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Defining the Momioime: Promiscuous Information Transfer by Mobile Mitochondria and Mitochondrial Genome

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Abstract

Mitochondria are complex intracellular organelles that have long been identified as the powerhouses of eukaryotic cells because of the central role they play in oxidative metabolism. A resurgence of interest in the study of mitochondria during the past decade has revealed that mitochondria also play key roles in cell signaling, proliferation, cell metabolism and cell death, and that genetic and/or metabolic alterations in mitochondria contribute to a number of diseases, including cancer. Mitochondria have been identified as signaling organelles, capable of mediating bidirectional intracellular information transfer: anterograde (from nucleus to mitochondria) and retrograde (from mitochondria to nucleus). More recently, evidence is now building that the role of mitochondria extends to intercellular communication as well, and that the mitochondrial genome (mtDNA) and even whole mitochondria are indeed mobile and can mediate information transfer between cells. We define this promiscuous information transfer function of mitochondria and mtDNA as “momioime” to include all mobile functions of mitochondria and the mitochondrial

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genome. Herein we review the “momiome” and explore its role in cancer development, progression, and treatment.

1. Introduction

Mitochondria are dynamic organelles comprising a network of long, filamentous structures that travel along a molecular highway of cytoskeletal elements [1, 2]. When stained with vital fluorescent dyes in living cells, mitochondria can be seen extending, contracting, fragmenting and fusing with one another as they move in three dimensions throughout the cytoplasm [1–3]. In contrast, electron micrographs of fixed tissue specimens show mitochondria as oval shaped particles similar in size to the bacterium *Escherichia coli* (1–2 microns long $\times$ 0.5–1.0 microns wide). Mitochondria are bound by two membranes. The outer membrane encloses the entire contents of the organelle, while the inner membrane, which has a much larger surface area and folds inward to form cristae, encloses the internal matrix compartment. The mitochondrial matrix contains the enzymes and cofactors involved in a number of important metabolic reactions and pathways, including the tricarboxylic acid (TCA) cycle, oxidative phosphorylation, fatty acid degradation, the urea cycle, and gluconeogenesis.

In mammalian cells, the matrix also contains up to 10,000 copies of a 16.6 kb closed circular double helical molecule of mitochondrial DNA (mtDNA). Although representing less than 1% of the total cellular DNA, mtDNA encodes two rRNAs, twenty-two tRNAs and thirteen highly hydrophobic polypeptide subunit components of four different respiratory enzyme complexes (I, III, IV and V), which are localized to the inner mitochondrial membrane. These enzyme complexes are essential for cellular respiration and, therefore, normal cell function. All other mitochondrial proteins, including those involved in the replication, transcription, and translation of mtDNA are encoded by nuclear genes and targeted to the mitochondrion by a specific transport system [4]. Interestingly, in humans and other mammals, mitochondrial genes display maternal inheritance (i.e. are inherited from the female parent).

Mitochondria have long been identified as the “powerhouses” of eukaryotic cells because of their central role in oxidative metabolism. It is in the mitochondrial matrix that acetyl coA, the metabolic byproduct of both carbohydrate and lipid metabolism, is further oxidized via the TCA cycle. The net metabolic yield of the cycle includes three molecules of reduced nicotinamide adenine dinucleotide (NADH) and one molecule of reduced flavin adenine dinucleotide (FADH₂), high-energy electron carriers that go on to serve as respiratory substrates for oxidative phosphorylation. In this process, electrons are transferred from NADH and FADH₂ to oxygen via four multi-subunit electron transfer chain (ETC) complexes located on the inner mitochondrial membrane (I, II, III, IV). Three of these enzyme complexes (I, III, and IV) also serve as proton pumps. At these sites, the energy derived from the transfer of electrons down the ETC is coupled to the translocation of protons from the matrix space outward to the space between the inner and outer mitochondrial membranes (i.e., inter-membrane space). Under normal physiological conditions, the inner mitochondrial membrane is impermeable to the backflow of protons

and an electrochemical gradient is established across the membrane. The energy stored in this proton gradient, the proton-motive force, is then used to drive the synthesis of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) and inorganic phosphate (P_i) via the inner membrane-bound enzyme, mitochondrial ATP synthase (complex V). It is by this mechanism that oxidative phosphorylation couples the oxidation of high-energy electron donors to the synthesis of ATP and supplies the vast majority of metabolic energy produced by a cell under aerobic conditions.

Mitochondria are among the main intracellular sources of reactive oxygen species (ROS). Under physiological conditions, approximately 1–2% of the molecular oxygen consumed is converted to ROS molecules as a byproduct of oxidative phosphorylation [5]. ROS production occurs when a small fraction of reducing equivalents from complex I or complex III of the mitochondrial electron transport chain “leak” electrons directly to molecular oxygen, generating the superoxide anion O_2^- . Mitochondrial superoxide dismutase converts the superoxide anion to H_2O_2 , which can then be reduced further to generate the highly reactive hydroxyl radical OH.

ROS play an important role as signaling molecules and are known to mediate changes in cell proliferation, differentiation, and gene transcription [6, 7]. Uncontrolled ROS activity, or oxidative stress, interferes with the integrity of biological membranes and can damage intracellular proteins, lipids, and DNA. The mitochondrial genome is especially susceptible to ROS damage due to its proximity to the site of ROS production (i.e., the ETC), and the fact that it has no introns or protective histones and a limited capacity for DNA repair. Oxidative stress can therefore impair mitochondrial function directly at the level of mitochondrial enzyme complexes, or indirectly as a consequence of its genotoxicity to mtDNA. Severe or prolonged oxidative stress can lead to irreversible oxidative damage and cell death [8]. It is generally accepted that oxidative stress in mitochondria throughout the human life span is an important factor in the aging process.

Mitochondria also play a key role in mediating intrinsic apoptosis, an energy-dependent cell death pathway that occurs in response to a variety of physiological or pathological cell stressors, such as toxins, viral infections, hypoxia, hyperthermia, free radicals, and DNA damage [9]. At the intracellular level, intrinsic apoptosis is induced by the loss of anti-apoptotic proteins, (e.g., Bcl-2 and Bcl-X_L) or by activation of pro-apoptotic proteins (e.g., Bax and Bak). The pathway involves mitochondrial outer membrane permeabilization (MOMP), a critical, irreversible step that commits the cell to ultimate destruction. As a direct consequence of MOMP, cytochrome c and other apoptogenic proteins are released from the mitochondrial inter-membrane space into the cytosol, where they activate a caspase cascade. The end result of this cascade is proteolytic cleavage of intracellular proteins, DNA degradation, formation of apoptotic bodies, and other morphological changes that are considered hallmarks of apoptotic cell death. The intrinsic apoptotic pathway plays a significant role in normal development, tissue remodeling, aging, wound healing, immune response, and maintaining homeostasis in the adult human body.

More recently, mitochondria have been identified as “signaling organelles”, capable of mediating bidirectional intracellular information transfer: anterograde (from nucleus to

mitochondria) and retrograde (from mitochondria to nucleus). Importantly, evidence is now building that the role of mitochondria extends to intercellular communication as well. This review explores the ever-expanding “momiome” (mobile functions of mitochondria and the mitochondrial genome), and its role in cancer development, progression, and treatment.

2. Mitochondria in intracellular information transfer

2.1. Retrograde (mitochondria to nucleus) information transfer

A number of germ-line mtDNA mutations have been found to be associated with an inherited predisposition to cancer. Among these, the human polymorphic variant in the NADH dehydrogenase 3 (ND3) gene at nt 10,398 (nt G10398A) is associated with an increased risk for invasive breast cancer in African-American women [10, 11], and a variant in a non-coding region of mtDNA (16189T>C) is associated with increased susceptibility to endometrial cancer [12]. In addition, the mtDNA haplogroup M7b2 is associated with an increased risk for hematopoietic cancers [13] and the U haplogroup is associated with increased risk of both renal and prostate cancers in North American Caucasian men [14].

Somatic mutations in mtDNA are also widespread in cancer [15]. The majority of these are homoplasmic in nature, suggesting that mutant mtDNA becomes the dominant form in tumor cells over time. Mutations in the displacement loop (or D-loop) region of mtDNA are especially common in human tumors [15–17]. The D-loop a triple stranded non-coding sequence of mtDNA (np 16024–516) that houses cis regulatory elements required for replication and transcription of the molecule. Mutations in the D-loop region alter the binding affinities of nuclear proteins involved in mtDNA replication and transcription, and can lead to the depletion of mtDNA content. Interestingly, several studies that measured mtDNA directly in paired normal and cancer cells have reported a decrease in mtDNA content in a variety of tumors [18–24], and depletion of mtDNA has been shown to correlate with tumor progression and prognosis in breast cancer patients [25].

Mutations in several mtDNA genes encoding the polypeptide subunits of oxidative phosphorylation enzymes are known to be of functional significance and to promote tumor growth *in vivo* [26–35]. For example, trans-mitochondrial hybrids (cybrids) harboring the ATP6T8993G mtDNA mutation in prostate cancer cells were found to generate tumors 7 times larger than wild type cybrids, which barely grew in mice [36]. Additionally, cybrids constructed using a common HeLa nucleus and mitochondria containing a point mutation in ATP synthase subunit 6 were conferred a growth advantage in early tumor stages after transplantation into nude mice [37]. It has been suggested that some of these alterations in mtDNA are adaptive mutations that confer a selective advantage under the harsh growth conditions of the tumor microenvironment [38], while others may be involved directly in tumor initiation and/or progression [36, 39].

Alterations in mtDNA copy number have also been identified in a variety of human cancers [25, 34, 40–52]. The importance of mitochondria-to-nucleus retrograde response evoked by alteration in mtDNA content has been demonstrated in studies employing ρ^0 cells, which have been entirely depleted of mtDNA content [20, 53]. One such study involved a comparative proteomic analysis of the osteosarcoma parental cell, its mtDNA depleted (ρ^0)

derivative, and a cybrid cell line in which mtDNA was restored. Results revealed marked changes in the cellular proteome of ρ^0 compared to parental cells, including quantitative changes in expression of several nuclear DNA encoded proteins. Protein expression was restored to wild type levels by reintroduction of mtDNA in cybrid cells, suggesting that these proteins play key roles in retrograde response [53]. In another study using the same osteosarcoma cell line, the ρ^0 derivative was found to display an increased tumorigenic phenotype compared to the parental cell line, as evidenced by increased anchorage independent growth [54]. The parental phenotype, which exhibited decreased anchorage independence, was restored by transfer of wild type mitochondrial DNA to the ρ^0 cells. This suggests that inter-genomic cross talk plays an important role in tumorigenesis and that retrograde mitochondria-to-nucleus signaling is an important factor in restoration of the non-tumorigenic phenotype.

Studies employing ρ^0 cells also implicate retrograde signaling in the regulation of nuclear DNA encoded gene expression. One study compared the expression of NADPH oxidase (Nox1), a major source of endogenous ROS, in the osteosarcoma 143B ρ^0 cell line and the isogenic cybrid cell line in which mitochondrial genes were restored by transfer of wild type mitochondria into ρ^0 cells [55]. Results showed that inactivation of mitochondrial genes by mtDNA depletion leads to down-regulation of Nox1, and the transfer of wild type mitochondrial genes restored the Nox1 expression to a level comparable to the parental cell line. Consistent with these results, superoxide anion levels were found to be low ρ^0 cells, and returned to parental levels in cybrid cells when Nox1 expression was restored by transfer of wild type mitochondria. In another study, depletion of mitochondrial genome in the osteosarcoma 143B ρ^0 cell line was shown to induce chromosomal instability and altered expression of APE1, a multifunctional protein that is involved in transcription and DNA repair in the nucleus and in the mitochondria [54]. Again, these changes could be reversed by exogenous transfer of wild type mitochondria in 143B ρ^0 cells. Furthermore, in a study employing the SK-Hep1 hepatoma cell line, manganese superoxide dismutase (MnSOD) expression was found to be greatly increased in SK-Hep1 ρ^0 cells compared to the parental cells [20]. Superoxide anion content increased during SK-Hep1 ρ^0 cell derivation but became normalized after establishment of ρ^0 phenotypes, suggesting that MnSOD induction is an adaptive process to increased O_2^- . Interestingly, these and other studies suggest a role for mitochondria in maintaining genomic stability in response to spontaneous or induced mitochondrial damage, and a putative mitochondria damage checkpoint (mito-checkpoint) that coordinates and maintains the proper balance between apoptotic and anti-apoptotic signals has been proposed [56].

2.2. Mitochondria and epigenetic regulation of the nuclear genome

Epigenetic modification of nuclear DNA is a long-studied and well-known means of regulation of nuclear gene expression that allows for temporal and spatial control of gene activity during the development of complex organisms without altering the genetic code [57]. One of the most common mechanisms for this type of control involves changes in DNA methylation status, whereby hyper-methylation of certain regulatory regions results in gene silencing and hypomethylation of these regions results in gene expression [58–60]. Histone modification (via acetylation, methylation, ubiquitination, phosphorylation, etc.),

microRNAs, and non-coding functional RNAs are also involved in the epigenetic modification of nuclear DNA [60, 61]. Epigenetic modifications of nuclear DNA mediate cellular responses to internal and external environmental cues, and have important implications for health, disease, and the natural ageing process [61–63].

Recent studies suggest that a variety of epigenetic changes in nuclear DNA can be influenced by mitochondria, thus demonstrating another important example of retrograde mitochondria-to-nucleus signaling. In one such study, mtDNA content was shown to influence nuclear DNA methylation [64]. Restriction Landmark Genomic Scanning analyses revealed that up to 10% of methylation-sensitive NotI restriction sites were differentially methylated in cells depleted of mtDNA compared to their parental cell lines, and that some but not all of the changes induced by the depletion of the mitochondrial genome could be reversed by reintroduction of wild-type mitochondria. In another study, mitochondrial content was measured as the integrated signal of a mitochondrial dye and determined to be proportional to the abundance of a number of mitochondrial proteins involved in energy production [65]. Here, single cell analysis revealed that alterations in mitochondrial content influence chromatin activation, mRNA abundance, translation, alternative splicing, and account for approximately 50% of the variability observed in cellular protein levels. All of these activities ultimately affect phenotypic variability among individuals within a clonal population of genetically identical cells.

Differences in mtDNA haplotypes have also been shown to affect nuclear DNA transcription, translation, and ultimately cell differentiation and phenotype [66]. In this study, chromosomal gene expression, differentiation, and mitochondrial metabolism were monitored in three mouse embryonic stem cell lines, each of which had identical nuclear chromosomes but different mtDNA haplotypes. Results showed that in pluripotent and differentiating embryonic stem cells, mtDNA haplotypes influence nuclear DNA methylation and chromosomal gene expression, and therefore play a role in determining cell fate.

Emerging evidence supports the idea that mitochondria-to-nucleus retrograde signaling pathways can also be mediated by a variety of mitochondrial metabolic intermediates (for reviews see Naviaux, 2008, and Wallace and Fan, 2011) [67, 68]. For example, variability in the amount of ATP, which is a natural consequence of changes in the number and/or functionality of mitochondria, has been suggested to play an important role in modulating the energetically costly process of eukaryotic gene expression [65]. The NAD^+/NADH ratio is another important retrograde signal. Metabolic reprogramming of skeletal muscle stem cells during the transition from quiescence to proliferation involves a shift from fatty acid and pyruvate oxidation to increased glycolysis and glutaminolysis. This has been shown to be associated with a decrease in both intracellular NAD^+ levels and activity of the histone deacetylase, sirtuin1, which then leads to an elevation of histone H4 acetylation and activation of muscle gene transcription and expression [69]. Additionally, a retrograde signaling pathway involving mitochondria generated reactive oxygen species (mtROS) has been reported to regulate the expression of genes involved in aging in *S. cerevisiae* [70]. In this pathway, mtROS were shown to inactivate a histone demethylase at subtelomeric heterochromatin through a series of protein kinases, which in turn inactivate the histone

demethylase, Rph1, and enhance binding of the silent information protein, Sir3p. This leads to transcriptional repression of subtelomeric genes and ultimately, the extension of chronological lifespan in budding yeast.

2.3. Epigenetic regulation of mitochondria

Epigenetic studies have traditionally been focused on the modification and regulation of nuclear DNA. However, one early clue suggesting the possibility of epigenetic regulation of the mitochondrial genome came from a study that identified and characterized a nuclear encoded, mitochondria targeted DNA methyltransferase, mtDNMT1 [71]. Data showed that in mouse embryonic fibroblasts and human colon carcinoma cells, mtDNMT1 was present in the mitochondrial matrix and bound to mtDNA. Data also indicated the mitochondrial DNMT1 was up-regulated by transcription factors that activate expression of nuclear-encoded mitochondrial genes in response to hypoxia, and by loss of p53, a tumor suppressor known to regulate mitochondrial metabolism. Furthermore, under conditions in which mtDNMT1 was overexpressed, there was a 10- to 20-fold enrichment of 5 methyl-cytosine (relative to IgG controls) in immunoprecipitated mtDNA samples. These results suggest that mtDNMT1 is responsible for mtDNA cytosine methylation and its expression is controlled by factors that regulate mitochondrial function.

Subsequently, other DNA methyltransferases were found to be associated with mitochondria. For example, DNMT3a was detected in mitochondrial fractions in mouse and human central nervous system [72], and its overexpression was shown to be associated with neurodegeneration in a mouse motor neuron-like hybrid cell line [72]. Furthermore, mtDNA methylation by DNMT3a is tissue specific and contributes to the degree of tissue inflammation seen in ALS pathology in mice [73]. Another DNA methyltransferase, DNMT3b, was observed in the mitochondrial fraction human HeLa and murine 3T3-L1 cultured cells [74].

Recently, a comparative analysis of human mitochondrial methylomes shows distinct patterns of epigenetic regulation in mitochondria [75]. A comprehensive genome-wide map of mtDNA methylation was generated through analysis of DNA methylation sites in the human mitochondrial genome from a total of 39 datasets (corresponding to 5 unique tissues) downloaded from the NIH Human Epigenome Roadmap project. The results of this analysis reveal a pattern and distribution of methyl-cytosines that are largely consistent and conserved across the human mitochondrial genome, with the exception of a few loci that are differentially methylated in different tissues and time-points. Additionally, results show that the clustering of methyl-cytosines near gene start sites could be temporally regulated, suggesting a potential regulatory role for methylation in mtDNA expression during development and beyond.

2.3.1. Mitochondria and microRNAs—MicroRNAs (miRNAs) are endogenous small (~22 nucleotides long) noncoding RNAs, which are involved in post-transcriptional control of gene expression [76]. More than 1100 human miRNAs are currently known (microrna.org), although the total number is predicted to be much higher. MicroRNAs are thought to directly control the expression of approximately 60% of the human genome and

to be involved in the regulation of a variety of essential cellular activities, such as metabolism, development, proliferation, differentiation, and apoptosis [77–79]. MicroRNAs are frequently dysregulated in human cancers and can act as either potent oncogenes or tumor suppressor genes [80–82]. Indeed, downregulation of a subset of miRNAs is commonly observed in tumor cells, suggesting a role for miRNAs in cancer. Recent studies report the presence of miRNAs and miRNA processing machinery in mitochondria [84, 85], suggesting a role for miRNAs in mitochondrial dysfunction as well [85, 86]. Since mitochondrial dysfunction is one of the most common and consistent phenotypes displayed in cancer [17, 19, 64, 82, 83], it is of interest to further explore the functional interaction between mitochondria and miRNAs, and its potential significance in the development and progression of this disease.

2.3.1.1. Regulation of mitochondrial function by miRNAs: There is ample evidence to indicate that miRNAs are involved in the regulation of mitochondrial metabolism. For example, miR-210 has been shown to target molecular components in both the mitochondrial electron transport chain and tri-carboxylic acid cycle, and thus reduce the rate of mitochondrial metabolism [87]. In addition, miR-338, regulates the expression of the nuclear encoded cytochrome c oxidase IV, and changes in expression of this protein are known to significantly alter mitochondrial oxygen consumption, metabolic activity, and ATP production [88]. The MicroRNAs miR-23a and miR-23b regulate mitochondrial glutaminase, and thus glutamine metabolism, energy production and biosynthesis [89]. Mitochondrial glutaminase converts glutamine, a major source for energy and nitrogen for biosynthesis, to glutamate, which may serve as a substrate for glutathione synthesis or be further catabolized through the tri-carboxylic acid cycle for the production of ATP or [89]. Mitochondrial dysfunction also appears to be related to insulin biosynthesis and function [90–92]. Sun et al. have recently reported that miR-15a regulates insulin biosynthesis by inhibiting expression of mitochondrial uncoupling-protein 2 (UCP2) [93]. Recently, we reported tumor-promoting role of UCP2 [94]. Together, these studies suggest that miR-15a may be a potential target for treatment of both diabetes and cancer

As previously stated, mtDNA is especially susceptible to mutation due to the lack of protective histones and limited DNA repair capacity in mitochondria, and the proximity of mtDNA to damaging mitochondrial ROS production. A number of miRNAs, including miR-335, miR-34a and miR-17*, are known to regulate the expression of mitochondrial antioxidant enzymes superoxide dismutase 2, thioredoxin reductase 2, and glutathione peroxidase 2 [95, 96]. Modulation of these miRNAs through their antigomers or premirs can concomitantly affect protein expression of these antioxidant enzymes and thereby affect tumorigenicity [95, 96].

Elevated CO₂ concentrations are known to occur in patients with severe lung disease [97, 98]. High CO₂ levels have been shown to be associated with decreased O₂ consumption and ATP production, impaired cell proliferation, and mitochondrial dysfunction [99, 100]. High CO₂ levels have also been shown to induce miR-183, which in turn decreases the expression of isocitrate dehydrogenase 2 (IDH2), a key enzyme of the TCA cycle, and impairs mitochondrial function and cell proliferation [101]. Overexpression of IDH2 or inhibition of miR-183 ameliorates the effects of high CO₂ on mitochondrial dysfunction and cell

proliferation [101]. Thus, miR-183 may prove to be an ideal target for development of effective treatment for conditions like chronic obstructive pulmonary disease, bronchopulmonary dysplasia, asthma and muscular dystrophies, which have elevated blood and tissue levels of CO₂ [98, 101].

2.3.1.2. Regulation of microRNAs by mitochondria: The translocation of nuclear-derived non-coding RNAs to mitochondria was hypothesized to occur as early as the 1960s [102], although initially these reports were not seriously considered.; More recent evidence, however, now demonstrates the trafficking of miRNAs and other biological molecules between the nucleus and mitochondria and the presence of miRNA processing machinery in mitochondria [54, 84, 85, 103, 104]. The Argonaute protein family plays a key role in both miRNA-mediated and small interfering (siRNA)-mediated RNA interference (RNAi) phenomena [105, 106]. One member of this family, Argonaute 2 (Ago2), is the endonuclease that cleaves RNA targets that bear complementarity to miRNAs or to siRNAs [107]. In an important study, Maniataki et al. reported a functional association of mitochondrial tRNA^{met} with Ago2 in the cytoplasm and speculated a possible cross-talk between mitochondria and RNAi [108]. They further speculated that mitochondrial tRNA^{met} might be a physical link that allows communication between mitochondria and miRNA or siRNA processing machinery [108]. Recently, Huang et al. also observed that mitochondrial activity is required for the assembly of active RNA-induced silencing complexes (RISC), and that inactivation of mitochondria leads to a strong decrease of miRNA-mediated RNAi efficiency [109]. They also suggested that mitochondria may serve as a reservoir of not only miRNAs but also of ATP for RISC assembly in the P-bodies [109]. Additional studies further support the role of mitochondria in miRNA processing and the presence of miRNAs in mitochondria [84–86, 110]., These include a mitochondrial miRNome made up of 20 miRNAs in mice liver mitochondria [85], a unique profile of 15 nuclear encoded miRNAs in rat liver mitochondria [86], and a specific subset of miRNAs as well as Ago2 in the mitochondria from HeLa cells [84]. Interestingly, these mitomiRs were found to lack preferential targeting of nuclear-encoded mitochondrial genes. Instead most have been predicted to have target sites within mtDNA-encoded protein genes [84]. Furthermore, human mtDNA seems to harbor sequences of some mitomiRs namely, miR-1974, miR-1977, and miR-1978 [84]. These studies provide strong evidence that mitochondria are novel players in the overall tuning of RNA interference mediated by miRNAs.

2.4. Transcription factor mediated mitochondria-nucleus crosstalk

We have earlier shown that mitochondrial dysfunction causes genetic and epigenetic changes in the nuclear DNA, resistance to cell-death, and tumorigenesis [54, 64, 111–113]. We and others have also identified a role of nuclear-encoded transcription factors in mitochondria-to-nucleus retrograde signaling [114–119]. Mitochondria relay the stress response to nucleus mainly through activation of protein kinases such as mTOR (mammalian target of rapamycin) and AMPK (AMP-activated protein kinase), increased production of ROS, and by release of Ca²⁺. These mitochondrial stress responders activate a variety of nuclear transcription factors [114–119], which protect against mitochondrial dysfunction by activating the expression of nuclear genes involved in the metabolic reprogramming or stress defense [120]. For example, the transcription factor and tumor suppressor protein p53

regulates cell cycle, apoptosis, and genomic stability [117, 121]. We have previously shown crosstalk between this protein and mitochondria [117–119, 122], identified down-regulation of p53 in p^0 cells [118], and observed that p53 regulates mitochondria-encoded COXII protein expression [119]. p53 also functions as a mito-checkpoint protein that regulates mtDNA copy number and mitochondrial biogenesis and, in the case of damaged/dysfunctional mitochondria, transiently blocks cell cycle progression [117]. Failure of this mito-checkpoint results in accumulation of genetic abnormalities in the nucleus [117]. It is therefore conceivable that downregulation of p53 with consequent mitochondrial dysfunction triggers nuclear genomic instability that leads to cellular transformation/cancer development [117, 123].

Mitochondrial dysfunction inhibits ATP synthesis and stimulates cellular AMPK, which regulates mitochondrial dynamics and induces mitophagy [124]. Mitochondrial retrograde response has also been linked to mTOR activity, which regulates mitochondrial quality control system via mitophagy [125]. Release of Ca^{2+} from stressed mitochondria activates different Ca^{2+} -regulated kinases, such as serine threonine kinase Akt1, protein kinase C, c-Jun N-terminal kinase (JNK), and p38 MAPK [114–116]. These kinases stimulate transcription of a number of factors, including CREB, ATF2, early growth response protein 1 (EGR1), NFAT, and CCAAT/enhancer-binding protein- δ (CEBP δ) [114–116]. Further, it has been observed that mitochondrial stress induced Akt1 mediated phosphorylation of heterogeneous ribonucleoprotein A2 (hnRNPA2), a transcriptional co-activator, is required for functional activities of the relevant transcription factors [116, 126]. Once activated these transcription factors facilitate reprogramming of nuclear gene expression and thus mitochondrial adaptation to stress [115, 116, 127, 128].

Another transcription factor, CEBP homologous protein (CHOP), also known as DNA damage inducible transcript 3 (DDIT3), is implicated in the mitochondrial unfolded protein response (UPR^{mt}). In the presence of over-expressed mutants of the mitochondrial protein ornithine transcarbamylase (OTC), CHOP forms heterodimers with CEBP β . The CHOP/CEBP β dimers then bind to and activate the promoters of the UPR^{mt} responsive genes [129, 130], which contain a CHOP binding site flanked by two mitochondrial unfolded protein response elements (MURE) [131]. Thus far, 11 MURE containing genes, which are upregulated upon mutant OTC expression, have been identified. These genes include Hsp60, Hsp10, mtDnaJ, ClpP, YME1L1, Tim17A, thioredoxin 2, endonuclease G, cytochrome C reductase, and NDUFB2 [131].

Mitochondrial dysfunction induced ROS production also plays an important role in mitochondria-to-nucleus retrograde response. Increased ROS levels in tumor cells stabilize and activate hypoxia-inducible factor-1 (HIF-1), which regulates the adaptation to low oxygen levels and aids in cell [132]. However, mitochondrial stress-induced p53-mediated ubiquitination and degradation of HIF-1 α in partial mtDNA-depleted cells has also been demonstrated [133]. These observations suggest that mitochondrial retrograde response induces cellular proliferation with or without activation of the HIF-1 dependent pathway [132, 133]. Increased levels of mitochondrial ROS are also involved in the activation of transcription factor NF- κ B and thereby promote cellular proliferation and survival in cancer cells [134]. ROS-mediated retrograde signaling also activates detoxification enzymes and

antioxidant proteins through activation of transcription factor nuclear factor erythroid 2-related factor 2 (NFE2L2; also known as NRF2), a master regulator of detoxification, antioxidation, and other cytoprotective mechanisms [135–138].

2.5. Insertion of mitochondrial DNA in the nuclear genome

The natural transfer of mtDNA into the nuclear genome of eukaryotic cells generates nuclear mitochondrial DNA (NUMT) copies [139]. NUMT insertion is a genetically frequent event that is estimated to occur at a rate of $\sim 5 \times 10^{-6}$ per germ cell per generation in humans [140]. Although NUMTs have been reported in at least 85 sequenced eukaryotic genomes [139, 141, 142], the exact mechanism(s) of NUMT accumulation in the nucleus is not yet known. In addition to mtDNA, the transfer of mitochondrial RNA (mtRNA) and mitochondrial proteins and peptides has also frequently been observed [143–150]. In fact, as early as 1965, Brandes et. al. observed the presence of intact mitochondria in the nucleus of a leukemic cell [145]. Later studies identified well-preserved mitochondria as nuclear inclusions [143–145, 148–150], and reported migration of mitochondria towards the nucleus in stress conditions [151–153].

In humans and other mammals, the distribution of germline NUMTs in the nuclear genome is non-random and is implicated in double-strand break repair [154–156]. To date, more than 700 germline NUMTs in the human genome have been identified [140, 157]. However, the role of NUMTs in cellular and organismal function and in human health and disease has yet to be elucidated. A handful of investigations suggest germline NUMT insertion into coding genes may lead to certain disease conditions [158]. These include severe plasma factor VII deficiency and bleeding diathesis [159], mucopolipodosis IV [160], Usher syndrome [161] and a rare Pallister-Hall syndrome [162]. NUMT insertions may reduce cellular fitness and lead to cellular dysfunction induced cell death, which may underlie these human diseases [163]. Little is known about the somatic NUMTs and their role in human pathology [164]. The increased rate of NUMT insertion during ageing in both yeast and mammals has also been identified [165–167].

We and others have demonstrated that interactions between mitochondria and the nucleus play a key role in tumorigenesis [54, 112, 127, 168–172]. However, the importance of mtDNA integration within the nuclear genome in cancer remains relatively unexplored. In our recent investigation, we analyzed the prevalence of NUMTs in colorectal cancer and have identified increased somatic transfer of mtDNA in colorectal tumors [173]. Our results also reveal an increased frequency of NUMT occurrence in tumors, suggesting NUMT may be used as a biomarker for tumorigenesis. In addition, we have identified that inactivation of *YME1L1* in colorectal tumors induces migration of mtDNA to the nuclear genome [173]. In yeast, Yme1 (yeast homolog of human YME1L1) aids in the removal of damaged mitochondria by mitophagy, a stringent mechanism that controls the quality of mitochondria and maintains a healthy pool of this organelle within the cells [174]. These observations lead us to suggest that compromised mitophagy is involved in the accumulation of mtDNA in the nucleus [174]. Indeed, compromised mitophagy due to loss of Yme1 [175] or acid endonuclease DNase II α [176] can lead to the cytoplasmic accumulation of incompletely digested mtDNA, which ultimately ends up in the nucleus. Our findings of increased levels

of somatic NUMTs in cancer is consistent with two previous studies that have also shown association between NUMTs and carcinogenesis [177, 178].

Interestingly, the transfer of mtDNA fragments to the nucleus has been shown to be a dynamic and reversible process in pluripotent stem cells [179]. Results show that induced pluripotent and embryonic stem cells contain high levels of mtDNA in the nucleus, and that differentiation of stem cells to somatic cells substantially reduces the number of mtDNA fragments in the nucleus to levels similar to those observed in normal somatic cells. This reversible accumulation of mtDNA in the nucleus of pluripotent cells suggests a novel mechanism by which mtDNA sequences dynamically regulate chromosomal DNA in pluripotent stem cells [179]. Another recent study suggests that mtDNA depletion induces stem cells characteristics and epithelial-mesenchymal transition (EMT) in breast cancer cells [180]. Based on our previous discussion about mitophagy, it seems plausible to hypothesize that compromised mitophagy during mtDNA depletion leads to increased accumulation of mtDNA sequences in the nucleus that enhance the expression of stem cell characteristics and promote tumor development and metastasis in cancer cells.

Fusion of the mitochondrial and nuclear membranes and encapsulation of mitochondria in the nucleus may be one mechanism by which mtDNA is transferred into the nuclear genome of eukaryotic cells [181, 182]. In fact, several studies provide evidence of encapsulation of mitochondria in the nucleus [143–146, 148–150], and disintegration of the nuclear envelope during mitosis has been shown to result in disruption of the physical barrier separating the nucleoplasm and cytoplasm, thus providing an opportunity for mitochondria to enter into the nucleus [183]. Interestingly, cancer cells often exhibit a ruptured nuclear envelope [184]. Furthermore, a decrease in the expression of lamins, which are important constituents of the nuclear membrane, has been shown to contribute to rupture of nuclear membrane in cancer cells [185]. It is likely that this decreased lamin facilitates the migration of mitochondria into the nucleus, resulting in eventual integration of mtDNA into the nuclear genome. Indeed, integrated mtDNA fragments have been identified in the *MYC* locus in HeLa cells [186] and in the nuclear genome of mouse embryonic fibroblasts [187]. In the latter case, integration of mtDNA into the nuclear genome appears to have led to malignant transformation [187]. More generally, insertion of NUMT in tumor suppressor gene(s) or in oncogene(s) may disrupt biochemical pathways and contribute to tumorigenesis. Further research in this area is needed in order to fully elucidate the role of NUMTs on cancer development.

3. Mitochondria in extracellular information transfer

3.1. Mitochondrial damage-associated molecular patterns

Recent studies have suggested that mtDNA-mediated signaling is fundamental for host immune defense against exogenous pathogens such as bacteria and viruses [188, 189]. An important aspect of the immune system is the capacity to discriminate self from non-self [190]. Since mitochondrial DNA evolved from prokaryotic bacteria-like ancestors, it has retained molecular motifs similar to those found in bacteria. When these motifs, or damage-associated molecular patterns (DAMPs), are released into the extracellular space during cell death and tissue injury, they activate innate and adaptive immune responses and contribute to inflammation and development of human pathologies [191, 192]. For example, recent

studies suggest that mtDNA functions as DAMPs in systemic inflammatory response syndrome associated with acute trauma [193], in the induction of lung inflammation in the rat [193], and in the induction of arthritis in mice [194].

A variety of mitochondria-secreted factors are also known to behave as DAMPs and to be associated with activation of inflammatory cells during different pathological conditions. These include: cytochrome c, a pro-apoptotic signaling molecule released from the mitochondria to cytosol [195, 196]; cardiolipin, an anionic phospholipid that is predominantly located in the inner mitochondrial membrane [197]; carbamoyl phosphate synthetase-1 (CPS-1), an enzyme localized in the mitochondrial matrix [198]; N-formyl peptides (NFPs), which are by-products of mitochondrial translation that are released from degenerating mitochondria [199]; extracellular ATP released from mitochondria of apoptotic cells [200, 201]; and mitochondrial ROS [202, 203].

Another mitochondria mediated extracellular response involves the formation of extracellular mtDNA traps, which are generated and released by several different leukocytes to aid in the innate immune response against pathogens such as bacteria, fungi, and parasites. It has been shown, for example, that lipopolysaccharide from gram-negative bacteria can activate eosinophils to rapidly release mitochondrial DNA in a catapult like manner [189, 204]. The release of mtDNA occurred in a reactive oxygen species-dependent manner, but did not involve eosinophil death. Significantly, in the extracellular space mtDNA and eosinophil granule proteins formed net-like structures, called eosinophil extracellular traps (EETs), which were found to bind and kill bacteria both *in vitro*, and under inflammatory conditions *in vivo* [205]. These data suggest a novel mechanism of eosinophil-mediated innate immune response that might be important in maintaining the intestinal barrier function. The presence of EETs was also detected in both infectious and non-infectious inflammatory skin diseases, and found to be particularly common in eosinophilic cellulitis, or Wells syndrome [206]. Activated neutrophils and mast cells have also been shown to form extracellular structures that bind and kill pathogens [207, 208]. Like EETs, both neutrophil extracellular traps (NETs) and mast cell extracellular traps (MCETs) appear to contain mtDNA and granular proteins that work together to exert strong antibacterial effects [207].

Despite these beneficial effects, extracellular traps have also been observed in inflammatory diseases and implicated in the initiation and/or potentiation of autoimmune diseases [207]. Interestingly, in one study mtDNA and other mitochondrial components secreted from live activated mast cells have been found to stimulate nearby mast cells, keratinocytes and endothelial cells to produce pro-inflammatory cytokines [209]. In addition, mast cell-derived mtDNA injected intraperitoneally in rats could be detected in their serum within four hours, implying that extracellular mitochondrial components can enter systemic circulation and possibly affect distant sites. It was proposed that the secretion of mitochondrial components from stimulated live mast cells may act as “autopathogens” contributing to the development of inflammatory diseases, and that neutralizing extracellular mtDNA sequences or other mitochondrial components may be a novel therapeutic approach to the treatment of these diseases. Recent studies have also identified the mechanism of mtDNA-mediated activation of immune response [188, 210–212]. Briefly, the presence of mtDNA in the cytosol is

sensed by the DNA sensor cGAS, which synthesizes its second messenger cGAMP and subsequently activates the endoplasmic reticulum membrane protein STING (stimulator of interferon genes). STING then translocates to the Golgi apparatus and the perinuclear endosomes, and subsequently phosphorylates and activates IRF3 [211, 212]. STING-IRF3-signaling elevates interferon-stimulated gene expression that potentiates type I interferon response to confer resistance against viruses [188]. It has also been demonstrated that herpesviruses induce mtDNA stress, which enhances antiviral signaling and type I interferon responses during infection [188]. All of the many and varied roles that mtDNA and other mitochondrial components play in microbial defense and autoimmune response have yet to be elucidated.

3.2. Extracellular ATP

There is now growing consensus that the extracellular ATP is a fundamental component of the tumor microenvironment that affects tumor growth and immune cell functions by regulating purinergic signaling. The steady-state concentration of ATP in the cytosol is 3–10 mM [213]. However, a small amount of this ATP pool (approximately 1%) is released extracellularly, to yield a concentration of ~10 nM ATP under basal conditions [213]. Interestingly, extracellular ATP has been implicated in a novel signaling mechanism [214] that is mediated by two types of extracellular purinergic receptors [215, 216]. Immune cells and most tumor cells express plasma membrane receptors for both extracellular ATP and adenosine, which dictate host and tumor responses [213]. Furthermore, it is known that a high concentration of ATP is characteristic of the tumor microenvironment [217, 218], and that adenosine, which is produced by sequential hydrolysis of extracellular ATP in the tumor interstitium, is a major determinant of the immunosuppressive tumor milieu [219]. Disturbed ATP synthesis, metabolism, and associated purinergic signaling have been shown to trigger a coordinated set of responses that help the cell defend itself from physical harm or microbial attack [220]. These cell danger responses (CDR) include a variety of different cellular mechanisms, such as: the endoplasmic reticulum stress response [221]; the unfolded protein response [222]; the heat shock protein response [223]; the oxidative stress response [224]; the oxidative shielding response [225]; and the innate immunity and inflammatory response [203, 226]. Studies also support extracellular ATP as a novel proliferative agent and possible effector of neoplastic transformation [227–229]. Through activation of the purinergic P2Y₁ and P2Y₂ receptors, extracellular ATP has also been shown to act synergistically with growth factors to induce mitogenesis in non-transformed cells [227–229]. ATP mediated activation of the P2Y₂ receptors and thus elevation of intracellular calcium and cellular proliferation in human breast cancer cell line MCF-7 has also been identified [230]. Extracellular ATP mediates these effects via activation of a variety of different signaling pathways, including phosphorylation of growth factor receptors [231], the ERK cascade [232], phosphatidylinositol 3-kinase (PI3K) [233], protein kinase A [234] and other calcium depending pathways [235].

4. Mitochondria in intercellular information transfer

4.1. Direct intercellular transfer of mitochondria

Direct intercellular transfer of mtDNA and/or whole mitochondria has been shown to occur between mammalian cells. In one of the earliest studies to demonstrate this phenomenon, human lung carcinoma cells were depleted of mtDNA, which rendered the cells incapable of aerobic respiration and growth (ρ^0 cells) except in a permissive medium to supplement anaerobic glycolysis [236]. When the ρ^0 cells were subsequently co-cultured with adult non-hematopoietic stem/progenitor cells from human bone marrow or with skin fibroblasts, the co-cultures produced clones of rescued ρ^0 cells with functional mitochondria. These clones were capable of propagating exponentially in a restrictive medium similar to the parental cell line with functional mitochondria, and genetic analysis revealed that 99 of 102 (97%) of them contained mtDNA from the donor cells. Our group demonstrated the xenogenic transfer of isolated murine mitochondria to human ρ^0 cells [237]. The presence of donor mitochondria within recipient cells was identified and its functional internalization was demonstrated by the restoration of mitochondrial respiration in ρ^0 human cells [237]. A later study demonstrated that intercellular mitochondrial transfer could be replicated in different types of cells and under different experimental conditions [238]. Using biochemical selection methods, it was shown that human mesenchymal stem cells (MSCs) can transfer mitochondria to human bone osteosarcoma cells lacking mtDNA (ρ^0), and that all recuperated cells were trans-mitochondrial cybrids containing the nuclear genome of osteosarcoma cells and mtDNAs from the MSCs. The same phenomenon was shown to take place under conditions in which severe mitochondrial dysfunction in osteosarcoma cells, but no mtDNA depletion, was caused by the mitochondrial toxin rhodamine 6G. Interestingly, mtDNA transfer from MSCs to osteosarcoma cells harboring pathogenic mtDNA mutations such as A3243G mutation or 4,977 bp deletion was not observed, suggesting that mitochondrial transfer may occur only when mitochondrial function is virtually absent in the recipient cell.

The most common mechanism by which intercellular mtDNA and/or whole mitochondria transfer occurs is through actin-based cytoplasmic bridges, referred to as tunneling nanotubes (TNT) [239–241]. These ultrafine plasma membrane protrusions (with a width of 50–200 nm and a length up to several cell diameters) form connections between neighboring cells that allow intercellular transfer of various cellular components, including organelles, proteins, and membrane components. The specific intercellular transfer of intact mitochondria via TNTs has been shown to occur between a variety of cells types, including mesenchymal multi-potent stromal cells and renal tubular cells [242], and mesenchymal stem cells and vascular smooth muscle cells [243].

There is considerable evidence to demonstrate that intercellular mitochondrial transfer can result in the phenotypic modulation of tumor cells [244–246]. In one study, for example, it was shown that pheochromocytoma cells stressed with ultraviolet light (UV) could be rescued from early stages of apoptosis when co-cultured with untreated pheochromocytoma cells [246]. Mitochondria were transferred through TNTs, which were formed by stressed cells that had lost cytochrome c but had not yet entered into the execution phase of

apoptosis. Significantly, only TNT-mediated transfer of functional mitochondria could rescue UV-stressed cells in co-culture, whereas untreated cells carrying defective mitochondria were unable to do so. In another study, the formation of TNTs and preferential transfer of mitochondria from endothelial to breast and ovarian cancer cells resulted in the acquisition of chemoresistance by the cancer cells [245].

Studies have also suggested both unidirectional [245, 247] and bidirectional movement of mitochondria [248] through TNTs. To a lesser extent, the intercellular transfer of mtDNA has also been shown to occur via exosomes, which are cell-derived, membrane bound micro-vesicles [209, 249, 250], and by connexin 43-containing gap junctional channels [251]. The transfer of mitochondria has been shown to occur between proximal and distant cultured mesothelioma cells [248], and between primary human laryngeal squamous carcinoma cells [252]. It has been suggested that the sharing of mitochondria between cancer cells may provide a means for fueling cancer cell maintenance and proliferation [248]. It is intriguing to consider the many ways in which the horizontal transfer of mtDNA might contribute to the genetic and biochemical plasticity and ultimate adaptability of cancer cells. The extent to which mitochondria transfer from normal cells to cancer cells or vice versa occurs *in vivo* is unknown, as are its functional consequences for the initiation and progression of the disease. These will undoubtedly be areas of great interest and importance to researchers for years to come.

Although the transfer of mitochondria between cells is mostly confirmed in *in vitro* studies, a few recent studies also support *in vivo* transfer of mitochondria. Canine transmissible venereal tumor (CTVT) in dogs present a classical example of mitochondrial transfer *in vivo*. CTVT, an infectious cell line circulating in many dog populations, was originated about 11,000 years ago [253, 254]. Phylogenetic analyses of mtDNA sequences from CTVT samples in dogs and mtDNA sequences from host animals indicate that these tumors have acquired mitochondria from their host and that probably helps CTVT cells in maintaining fitness of their mitochondria [253, 254]. Indeed, our group has earlier demonstrated the transfer of isolated mouse mitochondria to human ρ^0 cells upon simple co-incubation and demonstrated restoration of mitochondrial respiration in ρ^0 human cells [237]. Most recently, mitochondrial genome acquisition was also shown to restore the respiratory function and tumorigenic potential of cancer cells without mitochondrial DNA [247]. Using metastatic murine tumor models with mtDNA deletion to simulate severe mtDNA damage, a long lag in tumor formation was found for both ρ^0 melanoma and ρ^0 breast carcinoma cells grown either subcutaneously or intravenously in mice. In both models, the initiation of tumor growth was associated with mtDNA acquisition from the host, indicating horizontal transfer of mitochondria or mtDNA *in vivo*. Notably, the progressive recovery of mitochondrial respiration was found to correlate with the cells' tumorigenicity, rising from undetectable levels of respiration in ρ^0 cells to low levels in primary tumor cells derived from ρ^0 cells and then to even higher levels of respiration in circulating tumor cells [247]. However, due to technical limitations, this study does not provide direct evidence of mitochondrial transfer between cells [247]. In a subsequent *in vivo* study from the same group using C57BL/6^{su9DsRed2} mice that carrying mitochondrially-imported red fluorescence protein and B16 ρ^0 murine melanoma cells with blue fluorescent nuclei, it was

shown that B16p⁰ cells expressing nuclear blue fluorescent protein acquire red fluorescent mitochondria when implanted into transgenic C57BL/6^{su9DsRed2} mice [255].

There is a growing body of evidence to indicate that mitochondrial transfer is involved in the rescue and/or protection of a variety of diseased and damaged cells. For example, using an *in vitro* ischemia-reperfusion model, investigators demonstrated that oxygen/glucose deprivation and re-oxygenation of human umbilical vein endothelial cells induced an almost unidirectional transfer of mitochondria from mesenchymal stem cells to injured endothelial cells, which resulted in the rescue of aerobic respiration and protection of endothelial cells from apoptosis [256]. In one *in vivo* mouse model of acute lung injury, the transfer of mitochondria from bone marrow derived stromal cells was shown to increase alveolar ATP and protect alveolar epithelium from acute lung injury [251]. Mitochondrial transfer from normal cells has also been found to attenuate cigarette smoke induced damage of airway epithelial cells [257], and to reprogram adult cardiomyocytes toward a progenitor-like state [258]. In another *in vivo* mouse model of rotenone induced airway injury and allergic airway inflammation, the transfer of mitochondria from mesenchymal stem cells was shown to rescue injured epithelial cells [259]. Furthermore, in the same study, it was found that the mitochondrial Rho-GTPase, Miro1, regulates intercellular mitochondrial movement from mesenchymal stem cells to epithelial cells, and its over-expression leads to increased stem cell repair. As a mitochondrial outer membrane protein containing two GTPase domains and two helix-loop-helix Ca²⁺-binding domains [260, 261], Miro1 serves as a main component of mitochondrial trafficking machinery that anchors to the outer mitochondrial membrane and attaches mitochondria to motor proteins involved in mitochondrial transport [259]. Interestingly, Miro1 has been shown to be involved in a variety of other important cellular functions. For example, Miro1 knockout mice die soon after birth (postnatal day 0) due to postnatal respiratory failure [262], suggesting that the protein plays an important role in early development. Miro1 has also been shown to regulate mitochondrial morphology in yeast, flies, plants and mammals [264–266], and in a functional study, overexpression of human Miro1 resulted in collapsed mitochondrial network and the perinuclear aggregation of mitochondria [264]. In addition, Miro1 has been shown to regulate intra-mitochondrial matrix Ca²⁺ levels [263], to play a role in the maintenance of the integrity and function of the mitochondria-endoplasmic reticulum contact sites, which mediate calcium transfer from the endoplasmic reticulum to mitochondria through calcium transporters [260, 263], and to play an important role in mitotic redistribution of the mitochondrial network during cytokinesis [267]. Finally, a recent study also supports a role of Miro1 in prostate cancer cell migration and proliferation by suppressing the expression of SMAD4 [268].

The horizontal movement of genetic material between organisms other than by descent, has also long been recognized as a mechanism for genetic variability, adaptation and evolution in prokaryotes. Early estimates suggest that horizontal gene transfer (HGT) has contributed anywhere from 2–30% of the genome in certain prokaryotes [269, 270]. It has been proposed that once acquired, horizontally transferred genes can be vertically inherited within a group, thus having a substantial cumulative effect of HGT on longer evolutionary time scales [271]. Evidence also indicates that multiple mitochondrial genes can be transferred from a parasitic plant to host plant via a single horizontal gene transfer event, and that these genes can be integrated into the mitochondrial genome [272]. The authors suggest that since

this HGT probably involved a large segment of mitochondrial DNA, transfer via fusion of native and foreign mitochondria by direct plant-to-plant contact or by a relatively large organismal vector was more likely than transfer via naked DNA or a viral vector. Advances in the use of mtDNA polymorphism markers as well as transgenic animals and cells expressing mitochondrially-targeted fluorescent proteins have helped to establish the existence of intercellular mitochondrial transfer. However, technical limitations in the study of live imaging of mitochondrial transfer through TNTs remains a bottleneck for further characterization of the process *in vivo*. Recent studies have established a methodology for confocal microscope imaging of TNTs in tumor samples [273, 274]. Technical advancements in intravital confocal imaging would provide further support in identifying the mechanisms of intercellular mitochondrial transfer in and between tumor cells and cells of the tumor microenvironment.

4.2. Transfer of mitochondria-derived peptides

Humanin (HN) is a mitochondria-derived, locally active polypeptide with neuroprotective, anti-apoptotic, and anti-necrotic effects. It was first discovered in unaffected brain tissue of a patient with sporadic Alzheimer's disease and found to protect against neuronal cell death caused by multiple different types of familial Alzheimer's disease genes and by A β amyloid [275]. Subsequently, HN has been found in a variety of tissues and to exert multiple and wide-ranging effects on cell metabolism, survival, stress response, and inflammation *in vivo* and *in vitro* [275–280]. HN is a short polypeptide encoded within an open reading frame (ORF) found within the 16S rRNA gene of mtDNA. However, there is evidence for potential functionality of nuclear-encoded HN isoforms as well [281]. Recently, the 24-amino acid rat HN homologue, Rattin, was definitively shown to be derived and translated from an ORF within the 16S rRNA gene of mtDNA [282]. It has been proposed that HN is involved in mitochondria-to-nucleus retrograde control of cellular homeostasis and integrity [283]. Within a cell, HN binds to and interferes with a number of pro-apoptotic signaling molecules including Bax and Bid, to suppress cytochrome c release and inhibit the apoptotic pathway [284]. HN is also secreted, with measureable levels detected in plasma, cerebrospinal fluid, and seminal fluid [285]. When secreted outside the cell, HN exerts its effects by binding to specific trans-membrane receptors.

To date, multiple *in vitro* and *in vivo* studies demonstrate that HN and its analogs can protect against Alzheimer's disease related neuronal cell death and functional impairments, and suggest a potential role for HN in Alzheimer's disease therapy. HN and its analogs have also been found to play a cytoprotective role in a number of other diseases, especially those that are age related and/or involve oxidative stress and mitochondrial dysfunction [285], including: cardiovascular disease (CVD); stroke; inflammation; and type 2 diabetes. Interestingly, HN levels have been found to be considerably elevated in skeletal muscles of patients with two diseases caused by mtDNA abnormalities: mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) [286], and chronic progressive external ophthalmoplegia [278]. HN has also been shown to restore ATP levels in human lymphocytes harboring the MELAS associated A3243G mutant mtDNA [287]. These data suggest that an increase in HN expression may be a protective response to defects in energy production in cells harboring mitochondrial abnormalities.

Humanin may well be the first small peptide of its kind representing a putative set of novel mitochondrial-derived peptides that are involved in retrograde signaling as well as mitochondrial gene expression [283]. Recently, another mitochondrial-derived peptide has been characterized. MOTS-c is a 16-amino acid peptide encoded by the ORF of the 12S rRNA-c gene of mtDNA that has been shown to regulate insulin sensitivity and metabolic homeostasis [288], and may be involved in conferring exceptional longevity in humans [289]. It has been estimated that there may be from 100 to over 500 ORFs in mtDNA, and it is thus likely that additional mitochondrial-derived peptides have yet to be discovered [290]. Further research in this area will contribute not only to a better understanding of retrograde signaling, but also to the potential use of mitochondria-derived peptides as therapeutic agents in the treatment of human disease.

4.3. Transfer of exosomal mitochondria

Most cell types release small extracellular vesicles (EVs), which were originally considered as a waste disposal system but are now emerging as yet another class of signal mediators. EVs carry signals in their limiting membrane and/or in their interior lumen [291], and provide an excellent medium for intercellular communication in a number of physiological and pathological processes [292]. These vesicles range from 40 to 1000nm and, depending on their size, origin and molecular composition, can be categorized as micro-vesicles, exosomes, or apoptotic bodies. Exosomes are smaller EVs, with a diameter ranging from 40–100nm, that can be released either constitutively or in a regulated fashion [293]. Although larger EVs can contain entire mitochondria and mtDNA [294, 295], exosomes contain mostly small RNAs [296] genomic and mtDNA and proteins [249, 250, 297, 298]. Exosomes have been associated with several tumor-promoting activities, including modification of tumor microenvironment, promotion of cell invasiveness, and creation of a metastatic niche [299]. Our unpublished results demonstrate that mtDNA carrying exosomes play an important role in the tumor promoting properties of cells (e.g., cell migration, invasion and clone formation). Earlier studies have shown that exosomes activate oncogenic pathways and help in providing a favorable environment for circulating tumor cells in the development of metastasis [299]. Roles for exosomes in both adaptive and innate immune responses, and in the spread, survival and propagation of HIV-1 virus particles have been identified [300].

4.4. Transfer of mitochondria-derived vesicles

Mitochondria are also known to release small mitochondrial-derived vesicles (MDVs), ranging in size from 70 to 150nm. MDVs are generated through the selective incorporation of mitochondrial protein and lipid cargoes of outer membrane, inner membrane, and matrix contents, which are then transported from mitochondria to other intracellular organelles [301–303]. Initially, MDVs were believed only to mediate a mechanism of mitochondrial quality control, similar to the mitochondrial proteases, ubiquitin-mediated proteasomal degradation, and mitophagy. However, recent studies demonstrating involvement of the Parkinson's disease-associated proteins Vps35, Parkin, and PINK1 in the biogenesis of a subset of MDVs link this novel trafficking pathway to human disease [304–306] This emerging new area of mitochondrial biology will undoubtedly provide further insights about the importance of MDVs in mitochondrial homeostasis and human pathologies.

5. Mitochondria information transfer in cancer development, progression, and treatment

5.1. Mitochondrial regulation of epithelial-to-mesenchymal transition

Recent studies suggest that mtDNA mutations regulate the metastatic potential of cancer cells [39, 308], and that the mitochondrial genetic background imparts a significant effect on cancer tumorigenicity and metastatic severity [309]. It has also been shown that intercellular transfer of mitochondria can change the mitochondrial status of the tumor cells [247], which may dictate the underlying mechanism of the development of resistance to the therapeutic agents [247]. Epithelial-to-mesenchymal transition (EMT) provides metastatic potential to tumors and renders them resistant to therapies targeted to the primary cancers. Available literature supports a role for mitochondria in the EMT process [180, 310–312]. As stated previously, mtDNA content and/or copy number is frequently reduced in tumors [44, 313]. A recent study has shown that mtDNA copy number reduction in breast cancer cells activates mitochondria-to-nucleus Ca^{2+} /Calcineurin-mediated retrograde signaling, which leads to loss of epithelial marker genes expression and transcriptional activation of mesenchymal genes and induction of EMT [180]. A role for mtDNA depletion in the induction of EMT and progressive tumor phenotypes has also been demonstrated [311].

The multifunctional cytokine, TGF- β , is known to be one of the most potent activators of EMT during tumor progression [312, 314, 315]. TGF- β stimulation increases mitochondrial ROS and decreases mitochondrial membrane potential and intracellular glutathione levels. It has been shown that ROS produced in mitochondria regulate expression of genes associated with EMT through a mechanism involving a thiol reaction, and that approximately 15% of the TGF- β -inducible genes are affected by mitochondrial depletion [312]. The EMT marker gene fibronectin and high mobility group AT-hook 2 (HMGA2), a central mediator of EMT and metastatic progression, have been shown to be inhibited by exogenous expression of mitochondrial antioxidant thioredoxin (TXN2) [312]. Another study implicates a role for mitochondrial antioxidant enzyme, superoxide dismutase 2 (SOD2), in the regulation of EMT [310]. These observations suggest a novel mitochondria-dependent mechanism that regulates TGF- β -mediated gene expression associated with EMT [310, 312].

Studies also indicate that EMT and autophagy are linked in a complex relationship [315, 316], and that TGF- β is one of the major signaling pathways that converge on the regulation of these two processes [317–319]. It appears that during the early stages of tumor development, TGF- β promotes autophagy and cell death and suppresses tumor growth; later, when the tumor has settled, TGF- β restrains autophagy, induces EMT, and promotes metastatic spreading [315]. Furthermore, cells that undergo EMT require autophagy activation to survive during the metastatic spreading [320]. However, autophagy also acts as an oncosuppressive signal, which tends to inhibit EMT and metastasis by selectively destabilizing crucial mediators of this process [321, 322].

As previously indicated, mitophagy is the selective degradation of mitochondria by autophagy and a stringent mechanism that controls the quality of mitochondria in cells by degrading dysfunctional mitochondria. A healthy population of mitochondria provides the

required energy supply to cancer cells to reorganize the cytoskeleton and to sustain cell movement during EMT. Therefore, a functional interaction between mitochondria and cytoskeleton is one of the crucial regulatory centers at the crossroad between mitophagy and EMT.

A recent study suggests another link between mitochondrial dysfunction and EMT induction [323]. In this study, Tu translation elongation factor, mitochondrial (TUFM), was identified as a key factor in the translational expression of mtDNA that also plays an important role in the control of mitochondrial function and regulation of EMT [323]. In addition, the TUFM expression level was shown to positively correlate with E-cadherin, and to decrease during the progression of human lung cancer. TUFM knockdown reduced mitochondrial respiratory chain activity, and increased glycolytic function and EMT, suggesting that mitochondrial status plays an important role in EMT [323]. It is therefore plausible to suggest that changed mitochondrial status due to intercellular mitochondrial transfer might play an important role in EMT and thus cancer development and metastasis.

5.2. Mitochondrial regulation of resistance to apoptosis

Mitochondria are at the crossroads of death-inducing and life-sustaining cellular pathways, and an imbalance in the regulation of these pathways can lead to malignancy. Cancer cells have necessarily evolved a variety of adaptive mechanisms, which provide them the ability to evade death-inducing apoptotic pathway and thus confer a survival advantage. One such adaptive mechanism involves resistance to mitochondrial membrane permeabilization due to blockage of the permeability transition pore complex and the consequent inhibited release of apoptotic proteins, such as Cyt C, Smac/DIABLO and AIF, from intermembrane space [324]. In fact, upregulation of the anti-apoptotic proteins Bcl-2, Bcl-X_L and Mcl-1 [325], and downregulation of the pro-apoptotic protein Bax [326], have been found to be a frequent cause of apoptosis resistance in cancer cells.

As one of the hallmarks of cancer, mitochondrial dysfunction is known to induce chromosomal rearrangements that lead to genomic instability and cellular transformation [118, 307]. Mitochondrial DNA alterations and depletions have also been shown to confer resistance to apoptosis. We previously demonstrated that G10398A mtDNA polymorphism, which is present in African-American women, confers resistance to apoptosis and promotes aggressive breast cancer [11]. Other studies have identified a link between mtDNA depletion and apoptosis resistance. In one study, mtDNA depletion in myocytes markedly increased anti-apoptotic Bcl-2 protein, and reduced processing of p21 Bid to the active truncated tBid, a mitochondrially active protein required for release of Cyt-C from mitochondria [327]. In another study, mtDNA-depleted p⁰ human osteosarcoma cells displayed resistance to apoptosis even after treatment with a variety of apoptogenic molecules, such as staurosporine, doxorubicin, daunomycin and quercetin [328]. These observations suggest that dysfunctional mitochondria due to mtDNA mutations or mtDNA depletion in cells confer apoptosis resistance and promote cancer development. The rise of apoptosis resistance in cancer cells contributes to the development of resistance to conventional chemotherapy and poses a major challenge for the management of cancer. Development of

therapeutic molecules to restore apoptosis by blocking anti-apoptotic and activation of pro-apoptotic proteins are currently under clinical evaluations.

5.3. Mitochondria in cancer prevention and therapy

Of further importance to this review is the recent establishment of successful procedures for the transfer of isolated mitochondria to whole cells *in vitro*, which can be exploited as the therapeutic intervention for cancer. Our group has demonstrated the feasibility of xenogenic transfer of isolated murine mitochondria to human ρ^0 cells that were devoid of mtDNA [237]. In this study, the presence of donor mitochondria within recipient cells was detected by fluorescence microscopy and its functional internalization was demonstrated by the restoration of mitochondrial respiration in ρ^0 human cells. Although this study addresses the question of whether exogenous mitochondria isolated from one species can adapt and survive in the recipient cell from other species, further research is necessary to establish the long-term compatibility between xenogeneic mitochondria/mtDNA and the host nuclear genome. Another study by Spees *et al.*, demonstrated that co-culturing of A549 ρ^0 cells (devoid of mtDNA) with adult non-hematopoietic stem/progenitor cells from human bone marrow or with skin fibroblasts render the A549 ρ^0 cells capable of growing in a restrictive medium similar to the parental cell line with functional mitochondria [236]. Genetic analysis of these co-cultured A549 ρ^0 cells revealed the presence of mtDNA from the donor cells. Later, Elliott *et al.* demonstrated that the mitochondria purified from untransformed mammary epithelial MCF-12A cells could enter human breast cancer cell lines and suppress cancer cell proliferation and increase sensitivity to doxorubicin, abraxane, or carboplatin chemotherapy [329]. These pioneering studies created a niche for the therapeutic use of mitochondrial transfer in cancer treatment [236, 237, 329]. Recently, a new protocol for the direct transfer of isolated mitochondria to a variety of recipient cancer cell types was developed and validated by imaging, fluorescence-activated cell sorting and mtDNA analysis [330]. Using this protocol, the transfer of minute amounts of mesenchymal stem/stromal cell mitochondria to cancer cells resulted in enhanced oxidative phosphorylation activity and proliferation and invasion in the recipient cancer cells [330].

The importance of mitochondria transfer as a therapeutic strategy has also been shown in other human diseases. In one study using a rabbit model, viable respiration-competent mitochondria, which were isolated from tissue unaffected by ischemia and then injected into the ischemic zone just before reperfusion, significantly enhanced post-ischemic functional recovery and cellular viability [331]. Recent reports also suggest the feasibility of treatment of certain mitochondrial diseases by delivering healthy mitochondria from normal donors. For example, MERRF is a mitochondrial disease characterized by myoclonic epilepsy with ragged red fibers and caused by point mutation in the tRNA genes encoded by mtDNA. Notably, enhanced mitochondrial function was shown to occur in cells derived from patients with MERRF syndrome after the delivery to these cells of wild-type mitochondria isolated from normal donors [332]. Defective mitochondrial respiration has long been implicated in the etiology and pathogenesis of Parkinson's disease (PD) [333]. A recent study has demonstrated that allogeneic and xenogeneic transplantation of peptide-labeled mitochondria into neurotoxin-induced PD rat model improved the locomotive activity [334]. Interestingly, this increase in locomotive activity was accompanied by a marked decrease in

dopaminergic neuron loss in the substantia nigra pars compacta, restoration of mitochondrial complex I protein and mitochondrial dynamics, and decreased oxidative DNA damage [334].

To date, several different approaches have been utilized to transplant, replace, or transfer mitochondria into patients diagnosed with diseases that are characterized by mitochondrial dysfunction. These approaches include peptide-mediated mitochondrial delivery [332], cell-cell fusion [335], co-culture [236], microinjection [336], photothermal nanoblade [337], and import of mitochondria via liposome-modified RNA import complex [338]. It is now reasonable to assume that these methods can be used as tools to further examine the benefits of internalization of healthy mitochondria by diseased or damaged cells, to understand the impact that intercellular transfer of mitochondria or mtDNA might have on healthy cells, and to assess the practical applicability of intercellular transfer of mitochondria or mtDNA in the treatment and prevention of diseases involving heritable or acquired defects in mitochondria. In short, there is ample evidence to suggest that restoration of mitochondrial function, either through the use of mitochondria-targeted therapeutic agents or by direct transfer of mtDNA or healthy mitochondria to diseased cells, may yet be a viable therapeutic strategy for cancer and other diseases.

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Fig. 1.

Mutations in mtDNA sequence and alterations in mtDNA content have been identified in a wide variety of human cancers. These alterations are now known to trigger mitochondria-to-nucleus retrograde response (discussed in detail in text). Both somatic and germ-line mtDNA mutations have been reported in breast [32], brain [29], bladder [27], colorectal [33], head & neck [27], lung [27], ovarian [30], prostate [26, 28, 34], and thyroid [31, 35] cancers. Depletion in mtDNA has been reported in breast [47], colorectal [46], gastric [34, 46] hepatocellular [46], kidney [48, 51], lung [46], ovarian [50], and prostate [44] cancers. An increase in mtDNA content has been reported in Burkitt's lymphoma [45], chronic lymphocytic leukemia [45], head & neck cancer [45], non-Hodgkin's lymphoma [45], small lymphocytic lymphoma [45], and papillary thyroid carcinoma [47, 49].

Fig. 2. Information Transfer by Mobile Mitochondria and Mitochondrial Genome, aka the “Momiome”

Mitochondria have been identified as important signaling organelles which help to maintain cellular homeostasis. Alterations in signaling pathways may play a crucial role in tumorigenesis. *I. Intracellular information transfer.* Mitochondria are capable of mediating both anterograde (from nucleus to mitochondria) and retrograde (from mitochondria to nucleus) bidirectional intracellular information transfer. Evidence in support of these phenomena includes: the presence of nuclear genome-encoded epigenetic DNA modification machinery in mitochondria; identification of mtDNA-encoded miRNAs capable of altering nuclear gene expression; nuclear transcription factor mediated mitochondria-nuclear crosstalk; and accumulation of mtDNA in the nucleus (NUMT). *II. Extracellular information transfer.* During stress conditions mitochondria release their DNA and other molecules into the extracellular milieu. Extracellular release of ATP triggers different signaling mechanisms in the parent cell and/or neighboring cells that regulate tumor growth and immune cell functions. Damage-associated molecular patterns (DAMPs) can activate innate and adaptive immune responses and contribute to inflammation and the development of different human pathologies, including cancer. *III. Intercellular information transfer.* Mitochondria also play a crucial role in intercellular information exchange via mitochondria-derived vesicles, peptides, and exosomes, and via whole mitochondria transfer through tunneling nanotubes (TNTs) between neighboring cells.