Mitochondrial Heteroplasmy and Disease

Subjects: Biochemistry & Molecular Biology

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Given the relevance of mitochondria in numerous physiological and pathological mechanisms, such as adenosine triphosphate (ATP) synthesis, apoptosis, metabolism, cancer progression, and drug resistance, mitochondrial genome (mtDNA) analysis has become of great interest in the study of human diseases, including cancer. A high number of variants and mutations have been identified in different types of tumors, which coexist with normal alleles, a phenomenon named heteroplasmy. This mechanism is considered an intermediate state between the fixation or elimination of the acquired mutations. It is suggested that mutations, which confer adaptive advantages to tumor growth and invasion, are enriched in malignant cells.

Keywords: heteroplasmy ; heteroplasmy shifting ; mitochondrial DNA ; mitochondrial mutations ; cancer

1. Introduction

Despite the growing understanding of cancer biology and the constant effort to develop more effective diagnostic, follow-up and therapeutic strategies, these diseases still have important socio–economic implications worldwide [1]. To identify new diagnostic and prognostic biomarkers and even new potential molecular targets, current research focuses on the nuclear genome by detecting mutations and on gene expression and epigenomic signatures [2][3][4][5]; however, given the number of biological processes in which mitochondria participate (energy synthesis, metabolism, apoptosis and signaling pathways, among others), these organelles are gaining great relevance in addressing these questions [6]. More specifically, it has been shown that the mitochondrial DNA (mtDNA) of tumor cells accumulates many alterations, including punctual mutations, insertions, deletions, and variations in mtDNA copy number (mtCNV), which trigger the metabolic reprogramming of transformed cells as a biological strategy that favors tumor cell proliferation and survival [7][8][9][10][11][12][13]. Even though the mutational spectrum of mtDNA has already been studied in different types of cancer, the mechanism by which mtDNA mutations contribute to tumor development is not yet well known [14][15][16]. Additionally, heteroplasmy, defined as the presence of two or more mtDNA variants coexisting within the same cell, and the proportion of mutated mtDNA (the heteroplasmy level) are crucial for the expression of specific pathological phenotypes [17][18][19]. Heteroplasmy has been proposed as an intermediate phase between the fixation or elimination of newly acquired mtDNA mutations. However, the critical threshold to observe a biochemical defect in the respiratory chain or for disease expression is undisclosed in cancer and scarcely analyzed in the studies that characterize the mtDNA variant landscape. Interestingly, many studies have shown an association among heteroplasmic levels and risk and survival of cancer [20][21][22][23][24].

2. Mitochondrial Genome

The mitochondrion is a semi-autonomous organelle whose main function is the synthesis of cellular adenosine triphosphate (ATP). However, mitochondria also play roles in metabolism regulation, cell death, and signaling pathways involved in cell growth and proliferation [6]. The endosymbiotic theory indicates that the mitochondrion originated from endocytosis of an alpha-protobacterium by an ancestral pre-eukaryotic cell [6][25][26]. Throughout evolution, most of the mtDNA has migrated to the nucleus, leaving only a 16,569 base pair (bp) circular molecule [27]. This genome is constituted by two circular chains, a heavy strand (H) and a light strand (L) enriched in guanine and cytosine, respectively. mtDNA has 37 genes; two transcribe for ribosomal RNA (rRNA), 22 transcribe for transfer RNAs (tRNAs) and 13 transcribe for gene-encoding protein subunits of the enzyme complex of the oxidative phosphorylation system (OXPHOS) (**Table 1**). Additionally, the mitochondrial genome has a non-coding region of 1.1 kilobases (Kb), named D-Loop, which contains two hypervariable regions (HVR1 and HVR2) and sequences involved in the control of mtDNA replication and gene transcription [28][29]. The lack of histones, efficient DNA repair mechanisms, and the proximity to reactive oxygen species (ROS) generated by the OXPHOS system (mainly from Complex I and III) explain the high mutation rate observed in mtDNA, which is between 10 and 17 times higher than that of the nuclear genome (nDNA) [28][29][30][31]. Furthermore, mtDNA is a multicopy genome, displaying variable copy numbers over time, among cell types, tissues, subjects, physiological conditions. The estimated copy number in mammalians ranges from 100 to 10,000 molecules per cell

depending on the cell type and its energy requirement [32][33][34]. In humans, mtDNA is only inherited through the maternal line, and all alleles are passed down together as a single unit called haplotype, which could be shared in populations with common ancestry. In fact, a set of haplotypes or haplogroup is useful for identifying ethnic groups or populations [35]. Studies suggest that specific haplogroups have conferred environmental adaptive advantages but are also associated with diseases such as cancer [36][37][38][39][40][41][42].

Table 1. Encoded mitochondrial DNA genes.

Gene Symbol	Name	Function	OXPHOS Complex	Nucleotide Start Position	Nucleotide End Position
MT-ATP6	ATP synthase membrane subunit 6	Proton transmembrane transporter activity	V	8527	9207
MT-ATP8	ATP synthase membrane subunit 8	Proton transmembrane transporter activity		8366	8572
MT-CO1	Cytochrome c oxidase I	Electron transport Heme binding		5904	7445
MT-CO2	Cytochrome c oxidase II	Electron transport	IV	7586	8269
MT-CO3	Cytochrome c oxidase III	Electron transport		9207	9990
MT-CYB	Cytochrome b	Electron transport Heme binding	III	14747	15887
MT-ND1	NADH: ubiquinone oxidoreductase core subunit 1	Proton pumping Reduction site for ubiquinone		3307	4262
MT-ND2	NADH: ubiquinone oxidoreductase core subunit 2	Proton pumping		4470	5511
MT-ND3	NADH: ubiquinone oxidoreductase core subunit 3	Proton pumping	I	10059	10404
MT-ND4	NADH: ubiquinone oxidoreductase core subunit 4	Proton pumping		10760	12137
MT-ND4L	NADH: ubiquinone oxidoreductase core subunit 4L	Proton pumping		10470	10766

Gene Symbol	Name	Function	OXPHOS Complex	Nucleotide Start Position	Nucleotide End Position
MT-ND5	NADH:ubiquinone oxidoreductase core subunit 5	Proton pumping		12337	14148
MT-ND6	NADH:ubiquinone oxidoreductase core subunit 6	Proton pumping		14149	14673
MT-RNR1	12S rRNA	12S ribosomal RNA Small subunit	-	648	1601
MT-RNR2	16S rRNA	16S ribosomal RNA Large subunit	-	1671	3229
MT-TA	tRNA-Ala	tRNA for alanine	-	5587	5655
MT-TC	tRNA-Cys	tRNA for cysteine	-	5761	5826
MT-TD	tRNA-Asp	tRNA for aspartic acid	-	7518	7585
MT-TE	tRNA-Glu	tRNA for glutamic acid	-	14674	14742
MT-TF	tRNA-Phe	tRNA for phenylalanine	-	577	647
MT-TG	tRNA-Gly	tRNA for glycine	-	9991	10058
MT-TH	tRNA-His	tRNA for histidine	-	12138	12206
MT-TI	tRNA-Ile	tRNA for isoleucine	-	4263	4331
MT-TK	tRNA-Lys	tRNA for lysine	-	8295	8364
MT-TL1	tRNA-Leu (UUA/G) 1	tRNA for leucine 1	-	3230	3304
MT-TL2	tRNA-Leu (CUN) 2	tRNA for leucine 2	-	12266	12336
MT-TM	tRNA-Met	tRNA for methionine	-	4402	4469
MT-TN	tRNA-Asn	tRNA for asparagine	-	5657	5729
MT-TP	tRNA-Pro	tRNA for proline	-	15956	16023
MT-TQ	tRNA-Gln	tRNA for glutamine	-	4329	4400
MT-TR	tRNA-Arg	tRNA for arginine	-	10405	10469

Gene Symbol	Name	Function	OXPHOS Complex	Nucleotide Start Position	Nucleotide End Position
MT-TS1	tRNA-Ser (UCN) 1	tRNA for serine 1	-	7446	7514
MT-TS2	tRNA-Ser (AGU/C) 2	tRNA for serine 2	-	12207	12265
MT-TT	tRNA-Thr	tRNA for threonine	-	15888	15953
MT-TV	tRNA-Val	tRNA for valine	-	1602	1670
MT-TW	tRNA-Trp	tRNA for tryptophan	-	5512	5579
MT-TY	tRNA-Tyr	tRNA for tyrosine	-	5826	5891

ATP: adenosine triphosphate; NADH: nicotinamide adenine dinucleotide reduced; OXPHOS: oxidative phosphorylation system, I: NADH: ubiquinone oxidoreductase complex; III: cytochrome bc1 complex; IV: Cytochrome c Oxidase complex; V: Mitochondrial ATP synthase complex; -: no OXPHOS complex.

Even though mtDNA encodes only 13 of the approximately 1500 proteins that conform to the mitochondria, its maintenance is essential for mitochondrial biogenesis [6][43]. The presence of alterations in mtDNA correlates with an inefficient OXPHOS system, decreased ATP synthesis, and an increased ROS production rate, phenomena associated with pathological phenotypes [44][45][46][47][48].

3. Origins of Heteroplasmy and Its Impact on Disease

mtDNA replication, mediated by DNA polymerase γ (DNApoly), is continuous and cell-cycle-independent. Replication is the primary source of new mutations in mtDNA. Despite the high fidelity of DNApoly, the elevated replication rate and limited DNA repair mechanisms contribute to the maintenance of acquired mutations (point mutations, insertions, deletions, etc.) [10][49][50][51][52][53]. Due to the polyploid nature of mtDNA, mutations can be found in different proportions within a mitochondrion, cell, tissue, or individual, giving rise to heteroplasmy [18][31][45][54][55]. Heteroplasmy can be higher if the mutated allele frequency (MAF) ranges from 20% to 95% or lower if the MAF ranges from 0.5% to 20%. A MAF <0.5% corresponds to a rare variant. If the allele represents more than 95% of the mtDNA molecules, this is considered homoplasmic [54][56].

Heteroplasmy is maternally inherited, and its levels are determined during oogenesis. The proportion of mutated alleles differs between oocytes and then among offspring. Shifts in heteroplasmy levels have been observed in humans within a few generations, and a genetic bottleneck during the maternal transmission of mtDNA has been suggested to explain this phenomenon. The bottleneck could be derived from a reduction in the numbers of mtDNA molecules by three mechanisms: (a) passive reduction, where the mtDNA is destroyed through mitophagy processes; (b) mtDNA packaging into homoplasmic segregating units; and (c) focal replication, where specific populations of mtDNA are selected and replicated [57][58][59]. A bottleneck in oocytes, which divide rapidly after being fertilized, generates a heterogeneous distribution of mtDNA subpopulations in daughter cells [49][58][60][61]. Two main mechanisms by which heteroplasmy differs among cells have been described: vegetative segregation and clonal expansion. In the first case, changes in allelic frequencies occur through the mitochondria random distribution during mitosis; in the second case, present in post-mitotic cells or non-dividing cells, heteroplasmy depends on the mtDNA replication rate and other cellular processes such as mitochondrial fusion and fission, as well as mtDNA transference between cells (**Figure 1**) [49][57]. Thus, heteroplasmy is an extraordinarily complex and dynamic event that results from various stochastic and deterministic cellular processes [18][62][63][64][65][66]. Human pedigree analysis has shown that random genetic drift is involved in heteroplasmy and in combination with mitochondrial segregation, and the horizontal transfer of cell–cell mitochondria, modifies the allele frequencies of mtDNA over time. These frequencies are prone to increase or decrease depending on the effect of the variant [67]. In this context, heteroplasmy is a transitional event between the disappearance or fixation of alleles that alters the mitochondrial function or confers advantageous biochemical conditions that promote cell division (**Figure 2**) [57][68][69]. A scan of heteroplasmic sites in different tissues showed the allele-specificity and tissue-specificity of some variants, showing

evidence of the presence of positive and negative selection that promote or inhibit particular conditions of mitochondrial function [70][71]. Transversions (point mutations that change a purine A or G by a pyrimidine T or C) and non-synonymous amino-acid changes were more commonly identified in a low heteroplasmic state, which reinforces the fact that, due to their potential pathogenic nature, these changes are selected negatively to reduce the damage of protein subunits involved in mitochondrial function. In contrast, a positive selection of somatic heteroplasmic sites was observed both in liver tissue and in specific genes such as NADH: ubiquinone oxidoreductase core subunit 5 (*MT-ND5)*, suggesting that these mutations provide specific biochemical features to the tissue [70].

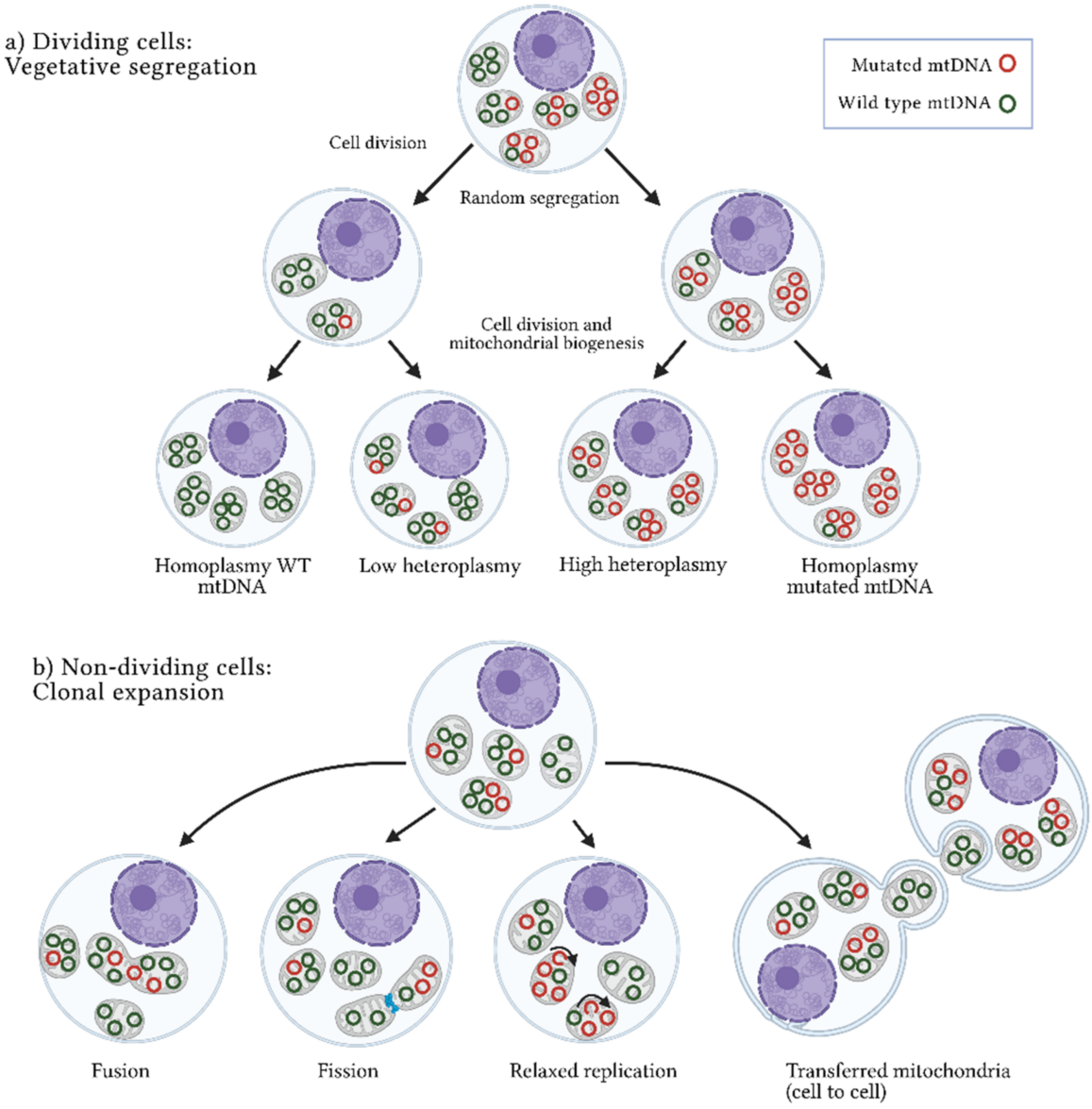

Figure 1. Heteroplasmy origin. Two mechanisms have been suggested to explain the origin and maintenance of the coexistence of wild-type and mutated mtDNA or heteroplasmy: (**a**) Vegetative segregation. In dividing cells, mitochondria are randomly distributed among daughter cells, resulting in different proportions of mutated mtDNA molecules between them. (**b**) Clonal expansion. In non-dividing cells, heteroplasmy is maintained through dynamic mitochondrial processes, such as fusion (union) or fission (separation) of mitochondria, relaxed replication (mtDNA replication independent of cell division), and intercellular mitochondrial transference. WT: wild-type; mtDNA: mitochondrial DNA molecules. Figure artwork created with BioRender.com.

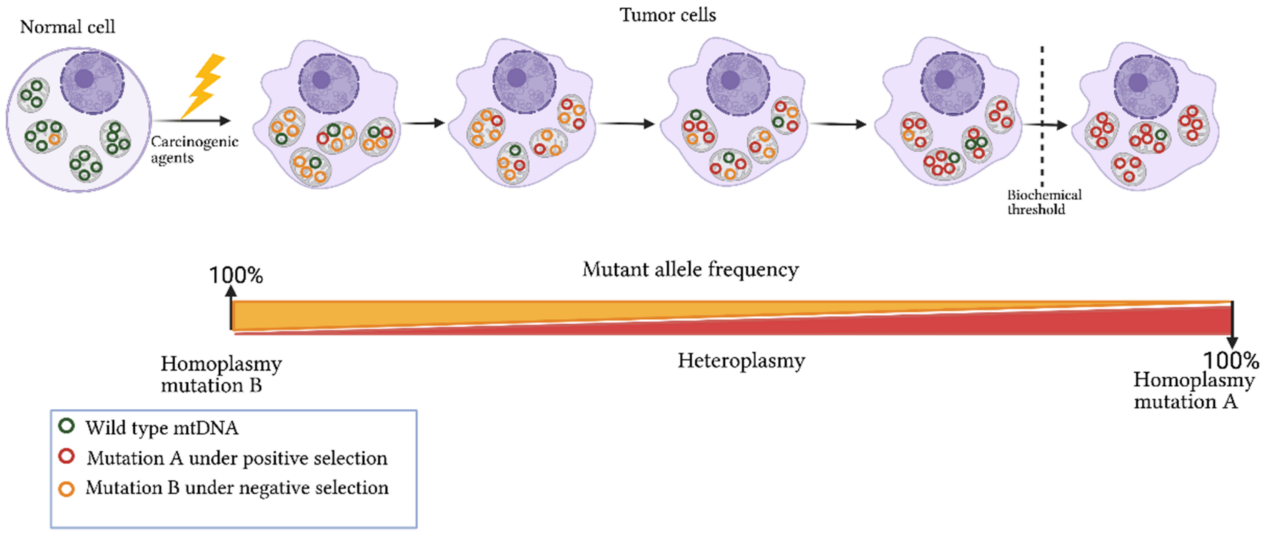

Figure 2. Dynamics of mitochondrial mutations in cancer. Exposure of a normal cell to carcinogenic agents leads to somatic mutation acquisition in mtDNA and changes in the germline mutation heteroplasmy. The frequency of acquired mutation can increase or decrease in tumor cells based on its nature and biological effect. For instance, if a mutation confers advantages to cell proliferation and survival, it will be selected and enriched in the tumor cell (mutation A). In contrast, a mutation compromising cell viability will be selected negatively (mutation B). Biochemical and phenotypic manifestation of the mtDNA mutations occurs only when a threshold level is exceeded. Figure artwork created with BioRender.com.

Heteroplasmy is a common phenomenon, and low levels of heteroplasmy are commonly found in healthy tissues; the presence of potentially pathogenic mutations is not always translated into changes in the cell function or in a specific phenotype [72][73][74]. The maintenance of normal mitochondrial function is explained by the existence of a “biochemical threshold”, a state where normal mtDNA buffers the damaging effect of mutated mtDNA molecules through the modulation of mitochondrial DNA replication, mitochondrial fission, and fusion processes [73][75]. The threshold is tissue-specific, and the level of the mutated allele (heteroplasmy level) required to produce a pathological phenotype is dependent on the nature of the mutation [57][74][76]. Many studies have reported that heteroplasmy levels of mutations positively correlate with ROS production and cellular damage that is potentially expressed as a wide range of clinical manifestations [57][62][77]. For example, individuals carrying the A3243G mutation in heteroplasmy levels of 20%–30% commonly have type II diabetes mellitus; ranges from 50% to 80% of the mutated allele are manifested in myopathies, lactic acidosis, or cardiomyopathies; in a homoplasmic state, A3243G carriers develop Leigh syndrome [78][79]. Additionally, the degree of heteroplasmy has been associated with different changes in the metabolic and epigenetic context [78].

References

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2021, 71, 209–249.
2. Fang, F.; Cardenas, H.; Huang, H.; Jiang, G.; Perkins, S.M.; Zhang, C.; Keer, H.N.; Liu, Y.; Nephew, K.P.; Matei, D. Genomic and Epigenomic Signatures in Ovarian Cancer Associated with Resensitization to Platinum Drugs. Cancer Res. 2018, 78, 631–644.
3. Alexandrov, L.B.; Nik-Zainal, S.; Wedge, D.C.; Aparicio, S.A.; Behjati, S.; Biankin, A.V.; Bignell, G.R.; Bolli, N.; Borg, A.; Borresen-Dale, A.L.; et al. Signatures of mutational processes in human cancer. Nature 2013, 500, 415–421.
4. Zhang, Z.; Yang, L.; Li, Y.; Wu, Y.; Li, X.; Wu, X. Four long noncoding RNAs act as biomarkers in lung adenocarcinoma. Open Med. 2021, 16, 660–671.
5. Ghafarpour, V.; Khansari, M.; Banaei-Moghaddam, A.M.; Najafi, A.; Masoudi-Nejad, A. DNA methylation association with stage progression of head and neck squamous cell carcinoma. Comput. Biol. Med. 2021, 134, 104473.
6. Protasoni, M.; Zeviani, M. Mitochondrial Structure and Bioenergetics in Normal and Disease Conditions. Int. J. Mol. Sci. 2021, 22, 586.
7. Hägg, S.; Jylhävä, J.; Wang, Y.; Czene, K.; Grassmann, F. Correction to: Deciphering the genetic and epidemiological landscape of mitochondrial DNA abundance. Qual. Life Res. 2021, 140, 863.

8. Chen, K.; Lu, P.; Beeraka, N.M.; Sukocheva, O.A.; Madhunapantula, S.V.; Liu, J.; Sinelnikov, M.Y.; Nikolenko, V.N.; Bulygin, K.V.; Mikhaleva, L.M.; et al. Mitochondrial mutations and mitoepigenetics: Focus on regulation of oxidative stress-induced responses in breast cancers. Semin. Cancer Biol. 2020.
9. Reznik, E.; Miller, M.L.; Şenbabaoğlu, Y.; Riaz, N.; Sarungbam, J.; Tickoo, S.K.; Al-Ahmadie, H.A.; Lee, W.; Seshan, V.E.; Hakimi, A.A.; et al. Mitochondrial DNA copy number variation across human cancers. eLife 2016, 5, e10769.
10. Basu, S.; Xie, X.; Uhler, J.P.; Hedberg-Oldfors, C.; Milenkovic, D.; Baris, O.R.; Kimoloi, S.; Matic, S.; Stewart, J.B.; Larsson, N.-G.; et al. Accurate mapping of mitochondrial DNA deletions and duplications using deep sequencing. PLoS Genet. 2020, 16, e1009242.
11. Zong, W.-X.; Rabinowitz, J.D.; White, E. Mitochondria and Cancer. Mol. Cell 2016, 61, 667–676.
12. Rao, S.G. Mitochondrial Changes in Cancer. Organotypic Models Drug Dev. 2016, 240, 211–227.
13. Bussard, K.M.; Siracusa, L.D. Understanding Mitochondrial Polymorphisms in Cancer. Cancer Res. 2017, 77, 6051–6059.
14. Yuan, Y.; Ju, Y.S.; Kim, Y.; Li, J.; Wang, Y.; Yoon, C.J.; Yang, Y.; Martincorena, I.; Creighton, C.J.; Weinstein, J.N.; et al. Comprehensive molecular characterization of mitochondrial genomes in human cancers. Nat. Genet. 2020, 52, 342–352.
15. Ju, Y.S.; Alexandrov, L.B.; Gerstung, M.; Martin, S.; Nik-Zainal, S.; Ramakrishna, M.; Davies, H.R.; Papaemmanuil, E.; Gundem, G.; Shlien, A.; et al. Origins and functional consequences of somatic mitochondrial DNA mutations in human cancer. eLife 2014, 3, 3.
16. Li, L.; Chen, L.; Li, J.; Zhang, W.; Liao, Y.; Chen, J.; Sun, Z. Correlational study on mitochondrial DNA mutations as potential risk factors in breast cancer. Oncotarget 2016, 7, 31270–31283.
17. Grandhi, S.; Bosworth, C.; Maddox, W.; Sensiba, C.; Akhavanfard, S.; Ni, Y.; LaFramboise, T. Heteroplasmic shifts in tumor mitochondrial genomes reveal tissue-specific signals of relaxed and positive selection. Hum. Mol. Genet. 2017, 26, 2912–2922.
18. Hahn, A.; Zuryn, S. The Cellular Mitochondrial Genome Landscape in Disease. Trends Cell Biol. 2019, 29, 227–240.
19. Tikochinski, Y.; Carreras, C.; Tikochinski, G.; Vilaca, S.T. Population-specific signatures of intra-individual mitochondrial DNA heteroplasmy and their potential evolutionary advantages. Sci. Rep. 2020, 10, 211.
20. Qi, Y.; Wei, Y.; Wang, Q.; Xu, H.; Wang, Y.; Yao, A.; Yang, H.; Gao, Y.; Zhou, F. Heteroplasmy of mutant mitochondrial DNA A10398G and analysis of its prognostic value in non-small cell lung cancer. Oncol. Lett. 2016, 12, 3081–3088.
21. Fendt, L.; Fazzini, F.; Weissensteiner, H.; Bruckmoser, E.; Schönherr, S.; Schäfer, G.; Losso, J.L.; Streiter, G.A.; Lamina, C.; Rasse, M.; et al. Profiling of Mitochondrial DNA Heteroplasmy in a Prospective Oral Squamous Cell Carcinoma Study. Cancers 2020, 12, 1933.
22. McMahon, S.; LaFramboise, T. Mutational patterns in the breast cancer mitochondrial genome, with clinical correlates. Carcinogenesis 2014, 35, 1046–1054.
23. Hopkins, J.F.; Sabelnykova, V.Y.; Weischenfeldt, J.; Simon, R.; Aguiar, J.; Alkallas, R.; Heisler, L.E.; Zhang, J.; Watson, J.D.; Chua, M.L.K.; et al. Mitochondrial mutations drive prostate cancer aggression. Nat. Commun. 2017, 8, 1–8.
24. Kloss-Brandstätter, A.; Schäfer, G.; Erhart, G.; Hüttenhofer, A.; Coassin, S.; Seifarth, C.; Summerer, M.; Bektic, J.; Klocker, H.; Kronenberg, F. Somatic Mutations throughout the Entire Mitochondrial Genome Are Associated with Elevated PSA Levels in Prostate Cancer Patients. Am. J. Hum. Genet. 2010, 87, 802–812.
25. Sagan, L. On the origin of mitosing cells. J. Theor. Biol. 1967, 14, 255–274.
26. Margulis, L. Symbiotic theory of the origin of eukaryotic organelles; criteria for proof. Symp. Soc. Exp. Biol. 1975, 29, 21–38.
27. Yamauchi, A. Rate of Gene Transfer From Mitochondria to Nucleus: Effects of Cytoplasmic Inheritance System and Intensity of Intracellular Competition. Genetics 2005, 171, 1387–1396.
28. Anderson, S.E.; Bankier, A.T.; Barrell, B.G.; De Bruijn, M.H.L.; Coulson, A.R.; Drouin, J.; Eperon, I.C.; Nierlich, D.P.; Roe, B.A.; Sanger, F.; et al. Sequence and organization of the human mitochondrial genome. Nature 1981, 290, 457–465.
29. Lee, S.R.; Han, J. Mitochondrial Nucleoid: Shield and Switch of the Mitochondrial Genome. Oxid. Med. Cell. Longev. 2017, 2017, 1–15.
30. Brandon, M.; Baldi, P.; Wallace, D.C. Mitochondrial mutations in cancer. Oncogene 2006, 25, 4647–4662.
31. Hou, X.-S.; Wang, H.-S.; Mugaka, B.P.; Yang, G.-J.; Ding, Y. Mitochondria: Promising organelle targets for cancer diagnosis and treatment. Biomater. Sci. 2018, 6, 2786–2797.

32. Castellani, C.A.; Longchamps, R.J.; Sun, J.; Guallar, E.; Arking, D.E. Thinking outside the nucleus: Mitochondrial DNA copy number in health and disease. Mitochondrion 2020, 53, 214–223.

33. O'Hara, R.; Tedone, E.; Ludlow, A.T.; Huang, E.; Arosio, B.; Mari, D.; Shay, J.W. Quantitative mitochondrial DNA copy number determination using droplet digital PCR with single-cell resolution. Genome Res. 2019, 29, 1878–1888.

34. D'Erchia, A.M.; Atlante, A.; Gadaleta, G.; Pavesi, G.; Chiara, M.; De Virgilio, C.; Manzari, C.; Mastropasqua, F.; Prazzoli, G.M.; Picardi, E.; et al. Tissue-specific mtDNA abundance from exome data and its correlation with mitochondrial transcription, mass and respiratory activity. Mitochondrion 2015, 20, 13–21.

35. Dong, J.; Wong, L.-J.; Mims, M.P. Mitochondrial inheritance and cancer. Transl. Res. 2018, 202, 24–34.

36. Lajbner, Z.; Pnini, R.; Camus, M.F.; Miller, J.; Dowling, D. Experimental evidence that thermal selection shapes mitochondrial genome evolution. Sci. Rep. 2018, 8, 9500.

37. Motoi, M.; Nishimura, T.; Egashira, Y.; Kishida, F.; Watanuki, S. Relationship between mitochondrial haplogroup and physiological responses to hypobaric hypoxia. J. Physiol. Anthr. 2016, 35, 12.

38. Chen, Y.; Gong, L.; Liu, X.; Chen, X.; Yang, S.; Luo, Y. Mitochondrial DNA genomes revealed different patterns of high-altitude adaptation in high-altitude Tajiks compared with Tibetans and Sherpas. Sci. Rep. 2020, 10, 1–9.

39. Toncheva, D.; Serbezov, D.; Karachanak-Yankova, S.; Nesheva, D. Ancient mitochondrial DNA pathogenic variants putatively associated with mitochondrial disease. PLoS ONE 2020, 15, e0233666.

40. Xiao, F.; Li, M.; Wang, J.; Liu, J.; Li, J.; Fang, H.; Lyu, J.; Shen, L. Association between mitochondrial DNA haplogroup variation and coronary artery disease. Nutr. Metab. Cardiovasc. Dis. 2020, 30, 960–966.

41. Grasso, D.; Zampieri, L.X.; Capelôa, T.; Van De Velde, J.A.; Sonveaux, P. Mitochondria in cancer. Cell Stress 2020, 4, 114–146.

42. Ma, L.; Fu, Q.; Xu, B.; Zhou, H.; Gao, J.; Shao, X.; Xiong, J.; Gu, Q.; Wen, S.; Li, F.; et al. Breast cancer-associated mitochondrial DNA haplogroup promotes neoplastic growth via ROS-mediated AKT activation. Int. J. Cancer 2018, 142, 1786–1796.

43. Song, J.; Herrmann, J.M.; Becker, T. Quality control of the mitochondrial proteome. Nat. Rev. Mol. Cell Biol. 2021, 22, 54–70.

44. Ishikawa, K.; Takenaga, K.; Akimoto, M.; Koshikawa, N.; Yamaguchi, A.; Imanishi, H.; Nakada, K.; Honma, Y.; Hayashi, J.-I. ROS-Generating Mitochondrial DNA Mutations Can Regulate Tumor Cell Metastasis. Science 2008, 320, 661–664.

45. Scheid, A.D.; Beadnell, T.C.; Welch, D.R. The second genome: Effects of the mitochondrial genome on cancer progression. Adv. Cancer Res. 2019, 142, 63–105.

46. Wu, C.-W.; Yin, P.-H.; Hung, W.-Y.; Li, A.F.-Y.; Li, S.-H.; Chi, C.-W.; Wei, Y.-H.; Lee, H.-C. Mitochondrial DNA mutations and mitochondrial DNA depletion in gastric cancer. Genes Chromosom. Cancer 2005, 44, 19–28.

47. Yadav, N.; Chandra, D. Mitochondrial DNA mutations and breast tumorigenesis. Biochim. Biophys. Acta BBA Bioenerg. 2013, 1836, 336–344.

48. Wallace, D.C. Bioenergetic Origins of Complexity and Disease. Cold Spring Harb. Symp. Quant. Biol. 2011, 76, 1–16.

49. Stewart, J.B.; Chinnery, P.F. Extreme heterogeneity of human mitochondrial DNA from organelles to populations. Nat. Rev. Genet. 2021, 22, 106–118.

50. Zheng, W.; Khrapko, K.; Coller, H.A.; Thilly, W.G.; Copeland, W.C. Origins of human mitochondrial point mutations as DNA polymerase gamma-mediated errors. Mutat. Res. 2006, 599, 11–20.

51. Wisnovsky, S.; Sack, T.; Pagliarini, D.J.; Laposa, R.R.; Kelley, S.O. DNA Polymerase theta Increases Mutational Rates in Mitochondrial DNA. ACS Chem. Biol. 2018, 13, 900–908.

52. Gustafson, M.A.; Sullivan, E.D.; Copeland, W.C. Consequences of compromised mitochondrial genome integrity. DNA Repair 2020, 93, 102916.

53. DeBalsi, K.L.; Hoff, K.E.; Copeland, W.C. Role of the mitochondrial DNA replication machinery in mitochondrial DNA mutagenesis, aging and age-related diseases. Ageing Res. Rev. 2017, 33, 89–104.

54. Jimenez-Morales, S.; Perez-Amado, C.J.; Langley, E.; Hidalgo-Miranda, A. Overview of mitochondrial germline variants and mutations in human disease: Focus on breast cancer (Review). Int. J. Oncol. 2018, 53, 923–936.

55. Stefano, G.B.; Bjenning, C.; Wang, F.; Wang, N.; Kream, R.M. Mitochondrial Heteroplasmy. Adv. Exp. Med. Biol. 2017, 982, 577–594.

56. Ahn, E.H.; Hirohata, K.; Kohrn, B.F.; Fox, E.J.; Chang, C.-C.; Loeb, L.A. Detection of Ultra-Rare Mitochondrial Mutations in Breast Stem Cells by Duplex Sequencing. PLoS ONE 2015, 10, e0136216.

57. Zhang, H.; Burr, S.; Chinnery, P.F. The mitochondrial DNA genetic bottleneck: Inheritance and beyond. Essays Biochem. 2018, 62, 225–234.

58. Nissanka, N.; Moraes, C.T. Mitochondrial DNA heteroplasmy in disease and targeted nuclease-based therapeutic approaches. EMBO Rep. 2020, 21, e49612.

59. Floros, V.I.; Pyle, A.; Dietmann, S.; Wei, W.; Tang, W.C.W.; Irie, N.; Payne, B.; Capalbo, A.; Noli, L.; Coxhead, J.; et al. Segregation of mitochondrial DNA heteroplasmy through a developmental genetic bottleneck in human embryos. Nat. Cell Biol. 2018, 20, 144–151.

60. Wei, W.; Chinnery, P.F. Inheritance of mitochondrial DNA in humans: Implications for rare and common diseases. J. Intern. Med. 2020, 287, 634–644.

61. Johnston, I.; Burgstaller, J.P.; Havlicek, V.; Kolbe, T.; Rülicke, T.; Brem, G.; Poulton, J.; Jones, N.S. Stochastic modelling, Bayesian inference, and new in vivo measurements elucidate the debated mtDNA bottleneck mechanism. eLife 2015, 4, e07464.

62. Naeem, M.M.; Sondheimer, N. Heteroplasmy Shifting as Therapy for Mitochondrial Disorders. In Mitochondria in Health and in Sickness; Urbani, A., Babu, M., Eds.; Springer: Singapore, 2019; pp. 257–267.

63. Jackson, M.V.; Krasnodembskaya, A.D. Analysis of Mitochondrial Transfer in Direct Co-cultures of Human Monocyte-derived Macrophages (MDM) and Mesenchymal Stem Cells (MSC). Bio-Protocol 2017, 7, e2255.

64. Brestoff, J.R.; Wilen, C.B.; Moley, J.R.; Li, Y.; Zou, W.; Malvin, N.P.; Rowen, M.N.; Saunders, B.T.; Ma, H.; Mack, M.R.; et al. Intercellular Mitochondria Transfer to Macrophages Regulates White Adipose Tissue Homeostasis and Is Impaired in Obesity. Cell Metab. 2021, 33, 270–282.e8.

65. Han, D.; Zheng, X.; Wang, X.; Jin, T.; Cui, L.; Chen, Z. Mesenchymal Stem/Stromal Cell-Mediated Mitochondrial Transfer and the Therapeutic Potential in Treatment of Neurological Diseases. Stem Cells Int. 2020, 2020, 1–16.

66. She, Z.; Xie, M.; Hun, M.; Abdirahman, A.S.; Li, C.; Wu, F.; Luo, S.; Wan, W.; Wen, C.; Tian, J. Immunoregulatory Effects of Mitochondria Transferred by Extracellular Vesicles. Front. Immunol. 2021, 11, 628576.

67. Burgstaller, J.P.; Kolbe, T.; Havlicek, V.; Hembach, S.; Poulton, J.; Piálek, J.; Steinborn, R.; Rülicke, T.; Brem, G.; Jones, N.S.; et al. Large-scale genetic analysis reveals mammalian mtDNA heteroplasmy dynamics and variance increase through lifetimes and generations. Nat. Commun. 2018, 9, 2488.

68. Lechuga-Vieco, A.V.; Latorre-Pellicer, A.; Johnston, I.G.; Prota, G.; Gileadi, U.; Justo-Méndez, R.; Acín-Pérez, R.; Martínez-De-Mena, R.; Fernández-Toro, J.M.; Jimenez-Blasco, D.; et al. Cell identity and nucleo-mitochondrial genetic context modulate OXPHOS performance and determine somatic heteroplasmy dynamics. Sci. Adv. 2020, 6, eaba5345.

69. Zaidi, A.A.; Wilton, P.R.; Su, M.S.-W.; Paul, I.M.; Arbeithuber, B.; Anthony, K.; Nekrutenko, A.; Nielsen, R.; Makova, K.D. Bottleneck and selection in the germline and maternal age influence transmission of mitochondrial DNA in human pedigrees. Proc. Natl. Acad. Sci. USA 2019, 116, 25172–25178.

70. Li, M.; Schröder, R.; Ni, S.; Madea, B.; Stoneking, M. Extensive tissue-related and allele-related mtDNA heteroplasmy suggests positive selection for somatic mutations. Proc. Natl. Acad. Sci. USA 2015, 112, 2491–2496.

71. He, Y.; Wu, J.; Dressman, D.C.; Iacobuziodonahue, C.A.; Markowitz, S.D.; Velculescu, V.; Diaz, L.A., Jr.; Kinzler, K.W.; Vogelstein, B.; Papadopoulos, N. Heteroplasmic mitochondrial DNA mutations in normal and tumour cells. Nat. Cell Biol. 2010, 464, 610–614.

72. Ye, K.; Lu, J.; Ma, F.; Keinan, A.; Gu, Z. Extensive pathogenicity of mitochondrial heteroplasmy in healthy human individuals. Proc. Natl. Acad. Sci. USA 2014, 111, 10654–10659.

73. Zekonyte, U.; Bacman, S.R.; Moraes, C.T. DNA-editing enzymes as potential treatments for heteroplasmic mtDNA diseases. J. Intern. Med. 2020, 287, 685–697.

74. Sacconi, S.; Salviati, L.; Nishigaki, Y.; Walker, W.F.; Hernandez-Rosa, E.; Trevisson, E.; Delplace, S.; Desnuelle, C.; Shanske, S.; Hirano, M.; et al. A functionally dominant mitochondrial DNA mutation. Hum. Mol. Genet. 2008, 17, 1814–1820.

75. Yapa, N.M.; Lisnyak, V.; Reljic, B.; Ryan, M.T. Mitochondrial dynamics in health and disease. FEBS Lett. 2021, 595, 1184–1204.

76. Ameele, J.V.D.; Li, A.Y.; Ma, H.; Chinnery, P.F. Mitochondrial heteroplasmy beyond the oocyte bottleneck. Semin. Cell Dev. Biol. 2020, 97, 156–166.

77. Stefano, G.B.; Kream, R.M. Mitochondrial DNA heteroplasmy in human health and disease. Biomed. Rep. 2016, 4, 259–262.

78. Kopinski, P.K.; Janssen, K.; Schaefer, P.M.; Trefely, S.; Perry, C.E.; Potluri, P.; Tintos-Hernandez, J.A.; Singh, L.N.; Karch, K.; Campbell, S.L.; et al. Regulation of nuclear epigenome by mitochondrial DNA heteroplasmy. Proc. Natl.

Acad. Sci. USA 2019, 116, 16028–16035.

79. McMillan, R.P.; Stewart, S.; Budnick, J.A.; Caswell, C.C.; Hulver, M.W.; Mukherjee, K.; Srivastava, S. Quantitative Variation in m.3243A > G Mutation Produce Discrete Changes in Energy Metabolism. Sci. Rep. 2019, 9, 1–11.

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