Mitochondrion: I am more than a fuel server

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Abstract: Apart from reliable management of the "powerhouse" of the cell, mitochondria faithfully orchestrate a diverse array of important and critical functions in governing cellular signaling, apoptosis, autophagy, mitophagy and innate and adaptive immune system. Introduction of instability and imbalance in the mitochondrial own genome or the nuclear encoded mitochondrial proteome would result in the manifestation of various diseases through alterations in the oxidative phosphorylation system (OXPHOS) and nuclear-mitochondria retrograde signaling. Understanding mitochondrial biology and dynamism are thus of paramount importance to develop strategies to prevent or treat various diseases caused due to mitochondrial alterations.

Keywords: Mitochondria; cancer; genetic disorders; therapy; biomarker

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Introduction

Mitochondria are unique cytoplasmic organelles faithfully generating fuel to support healthy living and carrying out normal metabolic function (1). Mitochondria possess their own DNA (mtDNA), strictly follow maternal inheritance and are integral part of the oxidative phosphorylation system (OXPHOS) in producing cellular ATP (1). They are the central regulators of OXPHOS system and constituted of five respiratory complexes (complex I-V) which are assembled from multiple polypeptides, some encoded by mtDNA and others by nuclear DNA (nDNA). The human mtDNA is a 16.5-kb double stranded closed circular molecule, which encodes 12S and 16S rRNAs, 22 tRNAs and 13 proteins essential for the mitochondrial respiratory complex (1) (*Figure 1*). Remarkably, intracellular and intercellular mitochondrial heterogeneity exist and each mitochondrion contain hundreds of copies of mtDNA and nearly all of these mtDNA copies remains identical or homoplasmic at birth. Notably, due to the lack of protective histones, rate of mutation in mtDNA is approximately 10 times higher than the nuclear DNA (nDNA) and comparatively easier to spot due to the high copy number particularly in the malignant cells. It is overwhelming to think from the evolutionary perspective about the retention of 13 mtDNA encoded proteins in the mitochondria, while more than 1,500 molecules are traveling from the nucleus to orchestrate diversified mitochondrial function efficiently.

Mitochondria in various cellular signaling

Appreciable number of studies in the past few decades uncovered diverse functions of mitochondria in regulating inflammation, innate and adaptive immune system, T cell function, macrophage polarization and mitophagy (2-8). Mitochondria appear to be intimately associated with immune system function by controlling various cellular responses. Inflammation is a natural response to infection or injury to tissues allowing a reasonable amount of time to clear infection or repairing injury. However, a chronic and uncontrolled inflammatory response could induce abnormal changes in the cellular or tissue microenvironment leading to even tumorigenesis (9). In pro-inflammatory microenvironment, mitochondria can elicit unique response known as mitochondrial danger-associated molecular pattern (mtDAMPs) through mtDNA, mtROS, ATP and cardiolipin, calreticulin production, indicative of disruption in mitochondrial homeostasis (10). Importantly, if the

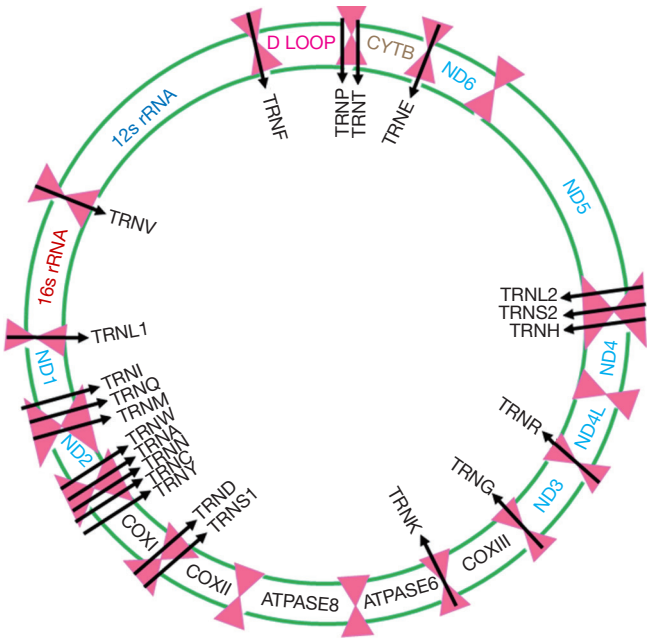

Figure 1 The human mitochondrial genome. The 16.5 Kb human mtDNA encodes for 13 proteins: CYTB (RCIII), ND6, ND5, ND4, ND4L, ND3, ND2, and ND1 (RCI), COXI, COXII and COXIII (RCIV), ATPASE6 and ATPASE8 (RCV), 12S and 16S rRNAs and 22 tRNAs (black arrows) essential for the mitochondrial respiratory complex.

release of mtDAMPs is sustained for a long enough time, it may promote tumorigenic growth and progression (10). However, various mtDAMPs released by the cancer cells can awake and trigger activation of immune cells, such as dendritic cells (DCs), cytotoxic lymphocytes (CTS) or phagocytic macrophages, which can eliminate tumor cells efficiently (10). Among these immune cells, macrophages are the integral components of the innate immune system and mitochondrial metabolism control activation, polarization and inflammatory response generated by the macrophages thereby engaging and directing them towards the mtDAMPs signaling (11). Other than the macrophages, a very recent study from Chandel laboratory has demonstrated a remarkable dependency of regulatory T cells (T_{reg}) on mitochondrial respiratory complex (RC) III for their classical immune suppressive function (12). The same group also uncovered a novel role of mitochondrial RC III in regulating endothelial cell proliferation during angiogenesis (13). Mitochondria are also potential mediator of anti-viral immune response through mitochondrial antiviral signaling protein (MAVS) (7). Mitophagy is a specialized form of autophagy in which damaged, dysfunctional or obsolete mitochondria are recognized by the autophagy machinery and eventually degraded by the lysosome (14). Mitophagy is regulated by various molecular pathways involving PINK, Parkin, BNIP3, NIX and FUNDC1 (14). Cancer cells can efficiently utilize mitophagy as a survival route and recycle intracellular components when stressed metabolically or exposed to treatment with various anticancer regimens (14).

Mitochondria, heterogeneity, tumorigenesis and health disparity

Unique existence of intracellular and intercellular mitochondrial heterogeneity exists within cells implicating the enormous complexity of mitochondrial signaling and function in multiple pathways. *Figure 2* shows both intracellular and intercellular mitochondrial heterogeneity in human urothelial carcinoma cells analyzed through transmission electron microscopy (15). Mitochondria from 4 different cells exhibit remarkable heterogeneity in their dynamics and distribution. Overwhelmingly, each mitochondrion in the same or different cells in turn may harbor variable copies of both wild type and mutant DNA (a state of heteroplasmy). Supporting this notion, majority of the mtDNA deep sequencing studies including ours have reported the presence of heteroplasmic mtDNA mutations (15-18).

A fundamental role of mitochondrial alterations in cancer evolution has been enunciated long ago by Otto Warburg (19,20). That obscured path has been uncovered recently, which continues to provide solid evidence that mtDNA mutations and changes in mitochondrial dynamics substantially contribute to tumorigenesis (21-28). To date, mitochondrial DNA mutation encompassing the coding and non-coding regions of the mitochondria have been detected in human malignancies of various anatomic origin (1,15-17,29-40). As mentioned above, most of these mutations were heteroplasmic in nature (1). Colorectal cancer (CRC) was the first studied neoplasm for mtDNA mutation and majority of the CRC mutations were centered in the non-coding tRNA and rRNA genes (41-44). In breast cancer (BC), the most frequently altered mtDNA regions were *ATP6*, *ATP8 (RCV) and ND5 (RCI)* (45-48). Recent studies in gastric carcinomas (GC) identified several mtDNA mutations encompassing the regulatory D-loop

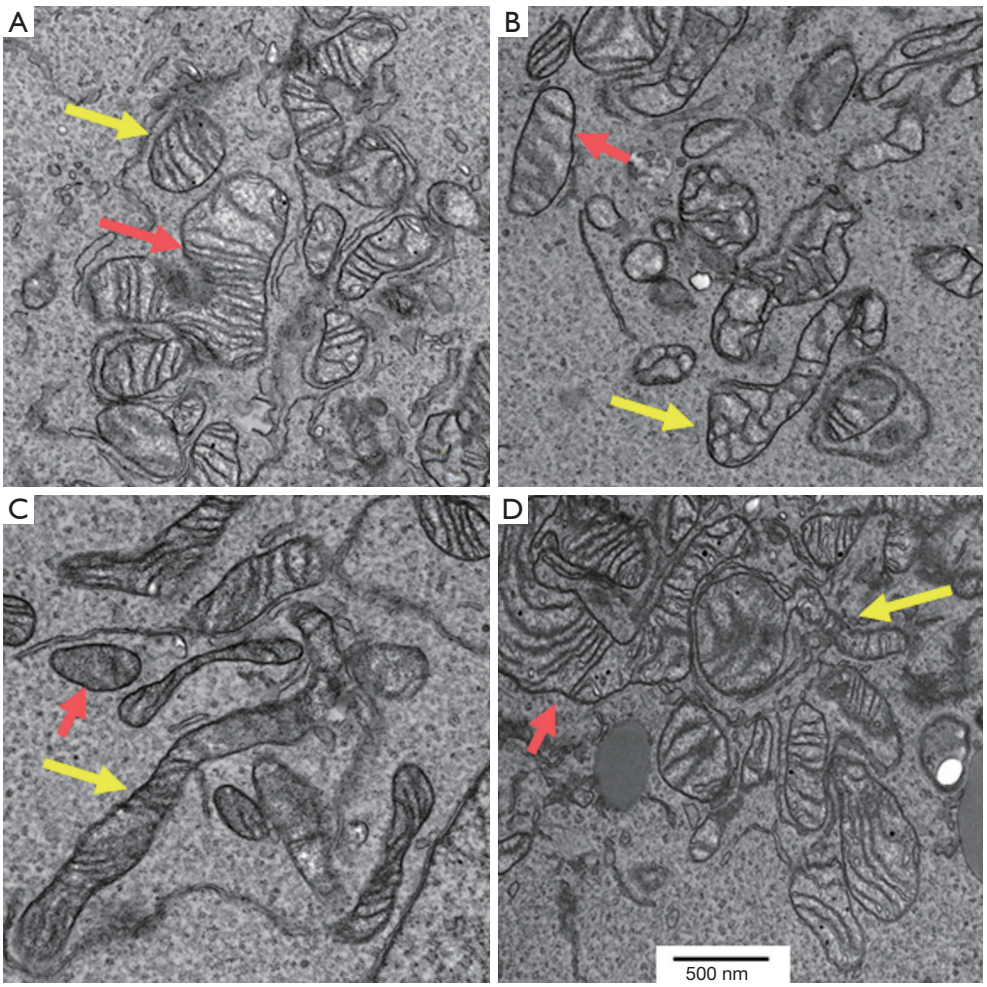

Figure 2 Mitochondrial heterogeneity. Transmission electron micrographs showing intracellular and intercellular mitochondrial heterogeneity (yellow *vs.* red arrows) in term of dynamics and distribution pattern in four different (A-D) urothelial carcinoma cells. Different cells were selected in a random fashion for the imaging. Magnification ×30,000.

and tRNA regions. On the other hand, non-coding rRNA, tRNA accompanied with both germ line and somatic mtDNA mutation from the respiratory complex (RC)-I, RCIV, RCIII regions were detected in head and neck cancer (49-52). Similarly in lung cancer, RCI and non-coding tRNA and rRNA mtDNA mutations were detected (53-57). Several groups have examined the extent of mtDNA mutations in prostate cancer and detected predominant mtDNA mutations in RCIV region along with non-coding mutations in rRNA and tRNA genes (39,58-62). A recent study identified RCI mutations exclusively in bone metastatic tissues from recurrent prostate cancer patients (18). In urothelial cell cancer, mtDNA mutations in protein-coding RCI (*ND3*, *ND4*, *ND5)* and RCIII (*CYTB*) have been reported (17,63-65). The human papilloma virus associated cervical cancer (CC) has also been studied and detected mtDNA mutations in D-loop, tRNA and rRNA genes and RCI (ND5) region (66-68). In addition to CC, mtDNA D-loop sequence variants were also detected in cervical intraepithelial neoplastic tissues suggesting a possible role of mtDNA alterations in early neoplastic transformation (68). The hurthle cell carcinoma develops from thyroid follicular cells, highly invasive in nature and harbor unique abundance of dysfunctional mitochondria (69). Higher abundance of mtDNA mutation (>2 mutations per positive samples) was detected in 24% (17/49) hurthle cell carcinoma subjects. The mutations were from various mtDNA regions including tRNA and coding RCI (ND6) and RCV (69)

(ATP8). Another interesting study identified RCI mutation as potential driver of hurthle cell carcinomas, where a total of 29 protein coding and 17 non-coding mtDNA mutations were detected (36). Although, numerous studies described above have identified non-coding (D-loop, tRNA, rRNA) and coding (RCI, III, IV and V) mtDNA mutations, only a limited number of studies have demonstrated their functional role in tumorigenesis.

In addition to mtDNA sequence variants, alteration in mtDNA copy number reflecting mitochondrial dysfunction has also been detected in various cancers including bladder, colorectal, gastric, head and neck, lung and prostate cancer (1,24,53,54,64,70). Functional studies with patient derived mtDNA mutations by us and others also revealed tumor growth and metastasis promoting and immune evasive role of mtDNA mutations confirming the contribution of mitochondrial alterations in tumorigenesis (53,62,65,71,72). On the other hand, tumor-derived clonal mtDNA mutations detected in urine, histopathologically normal surgical margins and salivary rinse samples from the same patients indicates their potential in biomarker development (30,51,64). Additionally, correlation between cancer promoting key nuclear genes such as EGFR, PSA and mtDNA mutations has also been established in lung and prostate cancer respectively (31,73). However, the fundamental and causative role of patients' derived mtDNA mutations in cancer initiation being within a heteroplasmic environment and their utilization in early cancer detection, monitoring and surveillance is yet to be established. Deciphering these critical contributions of mitochondria could open up novel avenues for therapeutic and biomarker development in clinical settings.

Cancer health disparity is a significant problem in various ethnic populations (74,75). Incidences of prostate, head and neck, uterine cervix and breast cancers are significantly higher among the African American with more aggressive outcomes and poor survival compared to the Caucasian American Population (74-78). Moreover, CC appears to be higher and more aggressive among the Hispanic/Latina women compared to the African American and Caucasian American women (78). The mitochondrial biological basis of this disparate outcome is yet to be established. In recent studies, an association between G10398A sequence variant in mitochondria encoded RCI (ND3, *Figure 1*) and increased risk of breast and prostate cancer among the African American subjects was reported (74). Among the Caucasian, detection of U haplogroup marker A12308G ($tRNA^{leu2}$) appeared to be associated with increased risk of prostate and renal cancer (74). In addition, co-detection of T4216C (RCI-ND1, *Figure 1*) and G10398 (RCI-ND3, *Figure 1*) appear to be associated with increase breast cancer risk among the African American women (74). Other than mitochondrial DNA (mtDNA) sequence variants, alterations in mtDNA copy numbers were found to be associated with cancer health disparities among the African American subjects including prostate cancer (74,79). However, a comprehensive analysis delineating the precise functional role of mtDNA alterations (both mutation and copy number changes) in cancer health disparities has yet to be done.

Mitochondrial alteration in genetic disease

Other than cancer, mtDNA alterations have been linked to various genetic diseases including mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), Leber's hereditary optic neuropathy (LHON), Leigh syndrome (LS), mitochondrial encephalopathy, Kearns-Sayre syndrome (KSS), progressive external ophthalmoplegia (PEO), Parkinson's, Alzheimer's, Huntington's disease, myopathy, cardiomyopathy, hepatopathy, hearing loss and gastrointestinal dysmotility (80-91). In addition to the mtDNA encoded genes, various nuclear encoded genes that function in mitochondria are linked with many of these diseases and involve *POLG*, *POLG2*, *TWINK*, *SLC25A4*, *TYMP*, *MPV17*, *OPA1*, *MFN2*, *DGUOK*, *RRM2B*, *TK2TFAM*, *PARKIN*, and *PINK1* (92). Unfortunately, majority of these diseases are not curable at this time. However, a recent study employing an adenovirus-associated gene delivery of mitochondria targeted zinc-finger nucleases (mtZFN), induced specific elimination of mutant mtDNA across the heart in mice bearing heteroplasmic mtDNA mutation m.5024C > T $tRNA^{Ala}$, causing a cardiac disease (93). This finding raises our hope for a new therapeutic avenue for effectively treating heteroplasmic mitochondrial diseases of diverse genetic origin (93).

Mitochondrial reactive oxygen species (ROS) and oncogenesis

Mitochondria are the major resources of ROS production during their metabolic function (94). Under normal condition, mitochondrial oxidant scavenging system

containing the dimutase, catalase and glutathione oxidase such as SOD2, Grx2, Trx, TrxR counterbalance ROS generation (9,94,95). However, impairment of mitochondrial function under various pathological conditions such as neoplastic transformation may sustain ROS production, with concomitant imbalance or loss of function of the ROS scavenging molecules such as SOD2 (9,94-96). In such conditions, abundant ROS generation could positively regulate diverse oncogenic signaling network, inhibit the function of various tumor suppressor genes and promote cancer progression (65,95,97-100) (*Figure 3*).

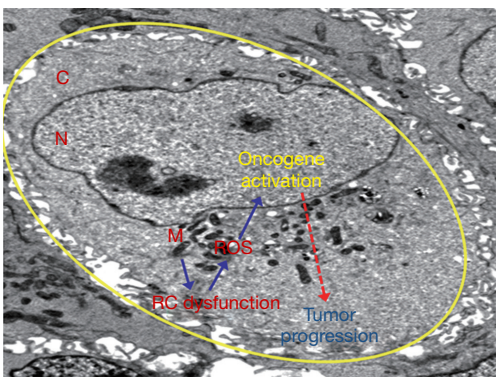

Figure 3 Mitochondria in oncogenesis. Mitochondria (M) harboring heterogeneous mtDNA mutations could induce respiratory complex (RC) dysfunction, which in turn promotes reactive oxygen species (ROS) production and subsequent activation of oncogenic pathways leading to tumorigenic progression. Transmission electron micrograph of mouse urothelial carcinoma cell (MB49) was utilized for mechanistic depiction. Magnification ×30,000. C: cytoplasm; N: Nucleus.

Conclusion and future perspective

Mitochondria have been able to attract considerable attention in this decade which continues to unravel their dynamic role in cell growth and signaling, immune modulation, neoplasia and various genetic diseases (*Figure 4*). However, the existence of enormous intracellular and intercellular mitochondrial as well as mtDNA heterogeneity in concert with complex nDNA-mtDNA signaling are enigmatic and pose significant challenges in designing appropriate treatment for different mitochondrial diseases. However, various models including transgenic animals, cybrids, allotropic mtDNA expression strategies and mitochondria targeted therapeutics are being developed with a view to study and correct these mitochondrial defects (89,90). Moreover, due to the occurrence of frequent RC specific coding and non-coding mtDNA mutations in various cancers and changes in mtDNA content, mtDNA alterations could be useful in developing mitochondria based novel molecular markers. With the advent of cutting age technologies for mitochondria genome sequencing and studying various aspect of mitochondria biology, the next decade would certainly advance our knowledge in the field of mitochondrial genomics and biology and will aid to develop better mitochondrial disease management strategies.

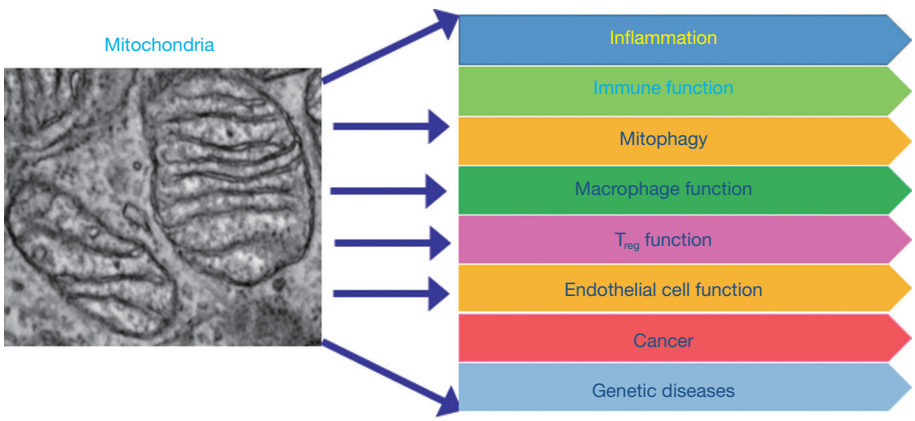

Figure 4 Dynamic role of mitochondria. Versatile functions of mitochondria in governing numerous important cellular processes. Alteration in mitochondrial homeostasis and function may lead to the development of cancer and various genetic diseases. Transmission electron micrograph of human urothelial carcinoma cell was utilized for describing mitochondrial function. Magnification ×30,000.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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