World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v19.i47.8880

World J Gastroenterol 2013 December 21; 19(47): 8880-8886
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (1): Hepatocellular carcinoma

Mitochondrial DNA alterations and mitochondrial dysfunction in the progression of hepatocellular carcinoma

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Author contributions: Hsu CC and Lee HC collected and analyzed the data; Hsu CC, Lee HC and Wei YH wrote the paper; Lee HC and Wei YH share equal contribution.
Supported by A Grant for the Center of Excellence for Cancer Research at Taipei Veterans General Hospital from the Ministry of Health and Welfare of the Executive Yuan, No. DOH102-TDC-111-007; A Grant from the Aim for the Top University Plan of the Ministry of Education and grants from the National Science Council of Taiwan, No. NSC101-2320-B-010-068-MY3 and No. NSC100-2320-B-010-024-MY3
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Received: August 23, 2013 Revised: November 1, 2013
Accepted: November 12, 2013
Published online: December 21, 2013

Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignancies and is ranked third in mortality among cancer-related diseases. Mitochondria are intracellular organelles that are responsible for energy metabolism and cellular homeostasis, and mitochondrial dysfunction has been regarded as a hallmark of cancer. Over the past decades, several types of mitochondrial DNA (mtDNA) alterations have been identified in human cancers, including HCC. However, the role of these mtDNA alterations in cancer progression is unclear. In this review, we summarize the recent findings on the somatic mtDNA alterations identified in HCC and their relationships with the clinicopathological features of HCC. Recent advances in understanding the potential roles of somatic mtDNA alterations in the progression of HCC are also discussed. We suggest that somatic mtDNA mutations and a decrease in the mtDNA copy number are common events in HCC and that a mitochondrial dysfunction-activated signaling cascade may play an important role in the progression of HCC. Elucidation of the retrograde signaling pathways in HCC and the quest for strategies to block some of these pathways will be instrumental for the development of novel treatments for this and other malignancies.

Key words: Hepatocellular carcinoma; Somatic mitochondrial DNA mutations; Mitochondrial dysfunction

Core tip: In this review, we summarize the recent findings on the somatic mtDNA alterations identified in hepatocellular carcinoma (HCC) and their relationships with the clinicopathological features of HCC. We suggest that somatic mtDNA mutations and a decrease in the mtDNA copy number are common events in HCC and that a mitochondrial dysfunction-activated signaling cascade may play an important role in the progression of HCC. Elucidation of the retrograde signaling pathways in HCC and the quest for strategies to block some of these pathways will be instrumental for the development of novel treatments for this and other malignancies.

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 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i47/8880.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i47.8880

INTRODUCTION

Hepatocellular carcinoma (HCC) is the one of most common cancers worldwide and is ranked third with respect to mortality[1,2]. There are approximately 434000 new cases of HCC per year[3]. Several risk factors have been suggested to be involved in the development of HCC, including aflatoxin exposure, alcohol consumption, chronic inflammation associated with viral hepatitis and familial tendency[4-8]. Moreover, inflammation and oxidative stress have been suggested to contribute to the carcinogenesis of HCC[9-11].

In the 1930s, the German biochemist Warburg[12] proposed that tumor cells prefer to utilize glycolysis rather than respiration as a primary energy source, even in the presence of abundant oxygen. This phenomenon was termed "aerobic glycolysis" or the "Warburg effect". He further proposed that defects in energy metabolism, especially in the mitochondria, are involved in the initiation or progression of cancer[13].

Mitochondria are cytoplasmic organelles that play multiple roles in energy metabolism and cellular homeostasis, including the generation of ATP *via* respiration and oxidative phosphorylation (OXPHOS), the production of reactive oxygen species (ROS), metabolic homeostasis, and the initiation and execution of apoptosis[14,15]. These roles are executed by proteins that are encoded by genes in the nucleus and mitochondria. Mitochondrial DNA (mtDNA) is a 16.6-kb, double-stranded circular DNA that contains genes for 22 transfer RNAs, 2 ribosomal RNAs and 13 polypeptides that comprise the respiratory enzyme complexes[16]. In addition to the coding region, mtDNA contains a non-coding region called the "D-loop", which is approximately 1.1 kb, encompasses nucleotide position (np) 16024-np 576, and controls the replication and transcription of the mtDNA[17].

Due to its lack of protective histone proteins, a limited DNA repair system and its spatial proximity to a high level of ROS, mtDNA sustains a 10-fold higher level of damage than that of nuclear DNA (nDNA)[18-20]. Somatic mutation and damage to mtDNA can lead to impairment of the OXPHOS system and enhanced ROS generation, which in turn accelerates the occurrence of DNA mutations. This scenario has been proposed to contribute to the initiation and progression of tumors[21,22].

Over the past decade, somatic mtDNA mutations have been identified in several types of cancer, including HCC[23-27]. Some of the acquired mtDNA mutations have been suggested to cause mitochondrial dysfunction, increase the production of ROS, and promote tumor growth[28,29].

In this article, we review the recent findings on somatic mtDNA alterations in HCC. In addition, we discuss the potential roles of mtDNA alterations and mitochondrial dysfunction in the progression and metastasis of HCC.

SOMATIC MITOCHONDRIAL DNA ALTERATIONS IN HCC

Over the past decade, several types of somatic mtDNA alterations have been identified in human HCC. These mtDNA alterations include point mutations, deletions, insertions and copy number changes.

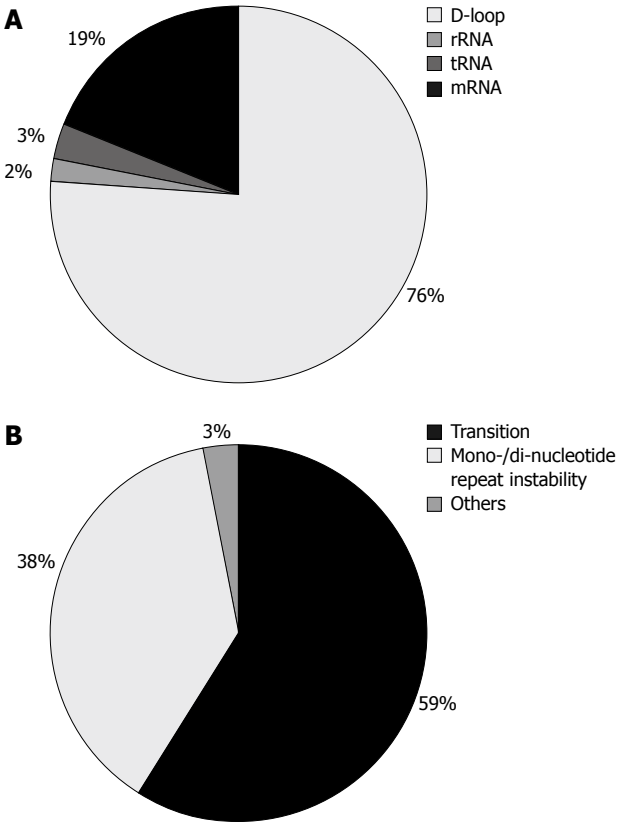

Figure 1 The location distribution of the identified somatic point mutations (A) and the types of somatic point mutations (B) in the mitochondrial DNA in hepatocellular carcinoma. Data adapted from Yin *et al*[29] and Wong *et al*[30].

Point mutations

Screening for somatic point mutations in the whole mitochondrial genomes of HCC samples[29,30] revealed that approximately 52% of HCC patients carry at least one homoplasmic or heteroplasmic point mutation in their tumor tissue mtDNA. Of the identified point mutations, 76% are located in the D-loop region, 2% are located in rRNA genes, 3% are located in tRNA genes and 19% are located in mRNA genes (Figure 1A). The incidence and location distribution of the point mutations are consistent with those observed in other cancer types[25].

The D-loop region is a hot spot for somatic mtDNA mutations in HCC and other cancers. It was reported that the D-loop region of mtDNA, especially the mononucleotide repeat in the np 303-309 poly-C sequence, is the most susceptible site to oxidative damage compared with the other regions of the mtDNA, implying that oxidative damage contributes to point mutations in the D-loop and/or the instability of the mononucleotide or dinucleotide repeats in the mtDNA. However, the unique G-to-T transversion caused by oxidative DNA damage is not detected in HCC[29,30]. Among the mtDNA mutations that have been identified in HCC, approximately 59% are transition mutations (G/A-to-A/G or C/T-to-T/C) and

38% are mono- or di-nucleotide instabilities (Figure 1B), suggesting that oxidative damage *per se* is not the major factor responsible for point mutations in HCC. The presence of hepatitis B infection, liver cirrhosis, alcohol abuse or their combination may affect the qualitative changes in the mtDNA in HCC[30].

Because the D-loop region controls the replication and transcription of the mtDNA, mutations in the D-loop region may influence the mtDNA copy number and the expression of the mitochondrial genome[31]. It has been shown that the occurrence of point mutations in the D-loop, especially near the replication origin of the heavy-strand (OH) of the mtDNA, affects the mtDNA copy number in HCC[32]. In addition, Nishikawa *et al*[33] reported that the number of mtDNA mutations in the D-loop region is positively correlated with a poor HCC differentiation grade. These findings suggest that the somatic mutations in the mtDNA D-loop region may affect mitochondrial function by decreasing the mtDNA copy number and/or transcription in HCC, thereby leading to HCC progression.

Among the mutations in the coding region, the nonsense mutation G3842A creates a premature stop codon and the missense mutations T6787C, G7976A, G9267A, and A11708G result in amino acid substitutions in the highly evolutionally conserved regions of the affected mitochondrial genes. Moreover, the base-pair deletion and insertion 11032delA and 12418insA may lead to a frame-shift mutation, and the tRNA mutations T1659C in $tRNA^{Val}$ and G5650A in $tRNA^{Ala}$ may alter the tRNA structure and were shown to associate with mitochondrial disorders[29]. Therefore, these mtDNA point mutations may result in mitochondrial dysfunction in HCC.

Deletions

Among the large-scale deletions identified in the mtDNA in different cancer types[32,34-37], the 4977-bp deletion is the most common mtDNA deletion in tumors[23,38-43]. Consistent with findings in other types of cancer, the incidence of the 4977-bp deletion and its accumulation level are lower in the malignant tissues than the non-tumor tissues of HCC patients[23,39]. Moreover, gender and a long-term history of alcohol consumption in HCC patients may affect the accumulation of the 4977-bp-deleted mtDNA[23]. Although the role of mtDNA deletion in HCC is unclear, it has been suggested that the observed decrease in mtDNA with a deletion is the result of the tumor cells adapting to a new microenvironment during hepatocarcinogenesis[25,44].

In addition, a 50-bp deletion was previously reported in one HCC patient[32]. This deletion is flanked by a 9-bp direct repeat in the D-loop region of the mtDNA. The mtDNA deletion appeared to be homoplasmic in the HCC tissue but was not detected in the corresponding non-tumor liver tissue. The tumor-specific accumulation of this deletion does not seem to be similar to that of the 4977-bp deletion in cancers. Because this deletion partly truncates the regulatory region of the mtDNA, the mtDNA copy number in the HCC tissue was found to be significantly reduced compared with that in the non-tumor liver tissue[32]. This mtDNA deletion may lead to mitochondrial dysfunction *via* mtDNA depletion and/or impairment of the transcription of mitochondrial genes.

Insertions

Two small insertions (approximately 260 bp and approximately 520 bp) have been identified as a tandem duplication and a tandem triplication and are flanked by two poly-cytosine (poly-C) sequences at np 303-309 and np 568-573 in the D-loop region of the mtDNA in various human cancers, including HCC[35]. This tandem duplication or triplication was detected in approximately 4% of HCCs and is highly correlated with the presence of length variation in the poly-C at np 568[44]. However, these insertions have also been found in somatic tissues in elderly subjects and, thus, are not specific for cancer tissues.

Copy number changes

A decrease in the mtDNA copy number is a common event in HCC[23,32,45,46]. Over 60% of HCCs have a lower mtDNA copy number than their corresponding non-tumor liver tissues. As mentioned above, it was observed that the reduction in the mtDNA copy number is associated with point mutations located near the replication origin in the D-loop region of the mtDNA[32]. Moreover, it was suggested that the decrease in the mtDNA copy number in HCC may be related to or result from the altered expression of genes involved in mitochondrial biogenesis, such as peroxisome proliferator-activated recept activator-1 (PGC-1) and mitochondrial single-stranded DNA binding protein (mtSSB)[23]. These results suggest that the mtDNA mutations in the D-loop region and the impairment of mitochondrial biogenesis contribute to the decrease in the mtDNA copy number in HCC[34].

The reduction in the mtDNA copy number seems to be more frequently observed in female patients with HCC compared with male patients with HCC[23]. This difference between male and female HCC patients could be a result of clinical manifestation, progression and/or mortality rate[23]. Yamada *et al*[46] showed that the low mtDNA copy number in HCC is significantly correlated with large tumor size and liver cirrhosis. In addition, HCC patients with a lower mtDNA copy number in their tumors tend to show poorer 5-year survival compared with patients with a higher mtDNA copy number[46]. It was also suggested that hepatitis B infection, liver cirrhosis, and alcohol abuse affect quantitative changes in the mtDNA in HCC[29]. Recently, it was reported that there is an association between the mtDNA content in the peripheral blood leukocytes and hepatitis B virus-related hepatocellular carcinoma[47], which suggests that the mtDNA copy number in the peripheral blood leukocytes could be used as a predictor of HCC occurrence.

POTENTIAL ROLES OF MITOCHONDRIAL DNA MUTATIONS AND MITOCHONDRIAL DYSFUNCTION IN HCC PROGRESSION

Several types of somatic mtDNA alterations have been identified in HCC, but the roles of these mtDNA alterations in HCC progression are unclear. Evidence from several lines of research has substantiated the pathological role of mtDNA mutation and mitochondrial dysfunction in HCC.

The majority of the somatic point mutations in the mitochondrial coding region and the decrease in the mtDNA copy number may cause mitochondrial dysfunction in HCC. These findings provide a molecular basis for the Warburg effect. In addition, it has been shown that the low mtDNA copy number in HCC is significantly correlated with large tumor size, liver cirrhosis, and poor 5-year survival[46]. Therefore, it is possible that mtDNA mutations and a decrease in the mtDNA copy number and, thereby, mitochondrial dysfunction modify the progression of HCC.

In the human SK-Hep1 hepatoma cell line, mtDNA depletion was demonstrated to induce resistance to oxidative stress and chemotherapeutic agents through an adaptive increase in the expression of manganese superoxide dismutase (MnSOD) and other antioxidant enzymes[48]. Moreover, chloramphenicol was found to inhibit mitochondrial protein synthesis in human hepatoma HepG2 cells and to render these cancer cells resistant to mitomycin-induced apoptosis[49]. Using similar approaches, respiratory inhibitors and an uncoupler of mitochondrial respiration as well as inhibitors of mtDNA replication or protein synthesis in the mitochondria were found to induce mitochondrial dysfunction and cisplatin resistance in human hepatoma HepG2 cells and to promote cell migration in other hepatoma cells *via* a paracrine signaling pathway[50]. It was further demonstrated that the mitochondrial dysfunction-induced upregulation of amphiregulin contributes to the cisplatin resistance and cell migration of hepatoma cells[50]. In addition, these treatments also induced changes in the expression of genes that affect the metastatic ability of cancers, including the integrin pathway, the PDGF signaling pathway and the cadherin signaling pathway[51]. On the other hand, the overexpression of PGC-1 in HepG2 cells was found to elevate mitochondrial protein expression and to reduce cell mobility *via* increased E-cadherin expression[52,53]. These findings support the hypothesis that mtDNA mutations and mitochondrial dysfunction contribute to the malignant progression of HCC.

Mitochondrial dysfunction increases ROS production and Ca^{2+} mobilization and reduces ATP generation, which may be involved in the malignant changes induced by mtDNA mutations and mitochondrial dysfunction in HCC. It has been demonstrated that antioxidants and calcium chelators can block mitochondrial dysfunction-induced amphiregulin expression and prevent cisplatin resistance and cell migration[50]. In addition, it was recently demonstrated that mitochondrial dysfunction-reduced intracellular ATP content represses the protein expression of hypoxia-inducible factor-1 (HIF-1) through the activation of the AMP-activated protein kinase (AMPK)-mTOR pathways in HepG2 cells[54]. HIF-1 is a nuclear transcription factor that plays a crucial role in cancer progression, including angiogenesis, invasion and metastasis[55]. These findings suggest that mitochondrial dysfunction regulates nuclear gene expression and phenotypic changes to face the different microenvironments of HCC. Therefore, the activation of retrograde signaling from the mitochondria to the nucleus may play an important role in the malignant progression of HCC.

Consistent findings were observed in other types of cancer. It has been reported that in some cancer cell lines, a pathogenic mtDNA mutation (*e.g.*, the T8993G transversion) promotes tumor growth in nude mice by preventing apoptosis[56-58]. Moreover, it was shown that the heteroplasmic 12418insA mutation, which has been identified in HCC[29] and other cancers[24,26,59], impairs mitochondrial respiratory function and promotes tumorigenesis by enhancing ROS production[60]. In addition, ROS-generating mtDNA mutations have been demonstrated to regulate tumor cell metastasis[61]. It was also shown that mtDNA depletion or mitochondrial dysfunction can enhance invasive phenotype changes[62-64] or chemo-resistance in some specific types of cancer[65]. The underlying mechanisms have been suggested to involve the communication between the mitochondria and the nucleus called "retrograde signaling"[66,67]. Several biomolecules have been identified to be involved in this signal transduction, including calcineurin, NFAT, ATF2, Akt, and NFκB/Rel, which then affect the expression of an array of nuclear genes[68,69]. The detailed mechanisms by which mtDNA mutations and mitochondrial dysfunction affect HCC progression await further investigation.

Although mtDNA alterations have been identified in HCC, it remains controversial whether mtDNA alterations are correlated with the initiation and progression of HCC. To dissect the role of mtDNA alterations in HCC, a larger sample size of HCC is required in future research. Moreover, some lines of evidence suggest that mitochondrial dysfunction and the dysfunctions caused by mtDNA alterations have the potential to contribute to tumor progression. However, whether a specific mtDNA mutation plays a driving force or is an indirect consequence of HCC progression requires further evaluation. Therefore, it is important to develop a strategy to dissect the role of specific mtDNA mutations in cancer progression and/or to exclude non-causal epiphenomena.

Because the coordination between the nDNA and mtDNA is important for the maintenance of mitochondrial structure and function[14,17], mutations in the nDNA-encoded genes that are responsible for mtDNA integrity and/or mitochondrial function may play an important role in tumorigenesis and cancer progression. For example, it was recently reported that defects in P53[70], mitochondrial DNA polymerase[71], and mitochondrial

deacetylase SIRT3[72] may affect mtDNA integrity and promote tumorigenesis. In addition, not only mtDNA mutations but also mitochondrial dysfunction caused by nDNA mutations, oncogenes, and tumor microenvironments (hypoxia and inflammation) are suggested to underlie energy metabolism reprogramming (or the Warburg effect)[73,74]. In summary, the interaction between mtDNA and nDNA may play an important role in the initiation and progression of HCC.

CONCLUSION

Several types of mtDNA alterations, including point mutations, deletions, insertions and copy number changes, have been identified in HCC. Somatic point mutations and depletions are the two most common of these mtDNA alterations in HCC. The low mtDNA copy number in HCC has been shown to be significantly correlated with large tumor size, liver cirrhosis, and poor 5-year survival[46]. However, the presence of somatic mtDNA point mutations in HCC does not seem to correlate with the patient's age or sex, the tumor size or grade, hepatitis virus infection, or the patient's survival[29,30]. This finding may result from the possibility that mtDNA point mutations do not always play a similar role in HCC progression. In addition, the heteroplasmic or homoplasmic level of the same mtDNA mutation may result in different consequences in tumorigenesis[60]. Therefore, the role of the specific mtDNA mutation and its level during HCC progression warrant further study.

The majority of the point mutations in the coding region of the mtDNA and the decrease in the mtDNA copy number likely cause mitochondrial dysfunction in HCC. These findings have provided solid evidence to substantiate the mechanism by which mitochondrial dysfunction is involved in metabolic reprogramming or the "Warburg effect" in cancer. Several lines of evidence have important implications in the pathological role of mtDNA mutation and mitochondrial dysfunction in HCC. Pharmacologic approaches to induce mitochondrial dysfunction can enhance chemo-resistance and promote metastasis, which may contribute to the malignant progression of HCC. Thus, the increased ROS production and Ca^{2+} mobilization and the reduced ATP generation induced by mitochondrial dysfunction may be involved in the malignant changes of HCC. However, the detailed mechanism by which mtDNA mutation and mitochondrial dysfunction affect HCC progression remains unclear. Elucidation of the retrograde signaling pathways in HCC and the search for strategies to block these pathways will be important for the development of novel treatments for this and other malignancies.

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ISSN 1007-9327