017). Archaea and the origin of eukaryotes. *Nature Reviews Microbiology*, *15*(12), 711–723. https://doi.org/10.1038/nrmicro.2017.133

Endoplasmic reticulum. (2024, November 2). In *Wikipedia*. https://en.wikipedia.org/wiki/Endoplasmic_reticulum

Evans, C. L. (2025, July 30). What can a cell remember? *Quanta Magazine.* https://www.quantamagazine.org/what-can-a-cell-remember-20250730/

Falkenberg, M., Larsson, N., & Gustafsson, C. M. (2024). Replication and transcription of human mitochondrial DNA. *Annual Review of Biochemistry, 93*(1), 47–77. https://doi.org/10.1146/annurev-biochem-052621-092014

Federico, A., Cardaioli, E., Da Pozzo, P., Formichi, P., Gallus, G. N., & Radi, E. (2012). Mitochondria, oxidative stress and neurodegeneration. *Journal of the Neurological Sciences, 322*(1–2), 254–262. https://doi.org/10.1016/j.jns.2012.05.030

Fleming, E., & Luo, Y. (2021). Co-delivery of synergistic antioxidants from food sources for the prevention of oxidative stress. *Journal of Agriculture and Food Research*, *3*, 100107. https://doi.org/10.1016/j.jafr.2021.100107

Frisbee, J. C., Lewis, M. T., & Wiseman, R. W. (2019). Skeletal muscle performance in metabolic disease: Microvascular or mitochondrial limitation or both? *Microcirculation*, *26*(5), e12517. https://doi.org/10.1111/micc.12517

Frost, B., & Dubnau, J. (2024). The role of retrotransposons and endogenous retroviruses in Age-Dependent Neurodegenerative Disorders. *Annual Review of Neuroscience*, *47*(1), 123–143. https://doi.org/10.1146/annurev-neuro-082823-020615

Fu, Q., Hajdinjak, M., Moldovan, O. T., Constantin, S., Mallick, S., Skoglund, P., … Pääbo, S. (2015). An early modern human from Romania with a recent Neanderthal ancestor. *Nature, 524*(7564), 216–219. doi:10.1038/nature14558

Gan, Z., Fu, T., Kelly, D. P., & Vega, R. B. (2018). Skeletal muscle mitochondrial remodeling in exercise and diseases. Cell Research, 28(10), 969–980. https://doi.org/10.1038/s41422-018-0078-7

Gardner, A., & Boles, R. G. (2011). Beyond the serotonin hypothesis: Mitochondria, inflammation and neurodegeneration in major depression and affective spectrum disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *35*(3), 730–743. https://doi.org/10.1016/j.pnpbp.2010.07.030

Gottwald, E. M., Duss, M., Bugarski, M., Haenni, D., Schuh, C. D., Landau, E. M., & Hall, A. M. (2018). The targeted anti-oxidant MitoQ causes mitochondrial swelling and depolarization in kidney tissue. *Physiological Reports, 6*(7), e13667. https://doi.org/10.14814/phy2.13667

Gray, M. W. (2017). Lynn Margulis and the endosymbiont hypothesis: 50 years later. *Molecular Biology of the Cell*, *28*(10), 1285–1287. https://doi.org/10.1091/mbc.e16-07-0509

Grazioli, S., & Pugin, J. (2018). Mitochondrial Damage-Associated molecular patterns: from inflammatory signaling to human diseases. *Frontiers in Immunology*, *9*. https://doi.org/10.3389/fimmu.2018.00832

Greenwood, V. (2024, March 6). Cellular self-destruction may be ancient. But why? *Quanta Magazine.* https://www.quantamagazine.org/cellular-self-destruction-may-be-ancient-but-

why-20240306/

Harold, F. M. (2001). *The way of the cell: Molecules, organisms, and the order of life.* Oxford.

Harold, F. M. (2014). *In search of cell history: The evolution of life's building blocks.* University of Chicago Press.

Hedberg-Oldfors, C., Lindgren, U., Basu, S., Visuttijai, K., Lindberg, C., Falkenberg, M., Larsson Lekholm, E., & Oldfors, A. (2021). Mitochondrial DNA variants in inclusion body myositis characterized by deep sequencing. Brain Pathology, 31(3), e12931. https://doi.org/10.1111/bpa.12931

Hedberg-Oldfors, C., Lindgren, U., Basu, S., Visuttijai, K., Lindberg, C., Falkenberg, M., Larsson Lekholm, E., & Oldfors, A. (2021). Mitochondrial DNA variants in inclusion body myositis characterized by deep sequencing. *Brain Pathology*, *31*(3). https://doi.org/10.1111/bpa.12931

Hernansanz-Agustín, P., Morales-Vidal, C., Calvo, E., Natale, P., Martí-Mateos, Y., Jaroszewicz, S. N., Cabrera-Alarcón, J. L., Acín-Pérez, R., López-Montero, I., Vázquez, J., & Enríquez, J. A. (2024). A transmitochondrial sodium gradient controls membrane potential in mammalian mitochondria. *Cell*. https://doi.org/10.1016/j.cell.2024.08.045

Herring, M. (2024, October 28). Meet the eukaryote, the first cell to get organized. *Quanta Magazine.* https://www.quantamagazine.org/meet-the-eukaryote-the-first-cell-to-get-organized-20241028/

Hoover, G., Gilbert, S., Curley, O., Obellianne, C., Lin, M. T., Hixson, W., Pierce, T. W., Andrews, J. F., Alexeyev, M. F., Ding, Y., Bu, P., Behbod, F., Medina, D., Chang, J. T., Ayala, G., & Grelet, S. (2025). Nerve-to-cancer transfer of mitochondria during cancer metastasis. *Nature*. https://doi.org/10.1038/s41586-025-09176-8

How cells repair their power plants. (2025, April 4). *ScienceDaily*. https://www.sciencedaily.com/releases/2025/04/250404140532.htm

Hroudova, J., Fisar, Z., & Raboch, J. (2013). Mitochondrial functions in mood disorders. In *Mood Disorders* (pp. 101–144). *InTech*. https://doi.org/10.5772/53254

Hu, M., & Shu, H. (2023). Mitochondrial DNA-triggered innate immune response: mechanisms and diseases. *Cellular and Molecular Immunology*, *20*(12), 1403–1412. https://doi.org/

10.1038/s41423-023-01086-x

Huang, C., & Zhang, Y. (Eds.). (2021). *Oxidative stress: Human diseases and medicine.* Springer.

Huang, Y., Xu, W., & Zhou, R. (2021). NLRP3 inflammasome activation and cell death. *Cellular and Molecular Immunology, 18*(9), 2114–2127. https://doi.org/10.1038/s41423-021-00740-6

Huntley, M. L., Gao, J., Termsarasab, P., Wang, L., Zeng, S., Thammongkolchai, T., Liu, Y., Cohen, M. L., & Wang, X. (2019). Association between TDP-43 and mitochondria in inclusion body myositis. *Laboratory Investigation*, *99*(7), 1041–1048. https://doi.org/10.1038/s41374-019-0233-x

Indo, H. P., Chatatikun, M., Nakanishi, I., Matsumoto, K., Imai, M., Kawakami, F., Kubo, M., Abe, H., Ichikawa, H., Yonei, Y., Beppu, H. J., Minamiyama, Y., Kanekura, T., Ichikawa, T., Phongphithakchai, A., Udomwech, L., Sukati, S., Charong, N., Somsak, V., … Majima, H. J. (2024). The roles of mitochondria in human being's life and aging. *Biomolecules*, *14*(10), 1317. https://doi.org/10.3390/biom14101317

Inflammasome. (2025, July 3).. In *Wikipedia*, The Free Encyclopedia. Retrieved 05:55, August 9, 2025, from https://en.wikipedia.org/w/index.php?title=Inflammasome&oldid=1298522627

Irazoki, A., Gordaliza-Alaguero, I., Frank, E., Giakoumakis, N. N., Seco, J., Palacín, M., Gumà, A., Sylow, L., Sebastián, D., & Zorzano, A. (2023). Disruption of mitochondrial dynamics triggers muscle inflammation through interorganellar contacts and mitochondrial DNA mislocation. *Nature Communications*, *14*(1). https://doi.org/10.1038/s41467-022-35732-1

Iu, E. C. Y., So, H., & Chan, C. B. (2024). Mitochondrial defects in sporadic inclusion body myositis—Causes and consequences. *Frontiers in Cell and Developmental Biology*, *12*, 1403463. https://doi.org/10.3389/fcell.2024.1403463

Iu, J., Smith, C., & Needham, M. (2024). Mitochondrial defects and inflammation in sporadic inclusion body myositis. Frontiers in Neurology, 15, Article 1267843. https://doi.org/10.3389/fneur.2024.1267843

Jackson, B. T., & Finley, L. W. (2024). Metabolic regulation of the hallmarks of stem cell

biology. *Cell Stem Cell*, *31*(2), 161–180. https://doi.org/10.1016/j.stem.2024.01.003

Jarry, J. (2025, February 14). Mitochondrial dysfunction is a bit of a fad. *Office for Science and Society*. https://www.mcgill.ca/oss/article/medical-critical-thinking-health-and-nutrition/mitochondrial-dysfunction-bit-fad

Jenkins, B. C., Neikirk, K., Katti, P., Claypool, S. M., Kirabo, A., McReynolds, M. R., & Hinton, A. (2024). Mitochondria in disease: Changes in shapes and dynamics. *Trends in Biochemical Sciences*, *49*(4), 346–360. https://doi.org/10.1016/j.tibs.2024.01.011

Jeon, Y. M., Kwon, Y., Lee, S., Kim, S., Jo, M., Lee, S., Kim, S. R., Kim, K., & Kim, H. J. (2021). Vitamin B12 Reduces TDP-43 Toxicity by alleviating oxidative stress and mitochondrial dysfunction. *Antioxidants*, *11*(1), 82. https://doi.org/10.3390/antiox11010082

Johnston-Carey, H. K., Pomatto, L. C. D., & Davies, K. J. A. (2016). The Immunoproteasome in oxidative stress, aging, and disease. *Critical Reviews in Biochemistry and Molecular Biology*, *51*(4), 268–281. https://doi.org/10.3109/10409238.2016.1172554

Joshi, P. R., Vetterke, M., Hauburger, A., Tacik, P., Stoltenburg, G., & Hanisch, F. (2014). Functional relevance of mitochondrial abnormalities in sporadic inclusion body myositis. *Journal of Clinical Neuroscience*, *21*(11), 1959–1963. https://doi.org/10.1016/j.jocn.2014.05.051

Kakanj, P., Bonse, M., Kshirsagar, A., Gökmen, A., Gaedke, F., Sen, A., Mollá, B., Vogelsang, E., Schauss, A., Wodarz, A., & Pla-Martín, D. (2025). Retromer promotes the lysosomal turnover of mtDNA. *Science Advances*, *11*(14). https://doi.org/10.1126/sciadv.adr6415

Kamalanathan, A. S., Agarwal, V., Talamini, L., & Muller, S. (2025). Autophagy in myositis, a dysregulated pathway, and a target for therapy. Autoimmunity Reviews, 103817. https://doi.org/10.1016/j.autrev.2025.103817

Karam, M., Itani, M. M., Faraj, M., Jaffa, A. A., Jelwan, J., Aldeen, K. S., & Jaffa, A. A. (2024). Oxidative stress and cardiovascular disease: Implication of gender and age. In A. H. Eid, F. Kobeissy, & A. F. El-Yazbi (Eds.), *Oxidative stress in cardiovascular-metabolic diseases* (pp. 1–23). Springer Nature Switzerland. https://doi.org/10.1007/978-3-031-62131-4_1

Kauffman, S. A. (2019). *A world beyond physics: The emergence and evolution of life*. Oxford

University Press.

Keeling, P. J. (2014). The impact of history on our perception of evolutionary events: Endosymbiosis and the origin of eukaryotic complexity. *Cold Spring Harbor Perspectives in Biology*, *6*(2), a016196–a016196. https://doi.org/10.1101/cshperspect.a016196

Kelley, N., Jeltema, D., Duan, Y., & He, Y. (2019). The NLRP3 Inflammasome: An overview of mechanisms of activation and regulation. *International Journal of Molecular Sciences, 20*(13), 3328. https://doi.org/10.3390/ijms20133328

Kempf, A., Song, S. M., Talbot, C. B., & Miesenböck, G. (2019). A potassium channel β-subunit couples mitochondrial electron transport to sleep. *Nature*, 1–1. https://doi.org/10.1038/s41586-019-1034-5

Khelfi, A. (2024). Oxidative Stress in Inflammation. In S. Andreescu, R. Henkel, & A. Khelfi (Eds.), *Biomarkers of oxidative stress* (pp. 13–43). Springer Nature Switzerland. https://doi.org/10.1007/978-3-031-69962-7_2

Kim, J. Y., Kang, Y. C., Kim, M. J., Kim, S. U., Kang, H. R., Yeo, J. S., Kim, Y., Yu, S. H., Song, B., Hwang, J. W., Lee, Y. S., Byun, J. W., Yoo, D. H., Kim, H. S., Han, K., Kim, C. H., & Lee, E. Y. (2025). Mitochondrial transplantation as a novel therapeutic approach in idiopathic inflammatory myopathy. *Annals of the Rheumatic Diseases,* S0003496725000706. https://doi.org/10.1016/j.ard.2024.11.005

Kim, K. H., & Lee, C. B. (2024). Socialized mitochondria: Mitonuclear crosstalk in stress. *Experimental & Molecular Medicine*, *56*(5), 1033–1042. https://doi.org/10.1038/s12276-024-01211-4

Kim, S., Park, S. G., Kim, J., Hong, S., Cho, S., Lim, S., Kim, E., Ju, S., Lee, S. B., Kim, S. P., Jeong, T. Y., Oh, Y., Han, S., Kim, H., Lee, T. C., Kim, H., Yoon, W. K., An, T. H., Oh, K., . . . Lee, H. (2024). Comprehensive phenotypic assessment of nonsense mutations in mitochondrial ND5 in mice. *Experimental & Molecular Medicine.* https://doi.org/10.1038/s12276-024-01333-9

Kleefeld, F., Cross, E., Lagos, D., Schoser, B., Hentschel, A., Ruck, T., Nelke, C., Walli, S., Hahn, K., Hathazi, D., Mammen, A. L., Casal-Dominguez, M., Gut, M., Gut, I. G., Heath, S., Schänzer, A., Goebel, H. H., Pinal-Fernandez, I., Roos, A., … Horvath, R. (2024). Mitochondrial leakage and mtDNA damage trigger early immune response in

Inclusion Body Myositis. *bioRxiv* 2024.08.05.606624; https://doi.org/10.1101/2024.08.05.606624

Kleefeld, F., Cross, E., Lagos, D., Walli, S., Schoser, B., Hentschel, A., Ruck, T., Nelke, C., Hahn, K., Hathazi, D., Mammen, A. L., Casal-Dominguez, M., Gut, M., Gut, I. G., Heath, S., Schänzer, A., Goebel, H.-H., Pinal-Fernandez, I., Roos, A., … Horvath, R. (2025). Mitochondrial damage is associated with an early immune response in inclusion body myositis. *Brain*, *148*(9), 3199–3214. https://doi.org/10.1093/brain/awaf118

Kleefeld, F., Uruha, A., Schänzer, A., Nishimura, A., Roos, A., Schneider, U., Goebel, H. H., Schuelke, M., Hahn, K., Preusse, C., & Stenzel, W. (2022). Morphologic and molecular patterns of polymyositis with mitochondrial pathology and inclusion body myositis. *Neurology*, *99*(20). https://doi.org/10.1212/WNL.0000000000201103

Klemmensen, M. M., Borrowman, S. H., Pearce, C., Pyles, B., & Chandra, B. (2023). Mitochondrial dysfunction in neurodegenerative disorders. *Neurotherapeutics, 21*(1), e00292. https://doi.org/10.1016/j.neurot.2023.10.002

Neurological and neuromuscular syndromes are the most frequent clinical presentations of mitochondrial disorders [2]. Although the density of mitochondria may be lower in neurons than it is in other cells, such as myocytes, the brain consumes almost ten times more oxygen and glucose compared to other tissues [3]. A resting cortical neuron consumes 4.7 billion ATP molecules per second 4], highlighting the dependence of the nervous system on mitochondria for its proper functioning. Mitochondria get transported across the neuron by miniature motors along tubular tracks to produce ATP where it's needed most. The highest demand for ATP in a neuron is usually in synapses, although some remain in basic housekeeping locations [4].

Knoll, A. H. (2015). *Life on a young planet*. Princeton University Press.

Know, L. (2018). *Mitochondria and the future of medicine: The Key to Understanding Disease, Chronic Illness, Aging, and Life Itself*. Chelsea Green Publishing.

Koene, S., & Smeitink, J. (2009). Mitochondrial medicine: Entering the era of treatment. *Journal of Internal Medicine*, *265*(2), 193–209.

Koonin, E. V. (2010). The origin and early evolution of eukaryotes in the light of phylogenomics. *Genome Biology*, *11*(5), 209. https://doi.org/10.1186/gb-2010-11-5-209

Kramer, P., & Bressan, P. (2015). Humans as superorganisms: How microbes, viruses, imprinted genes, and other selfish entities shape our behavior. *Perspectives on Psychological Science, 10*(4), 464–481. https://doi.org/10.1177/1745691615583131

Kramer, P., & Bressan, P. (2017). Our (Mother's) mitochondria and our mind. *Perspectives on Psychological Science, 13*(1), 88–100. https://doi.org/10.1177/1745691617718356

Kremer, L. S., Golder, Z., Barton-Owen, T., Papadea, P., Koolmeister, C., Chinnery, P. F., & Larsson, N.-G. (2025). The bottleneck for maternal transmission of mtDNA is linked to purifying selection by autophagy. ScieNce AdvANceS.

Kummer, K., Bertram, I., Zechel, S., Hoffmann, D. B., & Schmidt, J. (2023). Inflammasome in skeletal muscle: NLRP3 is an inflammatory cell stress component in inclusion body myositis. *International Journal of Molecular Sciences, 24*(13), 10675. https://doi.org/10.3390/ijms241310675

Kuszak, A. J., Espey, M. G., Falk, M. J., Holmbeck, M. A., Manfredi, G., Shadel, G. S., Vernon, H. J., & Zolkipli-Cunningham, Z. (2017). Nutritional interventions for mitochondrial OXPHOS deficiencies: Mechanisms and model systems. *Annual Review of Pathology Mechanisms of Disease, 13*(1), 163–191. https://doi.org/10.1146/annurev-pathol-020117-043644

Lambert, J. (2018, December 11). What a newfound kingdom means for the tree of life. *Quanta Magazine*. https://www.quantamagazine.org/what-a-newfound-kingdom-means-for-the-tree-of-life-20181211/

Landau, E. (2025, May 19). 'Turbocharged' mitochondria power birds' epic migratory journeys. *Quanta Magazine.* https://www.quantamagazine.org/turbocharged-mitochondria-power-birds-epic-migratory-journeys-20250519/

Lane, N. (2002). *Oxygen: The molecule that made the world*. Oxford University Press, USA.

Lane, N. (2005). *Power, sex, suicide: Mitochondria and the meaning of life.* OUP Oxford.

Lane, N. (2015). *The vital question: Energy, evolution, and the origins of complex life.* W. W. Norton & Company.

Lane, N. (2017). Origin of the Eukaryotic Cell. *Molecular Frontiers Journal*, *01*(02), 108–120. https://doi.org/10.1142/S2529732517400120

Lane, N. (2018). *Power, sex, suicide: Mitochondria and the meaning of life* (2nd ed.). Oxford

University Press.

Lanese, N. (2025, July 9). 8-year-old with rare, fatal disease shows dramatic improvement on experimental treatment. *Live Science*. https://www.livescience.com/health/medicine-drugs/8-year-old-with-rare-fatal-disease-shows-dramatic-improvement-on-experimental-treatment

Lanese, N. (2025, May 1). Scientists just discovered a single molecule that may treat rare, devastating mitochondrial diseases. *Live Science*. https://www.livescience.com/health/medicine-drugs/scientists-just-discovered-a-single-molecule-that-may-treat-rare-devastating-mitochondrial-diseases

Larsson, N. G. (2009). Introduction: Euromit VII–summarizing 50 years of research on mitochondrial disease. *Journal of Internal Medicine*, *265*(2), 170–173.10.1111/j.1365-2796.2008.02064.x

Lauletta, A., Bosco, L., Merlonghi, G., Falzone, Y. M., Cheli, M., Bencivenga, R. P., Zoppi, D., Ceccanti, M., Kleefeld, F., Léonard-Louis, S., Stenzel, W., Benveniste, O., Maggi, L., Previtali, S. C., & Garibaldi, M. (2025). Mitochondrial pathology in inflammatory myopathies: a marker of worse clinical outcome. *Journal of Neurology, 272*(7). https://doi.org/10.1007/s00415-025-13192-z

Lax, N. Z., Turnbull, D. M., & Reeve, A. K. (2011). Mitochondrial mutations: Newly discovered players in neuronal degeneration. *The Neuroscientist, 17*(6), 645-658. https://doi.org/10.1177/1073858411385469

Leermakers, P. A., & Gosker, H. R. (2016). Skeletal muscle mitophagy in chronic disease: Implications for muscle oxidative capacity? *Current Opinion in Clinical Nutrition & Metabolic Care*, *19*(6), 427–433. https://doi.org/10.1097/MCO.0000000000000319

Lei, Y., Gan, M., Qiu, Y., Chen, Q., Wang, X., Liao, T., Zhao, M., Chen, L., Zhang, S., Zhao, Y., Niu, L., Wang, Y., Zhu, L., & Shen, L. (2024). The role of mitochondrial dynamics and mitophagy in skeletal muscle atrophy: From molecular mechanisms to therapeutic insights. Cellular & Molecular Biology Letters, 29(1), 59. https://doi.org/10.1186/s11658-024-00572-y

Levin, J., & Strogatz, S. (2025, March 20). *How did multicellular life evolve? Quanta Magazine*.

https://www.quantamagazine.org/how-did-multicellular-life-evolve-20250320/

Li, J., Wang, Z., Li, C., Song, Y., Wang, Y., Bo, H., & Zhang, Y. (2022). Impact of Exercise and Aging on Mitochondrial Homeostasis in Skeletal Muscle: Roles of ROS and Epigenetics. Cells, 11(13), 2086. https://doi.org/10.3390/cells11132086

Li, Q., Weiss, K., Niwa, F., Riemer, J., & Hoppe, T. (2025). Leucine inhibits degradation of outer mitochondrial membrane proteins to adapt mitochondrial respiration. Nature Cell Biology, 27(11), 1889–1901. https://doi.org/10.1038/s41556-025-01799-3

Lin, L., Ren, R., Xiong, Q., Zheng, C., Yang, B., & Wang, H. (2024). Remodeling of T-cell mitochondrial metabolism to treat autoimmune diseases. *Autoimmunity Reviews, 23*(6), 103583. https://doi.org/10.1016/j.autrev.2024.103583

Lindgren, A. U., Roos, S., Hedberg Oldfors, C., Moslemi, A.-R., Lindberg, C., & Oldfors, A. (2014). Mitochondrial pathology in inclusion body myositis. *Neuromuscular Disorders, 2015*. http://dx.doi.org/10.1016/j.nmd.2014.12.010

Lindgren, A. U., Roos, S., Hedberg Oldfors, C., Moslemi, A.-R., Lindberg, C., & Oldfors, A. (2015). Mitochondrial pathology in inclusion body myositis. *Neuromuscular Disorders, 25*(4), 281–288. https://doi.org/10.1016/j.nmd.2014.12.010

Lisci, M., Barton, P. R., Randzavola, L. O., Ma, C. Y., Marchingo, J. M., Cantrell, D. A., Paupe, V., Prudent, J., Stinchcombe, J. C., & Griffiths, G. M. (2021). Mitochondrial translation is required for sustained killing by cytotoxic T cells. *Science*, *374*(6565), eabe9977. https://doi.org/10.1126/science.abe9977

Liu, J., Jia, Z., & Gong, W. (2021). Circulating mitochondrial DNA stimulates innate immune signaling pathways to mediate acute kidney injury. *Frontiers in Immunology*, *12*. https://doi.org/10.3389/fimmu.2021.680648

Liu, S., D'Amico, D., Shankland, E., Bhayana, S., Garcia, J. M., Aebischer, P., Rinsch, C., Singh, A., & Marcinek, D. J. (2022). Effect of urolithin A supplementation on muscle endurance and mitochondrial health in older adults: A randomized clinical trial. *JAMA Network Open*, *5*(1), e2144279. https://doi.org/10.1001/jamanetworkopen.2021.44279

López-García, P., & Moreira, D. (2015). Open questions on the origin of eukaryotes. *Trends in Ecology & Evolution*, *30*(11), 697–708. https://doi.org/10.1016/j.tree.2015.09.005

Lv, J., Li, Y., Shi, S., Xu, X., Wu, H., Zhang, B., & Song, Q. (2022). Skeletal muscle mitochon-

drial remodeling in heart failure: An update on mechanisms and therapeutic opportunities. Biomedicine & Pharmacotherapy, 155, 113833. https://doi.org/10.1016/j.biopha.2022.113833

Ma, Z., Xu, Q., & Xu, X. (2025). The pathophysiological role of mitochondrial oxidative stress in rheumatic diseases. *Journal of Inflammation Research*, Volume 18, 12021–12044. https://doi.org/10.2147/JIR.S534574

Distinct from nuclear genomic transmission patterns, mtDNA strictly adheres to maternal inheritance. Of clinical significance, pathogenic variants in oxidative phosphorylation-related mitochondrial genes underpin the multifaceted clinicopathological manifestations observed in numerous degenerative disorders and metabolic syndromes. Following cellular damage, while autolysosomal DNase II typically processes mtDNA fragments into metabolically inert nucleotides, emerging evidence implicates these degradation products in rheumatic pathogenesis. Specifically, oxidatively modified mtDNA escaping lysosomal clearance demonstrates dual functionality: extracellularly, these fragments act as DAMPs that engage Toll-like receptor 9 (TLR9) and NALP3 inflammasomes to propagate pro-inflammatory cascades via caspase-1 activation; intracellularly, they stimulate mitophagy through retrograde signaling upon mitochondrial extrusion.

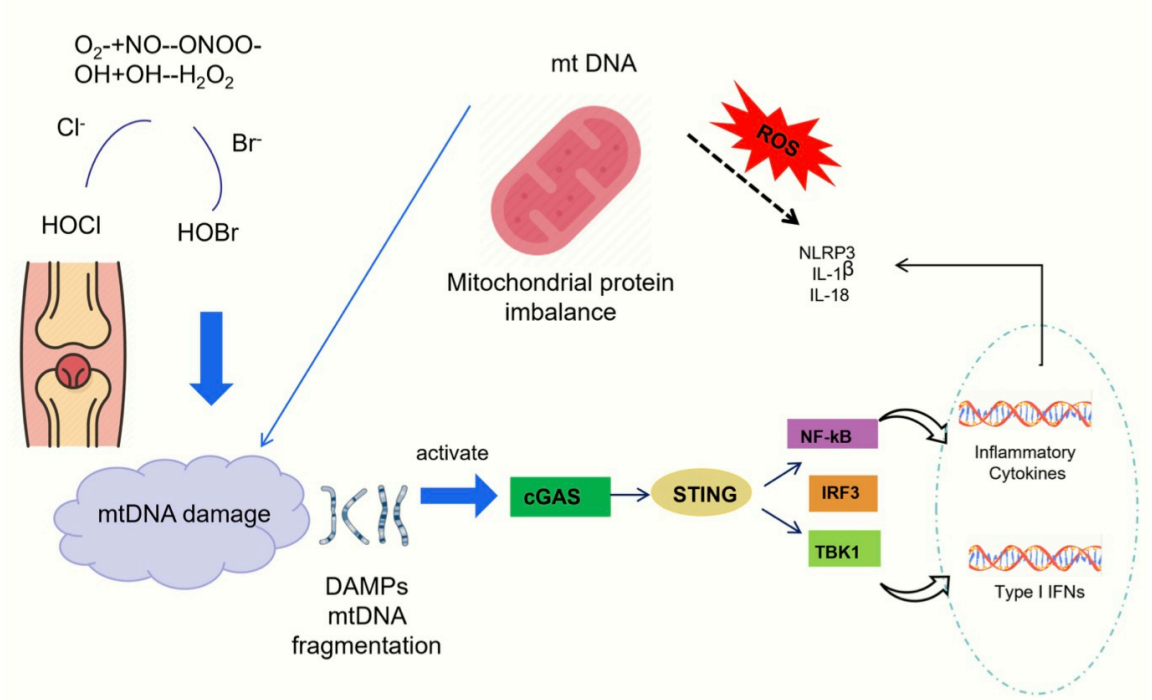

Figure 2 Proposed model for mitochondria-centered pathogenesis in ROS-induced rheumatic diseases.

The clinical deployment of antioxidants necessitates careful risk-benefit assessment due to their potential to disrupt physiological redox signaling. ROS serve as essential secondary messengers regulating immune cell differentiation, autophagic processes, and inflammatory responses. 213,214 Non-selective antioxidants may compromise antimicrobial defense by inhibiting neutrophil extracellular trap formation (NET), dysregulate T-cell homeostasis through altered Treg/Th17 balance, and impair hypoxia-inducible factor (HIF)-mediated tissue repair.

Future translational initiatives must prioritize mitochondrially-targeted antioxidants, which achieve >100-fold organellar accumulation to maximize therapeutic efficacy while minimizing systemic toxicity.

This review positions ROS as a central driver of mitochondrial impairment and mtDNA damage, while highlighting the inadequacy of empirical antioxidant approaches. Despite their therapeutic utility in conditions like rheumatoid arthritis, antioxidants exhibit dose-dependent paradoxes—high concentrations may provoke mitochondrial toxicity via pore activation—necessitating human validation of preclinical targets to resolve contradictory

evidence.

Macken, W. L., Vandrovcova, J., Hanna, M. G., & Pitceathly, R. D. S. (2021). Applying genomic and transcriptomic advances to mitochondrial medicine. *Nature Reviews Neurology*. https://doi.org/10.1038/s41582-021-00455-2

Maresca, A., Del Dotto, V., Romagnoli, M., La Morgia, C., Di Vito, L., Capristo, M., Valentino, M. L., & Carelli, V. (2020). Expanding and validating the biomarkers for mitochondrial diseases. *Journal of Molecular Medicine*. https://doi.org/10.1007/s00109-020-01967-y

Margulis, L., & Sagan, D. (1997a). *Microcosmos: Four billion years of microbial evolution.* University of California Press.

Margulis, L., & Sagan, D. (1997b). *Slanted truths: Essays on Gaia, symbiosis and evolution.* Copernicus.

Margulis, L., & Sagan, D. (2000). *What is life?* University of California Press.

Margulis, L., & Sagan, D. (2002). *Acquiring genomes: A theory of the origins of species.* Basic Books.

Marques, E., Kramer, R., & Ryan, D. G. (2024). Multifaceted mitochondria in innate immunity. *Npj Metabolic Health and Disease*, *2*(1). https://doi.org/10.1038/s44324-024-00008-3

Martin, W. F., & Mentel, M. (2010) The Origin of Mitochondria. Nature Education 3(9):58

Martin, W. F., Tielens, A. G. M., & Mentel, M. (2021). *Mitochondria and anaerobic energy metabolism in eukaryotes.* De Gruyter. https://doi.org/10.1515/9783110612417

Matsuhashi, T., Sato, T., Kanno, S., Suzuki, T., Matsuo, A., Oba, Y., Kikusato, M., Ogasawara, E., Kudo, T., Suzuki, K., Ohara, O., Shimbo, H., Nanto, F., Yamaguchi, H., Saigusa, D., Mukaiyama, Y., Watabe, A., Kikuchi, K., Shima, H., . . . Abe, T. (2017). Mitochonic acid 5 (MA-5) facilitates ATP synthase oligomerization and cell survival in various mitochondrial diseases. *EBioMedicine, 20*, 27–38. https://doi.org/10.1016/j.ebiom.2017.05.016

McArthur, E., Rinker, D. C., & Capra, J. A. (2021). Quantifying the contribution of Neanderthal introgression to the heritability of complex traits. *Nature Communications, 12*(1), 4481. https://doi.org/10.1038/s41467-021-24582-y

McBride, H. M., Neuspiel, M., & Wasiak, S. (2006). Mitochondria: more than just a powerhouse. *Current Biology*, *16*(14), R551–R560. https://doi.org/10.1016/j.cub.2006.06.054

McFarland, R., & Turnbull, D. M. (2009). Batteries not included: Diagnosis and management of

mitochondrial disease. *J Intern Med*, *265*(2), 210–228. doi: 10.1111/j.1365-2796.2008.02066.x

McRae, M. (2024, August 29). Mitochondria dump DNA in the brain, potentially cutting years off our lives. *ScienceAlert*. https://www.sciencealert.com/mitochondria-dump-dna-in-the-brain-potentially-cutting-years-off-our-lives

McWilliams, T. G., & Suomalainen, A. (2019). Mitochondrial DNA can be inherited from fathers, not just mothers. *Nature*, *565*(7739), 296–297. https://doi.org/10.1038/d41586-019-00093-1

Means, C., & Means, C. (2024). *Good energy: The surprising connection between metabolism and limitless health*. Penguin.

Miller, K. N., Li, B., Pierce-Hoffman, H. R., Patel, S., Lei, X., Rajesh, A., Teneche, M. G., Havas, A. P., Gandhi, A., Macip, C. C., Lyu, J., Victorelli, S. G., Woo, S., Lagnado, A. B., LaPorta, M. A., Liu, T., Dasgupta, N., Li, S., Davis, A., . . . Adams, P. D. (2025). p53 enhances DNA repair and suppresses cytoplasmic chromatin fragments and inflammation in senescent cells. *Nature Communications*, *16*(1). https://doi.org/10.1038/s41467-025-57229-3

Miller, V. J., LaFountain, R. A., Barnhart, E., Sapper, T. S., Short, J., Arnold, W. D., Hyde, P. N., Crabtree, C. D., Kackley, M. L., Kraemer, W. J., Villamena, F. A., & Volek, J. S. (2020). A ketogenic diet combined with exercise alters mitochondrial function in human skeletal muscle while improving metabolic health. *American Journal of Physiology-Endocrinology and Metabolism*, *319*(6), E995–E1007. https://doi.org/10.1152/ajpendo.00305.2020

Miranda, D. R. (2023, February 7). Scientist challenges David Sinclair's Best-Selling book on aging. *NAD+ Aging Science.* https://www.nad.com/news/charles-brenner-critiques-david-sinclairs-best-selling-book-on-aging

Mitochondria are flinging their DNA into our brain cells. (2024, August 22). *ScienceDaily*. https://www.sciencedaily.com/releases/2024/08/240822142624.htm

Mitochondria may hold the key to curing diabetes. (2025, February 7). *ScienceDaily*. https://www.sciencedaily.com/releases/2025/02/250207152714.htm

Mitochondrial gene editing reveals links to memory. (2024, November 22). *Neuroscience News.* https://neurosciencenews.com/mitochondrial-gene-editing-memory-28112/

Mitochondrion. (2024, November 1). In *Wikipedia*. https://en.wikipedia.org/wiki/Mitochondrion

Monzel, A. S., Enríquez, J. A., & Picard, M. (2023). Multifaceted mitochondria: moving mitochondrial science beyond function and dysfunction. Nature Metabolism, 5(4), 546–562. https://doi.org/10.1038/s42255-023-00783-1

Moreira, P. I., Honda, K., Zhu, X., Nunomura, A., Casadesus, G., Smith, M. A., & Perry, G. (2006). Brain and brawn: Parallels in oxidative strength. *Neurology*, *66*(2 Suppl 1),

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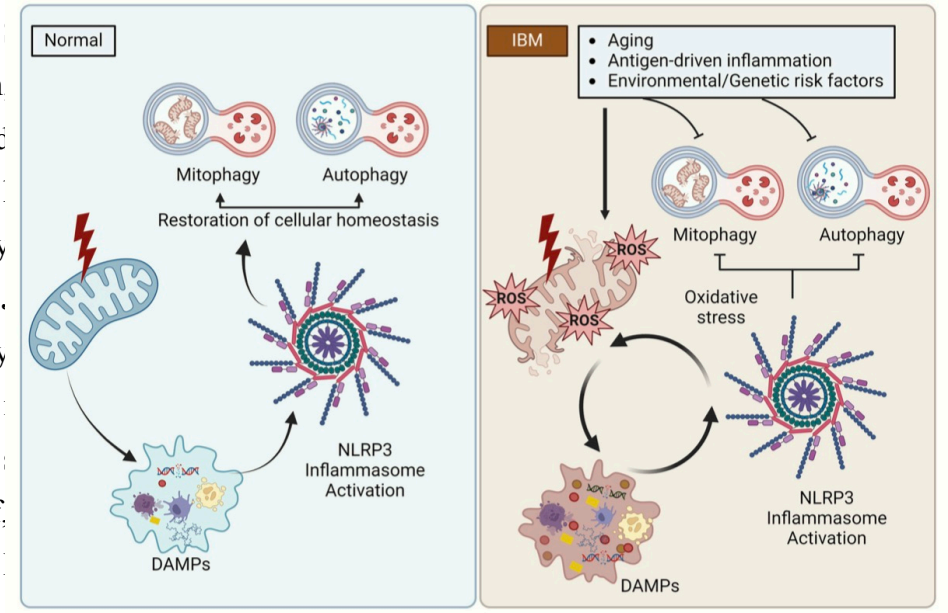

FIGURE 5 | The vicious cycle of inflammasome activation-mitochondrial dysfunction/altered mitophagy in inclusion body myositis. The release of mitochondrial damage-associated molecular patterns (DAMPs) results in the activation of the NLRP3 inflammasome. Under normal conditions, damaged mitochondria and the NRLP3 inflammasome are both subsequently removed by mitophagy and autophagy, reestablishing cellular homeostasis. In IBM, mitophagy and autophagy are altered, establishing a feedforward loop in which the inflammatory milieu results in additional oxidative stress and mitochondrial dysfunction with further release of mitochondrial DAMPs and subsequent aberrant NLRP3 inflammasome activation.

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Naddaf, E., Shammas, I., Dasari, S., Petterson, X. T., Springer, W., Trushina, E., & Lanza, I. R. (2025). Mitochondria-centred metabolomic map of inclusion body myositis: sex-specific alterations in central carbon metabolism. *Annals of the Rheumatic Diseases*. https://doi.org/10.1016/j.ard.2025.05.003

Nagai, A., Nagai, T., Yaguchi, H., Fujii, S., Uwatoko, H., Shirai, S., Horiuchi, K., Iwata, I., Matsushima, M., Ura, S., Anzai, T., & Yabe, I. (2022). Clinical features of anti-mitochondrial M2 antibody-positive myositis: Case series of 17 patients. *Journal of the Neurological Sciences*, *442*, 120391. https://doi.org/10.1016/j.jns.2022.120391

Nagy, S., Khan, A., Machado, P. M., & Houlden, H. (2023). Inclusion body myositis: From

genetics to clinical trials. *Journal of Neurology, 270*(3), 1787–1797. https://doi.org/10.1007/s00415-022-11459-3

Nathan, C., & Cunningham-Bussel, A. (2013). Beyond oxidative stress: An immunologist's guide to reactive oxygen species. *Nature Reviews Immunology, 13*(5), 349–361.

Navas, P., & Salviati, L. (Eds.). (2021). *Mitochondrial diseases: Theory, diagnosis and therapy*. Springer.

Nelke, C., Schroeter, C. B., Theissen, L., Preusse, C., Pawlitzki, M., Räuber, S., Dobelmann, V., Cengiz, D., Kleefeld, F., Roos, A., Schoser, B., Brunn, A., Neuen-Jacob, E., Zschüntzsch, J., Meuth, S. G., Stenzel, W., & Ruck, T. (2023). Senescent fibro-adipogenic progenitors are potential drivers of pathology in inclusion body myositis. Acta Neuropathologica, 146(5), 725–745. https://doi.org/10.1007/s00401-023-02637-2

Neuzil, J., Pervaiz, S., & Fulda, S. (Eds.). (2014). *Mitochondria: The anti-cancer target for the third millennium*. Springer.

Nicholls, T. J., Rorbach, J., & Minczuk, M. (2013). Mitochondria: Mitochondrial RNA metabolism and human disease. *The International Journal of Biochemistry & Cell Biology*, *45*(4), 845–849. http://www.ncbi.nlm.nih.gov/pubmed/23333854

Nicod, J., Wagner, S., Vonberg, F., Schlicht, K. F., Tadic, A., Mott, R., Lieb, K., & Flint, J. (2015). The amount of mitochondrial DNA in blood reflects the course of a depressive episode. *Biological Psychiatry*. http://dx.doi.org/10.1016/j.biopsych.2015.12.019 http://linkinghub.elsevier.com/retrieve/pii/S0006322315010847

Nield, D. (2025, October 4). Mitochondria dump their rubbish DNA, and it could be costing us our health. *ScienceAlert*. https://www.sciencealert.com/mitochondria-dump-their-rubbish-dna-and-it-could-be-costing-us-our-health

NLRP3. (2025, July 19). In *Wikipedia*, The Free Encyclopedia. Retrieved 07:35, August 9, 2025, from https://en.wikipedia.org/w/index.php?title=NLRP3&oldid=1301328739

Notarnicola, A., Hellstrom, C., Horuluoglu, B., Pin, E., Preger, C., Bonomi, F., De Paepe, B., De Bleecker, J. L., Van Der Kooi, A. J., De Visser, M., Sacconi, S., Machado, P., Badrising, U. A., Rietveld, A., Pruijn, G., Rothwell, S., Lilleker, J. B., Chinoy, H., Benveniste, O., … Lundberg, I. E. (2024). Autoantibodies against a subunit of mitochondrial respiratory chain complex I in inclusion body myositis. *Journal of Autoimmunity, 149,* 103332.

https://doi.org/10.1016/j.jaut.2024.103332

Nuccio, A., Nogueira-Ferreira, R., Moreira-Pais, A., Attanzio, A., Duarte, J. A., Luparello, C., & Ferreira, R. (2024). The contribution of mitochondria to age-related skeletal muscle wasting: A sex-specific perspective. Life Sciences, 336, 122324. https://doi.org/10.1016/j.lfs.2023.122324

Oikawa, Y., Izumi, R., Koide, M., Hagiwara, Y., Kanzaki, M., Suzuki, N., Kikuchi, K., Matsuhashi, T., Akiyama, Y., Ichijo, M., Watanabe, S., Toyohara, T., Suzuki, T., Mishima, E., Akiyama, Y., Ogata, Y., Suzuki, C., Hayashi, H., Kodama, E. N., . . . Abe, T. (2020). Mitochondrial dysfunction underlying sporadic inclusion body myositis is ameliorated by the mitochondrial homing drug MA-5. *PLoS ONE*, *15*(12), e0231064. https://doi.org/10.1371/journal.pone.0231064

Oldfors, A., Moslemi, A. R., Fyhr, I., Holme, E., Larsson, N., & Lindberg, C. (1995). Mitochondrial DNA deletions in muscle fibers in inclusion body myositis. *Journal of Neuropathology & Experimental Neurology*, *54*(4), 581–587. https://doi.org/10.1097/00005072-199507000-00012

Oldfors, A., Moslemi, A. R., Jonasson, L., Ohlsson, M., Kollberg, G., & Lindberg, C. (2006). Mitochondrial abnormalities in inclusion-body myositis. *Neurology*, *66*(1_suppl_1). https://doi.org/10.1212/01.wnl.0000192127.63013.8d

Olguín, H. J., Guzmán, D. C., García, E. H., & Mejía, G. B. (2016). The role of dopamine and its dysfunction as a consequence of oxidative stress. *Oxidative Medicine and Cellular Longevity*, *2016*, 1–13. https://doi.org/10.1155/2016/9730467

Pacold, M. (2025). Molecule eases neurological symptoms of mitochondrial deficiency in coenzyme Q10. *Nature*, d41586-025-02289–0. https://doi.org/10.1038/d41586-025-02289-0

Palma, F. R., Gantner, B. N., Sakiyama, M. J., Kayzuka, C., Shukla, S., Lacchini, R., Cunniff, B., & Bonini, M. G. (2024). ROS production by mitochondria: Function or dysfunction? *Oncogene, 43*(5), 295–303. https://doi.org/10.1038/s41388-023-02907-z

Papadimas, G. K., Kokkinis, C., Xirou, S., Chrysanthou, M., Kararizou, E., & Papadopoulos, C. (2019). Polymyositis with mitochondrial pathology or atypical form of sporadic inclusion body myositis: Case series and review of the literature. *Rheumatology International*,

39(8), 1459–1466. https://doi.org/10.1007/s00296-019-04314-8

Patin, E., & Quintana-Murci, L. (2025). Tracing the evolution of human immunity through ancient DNA. *Annual Review of Immunology, 43*(1), 57–82. https://doi.org/10.1146/annurev-immunol-082323-024638

Paul, S., Saha, D., & Bk, B. (2021). Mitochondrial dysfunction and mitophagy closely cooperate in neurological deficits associated with Alzheimer's disease and type 2 Diabetes. *Molecular Neurobiology*, *58*(8), 3677–3691. https://doi.org/10.1007/s12035-021-02365-2

Pearce, S., Nezich, C. L., & Spinazzola, A. (2013). Mitochondrial diseases: Translation matters. *Molecular and Cellular Neurosciences*, *55*, 1–12. http://www.ncbi.nlm.nih.gov/pubmed/22986124

Pernas, L., & Scorrano, L. (2016). Mito-Morphosis: Mitochondrial fusion, fission, and cristae remodeling as key mediators of cellular function. *Annual Review of Physiology*, *78*(1), 505–531. https://doi.org/10.1146/annurev-physiol-021115-105011

Picard, M. (2025, June). The social lives of mitochondria: When these energy giving organelles thrive, so do we. *Scientific American*, 50–57.

Picard, M., & Sandi, C. (2020). The social nature of mitochondria: Implications for human health. *Neuroscience & Biobehavioral Reviews, 120*, 595–610. https://doi.org/10.1016/j.neubiorev.2020.04.017

Picca, A., Faitg, J., Auwerx, J., Ferrucci, L., & D'Amico, D. (2023). Mitophagy in human health, ageing and disease. *Nature Metabolism, 5*(12), 2047–2061. https://doi.org/10.1038/s42255-023-00930-8

Qu, C., Keijer, J., Adjobo-Hermans, M. J. W., Van De Wal, M., Schirris, T., Van Karnebeek, C., Pan, Y., & Koopman, W. J. H. (2021). The ketogenic diet as a therapeutic intervention strategy in mitochondrial disease. *The International Journal of Biochemistry & Cell Biology*, *138*, 106050. https://doi.org/10.1016/j.biocel.2021.106050

Raval, P. K., Martin, W. F., & Gould, S. B. (2023). Mitochondrial evolution: Gene shuffling, endosymbiosis, and signaling. *Science Advances*, *9*(32), eadj4493. https://doi.org/10.1126/sciadv.adj4493

Reichert, A. S. (Ed.). (2024). *The dynamic nature of mitochondria: From ultrastructure to health and disease.* CRC Press.

Riley, J. S., & Tait, S. W. (2020). Mitochondrial DNA in inflammation and immunity. *EMBO Reports*, *21*(4). https://doi.org/10.15252/embr.201949799

Rocheleau, J. (2025). Mighty mitochondria: Cell powerhouses harnessed for healing. *Knowable Magazine*. https://doi.org/10.1146/knowable-070825-1

Roger, A. J., Muñoz-Gómez, S. A., & Kamikawa, R. (2017). The origin and diversification of mitochondria. *Current Biology*, *27*(21), R1177–R1192. https://doi.org/10.1016/j.cub.2017.09.015

Rohman, M. (2025, February 6). Mitochondria's secret power unleashed in the battle against inflammation. *SciTechDaily*. https://scitechdaily.com/mitochondrias-secret-power-unleashed-in-the-battle-against-inflammation/

Rohman, M. (2025, January 23). Mitochondria may be a promising therapeutic target for inflammatory diseases. *Medical Xpress* - medical research advances and health news. https://medicalxpress.com/news/2025-01-mitochondria-therapeutic-inflammatory-diseases.html

Romani, M., Sorrentino, V., Oh, C. M., Li, H., de Lima, T. I., Zhang, H., Shong, M., & Auwerx, J. (2021). NAD+ boosting reduces age-associated amyloidosis and restores mitochondrial homeostasis in muscle. *Cell Reports*, *34*(3), 108660. https://doi.org/10.1016/j.celrep.2020.108660

Rygiel, K. A., Miller, J., & Schaefer, A. M. (2015). Pathogenesis and clinical significance of mitochondrial abnormalities in inclusion body myositis. Frontiers in Aging Neuroscience, 7, 7. https://doi.org/10.3389/fnagi.2015.00007

Rygiel, K. A., Miller, J., Grady, J. P., Rocha, M. C., Taylor, R. W., & Turnbull, D. M. (2015). Mitochondrial and inflammatory changes in sporadic inclusion body myositis. *Neuropathology and Applied Neurobiology*, *41*(3), 288–303. https://doi.org/10.1111/nan.12149

Rygiel, K. A., Tuppen, H. A., Grady, J. P., Vincent, A., Blakely, E. L., Reeve, A. K., Taylor, R. W., Picard, M., Miller, J., & Turnbull, D. M. (2016). Complex mitochondrial DNA rearrangements in individual cells from patients with sporadic inclusion body myositis. *Nucleic Acids Research*, *44*(11), 5313–5329. https://doi.org/10.1093/nar/gkw382

Sagan, L. (1967). On the origin of mitosing cells. *Journal of Theoretical Biology*, *14*(3),

225-274. https://doi.org/10.1016/0022-5193(67)90079-3

Sajdel-Sul, E. M., Lipinski, B., Windom, H., Audhya, T., & McGinnis, W. (2008). Oxidative Stress in Autism: Elevated Cerebellar 3-nitrotyrosine Levels. *American Journal of Biochemistry and Biotechnology*, *4*(2), 73–84. https://doi.org/10.3844/ajbbsp.2008.73.84

San-Millán, I. (2023). The key role of mitochondrial function in health and disease. *Antioxidants, 12*(4), 782. https://doi.org/10.3390/antiox12040782

Scheffler, I. E. (2001). A century of mitochondrial research: Achievements and perspectives. *Mitochondrion*, *1*(1), 3–31. https://doi.org/10.1016/S1567-7249(00)00002-7

Schuler, M. H., English, A. M., Xiao, T., Campbell, T. J., Shaw, J. M., & Hughes, A. L. (2021). Mitochondrial-derived compartments facilitate cellular adaptation to amino acid stress. *Molecular Cell*, *81*(18), 3786-3802.e13. https://doi.org/10.1016/j.molcel.2021.08.021

Sercel, A. J., Sturm, G., Gallagher, D., St-Onge, M. P., Kempes, C. P., Pontzer, H., Hirano, M., & Picard, M. (2024). Hypermetabolism and energetic constraints in mitochondrial disorders. *Nature Metabolism*, *6*(2), 192–195. https://doi.org/10.1038/s42255-023-00968-8

Shabrokh, E., Kavanaugh, J., McMillan, R., Pittman, J., Hulver, M., & Frisard, M. (2014). Mitochondrial dysregulation in skeletal muscle from patients diagnosed with Alzheimer's disease and sporadic inclusion body myositis. *Open Journal of Molecular and Integrative Physiology*, *04*(02), 11–19. https://doi.org/10.4236/ojmip.2014.42002

Shi, G., Miller, C., Kuno, S., Rey Hipolito, A. G., El Nagar, S., Riboldi, G. M., Korn, M., Tran, W. C., Wang, Z., Ficaro, L., Lin, T., Spillier, Q., Gamallo-Lana, B., Jones, D. R., Snuderl, M., Song, S. C., Mar, A. C., Joyner, A. L., Sillitoe, R. V., … Pacold, M. E. (2025). Coenzyme Q headgroup intermediates can ameliorate a mitochondrial encephalopathy. *Nature*. https://doi.org/10.1038/s41586-025-09246-x

Pacold, M. (2025). Molecule eases neurological symptoms of mitochondrial deficiency in coenzyme Q10. *Nature*, d41586-025-02289–0. https://doi.org/10.1038/d41586-025-02289-0 [This is a summary of: Shi, G. et al. Coenzyme Q headgroup intermediates can ameliorate a mitochondrial encephalopathy *Nature* https://doi.org/10.1038/s41586-025-09246-x (2025).]

This study examines an extremely rare mitochondrial disease (with only 2000 known

cases) caused by a CoQ10 deficiency, known as HPDL encephalopathy. Using a mouse model, the study explored methods to treat CoQ10 deficiency that are more effective than CoQ10 supplements. The study used CoQ10 precursors (4-HMA and 4-HB) rather than CoQ10 itself. Implications for IBM: It is speculated that if IBM-related mitochondrial dysfunction involves impaired CoQ10 biosynthesis, supplementation with 4-HB and 4-HMA, rather than CoQ10 itself, might be a more effective way to address CoQ10 deficiency and mitochondrial dysfunction.

Shimazaki, R., Uruha, A., Kimura, H., Nagaoka, U., Kawazoe, T., Yamashita, S., Komori, T., Miyamoto, K., Matsubara, S., Sugaya, K., Nagao, M., & Isozaki, E. (2020). Rimmed vacuoles in myositis associated with antimitochondrial antibody. *Journal of Clinical Neurology (Korea)*, *16*(3), 510–512. https://doi.org/10.3988/jcn.2020.16.3.510

Sinclair, D. A. (2019). Lifespan: Why we age - and why we don't have to. HarperThorsons.

Sinha, P., Islam, M. N., Bhattacharya, S., & Bhattacharya, J. (2016). Intercellular mitochondrial transfer: bioenergetic crosstalk between cells. *Current Opinion in Genetics & Development, 38,* 97–101. https://doi.org/10.1016/j.gde.2016.05.002

Smith, J. M., & Szathmáry, E. (1999). *The origins of life: From the birth of life to the origin of language.* Oxford University Press, USA.

Song, N., Mei, S., Wang, X., Hu, G., & Lu, M. (2024). Focusing on mitochondria in the brain: from biology to therapeutics. *Translational Neurodegeneration, 13*(1). https://doi.org/10.1186/s40035-024-00409-w

Mitochondria are essential for brain functions, as they produce adenosine triphosphate (ATP) to be used by brain cells. Insufficient ATP supply will lead to brain cell death. Reactive oxygen species (ROS) are toxic byproducts of ATP generation, produced along with the respiration process. In physiological states, the ROS are maintained at a controllable steady-state level and facilitate normal redox signaling of the brain cells. Excessive production of ROS will oxidize the brain lipids and neurotransmitters to induce enrichment of unsaturated lipids, neurotransmitter auto-oxidation, RNA oxidation, etc.. Interestingly, mitochondria also possess antioxidant enzymes and endogenous antioxi-

dants to balance cellular oxidation and reduction states. In addition, the membrane dynamics, genetic information storage and the quality control system of mitochondria are closely related to the homeostasis of the brain. Even in resting states or when neurons are not releasing neurotransmitters to each other, the brain consumes 20% of the body's overall energy. As mentioned above, the brain has an extremely high metabolic demand. It utilizes approximately 20% of the body's total oxygen and glucose consumption with only 2% weight. About 70% of the calculated energy expenditures are used to support neuronal signaling including resting potentials, action potentials, postsynaptic receptor activation, glutamate cycling, and postsynaptic Ca 2 + signaling, while the remainder is for non-signaling activities like biomacromolecule turnover, axonal transport, mitochondrial proton leak and actin cytoskeleton remodeling (Fig. 1a). Neurons display most of the energy consumption. They generate ATP predominantly within mitochondria through oxidative phosphorylation (OXPHOS), with a small portion of ATP from aerobic glycolysis in the cytoplasm. A

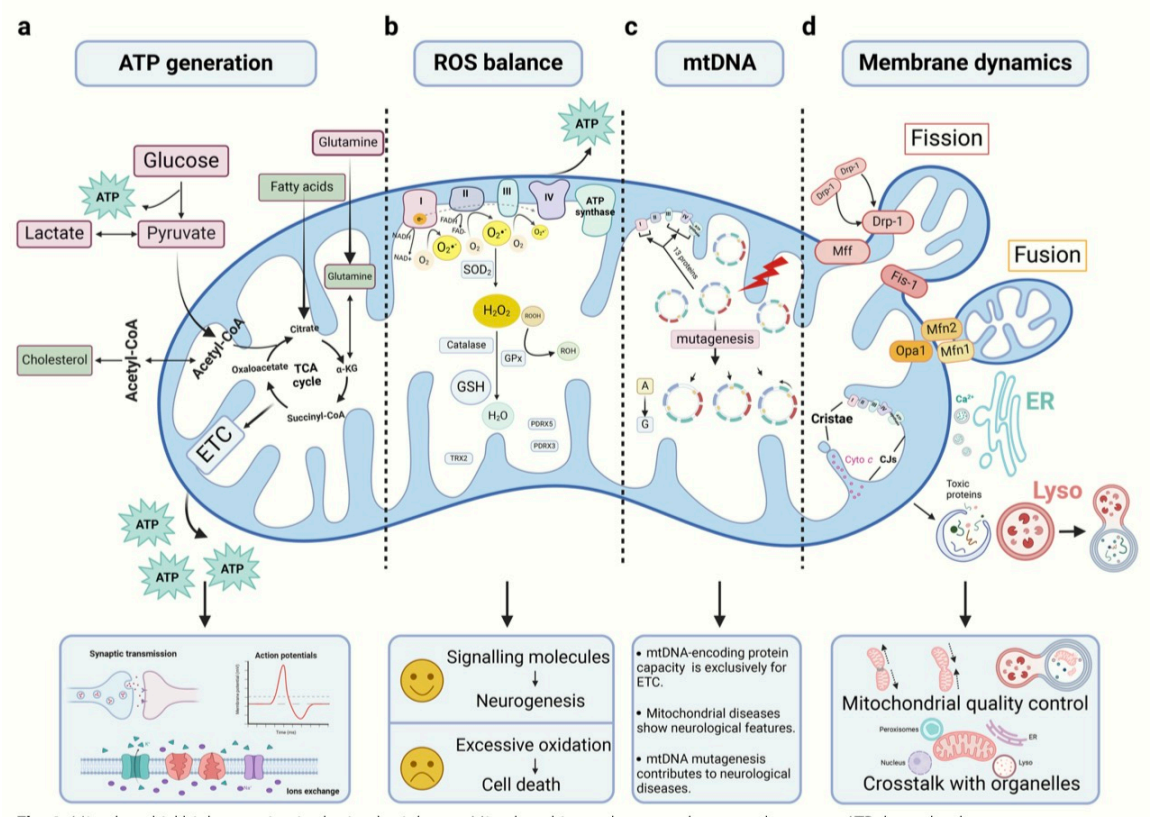

Fig. 1 Mitochondrial biology maintains brain physiology. a Mitochondria are the power house and generate ATP through relevant processes of glucose, FA and amino acid metabolism. They tightly support normal brain functions dominated by neuronal activity including synaptic transmission, neuroelectrical activity, and ion exchange. b The mitochondrial ETC is the site of mitochondrial ROS generation. During oxidative metabolism, electrons combine prematurely with oxygen to form O2 •− , which is dismutated to H2 O 2 by SOD2 and then converted to H2 O by catalase and GPx. There are also mitochondria-targeted antioxidants essential for controlling ROS homeostasis in the brain, such as PDRX3, PDRX5 and TRX2. c The entire protein-coding capacity of mtDNA is devoted to the synthesis of mitochondrial complexes except complex II. Mutagenesis in mitochondrial genome occurs at a much higher rate than that in the nuclear genome, leading to the collapse of mitochondrial functions, which is closely related to neurological diseases. d Mitochondrial membrane dynamics including mitochondrial fission/fusion, membrane interactions with other organelles and ultra-structural membrane remodeling, renders the multifaceted involvement of mitochondria in cell biology. ATP, adenosine triphosphate; cyto c, cytochrome c; ER, endoplasmic reticulum; ETC, electron transport chain; FAs: fatty acids; GPx, glutathione peroxidases; GSH, glutathione; H2 O2 , hydrogen peroxide; lyso, lysosome; O2 •− , superoxide; PDRX, peroxiredoxin; ROH, organic alcohol; ROS, reactive oxygen species; SOD2, manganese-dependent superoxide dismutase; TCA, tricarboxylic acid; TRX, thioredoxin.

Sorrentino, V., Menzies, K. J., & Auwerx, J. (2018). Repairing mitochondrial dysfunction in disease. *Annual Review of Pharmacology and Toxicology, 58*(1), 353–389. https://doi.org/10.1146/annurev-pharmtox-010716-104908

Stoolman, J. S., Grant, R. A., Billingham, L. K., Poor, T. A., Weinberg, S. E., Harding, M. C., Lu, Z., Miska, J., Szibor, M., Budinger, G. S., & Chandel, N. S. (2025). Mitochondria complex III–generated superoxide is essential for IL-10 secretion in macrophages. *Science Advances, 11*(4), eadu4369. https://doi.org/10.1126/sciadv.adu4369

Stowe, D. F. (2025). *Evolution of Bioenergetics from Elements to Life: Emergence of High Energy Mitochondria*.

Sugiura, A., Mattie, S., Prudent, J., & McBride, H. M. (2017). Newly born peroxisomes are a hybrid of mitochondrial and ER-derived pre-peroxisomes. *Nature*, *542*(7640), 251–254. https://doi.org/10.1038/nature21375

Suomalainen, A., & Battersby, B. J. (2018). Mitochondrial diseases: The contribution of organelle stress responses to pathology. *Nature Reviews Molecular Cell Biology*, *19*(2), 77–92. https://doi.org/10.1038/nrm.2017.66

Suomalainen, A., & Nunnari, J. (2024). Mitochondria at the crossroads of health and disease. *Cell*, *187*(11), 2601–2627. https://doi.org/10.1016/j.cell.2024.04.037

Švorcová, J., & Markoš, A. (2019). *Epigenetic processes and the evolution of life.* CRC Press.

Swanson, K. V., Deng, M., & Ting, J. P. (2019). The NLRP3 inflammasome: molecular activation and regulation to therapeutics. *Nature Reviews. Immunology, 19*(8), 477–489. https://doi.org/10.1038/s41577-019-0165-0

Taylor, R. W., Schaefer, A. M., Barron, M. J., McFarland, R., & Turnbull, D. M. (2004). The diagnosis of mitochondrial muscle disease. *Neuromuscular Disorders*, *14*(4), 237–245. 10.1016/j.nmd.2003.12.004

Temiz, P., Weihl, C. C., & Pestronk, A. (2009). Inflammatory myopathies with mitochondrial pathology and protein aggregates. *Journal of the Neurological Sciences*, *278*(1–2), 25–29. http://dx.doi.org/10.1016/j.jns.2008.11.010

Temme, S., Zacharias, M., Neumann, J., Wohlfromm, S., König, A., Temme, N., Springer, S., Trowsdale, J., & Koch, N. (2014a). A novel family of human leukocyte antigen class II receptors may have its origin in archaic human species. *Journal of Biological Chemistry, 289*(2), 639–653. https://doi.org/10.1074/jbc.M113.515767

The cell's powerhouses: Molecular machines enable efficient energy production. (2025, March 20). ScienceDaily. https://www.sciencedaily.com/releases/2025/03/250320144617.htm

The citric acid cycle. (n.d.). *Khan Academy*. https://www.khanacademy.org/science/biology/cellular-respiration-and-fermentation/pyruvate-oxidation-and-the-citric-acid-cycle/a/the-citric-acid-cycle

Torralba, D., Baixauli, F., & Sánchez-Madrid, F. (2016). Mitochondria know no boundaries: Mechanisms and functions of intercellular mitochondrial transfer. *Frontiers in Cell and Developmental Biology,* 4. https://doi.org/10.3389/fcell.2016.00107

Tresse, E., Marturia-Navarro, J., Sew, W. Q. G., Cisquella-Serra, M., Jaberi, E., Riera-Ponsati, L., Fauerby, N., Hu, E., Kretz, O., Aznar, S., & Issazadeh-Navikas, S. (2023). Mitochondrial DNA damage triggers the spread of Parkinson's disease-like pathology. *Molecular Psychiatry.* https://doi.org/10.1038/s41380-023-02251-4

Trumpff, C., Michelson, J., Lagranha, C. J., Taleon, V., Karan, K. R., Sturm, G., Lindqvist, D., Fernström, J., Moser, D., Kaufman, B. A., & Picard, M. (2021). Stress and circulating cell-free mitochondrial DNA: A systematic review of human studies, physiological considerations, and technical recommendations. *Mitochondrion, 59,* 225–245. https://doi.org/10.1016/j.mito.2021.04.002

Trumpff, C., Monzel, A. S., Sandi, C., Menon, V., Klein, H., Fujita, M., Lee, A., Petyuk, V. A., Hurst, C., Duong, D. M., Seyfried, N. T., Wingo, A. P., Wingo, T. S., Wang, Y., Thambisetty, M., Ferrucci, L., Bennett, D. A., De Jager, P. L., & Picard, M. (2024). Psychosocial experiences are associated with human brain mitochondrial biology. *Proceedings of the National Academy of Sciences, 121*(27). https://doi.org/10.1073/pnas.2317673121

Tucker, D., Lu, Y., & Zhang, Q. (2018). From mitochondrial function to neuroprotection—An emerging role for methylene blue. *Molecular Neurobiology, 55*(6), 5137–5153. https://doi.org/10.1007/s12035-017-0712-2

Twig, G., Hyde, B., & Shirihai, O. S. (2008). Mitochondrial fusion, fission and autophagy as a quality control axis: The bioenergetic view. *Biochimica et Biophysica Acta (BBA) - Bioenergetics*, *1777*(9), 1092–1097. https://doi.org/10.1016/j.bbabio.2008.05.001

Urbani, A., & Babu, M. (Eds.). (2019). *Mitochondria in health and in sickness.* Springer Nature.

Uvizl, M., Puechmaille, S. J., Power, S., Pippel, M., Carthy, S., Haerty, W., Myers, E. W., Teeling, E. C., & Huang, Z. (2024). Comparative genome microsynteny illuminates the fast evolution of nuclear mitochondrial segments (NUMTs) in mammals. *Molecular Biology and Evolution, 41*(1), msad278. https://doi.org/10.1093/molbev/msad278

van der Giezen, M. (2011). Mitochondria and the rise of eukaryotes. *BioScience*, *61*(8), 594–601. https://doi.org/10.1525/bio.2011.61.8.5

Vekaria, H. J., Talley Watts, L., Lin, A.-L., & Sullivan, P. G. (2017). Targeting mitochondrial dysfunction in CNS injury using Methylene Blue; Still a magic bullet? *Neurochemistry International, 109*, 117–125. https://doi.org/10.1016/j.neuint.2017.04.004

Vekshin, N. (2020). *Biophysics of mitochondria.* Springer.

Vidali, S., Aminzadeh, S., Lambert, B., Rutherford, T., Sperl, W., Kofler, B., & Feichtinger, R. G. (2015). Mitochondria: The ketogenic diet—A metabolism-based therapy. *The International Journal of Biochemistry & Cell Biology*, *63*, 55–59. https://doi.org/10.1016/j.biocel.2015.01.022

Vosseberg, J., Van Hooff, J. J. E., Köstlbacher, S., Panagiotou, K., Tamarit, D., & Ettema, T. J. G. (2024). The emerging view on the origin and early evolution of eukaryotic cells. *Nature*, *633*(8029), 295–305. https://doi.org/10.1038/s41586-024-07677-6

Walker, E. M., Pearson, G. L., Lawlor, N., Stendahl, A. M., Lietzke, A., Sidarala, V., Zhu, J., Stromer, T., Reck, E. C., Li, J., Levi-D'Ancona, E., Pasmooij, M. B., Hubers, D. L., Renberg, A., Mohamed, K., Parekh, V. S., Zhang, I. X., Thompson, B., Zhang, D., . . . Soleimanpour, S. A. (2025). Retrograde mitochondrial signaling governs the identity and maturity of metabolic tissues. *Science*. https://doi.org/10.1126/science.adf2034

Wallace, D. C., & Fan, W. (2010). Energetics, epigenetics, mitochondrial genetics. *Mitochondrion*, *10*(1), 12–31. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3245717%5C&tool=pmcentrez%5C&rendertype=abstract

Waltz, F., Righetto, R. D., Lamm, L., Salinas-Giegé, T., Kelley, R., Zhang, X., Obr, M., Khavnekar, S., Kotecha, A., & Engel, B. D. (2025). In-cell architecture of the mitochondrial respiratory chain. *Science*, *387*(6740), 1296–1301. https://doi.org/10.1126/science.ads8738

Wang, L., Han, J., Fearnley, L. G., Milton, M., Rafehi, H., Reid, J., Gerring, Z. F., Masaldan, S., Lang, T., Speed, T. P., & Bahlo, M. (2024). Peripheral immune cell abundance differences link blood mitochondrial DNA copy number and Parkinson's disease. *Npj Parkinson's Disease, 10*(1), 219. https://doi.org/10.1038/s41531-024-00831-x

Wang, L., Sharif, H., Vora, S. M., Zheng, Y., & Wu, H. (2021). Structures and functions of the inflammasome engine. *Journal of Allergy and Clinical Immunology, 147*(6), 2021–2029. https://doi.org/10.1016/j.jaci.2021.04.018

Ward, P., & Kirschvink, J. (2015). *A new history of life: The radical new discoveries about the origins and evolution of life on earth*. Bloomsbury Publishing USA.

Watson, T. (2025). Cancer cells get power boost by stealing mitochondria from nerves. *Nature*.

https://doi.org/10.1038/d41586-025-01941-z

Wei, K., Chen, T., Fang, H., Shen, X., Tang, Z., & Zhao, J. (2024). Mitochondrial DNA release via the mitochondrial permeability transition pore activates the cGAS-STING pathway, exacerbating inflammation in acute Kawasaki disease. *Cell Communication and Signaling*, *22*(1). https://doi.org/10.1186/s12964-024-01677-9

Wei, X., Robles, C. R., Pazokitoroudi, A., Ganna, A., Gusev, A., Durvasula, A., Gazal, S., Loh, P. R., Reich, D., & Sankararaman, S. (2023). The lingering effects of Neanderthal introgression on human complex traits. *eLife*, 12, e80757. https://doi.org/10.7554/eLife.80757

Wen, S., Zhu, D., & Huang, P. (2013). Targeting cancer cell mitochondria as a therapeutic approach. *Future Medicinal Chemistry*, *5*(1), 53–67. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3587793%5C&tool=pmcentrez%5C&rendertype=abstract

Westermann, B. (2010). Mitochondrial fusion and fission in cell life and death. *Nature Reviews Molecular Cell Biology, 11*(12), 872–884. https://doi.org/10.1038/nrm3013

Winkler, M., von Landenberg, C., Kappes-Horn, K., Neudecker, S., Kornblum, C., & Reimann, J. (2021). Diagnosis and clinical development of sporadic inclusion body myositis and polymyositis with mitochondrial pathology: A single-center retrospective analysis. *Journal of Neuropathology & Experimental Neurology*, nlab101. https://doi.org/10.1093/jnen/nlab101

Wu, S., Yang, T., Ma, M., Fan, L., Ren, L., Liu, G., Wang, Y., Cheng, B., Xia, J., & Hao, Z. (2024). Extracellular vesicles meet mitochondria: Potential roles in regenerative medicine. *Pharmacological Research, 206,* 107307. https://doi.org/10.1016/j.phrs.2024.107307

Yang, L., Youngblood, H., Wu, C., & Zhang, Q. (2020). Mitochondria as a target for neuroprotection: role of methylene blue and photobiomodulation. *Translational Neurodegeneration, 9*(1). https://doi.org/10.1186/s40035-020-00197-z

Ye, K., Lu, J., Ma, F., Keinan, A., & Gu, Z. (2014). Extensive pathogenicity of mitochondrial heteroplasmy in healthy human individuals. *Proceedings of the National Academy of Sciences, 111*(29), 10654–10659. https://doi.org/10.1073/pnas.1403521111

Zanini, G., Selleri, V., Lopez Domenech, S., Malerba, M., Nasi, M., Mattioli, A. V., & Pinti, M. (2023). Mitochondrial DNA as inflammatory DAMP: A warning of an aging immune

system? *Biochemical Society Transactions, 51*(2), 735–745. https://doi.org/10.1042/BST20221010

Zhang, G., Wei, H., Zhao, A., Yan, X., Zhang, X., Gan, J., Guo, M., Wang, J., Zhang, F., Jiang, Y., Liu, X., Yang, Z., & Jiang, X. (2025). Mitochondrial DNA leakage: underlying mechanisms and therapeutic implications in neurological disorders. *Journal of Neuroinflammation*, *22*(1). https://doi.org/10.1186/s12974-025-03363-0

Zhou, W., Karan, K. R., Gu, W., Klein, H. U., Sturm, G., De Jager, P. L., Bennett, D. A., Hirano, M., Picard, M., & Mills, R. E. (2024). Somatic nuclear mitochondrial DNA insertions are prevalent in the human brain and accumulate over time in fibroblasts. *PLOS Biology*, *22*(8), e3002723. https://doi.org/10.1371/journal.pbio.3002723

Zimmer, K. (2021, July 8). *'Social' Mitochondria, Whispering between cells, Influence Health | Quanta Magazine*. https://www.quantamagazine.org/social-mitochondria-whispering-between-cells-influence-health-20210706/

Zong, Y., Li, H., Liao, P., Chen, L., Pan, Y., Zheng, Y., Zhang, C., Liu, D., Zheng, M., & Gao, J. (2024). Mitochondrial dysfunction: Mechanisms and advances in therapy. *Signal Transduction and Targeted Therapy, 9*(1), 124. https://doi.org/10.1038/s41392-024-01839-8

Zuo, X., Zhou, J., Li, Y., Wu, K., Chen, Z., Luo, Z., Zhang, X., Liang, Y., Esteban, M. A., Zhou, Y., & Fu, X. D. (2021). TDP-43 aggregation induced by oxidative stress causes global mitochondrial imbalance in ALS. *Nature Structural & Molecular Biology*, *28*(2), 132–142. https://doi.org/10.1038/s41594-020-00537-7

Zweers, H., Van Wegberg, A. M. J., Janssen, M. C. H., & Wortmann, S. B. (2021). Ketogenic diet for mitochondrial disease: A systematic review on efficacy and safety. *Orphanet Journal of Rare Diseases*, *16*(1), 295. https://doi.org/10.1186/s13023-021-01927-w