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Research Progress of Mitochondrial DNA and Cancer

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Abstract: Mitochondrial DNA mutation will lead to a series of diseases, and Defective mitochondrial DNA will lead to organ dysfunction.The increase of mutation frequency caused by nuclear DNA repair defect, replication error, carcinogen exposure and aging is generally considered to drive the occurrence of cancer.In contrast, the status and role of mitochondrial genome mutation in cancer are not clear.We reviewed the variation in number and structure of mtDNA in colorectal cancer, liver cancer, breast cancer , aiming to illustrate the important role of mtDNA in the occurrence and development of cancer, and to provide some reference for early diagnosis, treatment and prognosis evaluation of cancer.

Keywords: Mitochondrial DNA Mutation; Mitochondrial DNA Copy Number; Cancer

Introduction

Mitochondria possess their own DNA, which encodes many key proteins used for the assembly and activity of mitochondrial respiratory complexes. The mtDNA does not bind to histones or form chromosomes, but instead forms a mtDNA-protein complex with many proteins, forming a nucleoid uniformly distributed in the mitochondrial matrix, which is essential for mitochondrial function. Since the structural characteristics of mtDNA are different from nuclear DNA with more than ten times more than nuclear DNA, defects or mutations in mtDNA cause a series of diseases and damaged mtDNA can be eliminated by mitophagy[1]. Mitochondria have been shown to play an important role in apoptosis, a fundamental biological process in which cells die in a controlled manner, playing a key role in cancer development and the cellular response to anticancer drugs. Therefore, it is important to understand the biological characteristics of mtDNA and its role in tumor development and development. Otto Warburg The observation that cancer has acquired the unusual property of absorbing and fermenting glucose into lactate in the presence of oxygen raises defects in mitochondrial respiration as the underlying basis for aerobic glycolysis and cancer. However, not all tumors have this aerobic glycolytic property, and it is now clear that defects in mitochondrial respiration are generally not often the cause of aerobic glycolysis[2]. In recent years, the research on mtDNA in cancer has attracted much attention, and many studies explain the role of mtDNA mutations and mtDNA copy number variants in cancer occurrence[3,4]. Therefore, this paper outlines the variant characteristics of mtDNA in multiple cancers and its role in cancer development, aiming to further elucidate the complex relationship between mtDNA and cancer,It provides some reference basis for the early diagnosis, treatment and prognosis evaluation of cancer.

1. Basic knowledge of mitochondria:

Mitochondria is a bilayer membrane organelle that generates about 90% of its cellular energy in mammalian cells, by oxidative phosphorylation (OXPHOS), in the form of adenosine triphosphate (ATP). Mitochondria also play important roles in a range of signaling pathways, including the tricarboxylic acid cycle (TCA), β -oxidation of fatty acids, and cell death in cell apoptosis[5,6]And the cell cycle[7,8]Play an important role in the process.

Unlike other organelles in mammalian cells, mitochondria have their own genetic material, which encodes a range of key proteins associated with mitochondrial respiration. Each mitochondrion contains one or more copies of mtDNA, located in the mitochondrial matrix[9]. significantly different from the structure of nuclear DNA, mtDNA is closed circular duplex DNA, the outer ring is rich in purine, called heavy chain (H chain), and the inner ring is rich in pyrimidine, called light chain (L chain). Therefore, the component of mtDNA is highly asymmetric. In human cells, mtDNA consists of 16,569 base pairs and encodes 37 genes, including 13 polypeptides, two ribosomal RNA, and 22 transport RNA[10]. Most of the non-coding DNA of the human mitochondrial genome is located within an ~ 1 kb region called the non-coding

region (NCR). The NCR is the most strongly polymorphic site in the mtDNA, with several known polymorphic sites within the two hypervariable regions (HVR) of the NCR[11]. Non-coding regions (NCR) exert a regulatory function in the mtDNA, exerting control on transcription and translation. The mtDNA control region contains the replication origin of one strand and the transcription origin of both strands, the control region is also the location of the mtDNA displacement loop (D-loop), and the mtDNA replication begins at the D loop, which also contains the promoter of the transcript adjacent to the D loop. Although the exact function of the D-loop is unknown, it is noteworthy that this region is highly sequence variability[12], And has been shown to be associated with the incidence of specific types of cancer[13]。

Mitochondrial dysfunction, often characterized by the loss of oxidative phosphorylation efficiency, is a hallmark of aging and various chronic diseases[14]. Mitochondrial dysfunction leads to inefficient cellular energy production and increased levels of reactive oxygen species (ROS), which may damage lipids, proteins, and nucleic acids[15]. Mitochondrial dysfunction also affects the expression of nuclear genes involved in metabolism, growth, differentiation, and apoptosis[16]. A major limitation of the routine assessment of mitochondrial dysfunction in clinical practice is the lack of reliable measures of mitochondrial dysfunction that can be used in the clinic. And mitochondrial DNA copy number (mtDNA-CN) is a promising biomarker of mitochondrial dysfunction and is likely to be widely used in clinical practice.

2. Mitochondrial DNA variants and cancer:

During cancer development, tumor cells not only undergo metabolic changes to support cell growth, but also other types of mtDNA damage. The mtDNA mutations have been identified in all types of human tumors, including the non-coding and coding regions of mtDNA. Larman et al studied different cancer types and found that the frequency of somatic mtDNA mutations ranged from 13% in glioblastoma to 63% in rectal adenocarcinoma[17]. There are data suggesting that at least one observed tumor mtDNA mutation can confer a selective advantage to cancer cells, further supporting the hypothesis that mtDNA somatic mutations play an important role in promoting tumor cell proliferation[18]. In addition to the structural abnormalities in mtDNA, mtDNA copy number changes have also been frequently described in cancer. For example, elevated mtDNA content was found in primary head and neck squamous cell carcinoma, papillary thyroid carcinoma, and endometrial carcinoma, while gastric cancers exhibited mtDNA depletion. The mtDNA copy number in a cancer may depend on the specific mutation site associated with this cancer. Thus, increased mtDNA copy number can serve as a compensatory response to mitochondrial dysfunction or mutations in nuclear genes indirectly involved in the control of mtDNA copy number. Conversely, mutations in the D loop region that controls mtDNA replication are expected to result in copy number reduction. In many cases, fewer mtDNA copies were accompanied by a reduction in mitochondrial gene expression, suggesting an inhibition of mitochondrial activity in these tumor types. The mtDNA damage causes not only mtDNA copy number changes, but also new point mutations and deletions in mtDNA, impaired mitochondrial function, and changes in cellular and tissue functions. Indeed, Reznik et al found that mtDNA copy number is associated with the incidence of key driver mutations leading to cell carcinogenesis[19]. It is noteworthy that although mtDNA copy number affects the transcript level of mtDNA genes, not all cancer types exhibit a correlation between mitochondrial gene expression and mtDNA copy number.

3. Molecular characterization of mtDNA in intestinal cancer:

Although colonoscopy is widely used for early detection and resection of colorectal adenomas, a precursor to most colorectal cancers, colorectal cancer remains a cause of cancer death and is the only major cancer that affects essentially equally in men and women[20]. Oxidative stress of reactive oxygen species (ROS) is believed to have an important role in colorectal cancer. In addition, several studies have identified oxidative stress as an important risk factor for colorectal adenoma, suggesting that abnormal oxidative stress may be important in early colorectal carcinogenesis. ROS are mainly derived from mitochondria, and they are by-products of aerobic respiration. Under physiological conditions, the amount of cellular mitochondrial DNA remains relatively stable, and it has been found that qualitative and quantitative mtDNA changes, such as somatic mitochondrial mutations and mtDNA copy number changes in colorectal tumor tissue, may play an important role in colorectal carcinogenesis[21,22]. Similarly, changes in mtDNA copy number in non-neoplastic tissues (e. g., peripheral blood) may reflect the end result of interactions between genetic and environmental factors that may increase oxidative stress and colorectal cancer risk. In support of this hypothesis, some studies have found an association between mtDNA copy number in peripheral blood and multiple

cancers[23,24]. In particular, a case-control study in the Singapore Chinese Health cohort[25]And a prospective nested case cohort study[26], Both found that mtDNA copy number in the peripheral blood was associated with an increased risk of colorectal cancer. Despite the association between mtDNA copy number and CRC, it is unclear whether the altered mtDNA copy number is a risk factor for CRC or a biomarker for a confirmed diagnosis of CRC.

Colorectal cancer is the result of the accumulation of multiple genetic alterations, for example point mutations, copy number variations and epigenetic modifications[27]. To date, two major pathways of colorectal carcinogenesis have been precisely described. The first pathway involves chromosomal instability (CIN) and is mainly characterized by the continuous accumulation of genetic alterations in APC, KRAS, and p53[28], The second pathway is the microsatellite instability (MSI)[29]. There is increasing evidence for the functional role of mtDNA abnormalities (including point mutations, deletions, inversions, and copy number alterations) in mitochondrial dysfunction and colorectal carcinogenesis. However, it is unclear whether these mutations initiate or promote tumorigenesis, or whether they are simply a result of genomic instability. Peripheral blood mitochondrial DNA content is associated with risk of colorectal cancer and is proposed as potential biomarkers, however, some studies have failed to confirm this association, suggesting that relative mtDNA copy number in peripheral blood is more likely to be considered as markers of early CRC occurrence than a biomarker that can be used to assess CRC risk[30]。

The molecular mechanisms leading to mtDNA copy number changes are still under investigation. In a study of 65 colorectal cancers, it has been proposed that hypomethylation of the D-loop region may be involved in the regulation of mtDNA copy number[31]. Recently, it has been reported that polymorphisms within the nuclear-encoded polymerase γ gene (POLG) may contribute to reducing a key component of the mitochondrial genome maintenance machinery, resulting in mitochondrial copy number changes[32]. The D loop region contains essential transcription and replication elements and is a well-known somatic mutation hotspot in colorectal tumors. This region is formed by two hypervariable regions, the HV-I (nt.16024-16383) and HV-II (nt.57-333)[33]. MtDNA variants in the D-Loop region are associated with risk and survival in colorectal cancer patients and, therefore, they are proposed as valuable markers for assessment of colorectal cancer outcome[34]. Mitochondrial microsatellite instability (mtMSI), the change in the length of the D loop repeat between normal and tumor tissues, has been described as a common molecular event in colorectal carcinogenesis (approximately 30% of colorectal tumors), but its prognostic value remains controversial[35]。

4. Molecular characterization of mtDNA in liver cancer:

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, with the third highest mortality rate[36,37]. About 434000 new cases of HCC each year[38]. Several risk factors have been proposed to participate in the development of HCC, including aflatoxin exposure, alcohol consumption, viral hepatitis, etc.

Several types of somatic mtDNA alterations have been identified in human HCC, and these mtDNA alterations include point mutations, deletions, insertions, and copy number changes. Screening for somatic point mutations in the whole mitochondrial genome of HCC samples indicates that approximately 52% of HCC patients carry at least one homogenous or heterogeneous point mutation in their tumor tissue mtDNA. Of the identified point mutations, 76% are located in the D-loop regions, 2% in rRNA genes, 3% in tRNA genes, and 19% in mRNA genes[39]. The D-loop region is a hot spot for somatic mtDNA mutations in HCC and other cancers. That the D loop regions of mtDNA, especially mononucleotide repeats in the np 303-309 poly-C sequence, are the sites most susceptible to oxidative damage compared to other regions of mtDNA, implies that oxidative damage contributes to point mutations in the D loop and the instability of mononucleotide or dinucleotide repeats in mtDNA. And because the D-loop region controls mtDNA replication and transcription, mutations in the D-loop region may affect mtDNA copy number and expression of the mitochondrial genome. Thus, somatic mutations in the mtDNA D-loop region may affect mitochondrial function by reducing mtDNA copy number and transcription in HCC, thus leading to HCC progression. The reduction in mitochondrial DNA copy number is a common event in HCC, with more than 60% of HCC having lower mtDNA copy numbers than their corresponding normal liver tissue.

Several types of somatic mtDNA alterations have been identified in HCC, but the role of these mtDNA alterations in HCC progression

is still unclear, and some studies confirm the pathological role of mtDNA mutations and mitochondrial dysfunction in HCC. Most somatic point mutations in mtDNA copy number and reduction in the mitochondrial coding region may contribute to mitochondrial dysfunction in HCC, and these findings provide a molecular basis for the Warburg effect. Furthermore, it has been shown that low mtDNA copy number in HCC is significantly associated with large tumor size, liver cirrhosis, and poor 5-year survival[40]. Thus, mtDNA mutations and reduced mtDNA copy number and mitochondrial dysfunction may alter the progression of HCC. However, the presence of somatic mtDNA point mutations in HCC does not seem to be associated with patient age or sex, tumor size or grade, hepatitis virus infection, or survival of patients[41]. Furthermore, heterogeneous or homogeneous levels of the same mtDNA mutation may lead to different consequences of tumorigenesis. Therefore, the role of specific mtDNA mutations and their levels during HCC progression warrants further investigation.

5. Molecular features of mtDNA in breast cancer:

With regard to breast cancer, multiple studies have investigated the effect of mtDNA content on phenotype, prognosis, and drug response. Lower mtDNA content was observed in approximately 70% of breast cancer specimens when compared to the surrounding normal epithelium[42,43]. There are indications that low mtDNA content in breast cancer may produce a more aggressive phenotype and altered treatment response. Depletion of mtDNA in in vitro models affects the mRNA and protein expression levels of several genes involved in epithelial stromal transition (EMT)[44,45], The transition to a mesenchymal phenotype has been recognized as an important mechanism for promoting cancer metastasis[46]. Thus, the low mtDNA content used as a marker of the mesenchymal phenotype may identify tumor aggressiveness.

Somatic mtDNA variation is frequently observed in primary breast tumors[47]. Most of these variants are single-nucleotide variants rather than small insertions or deletions, which are distributed along the entire mitochondrial genome and show great heterogeneity between cases. To date, no somatic mtDNA mutations have been described that clearly affect breast cancer tumorigenesis or progression. With more somatic mtDNA variants in the primary tumors of patients diagnosed at a higher age. Furthermore, there is substantial heterogeneity in somatic mtDNA variants within primary breast tumors. Although mtDNA content in primary breast tumors is not associated with any traditional clinicopathological marker, low mtDNA levels in primary breast tumors indicate that cancers are more aggressive[48]。

6. Summary and Outlook:

Mutations in mtDNA affect tumor development and progression, which makes the presence of the mitochondrial genome add to both the unique and complex biological properties of this organelle. In recent years, with the vigorous development of next-generation sequencing technology and single-cell sequencing technologies, the biological characteristics of mtDNA in tumors have been gradually elucidated. The structure of mtDNA, mtDNA copy number and others have unique changes in the development of cancer. The mtDNA abnormalities (including point mutations, deletions, inversion, and copy number alterations) have a role in mitochondrial dysfunction and colorectal carcinogenesis, The mtDNA copy number in the peripheral blood is associated with an increased risk of colorectal cancer, The D loop region contains essential transcriptional and replication elements, Is a well-known hotspot of somatic mutations in colorectal tumors, Variation in this region is associated with risk and survival in colorectal cancer patients; Several types of somatic mtDNA alterations have been identified in human HCC, These mtDNA alterations include point mutations, deletions, insertions, and copy number changes, Somatic mutations in the mtDNA D-loop region may affect mitochondrial function by reducing mtDNA copy number and transcription in HCC, Thus leading to the HCC progression, besides, Low mtDNA copy number in HCC was associated with tumor size and cirrhosis of the liver; Single-nucleotide variants in somatic mtDNA are frequently observed in primary breast tumors, Low mtDNA content can be used as a mesenchymal phenotype marker, And then identify the aggresnature of the tumor. As mtDNA has certain clinical significance in many kinds of cancers, this paper reviews the features of mtDNA variation in cancer, and provides relevant basic information for clinical and scientific research staffIt provides some reference basis for the early diagnosis, treatment and prognosis evaluation of cancer.

References

[1] Yan C, Duanmu X, Zeng L, Liu B, Song Z.Mitochondrial DNA: Distribution, Mutations, and Elimination. Cells. 2019; 8(4):379.

[2] Zong WX, Rabinowitz JD, White E.Mitochondria and Cancer. Mol Cell. 2016; 61(5): 667-676.

[3] Yuan Y, Ju YS, Kim Y, et al.Comprehensive molecular characterization of mitochondrial genomes in human cancers [published correction appears in Nat Genet.2020 Feb 11;:] [published correction appears in Nat Genet.2020 Apr 27;:].Nat Genet. 2020; 52(3):342-352.

[4] Reznik E, Miller ML, Şenbabaoğlu Y, et al.Mitochondrial DNA copy number variation across human cancers.Elife.2016;5:e10769. Published 2016 Feb 22.

[5] Desagher S., Martinou J.C.Mitochondria as the central control point of apoptosis.Trends Cell Biol.2000;10:369–377.

[6] Suen D.F., Norris K.L., Youle R.J.Mitochondrial dynamics and apoptosis.Genes Dev. 2008; 22:1577–1590.

[7] Arakaki N., Nishihama T., Owaki H., Kuramoto Y., Suenaga M., Miyoshi E., Emoto Y., Shibata H., Shono M., Higuti T.Dynamics of mitochondria during the cell cycle.Biol.Pharm.Bull.2006;29:1962–1965.

[8] Finkel T., Hwang P.M.The Krebs cycle meets the cell cycle: Mitochondria and the G(1)-S transition.Proc.Natl.Acad.Sci. USA.2009;106:11825–11826.

[9] Mishra P., Chan D.C.Mitochondrial dynamics and inheritance during cell division, development and disease.Nat.Rev.Mol.Cell Biol.2014;15:634–646.

[10] Nicholls T.J., Gustafsson C.M. Separating and Segregating the Human Mitochondrial Genome. Trends Biochem.Sci.2018;43:869–881.

[11] Holt I.J., Reyes A.Human mitochondrial DNA replication.Cold Spring Harb. Perspect. Biol.2012;4:a012971.

[12] Ingman M., Kaessmann H., Paabo S., Gyllensten U.Mitochondrial genome variation and the origin of modern humans.Nature.2000;408:708–713.

[13] Yuan R.T., Sun Y., Bu L.X., Jia M.Y.Gene mutations in the D-loop region of mitochondrial DNA in oral squamous cell carcinoma. Mol. Med.Rep. 2015; 11: 4496 –4500.

[14] Nicolson GL. Mitochondrial Dysfunction and Chronic Disease: Treatment With Natural Supplements.Integr Med (Encinitas).2014;13(4):35-43.

[15] Guyatt AL, Burrows K, Guthrie PAI, et al.Cardiometabolic phenotypes and mitochondrial DNA copy number in two cohorts of UK women. Mitochondrion. 2018; 39: 9-19.

[16] Pello R, Martín MA, Carelli V, et al. Mitochondrial DNA background modulates the assembly kinetics of OXPHOS complexes in a cellular model of mitochondrial disease.Hum Mol Genet.2008 Dec 15;17(24):4001-11.

[17] Larman TC, DePalma SR, Hadjipanayis AG, Protopopov A, Zhang J, Gabriel SB, Chin L, Seidman CE, Kucherlapati R and Seidman JG; Cancer Genome Atlas Research Network: Spectrum of somatic mitochondrial mutations in five cancers. Proc Natl Acad Sci USA.109:14087–14091.

[18] Jiménez-Morales S, Pérez-Amado CJ, Langley E, Hidalgo-Miranda A. Overview of mitochondrial germline variants and mutations in human disease: Focus on breast cancer (Review). Int J Oncol.2018 Sep;53(3):923-936.

[19] Reznik E, Miller ML, Şenbabaoğlu Y, et al: Mitochondrial DNA copy number variation across human cancers.eLife.5:e107692016.

[20] Thyagarajan B, Guan W, Fedirko V, et al. No association between mitochondrial DNA copy number and colorectal adenomas. Mol Carcinog. 2016;55(8):1290-1296.

[21] Lin PC, Lin JK, Yang SH, et al. Expression of beta-F1-ATPase and mitochondrial transcription factor A and the change in mitochondrial DNA content in colorectal cancer: clinical data analysis and evidence from an in vitro study.Int J Colorectal Dis.2008;23(12):1223–1232.

[22] Chang SC, Lin PC, Yang SH, et al. Mitochondrial D-loop mutation is a common event in colorectal cancers with p53 mutations. Int J Colorectal Dis. 2009; 24(6): 623– 628.

[23] Xie H, Lev D, Gong Y, et al.Reduced mitochondrial DNA copy number in peripheral blood leukocytes increases the risk of soft tissue sarcoma. Carcinogenesis. 2013; 34(5): 1039–1043.

[24] He Y, Gong Y, Gu J, Lee JJ, Lippman SM, Wu X.Increased leukocyte mitochondrial DNA copy number is associated with oral

premalignant lesions: an epidemiology study. Carcinogenesis. 2014; 35(8):1760-1764.

[25] Qu F, Liu X, Zhou F, et al.Association between mitochondrial DNA content in leukocytes and colorectal cancer risk: A case-control analysis. Cancer. 2011; 117(14): 3148–3155.

[26] Thyagarajan B, Wang R, Barcelo H, Koh WP, Yuan JM.Mitochondrial Copy Number is Associated with Colorectal Cancer Risk. Cancer Epidemiol Biomarkers Prev.2012;21(9):1574–1581.

[27] Wang C, Zhao S, Du Y, Guo Z.Single nucleotide polymorphisms in the D-loop region of mitochondrial DNA is associated with colorectal cancer outcome. Mitochondrial DNA A DNA Mapp Seq Anal.2016 Nov;27(6):4361-4363.

[28] Pino MS, Chung DC. The chromosomal instability pathway in colon cancer. Gastroenterology. 2010 Jun; 138(6):2059-72.

[29] Akbari M, Sykora P, Bohr VA.Slow mitochondrial repair of 5'-AMP renders mtDNA susceptible to damage in APTX deficient cells.Sci Rep.2015 Aug 10;5:12876.

[30] Thyagarajan B, Guan W, Fedirko V, Barcelo H, Tu H, Gross M, Goodman M, Bostick RM.No association between mitochondrial DNA copy number and colorectal adenomas.Mol Carcinog.2016 Aug;55(8):1290-6.

[31] Gao J, Wen S, Zhou H, Feng S (2015) De-methylation of displacement loop of mitochondrial DNA is associated with increased mitochondrial copy number and nicotinamide adenine dinucleotide subunit 2 expression in colorectal cancer.Mol Med Rep 12(5):7033–7038

[32] Linkowska K, Jawień A, Marszałek A, et al. Mitochondrial DNA Polymerase γ Mutations and Their Implications in mtDNA Alterations in Colorectal Cancer.Ann Hum Genet.2015 Sep;79(5):320-328.

[33] Tipirisetti NR, Govatati S, Pullari P, et al. Mitochondrial control region alterations and breast cancer risk: a study in South Indian population. PLoS One. 2014 Jan 30; 9(1):e85363.

[34] Wang C, Zhao S, Du Y, Guo Z (2016) Single nucleotide polymorphisms in the D-loop region of mitochondrial DNA is associated with colorectal cancer outcome.Mitochondrial DNA A DNA Mapp Seq Anal 27(6):4361–4363.

[35] Venderbosch S, Van Vliet S, Craenmehr MH, Simmer F, de Haan AF, Punt CJ, Koopman M, Nagtegaal ID (2015) Mitochondrial microsatellite instability in patients with metastatic colorectal cancer.Virchows Arch 466(5):495–502.

[36] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM.Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010; 127: 2893–2917.

[37] Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet. 2012; 379:1245 –1255.

[38] World Health Organisation (WHO) Databank. WHO statistical information system[Internet]. Geneva: WHO.

[39] Hsu CC, Lee HC, Wei YH.Mitochondrial DNA alterations and mitochondrial dysfunction in the progression of hepatocellular carcinoma.World J Gastroenterol. 2013; 19(47): 8880-8886.

[40] Yamada S, Nomoto S, Fujii T, Kaneko T, Takeda S, Inoue S, Kanazumi N, Nakao A. Correlation between copy number of mitochondrial DNA and clinico-pathologic parameters of hepatocellular carcinoma.Eur J Surg Oncol. 2006; 32:303–307.

[41] Yin PH, Wu CC, Lin JC, et al. Somatic mutations of mitochondrial genome in hepatocellular carcinoma.Mitochondrion.2010;10:174–182.

[42] McMahon S, LaFramboise T. Mutational patterns in the breast cancer mitochondrial genome, with clinical correlates. Carcinogenesis. 2014; 35: 1046–54.

[43] Hollestelle A, Peeters JK, Smid M, et al. Loss of E-cadherin is not a necessity for epithelial to mesenchymal transition in human breast cancer.Breast Cancer Res Treat. 2013;138:47–57.

[44] Naito A, Cook CC, Mizumachi T, et al. Progressive tumor features accompany epithelial-mesenchymal transition induced in mitochondrial DNA-depleted cells. Cancer Sci. 2008; 99: 1584–8.

[45] Guha M, Srinivasan S, Ruthel G, et al. Mitochondrial retrograde signaling induces epithelial-mesenchymal transition and generates breast cancer stem cells. Oncogene.2014;33:5238–50.

[46] Thiery JP. Epithelial-mesenchymal transitions in tumour progression.Nat Rev Cancer. 2002; 2:442–54.

[47] Ebrahimi E, Almasi-Hashiani A, Ghaffari K, Shirkoohi R. Mitochondrial DNA copy number instability in ERBB2-amplified

breast cancer tumors. EXCLI J. 2018; 17: 149-158.

[48] Weerts MJA, Sleijfer S, Martens JWM.The role of mitochondrial DNA in breast tumors.Drug Discov Today.2019 May;24(5):1202-1208.

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