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An overview about mitochondrial DNA mutations in ovarian cancer

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ABSTRACT

Background: Ovarian tumour is the second most common form of cancer affecting female reproductive system and the most lethal of the gynaecological malignancies. Since past decades, tremendous efforts have been made to illuminate the molecular basis for initiation and progression of ovarian carcinoma. A low quantity of dysfunction in mitochondrial DNA (mtDNA) is considered to be a risk factor for variety of cancer types. Mitochondrial dysfunctions have been allied with varied metabolic diseases and for occurrence of cancer. Researches say that mtDNA have pivotal role in development of cancer but future work has to be carried out to know the exact significance of specific mitochondrial mutations linked with cancer and disease progression. Most of mtDNA mutations in gynecological cancers are observed in the D-loop region.

Objective: This review article provides a detailed summary about the ovarian cancer and mutations observed in mtDNA.

Result: Furthermore, this review offers some perspective as to the mtDNA origin of these mutations in ovarian cancer, their functional consequences in ovarian cancer development, to check for incidence rate for transmission of the disease through maternal lineages and possible diagnostic marker implication.

Contents

Abbreviations: mtDNA, Mitochondrial DNA; D-loop, Displacement loop; ND6, , NADH dehydrogenase subunit 6; ROS, , Reactive Oxygen Species.

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1. Introduction

Cancer development is known to be a result of the collection of genetic alterations including multiple genes and chromosomes. Ovarian cancer has emerged as the second most common form of gynaecological malignancies affecting women in India. Normally it occurs during 50–69 years of age for a female in her lifetime.[1] Almost 14,000 women are suffering from ovarian cancer annually which ends up as a global increase in incidence rates. There are 2 per cent chances of developing a lifetime risk for sporadic ovarian carcinoma. There are studies which have shown that patients with positive family history are at higher percent risk to acquire the cancer. Ovarian tumours are a heterogeneous group of neoplasms, divided into a number of different subgroups, depending largely on histological and cytological features. Many researches have been carried out in India to demonstrate the behaviour and etiology of the heterogeneous group of ovarian cancers. Epithelial ovarian cancer arises from the surface of the ovary. Serosal lining of the ovary continues with the peritoneal lining of the abdomino-pelvic cavity. Among the ovarian cancer subtypes the serous subtype of surface epithelium is considered to be highly lethal and frequent.[2] In ovarian cancer follicle-stimulating hormone receptor gene polymorphism is been considered for modulation of receptor sensitivity and susceptibility.

Familial ovarian carcinoma has been considered to be characterised by an elevated frequency during the past decades commensurate with physicians attention to the family history. Putative autosomal dominant inheritance of this heterogeneous problem is seeking great attention in maternal lineages. Mode of inheritance for autosomal dominant along with the risk of developing ovarian cancer in humans with a familial risk is as high as 50%.[3]

Approximately 10–20% of high grade ovarian cancers are been associated with germ line mutations in BRCA1/2 whereas 50% of them are been coupled with somatic alterations. Women with deletions such as heteroplasmic mutations have an increased chance of having affected children which especially depends on the nature and severity of phenotypic mutations on mtDNA along with heteroplasmy.[4] There are reports which have been suggested that mtDNA is inherited exclusively or almost from their maternal side, thus has important ramifications both for its genetic and evolution.[5] In individuals, different array of cells with mtDNA mutations can accumulate over the time. These mutations play vital role in ageing and cancer. Till now only a very little information about the origin, genetics and phenotypic effects of heteroplasmic mtDNA mutation in relation to cancer is known.

This review article will provide a brief summary about the current understanding of ovarian cancer in India along with the role played by mitochondria both in genetic and biological aspects. Furthermore, it reviews the reported mtDNA alterations in ovarian cancer and discusses possible mechanism by which mtDNA mutations emerge in cancer cells and its role in transmission of the disease through maternal lineages.

2. Mitochondrial DNA (mtDNA)

Mitochondria, the so-called "powerhouses" of cells are an unusual organelles which are surrounded by a double membrane and retain their own small genome. Mitochondrial genomes are very small but has varied variations which results in diverged evolutions. Mitochondrion is considered to be a metabolic organelle which possess their own genome i.e. mtDNA which is considered to be inherited only through the maternal descent.[6] The mitochondria is a double-membrane structure with a double-stranded genome capable of transcription, translation and protein assembly. There are reports which suggest that mtDNA can be replicated independent of nuclear DNA.[7] Defects in mitochondria plays a major role in progression and development of cancer. Warburg et al.[8] were the first to suggest the role of mitochondrial contribution in the progression of cancer pathogenesis where they observed that neoplastic cells showed prevalence during the anaerobic glycolysis process. Another study revealed that mitochondrion was involved in carcinogenesis process due to discovery of respiratory deficit in dividing cells which were characterised by rapid proliferation.[8–10]

3. Mutations in mtDNA

In many studies, it have been noted that mutations in mtDNA is focused on the D-loop region. In the mitochondrial genome, the D-loop is a control site for expression. Mutations in regulatory region in D-loop origin is associated with reduction in NADH dehydrogenase subunit 6 (ND6) expression and in the mtDNA copy number.[11] A combination of the mitochondrial DNA proteins forms the nucleoid complex, which protects against mutagenesis much less strong than those in nuclear genome.[12] Thus the high rate of mutations in mtDNA is 10–100 times higher than in the nuclear DNA.[13–15], is explained by production of ROS through the phosphorylation process. High susceptibility of mtDNA to mutation through ROS leads to inefficient repair system and lack of protective histones. The network of mitochondria is extremely dynamic which is precisely regulated during stressful conditions. This mutations in mtDNA due to increased accumulation results in ageing of tissues such as brain, skeletal muscle and fibroblasts as well as in many pathological conditions like neurologic, metabolic and age-related disorders.[13,16,17] Such forms of alterations are especially noted in pre-neoplastic lesions and in human cancers which includes breast cancer, ovarian cancer, colorectal cancer, hepatic cancer, gastric cancer, esophageal cancer, thyroid cancer and prostate cancer.[18,19]

4. Involvement of mtDNA in different cancers

Mutations in mtDNA have been discovered to play role in various types of human cancers which are:

4.1. Breast cancer

In an earlier study, a combination of temporal temperature gel electrophoresis along with direct DNA sequencing were used to screen complete mitochondrial genome mutations in 19 sets of breast cancer sample and controls. Out of 19 sets, 14 showed somatic mutations (74%) while the remaining of them were restricted to D-loop region (81.5%). Few mutations were also found in 16S rRNA, ND2 and ATPase 6 genes.[20]

4.2. Colorectal cancer

Polyak[21] carried out an experiment with 10 normal and malignant colon cells to sequence the entire mitochondrial genome. 7 out 10 samples showed somatic mutations in 12S rRNA, 16S rRNA, ND1, ND4L, ND5, Cytochrome *b*, COXI, COXII and COXIII genes.

4.3. Hepatic cancer

One of the previous study involving 19 hepatocellular carcinoma (HCC) patents revealed that in mtDNA, the D-loop region showed high frequency for mutations and thus suggested that this region in HCC could be used as a molecular marker for diagnosis.[22]

4.4. Gastric cancer

In a previous study, 32 gastric cancer samples were been examined and common deletion in mtDNA was reported in 54% of cases; most of the mutations corresponded to insertions/deletions in the D-loop region or transitions in ND1, ND4 and COXI. Thus suggesting that mtDNA alterations tend to be associated with gastric cancers.[23]

4.5. Esophageal cancer

Miyazono[24] carried out an experiment on adenocarcinomas of Barrett's esophagus and identified that 40% of cases showed alterations in D-loop region. Whereas in an another study only few D-loop mutations (5%) are been associated with esophageal carcinomas.[25]

4.6. Thyroid cancer

Since many years, it has been confirmed that abnormality in mitochondria is been associated with thyroid tumours.[26] In a preceding study, 21 thyroid tumour samples were been analysed which showed that somatic mutations were present in 23% of samples were the mutations occurred in genes coding for subunits of complex I of respirator chain.[19]

4.7. Prostate cancer

Only few studies have been carried out suggesting about the role of mtDNA in prostate cancer. In one of the study, the authors examined 34 malignant prostate specimens where the whole mtDNA has been amplified, which showed that average number of deletions increased with advanced age.[27] However, in other study involving 16 patients,[28] sequenced only the D-loop region, 16S rRNA and NADH subunits and found mutations only in 3 of them. Thus suggesting the presence of mutations in mtDNA in cancer cells is due to intrinsic susceptibility to damage and constitutive oxidative stress.

5. Role of mtDNA in ovarian cancer

In Ovarian cancer there are difficulties in detecting the exact location of primary tumour because of which most of the patients are been diagnosed in the advanced stages (stage III/IV). As ovarian cancer has the capacity of high recurrence rate; it still remains as the most leading cause of deaths in women.[29] Thus, new methods have to be invented to discover mechanism behind the pathogenesis of ovarian tumour. Recently[30] another author suggested that the aggressive behaviour of cancer cells and its prognosis might be related to functional disorders in mitochondria. The mutations rate in mtDNA in cancer cells is 10 times higher than that of nuclear DNA.[31] An unique adaptation can be taken by tumour cells during unrestrained growth by shifting from either oxidative phosphorylation to glycolysis or the Warburg effect,[32] in which somatic mutations occurs through the hypoxia activation inducible factor.[33] In mitochondrial genome, the variants which encodes 22 tRNAs, 2 rRNAs and 13 proteins which are involved in electron transport chain (ETC) complexes are vital for oxidative phosphorylation thus affecting in tumorigenesis.[34]

5.1. Prior works in mtDNA & ovarian cancers

Given that the vast majority of patients with ovarian cancers are females and in most cases the inheritance is been considered to be through their maternal lineages thus a fateful consequence with mutation in mtDNA might play a major role. A previous study.[35] by Wang et al reported that abnormal copy number of mtDNA was related with type and grade of ovarian cancer. Many preceding studies have established that several mutations in mtDNA in somatic form in mitochondrial respiratory complex I genes especially in D-loop region may act in predisposition for cancers.[36] Mitochondrial genome has two strands for encoding, which are light and a heavy strand where most of the genes are located in the heavy strands. MtDNA contains a non-coding region i.e. displacement loop (D-loop) with 1123bl length accommodated with transcription and replication process for both heavy and light strands. In the mitochondrial transcription and replication process, the main regulatory region is the D-loop site which encompasses essential and strongly conserved sequence elements as well as loci which communicates mutations rapidly.[37,38] D-loop region's mutations located in regulatory elements are been associated with reduction in ND6 expression especially in mtDNA copy number.[11] The most unstable micro satellite sequence in D-loop region of mtDNA is between 303 and 309; this region initiates replication of mtDNA heavy strand.[39] In a recent study, 3 out of 15 cases (20%) of ovarian carcinoma showed somatic mtDNA mutation in the D-loop which were homoplasmic.[40] Furthermore,[40] stated that there is a high incidence of somatic (60%) type of mutations in mtDNA in human ovarian carcinomas, where most of the mutations were homoplasmic and most were T3C or G3A transitions but only one showed a differential length in identical C residues. In one of the study, it has been reported that alterations in mtDNA in 15 primary ovarian cancers identified that D-loop, 12S rRNA, 16S rRNA and cytochrome *b* (G-A transition) regions were mutated.[41] Another study indicated that SNPs 254T/G, 259A/G, 275G/A, 366G/A, 411C/G, 414T/G, 418C/G, 441C/A, 476C/A, 524C/del, 530C/T were significantly coupled with an increased risk for acquiring epithelial ovarian cancer; thus concluding that SNP's in the D-loop region of mtDNA can be used as accurate diagnosing marker in ovarian cancer cases.[42] In a previous report, it has been found that among 102 ovarian tumour samples, almost 352 mtDNA variants were been observed over a span of 3.3 kb fragment which includes D-loop, 12S rRNA-tRNAphe, tRNAval, COX I, tRNAser, tRNAasp, COX II, tRNAlys, ATPase 6 and ATPase 8.[43]

Another interesting finding in ovarian tumour was the genetic alteration in the C-stretch region which is considered to be the hotspot for somatic mutations. Bragoszewski et al.[44] carried out an experiment on ovarian cancer samples and found that the sequence alterations in C-tract were either insertions or deletions of one or two base pairs. Similar results were reported in another study where c-stretch instability at np 303–315 was found in almost 97% of the cases thus suggesting that c-stretch variants as the mutations can occur in germ line origin in ovarian carcinoma.[18]

6. Key aspects of mtDNA as a diagnostic marker in ovarian cancer

Now-a-days it is been a trend to discover tumour markers which can be used for assessing both early diagnosis, recurrence of the disease and to monitor the treatment response. Till now no exact early detection marker is available to detect ovarian cancer because of which the number of deaths in women due to ovarian cancer is been increasing steadily. Though some preventive measures may reduce the risk for ovarian cancer, the majority of cases cannot be cured completely, especially in developing country like India where ovarian cancer is been diagnosed in late stages. Thus, early detection could prove important to improve the outcome and survival rate of women affected with ovarian cancer. In a recent study by,[45] it is established that serum CA125, serum HE4 and urine HE4 levels were increased in patients with ovarian

cancer. But the changes occur in molecular levels, thus suggesting that the marker should also be established in the DNA level. The main challenge regarding biomarkers for ovarian cancer diagnosis is to improve the accuracy for the detection of the malignancy at the earliest possible stage.

In ovarian tumour many researches have been carried out to study mutations in D-loop region of mtDNA which is considered to be highly polymorphoric and mutable region. Thus, many authors have suggested that mtDNA mutations can be served as both biomarkers of carcinogenesis and a predictive factor for the course of the disease. There are many evidences that mtDNA mutational variability in tumour has provided optimistic belief that mtDNA studies in ovarian cancer patients might be a promising search for developing reliable diagnostic marker.[46,47] In mtDNA the most reliable region for developing as a biomarker can be the D-loop region. The unstable C-stretch which is located in HV segment II region of D-loop along with length variations in this mono nucleotide sequences are the best common polymorphisms in cancer cases.

7. Conclusion

In closing, the Ovarian Carcinoma was considered to be the most deadly women's cancer in developing countries like India, but today has inspired many exciting basic science studies in epigenetics especially related to mutations observed in mtDNA. It is anticipated that the chapters in this review involves translating some of the novel discoveries of mutations in mtDNA, chances of transmission of the mutated mtDNA through maternal lineages in the disease, thus exhibiting as a beneficial source for treating women suffering with ovarian cancer.

Conflict of interest

The authors declared that there is no conflict of interest.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin*. 2009;59:225–249.
2. Nijman HW, Lambeck A, Burg van der SH, Zee van der AG, Daemen T. Immunologic aspect of ovarian cancer and p53 as tumor antigen. *J Transl Med*. 2005;3:34.
3. Ponder BAJ, Easton DF, Peto J. Risk ofovarian cancer associated with a family history: preliminary report of the OPCS. In: Sharp F, Mason WP, Leake RE, eds. *Ovarian Cancer: Biological and Therapeutic Challenges*. London: Chapman and Hall; 1993:3–6.
4. Wallace DC, Chalkia D. Mitochondrial DNA genetics and the heteroplasmy conundrum in evolution and disease. *Cold Spring Harb Perspect Biol*. 2013;5: a021220.
5. Howell N. Human mitochondrial diseases: answering questions and questioning answers. *Int Rev Cytol*. 1999;186:49–116.
6. Giles RE, Blanc H, Cann HM, Wallace DC. *Proc Natl Acad Sci USA*. 1980;77:6715–6719.
7. Lightowlers RN, Chinnery PF, Turnbull DM, Howell N. *Trends Genet*. 1997;13:450–455.
8. Warburg O. *The Metabolism of Tumors*. London, UK: Arnold Constable; 1932.
9. Warburg O. On the origin of cancer cells. *Science*. 1956;123:309–314.
10. Szent-Gyorgyi A. Electronic biology and cancer*Search and Discovery: A Tribute to Albert Szent-Gyorgyi*. New York: Kaminer B: Academic Press; 1977:329–335.
11. Coskun PE, Beal MF, Wallace DC. Alzheimer's brains harbor somatic mtDNA control-region mutations that suppress mitochondrial transcription and replication. *Proc Natl Acad Sci USA*. 2004;101:10726–10731.
12. Czarnecka AM, Gammazza AM, Di Felice V, Zummo G, Cappello F. Cancer as "Mitochondriopathy". *J Cancer Mol*. 2007;3:71–79.
13. Maximo V, Sobrinho-Simoes M. Hurthle cell tumours of the thyroid. A review with emphasis on mitochondrial abnormalities with clinical relevance. *Virchows Arch*. 2000;437:107–115.
14. Wallace DC, Brown MD, Lott MT. Mitochondrial DNA variation in human evolution and disease. *Gene*. 1999;238:211–230.
15. Fernandez-Silva P, Enriquez JA, Montoya J. Replication and transcription of mammalian mitochondrial DNA. *Exp Physiol*. 2003;88:41–56.
16. Melov S, Shoffner JM, Kaufman A, Wallace DC. Marked increase in the number and variety of mitochondrial DNA rearrangements in aging human skeletal muscle. *Nucleic Acids Res*. 1995;23:4122–4126.
17. Michikawa Y, Mazzucchelli F, Bresolin N, Scarlato G, Attardi G. Aging-dependent large accumulation of point mutations in the human mtDNA control region for replication. *Science*. 1999;286:774–779.
18. Aikhionbare FO, Khan M, Carey D, Okoli J, Go R. Is cumulative frequency of mitochondrial DNA variants a biomarker for colorectal tumor progression? *Mol Cancer*. 2004;3:30.
19. Yeh JJ, Lunetta KL, van Orsouw NJ, et al.. Somatic mitochondrial DNA (mtDNA) mutations in papillary thyroid carcinomas and differential mtDNA sequence variants in cases with thyroid tumours. *Oncogene*. 2000;19:2060–2066.
20. Tan DJ, Bai RK, Wong LJ. Comprehensive scanning of somatic mitochondrial DNA mutations in breast cancer. *Can Res*. 2002;62:972–976.
21. Polyak K, Li Y, Zhu H, et al.. Somatic mutations of the mitochondrial genome in human colorectal tumours. *Nat Genet*. 1998;20:291–293.
22. Nomoto S, Yamashita K, Koshikawa K, Nakao A, Sidransky D. Mito-chondrial D-loop mutations as clonal markers in multicentric hepatocellular carcinoma and plasma. *Clin Cancer Res*. 2002;8:481–487.
23. Maximo V, Soares P, Seruca R, Rocha AS, Castro P, Sobrinho-Simoes M. Microsatellite instability, mitochondrial DNA large deletions, and mitochondrial DNA mutations in gastric carcinoma. *Genes Chromosom Cancer*. 2001;32:136–143.
24. Miyazono F, Schneider PM, Metzger R, et al.. Mutations in the mitochondrial DNA D-Loop region occur frequently in adenocarcinoma in Barrett's esophagus. *Oncogene*. 2002;21:3780–3783.
25. Hibi K, Nakayama H, Yamazaki T, et al.. Mitochondrial DNA alteration in esophageal cancer. *Int J Cancer*. 2001;92:319–321.
26. Stefaneanu L, Tasca C. An electron-microscopic study of human thyroid cancer. *Endocrinologie*. 1979;17:233–239.
27. Jessie BC, Sun CQ, Irons HR, Marshall FF, Wallace DC, Petros JA. Accumulation of mitochondrial DNA deletions in the malignant prostate of patients of different ages. *Exp Gerontol*. 2001;37:169–174.
28. Jeronimo C, Nomoto S, Caballero OL, et al.. Mitochondrial mutations in early stage prostate cancer and bodily fluids. *Oncogene*. 2001;20:5195–5198.
29. Naora H, Montell DJ. Ovarian cancer metastasis: integrating insights from disparate model organisms. *Nat Rev Cancer*. 2005;5:355–366.
30. Gottlieb E, Tomlinson IP. Mitochondrial tumour suppressors: a genetic and biochemical update. *Nat Rev Cancer*. 2005;5:857–866.
31. Wallace DC. Mitochondrial DNA sequence variation in human evolution and disease. *Proc Natl Acad Sci USA*. 1994;91:8739–8746.
32. Koppenol WH, Bounds PL, Dang CV. Otto Warburg's contributions to current concepts of cancer metabolism. *Nat Rev Cancer*. 2011;11:325–337.
33. Semenza GL. Hypoxia-inducible factors in physiology and medicine. *Cell*. 2012;148:399–408.
34. Anderson S et al.. Sequence and organization of the human mitochondrial genome. *Nature*. 1981;290:457–465.
35. Wang Y, Liu VW, Xue WC, Cheung AN, Ngan HY. Association of decreased mitochondrial DNA content with ovarian cancer progression. *Br J Cancer*. 2006;95:1087–1091.
36. Ding C, Li R, Wang P, Jin P, Li S, Guo Z. Identification of qu pyp -Lp g DNA as a risk factor for lung cancer. *Mitochondrial DNA*. 2012;23:251–254.
37. Taanman JW. The mitochondrial genome: structure, transcription, translation and replication. *Biochem Biophys Acta*. 1999;1410:103–123.
38. Suzuki M, Toyooka S, Miyajima K, et al.. Alterations in the mitochondrial displacement Loop in lung cancers. *Clin Cancer Res*. 2003;9:5636–5641.
39. Lee DY, Clayton DA. Initiation of mitochondrial DNA replication by transcription and R-loop processing. *J Biol Chem*. 1998;273:30614–30621.
40. Liu VW, Shi HH, Cheung AN, et al.. High incidence of somatic mitochondrial DNA mutations in human ovarian carcinomas. *Can Res*. 2001;61:5998–6001.
41. Księżakowska K, Anna NS, Jacek RW. Mitochondrial DNA mutations in gynecological cancers. *Przegląd Menopauzalny*. 2011;6:436–442.
42. Liu S, Shi S, Li Y, et al.. Identification of sequence nucleotide polymorphisms in the D-loop region of mitochondrial DNA as a risk factor for epithelial ovarian cancer. *Mitochondrial DNA A DNA Mapp Seq Anal*. 2016;27:9–11.
43. MITOMAP. A human mitochondrial genome database. <http://www.mitomap.org>.
44. Bragoszewski P, Kupryjanczyk J, Bartnik E, et al.. Limited clinical relevance of mitochondrial DNA mutation and gene expression analyses in ovarian cancer. *BMC Cancer*. 2008;8:292.
45. Karakaya BK, Başer E, Bildaci B, et al.. Alternative tumor markers in the diagnosis of ovarian cancer. *Ginekol Pol*. 2016;87:565–569.
46. Salas A, Yao YG, Macaulay V, Vega A, Carracedo A, Bandelt HJ. A critical reassessment of the role of mitochondria in tumorigenesis. *PLoS Med*. 2005;2: e296.
47. Zanssen S, Schon EA. Mitochondrial DNA mutations in cancer. *PLoS Med*. 2005;2:e401.