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**Invited Mini Review**

# Mitochondrial noncoding RNA transport

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**Mitochondria are cytosolic organelles essential for generating energy and maintaining cell homeostasis. Despite their critical function, the handful of proteins expressed by the mitochondrial genome is insufficient to maintain mitochondrial structure or activity. Accordingly, mitochondrial metabolism is fully dependent on factors encoded by the nuclear DNA, including many proteins synthesized in the cytosol and imported into mitochondria via established mechanisms. However, there is growing evidence that mammalian mitochondria can also import cytosolic noncoding RNA via poorly understood processes. Here, we summarize our knowledge of mitochondrial RNA, discuss recent progress in understanding the molecular mechanisms and functional impact of RNA import into mitochondria, and identify rising challenges and opportunities in this rapidly evolving field. [BMB Reports 2017; 50(4): 164-174]**

## INTRODUCTION

As a primary site for energy generation, calcium signaling, and apoptotic factors, mitochondria are essential multifunctional organelles in eukaryotic cells. Derived from endosymbiotic bacterial ancestors, eukaryotic mitochondria have their own genome and are equipped with fully functional gene expression machineries (1, 2). To maintain their biogenesis and function, however, mitochondria require a large number of proteins that are encoded by the nuclear genome, translated in the cytosol, and subsequently imported into mitochondria. Accordingly, there has been a strong effort to elucidate the mechanisms of protein import into mitochondria (3-5).

Since the first discovery of cytosolic transfer RNAs (tRNAs) in mitochondria 50 years ago (6), evidence has accumulated supporting the notion that many types of RNA transcribed from nuclear DNA are actively delivered to mitochondria. Imported RNAs include different types of noncoding (nc)RNAs, such as tRNAs, *5S* rRNA, MRP RNA (*RMRP*), and RNase P RNA (*RPPH1*) (7-13), as well as microRNAs (mitomiRs) (14, 15). Their mobilization into mitochondria requires a range of protein factors (16-19), although the mechanisms that select and import RNAs into mitochondria, as well as the impact of imported RNAs on mitochondrial gene expression programs are largely unknown.

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## MITOCHONDRIAL TRANSCRIPTS AND THEIR FUNCTIONS

The mammalian mitochondrial genome (~12,500 bp) encodes 13 proteins, 22 tRNAs, and two ribosomal RNAs, *12S* rRNA and *16S* rRNA, which assemble the small (28S) and large (39S) subunits of the 55S mitochondrial ribosome (20). The mammalian mitochondrial DNA is transcribed as polycistronic precursor RNAs synthesized from both strands, the heavy (H) and the light (L) strands. The individual mitochondrial (mt-) rRNA and mt-mRNA sequences are regularly interspersed with mt-tRNA genes (21). The 13 proteins encoded by the mitochondrial genome function in the oxidative phosphorylation (OX-PHOS) complex (21, 22).

### *lncND5*, *lncND6*, and *lncCyt b*

Recently, two different laboratories reported whole-transcriptome analyses of purified human mitochondria and mitoplasts (23, 24). The studies identified numerous small RNAs and long noncoding RNAs (lncRNAs) transcribed from the mitochondrial genome. Among them, the lncRNAs *lncND5*, *lncND6*, and *lncCyt b* were identified as the counterpart antisense transcripts of the mitochondrial *ND5*, *ND6*, and *CYTB* mRNAs, respectively (23). *lncND5* and *lncCyt b* were transcribed from the L strand, and *lncND6* from the H strand of the mitochondrial DNA. Intriguingly, one of the known mitochondrial RNA processing proteins, the mitochondrial RNase P protein 1 (MRPP1) (25), was proposed to have a unique RNA processing function, influencing the maturation and abundance of lncRNA transcripts (24) (Table 1).

### *SncmtRNA* and *ASncmtRNAs*

Villegas *et al*. reported a human mitochondrial chimeric transcript called sense noncoding mitochondria ribosomal RNA (*SncmtRNA*) (26), structurally similar to a mouse

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mitochondrial RNA, containing a loop structure and a long inverted repeat (IR) linked to the 5′ end of the sense mitochondrial *16S* rRNA (27). Interestingly, *SncmtRNA* was only detected in proliferating cells but not in resting cells, suggesting that it might be a marker of cell proliferation (26). Two other ncRNAs that formed a similar chimeric structure with *SncmtRNA* but containing the antisense fragment of *16S* rRNA transcribed from the L-strand were later identified (*ASncmtRNA1* and *ASncmtRNA2*) (28).

Unlike the *SncmtRNA*, which is abundant in normal and cancerous proliferating cells, *ASncmtRNA1* and *ASncmtRNA2* were found expressed only in normal cells and were much less abundant in tumor cells (26, 28). A striking subsequent report found that both *SncmtRNA* and *ASncmtRNAs* were found in the nucleus associated with heterochromatin, suggesting the possibility that these mitochondrial lncRNAs participate in intraorganellar communication via retrograde signaling pathways (29). Recently, the *ASncmtRNA2* was found upregulated in senescent cells, where *ASncmtRNA2* delayed cell cycle progression through the G2/M cell cycle phases, possibly through the action of two microRNAs (*hsa-miR4485* and *hsa-miR1973*) derived from *ASncmtRNA2* (30) (Table 1, Fig. 1).

### *LIPCAR*

Very recently, a novel mitochondrial DNA-encoded lncRNA, *LIPCAR* (long intergenic noncoding RNA predicting cardiac remodeling) was identified in plasma of patients with left ventricular (LV) remodeling post-myocardial infarction (MI). *LIPCAR* levels declined in early stages after myocardial infarction, but increased in late stages, coinciding with LV remodeling. Increased levels of *LIPCAR* identified patients at high risk of heart failure or death, suggesting that *LIPCAR* was a possible biomarker for cardiac remodeling in patients who had an episode of acute MI (31) (Table 1, Fig. 1).

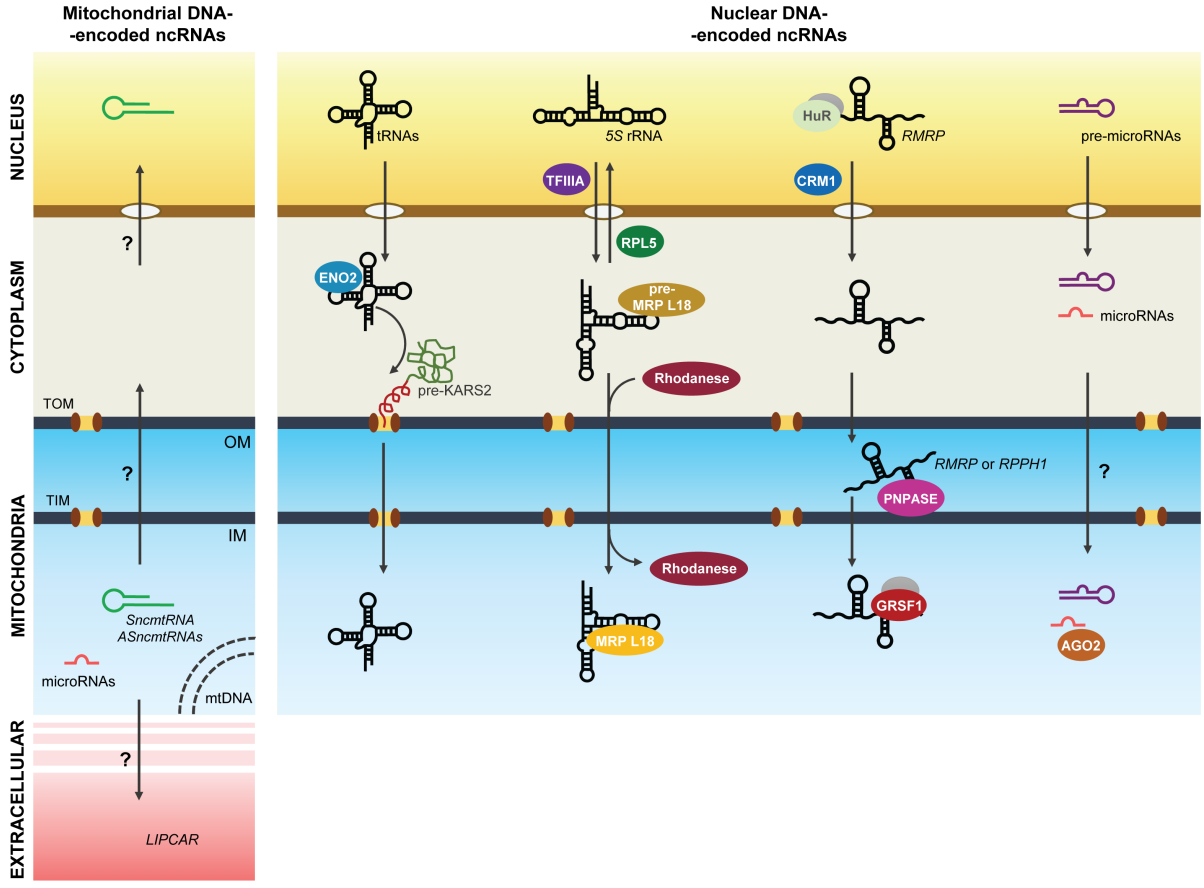


**Fig. 1.** Schematic of the ncRNAs transported through the mitochondrial outer and inner membranes (OM, IM). *Left*, ncRNAs synthesized in mitochondria but found elsewhere (nucleus and extracellular space); *right*, ncRNAs synthesized in the nucleus and found in mitochondria, including tRNAs, *5S* rRNA, lncRNAs like *RMRP*, and microRNAs and their precursors. Transport factors identified as mediators of these processes, including many ncRNA-interacting RBPs, are indicated. Yellow, nucleus; gray, cytoplasm; blue, mitochondria; pink, extracellular space.

## LOCALIZATION OF NUCLEAR DNA-ENCODED RNAs INTO MITOCHONDRIA

Although mitochondria synthesize dozens of RNAs from their own mitochondrial DNA, some nuclear DNA-encoded RNAs can be mobilized into mitochondria. As mentioned above, the import mechanism of cytoplasmic proteins into mitochondria has been studied in detail, but the mechanisms that import nuclear DNA-encoded RNAs into mitochondria are far less clear (32). Only a few noncoding transcripts are selectively transported into the mitochondrial matrix (17, 24). In this section, we discuss the current knowledge of the major mitochondria-localized ncRNAs: tRNA, *5S* rRNA (9, 11), MRP RNA (*RMRP*) (33), RNase P RNA (*RPPH1*) (12), and microRNAs (mitomiRs) (14, 15).

### tRNA ($tRNA^{Lys}$, tRK1)

The presence of nuclear DNA-encoded tRNAs in mitochondria was first suggested decades ago from a survey of the protozoan *Tetrahymena* (6). A following study in yeast *S. cerevisiae* also found that one of two mitochondrial tRNAs (isoacceptors of $tRNA^{Lys}$) originated from the nuclear DNA (34). Since this time, the traffic of nuclear DNA-encoded tRNAs to mitochondria has been observed in many organisms, including protozoa (35-40), yeast (41, 42), plants (43-48), and mammals (49). We now recognize that in most organisms at least a few cytosolic tRNA species are required for maintaining mitochondrial biogenesis (50, 51). Moreover, a cytoplasmic tRNA from yeast ($tRNA^{Lys}$; tRNALys acceptor 1, tRK1) was found to be internalized into human mitochondria (32, 52), suggesting that yeast and human mitochondria might share key components of RNA import (53).

Mitochondrial tRNA import occurs in higher organisms including human, even though mitochondrial DNA already encodes a full set of tRNAs required for the mitochondrial translation (52, 54, 55). The protein factors responsible for targeting the yeast tRNA tRK1 to mitochondria include the glycolytic enzyme enolase (ENO2P), which binds tRK1 to form a complex that is directed to the mitochondrial surface, whereupon the tRNA is handed over to the precursor of the mitochondrial lysyl-tRNA synthetase (preMSK or pre-LysRS) (56-58). The resulting complex tRNA-pre-LysRS is then internalized into the mitochondrial matrix through the protein import pathway, comprising the translocase of the translocase of the outer (TOM) and inner (TIM) mitochondrial membrane (the TOM/TIM complex) (59, 60). A recent study investigating the conformational change of the labeled $tRNA^{Lys}$ (tRK1) suggested that tRNA alters its structure upon binding to each carrier protein (ENO2P and pre-LysRS) of the import pathway (61). Both tRK1 and an artificial RNA containing the structural elements required for tRK1 mitochondrial import were targeted into human mitochondria with assistance by the cytosolic precursor of human mitochondrial lysyl-tRNA synthetase (pre-KARS2) and mammalian ENO2 (62). However, it is still unclear how tRNA and pre-LysRS remain bound during translocation through the the TOM and TIM complexes (63, 64), despite indications that the mitochondrial protein import machinery might accommodate proteins conjugated with RNAs (65) (Fig. 1).

### *5S* rRNA

Ancestral mitochondria were believed to have a complete set of rRNAs, but most mitochondrial rRNAs, including *5S* rRNA, were lost during evolution (66). Two proteins were found to regulate the intracellular distribution and ribosomal assembly of *5S* rRNA: the transcription factor TFIIIA, which binds to *5S* rRNA and mediates the nuclear export of *5S* rRNA and its ribosomal integration in *X. laevis* oocytes (67, 68), and the ribosomal protein L5, which forms the RNP complex *5S* rRNA-L5 (69), essential for delivering *5S* rRNA to the cytoplasm and assembling it into ribosomes (70, 71) (Fig. 1).

Other studies showed that a substantial portion of nuclear DNA-encoded *5S* rRNA is directed to mammalian mitochondria (9, 11). Entelis *et al*. proposed that cytosolic *5S* rRNA imported into mitochondria might substitute for its missing counterpart and form a functional mitochondrial ribosome (mitoribosome) large subunit (LSU) (32). Several proteins regulating *5S* rRNA import into mitochondria, as well as key *5S* rRNA motifs (helix I and helix IV-loop D) have been identified in recent years (72). For example, the mitochondrial enzyme Rhodanese bound the helix I sequence of *5S* rRNA and enhanced *5S* rRNA import, while Rhodanese depletion abolished *5S* rRNA import into mitochondria and decreased global mitochondrial translation, suggesting that the Rhodanese-driven localization of *5S* rRNA enhances mitochondrial function (73) (Fig. 1). Human MRP (mitochondrial ribosomal protein)-L18 was identified as another *5S* rRNA import factor. As observed for Rhodanese, the import sequence of *5S* rRNA directly interacted with mature MRP-L18 but also with its precursor, preMRP-L18, which contains a mitochondria-targeting sequence in its N-terminal region. The interaction between preMRP-L18 and *5S* rRNA in the cytosol causes a conformational change in *5S* rRNA that makes it recognized by Rhodanese and translocated into mitochondria. In the matrix, the innermost space in mitochondria, *5S* rRNA was proposed to associate with the mature MRP-L18 and with mitoribosomes, affecting mitochondrial translation efficiency (18) (Fig. 1).

### MRP RNA (*RMRP*)

The 267-nt long lncRNA *RMRP* is an RNA component of the mitochondrial RNA-processing endoribonuclease complex (RNase MRP), and its mutation causes the pleiotropic human disease cartilage-hair hypoplasia (CHH) (74). *RMRP* is broadly expressed in mouse and human tissues from an intronless nuclear gene (75), and resides in the nucleus and mitochondria. In the nucleus, *RMRP* is involved in the 5′end maturation of *5.8S* rRNA (76, 77) and influences yeast cell division cycle

**Table 1.** Mitochondrial noncoding RNAs

| Genome source | Noncoding RNA | Subcellular localization | Interacting proteins (RBPs) | Translocation Mechanism | Functions | References |
|---|---|---|---|---|---|---|
| Mitochondrial DNA | *lncND5* | Mitochondria | MRPP1 | Unknown | Mitochondrial gene expression | (23, 24) |
| | *lncND6* | | | | | |
| | *lncCyt b* | | | | | |
| | *SncmtRNA* | Nucleus, mitochondria | Unknown | | Unknown | (26, 29) |
| | *ASncmtRNA1* | | | | Unknown | (28, 29) |
| | *ASncmtRNA2* | | | | Cell cycle regulation | (28-30) |
| | *LIPCAR* | Extracellular (plasma) | | | Unknown | (31) |
| Nuclear DNA | tRNA | Cytoplasm, mitochondria | ENO2P, pre-KARS2 | Mitochondrial import | Mitochondrial translation | (62) |
| | *5S* rRNA | Cytoplasm, mitochondria | TFIIIA, RPL5, MRP L18, Rhodanese | Nuclear export/ mitochondrial import | | (67, 68, 73) |
| | MRP RNA (*RMRP*) | Nucleus, mitochondria | HuR, CRM1, GRSF1, PNPASE, hTERT | Nuclear export/ mitochondrial import | Ribosomal RNA (*5.8S*) maturation, cell division, mitochondrial RNA processing, mitochondrial DNA replication | (17, 19) |
| | RNase P RNA (*RPPH1*) | Nucleus, mitochondria | PNPASE | Mitochondrial import | Unknown | (17) |
| | miRNAs (mitomiRs) | Cytoplasm, mitochondria | AGO2 | Unknown | Mitochondrial gene expression | (14, 15, 105, 112) |

by binding the 5′untranslated region (UTR) of B-cyclin (*CLB2*) mRNA and degrading *CLB2* mRNA during mitosis (78). Human telomerase reverse transcriptase (hTERT) also associated with *RMRP* and synthesized a double-stranded RNA (*dsRMRP*) that was recognized by the endoribonuclease DICER1 and processed into short interfering (si) RNA (79).

There is strong evidence that *RMRP* is also found in mammalian mitochondria (17, 19, 23). The Clayton laboratory further proposed that *RMRP* was involved in mitochondrial RNA processing as well as in mitochondrial DNA replication (7, 8), although these functions are not fully understood. PNPASE (polynucleotide phosphorylase or 3′-to-5′ exoribonuclease and poly(A) polymerase) is a nuclear DNA-encoded protein that can be localized in the mitochondrial intermembrane space (IMS) (80-82). Recently, Wang *et al*. identified a novel function for mitochondrial PNPASE in regulating the import into the mitochondrial matrix of RNAs transcribed in the nucleus. Besides its impact on mitochondrial RNA processing, translation, and respiration, PNPASE can internalize RNAs including *RMRP*, *5S* rRNA, and RNase P RNA (*RPPH1*, described in the next section) from the IMS into the matrix. Interestingly, both *RMRP* and *RPPH1* were shown to share a stem loop structure recognized by PNPASE, which is critical for their translocation (17) (Table 1, Fig. 1).

Very recently, Noh *et al*. proposed a molecular mechanism whereby RBPs contributed to the intracellular and the suborganelle-specific distribution of lncRNP complexes. Their findings revealed that *RMRP* is exported from the nucleus to the cytosol by the RBP HuR through a CRM1 (chromosome region maintenance 1)-dependent nuclear export pathway. The exported *RMRP* was targeted into the mitochondrial matrix through unknown mechanisms, but once in the matrix, a nuclear DNA-encoded, mitochondria-resident RBP, GRSF1 (G-rich RNA sequence-binding factor 1), interacted with the imported *RMRP* and the resulting lncRNP complex was proposed to contribute to mitochondrial function by affecting the OX-PHOS system and mitochondrial DNA replication (19) (Table 1, Fig. 1).

### RNase P RNA (*H1* RNA, *RPPH1*)

RNase P RNA from bacteria, archaea, and eukarya was initially characterized as a catalytic subunit of a ribozyme capable of removing the 5′ leader sequence from tRNA precursors in the absence of protein subunits (83-85). An endoribonuclease protein complex that cleaves the *E. coli* $tRNA^{Tyr}$ at the same site as bacterial RNase P was partially purified from mammalian mitochondria and was named mtRNase P, to distinguish it

from its nuclear counterpart (nuRNase P) (86). Subsequent studies found that unlike mammalian nuRNase P and bacterial RNase P, which include an RNA component, mammalian mtRNase P does not (13, 87); however, other studies found an RNA similar to the *H1* RNA of nuRNase P bound to mammalian mtRNase P (12, 88). Despite controversy about its function, there is strong evidence that RNase P RNA is imported into the mitochondrial matrix (17, 19, 23) (Table 1, Fig. 1).

## MITOCHONDRIA-DIRECTED MicroRNAs (mitomiRs)

MicroRNAs (miRNAs) are small noncoding RNA molecules (~22 nucleotides long) that generally target and suppress mRNA stability and/or translation (89, 90). They are transcribed as primary (pri-)microRNAs, which are processed in the nucleus by the DROSHA/DGCR8 complex into precursor (pre-)microRNAs that are exported to the cytoplasm and further processed by DICER1 into mature microRNAs. MicroRNAs associated with the RBP AGO2 (argonaute 2), a component of the RNA-induced silencing complex (RISC), are directed to target mRNAs with which they share partial sequence complementarity (91-94). MicroRNAs can potentially interact with a wide range of target mRNAs and thus have emerged as potent posttranscriptional regulators involved in several cellular processes, including survival, death, division, differentiation, and senescence (95-101). In turn, they impact upon physiologic processes and diseases, such as cancer, cardiovascular disease, neurodegeneration, aging, inflammation, and diabetes (101-103). The recent discovery of microRNAs in mitochondria has expanded the spectrum of possible posttranscriptional functions of microRNAs and has led to a search for mechanisms of microRNA translocation to mitochondria. In this section, we review some of these microRNAs and their impact on mitochondrial functions.

### MicroRNAs and AGO2 in mitochondria

Generally, microRNAs function as the sequence specificity-conferring component of the RISC, which suppresses the stability and/or translation of target mRNAs in the cytosol. The RISC includes multiple RBPs such as AGO, TRBP1, TRBP2, and GW182. Accumulating evidence indicates that microRNAs and AGO2 exist in mitochondria (14, 15, 104), although the mechanisms through which microRNAs are imported into mitochondria as well as their functional impact are largely unknown. Pre-microRNAs have also been detected in mitochondria, suggesting that some aspects of microRNA biogenesis may occur in mitochondria (105-107). Moreover, the discovery of AGO2-bound microRNAs in mitochondria suggests that AGO2 may be important for the import of microRNAs into mitochondria possibly via co-import (108); interestingly, there is no evidence that other AGO proteins (e.g., AGO1 and AGO3) are imported to mitochondria (109). Crosslinking and immunoprecipitation (CLIP)-based analyses have further shown that AGO2 is associated with mitochondrial DNA-encoded transcripts (104). At present, the full mechanisms that govern these translocation events are not known.

### Function of mitomiRs

The vast majority of microRNAs found in mitochondria, collectively known as mitomiRs (110), are encoded by nuclear DNA, although a few microRNAs (specifically, miR-1974, miR-1977, and miR-1978) are encoded by mitochondrial DNA (14). Although the functions of most mitomiRs are unknown, they have been suggested to play roles in cell survival, cell division, and energy metabolism, as well as in disease processes like cancer (111). Among the few mitomiRs that have been studied functionally, the nuclear DNA-encoded miR-181c was found to translocate into mitochondria and to regulate mitochondrial gene expression. In rodents, overexpression of miR-181c, which targeted and downregulated *mt-COX1* (cytochrome c oxidase subunit 1) mRNA, led to higher ROS production, lower exercise capacity, and the appearance of cardiac dysfunction (112). Interestingly, the translocation of miR-1 into mitochondria with AGO2 led to increased translation of COX1 and the mitochondrial DNA-encoded NADH dehydrogenase 1 (ND1), suggesting that miR-1 coordinates gene expression networks in the cytoplasm and the mitochondria during muscle differentiation (109).

Next-generation sequencing (NGS) identified several microRNAs imported into mitochondria in 206 $\rho^o$ cells, such as miR-181c-5p and miR-146a-5p, which had many potential targets within the mitochondria, including RNAs transcribed from nuclear DNA and from mitochondrial DNA (112, 113). The mitochondria-localized miR-34a was recently found to control the integrity of the blood-brain barrier in cultured cerebrovascular endothelial cells by lowering mitochondrial oxidative phosphorylation and the levels of adenosine triphosphate and cytochrome c (114). However, miR-34a was also detected in the cytosol and thus its effect on the integrity of the blood-brain barrier might include miR-34a actions on cytosolic mRNAs. In a mouse model of diabetic heart and in HL-1 cells, Jagannathan *et al*. identified a pool of mitomiRs including miR-378, which translocated into mitochondria following a diabetic insult and downregulated the mitochondrially encoded F0 component ATP6, essential for cardiac pump function (115).

Together, these studies provide evidence that a substantial portion of microRNAs are imported into mitochondria and may influence mitochondrial gene expression programs widely. MitomiRs can enhance and reduce the expression of mRNAs originated from mitochondrial and nuclear transcription and in turn affect mitochondrial metabolic activity and cell homeostasis. It will be important to elucidate the mechanisms that govern microRNA localization in mitochondria, including the transport and interaction factors (e.g., RBPs and long noncoding RNAs), the mitochondria localization signals that tag microRNAs to mitochondria (e.g., RNA motifs), and the mitochondrial

transport machineries that mediate such transport. In addition, it will be critical to identify the mitochondrial interaction partners (AGO2 and likely other RBPs) that enable the mitochondrial functions of mitomiRs.

## CONCLUDING REMARKS

We have summarized our knowledge of noncoding RNAs mobilized into and out of mitochondria as well as their function. We discuss specific areas that warrant immediate attention as the field progresses.

### RNP complexes implicated in mitochondrial RNA mobilization

Recent advances in high-throughput sequencing technology have revealed vast numbers of lncRNAs expressed in cells (116) and follow-up studies have shown that they regulate gene expression programs transcriptionally, post-transcriptionally, and post-translationally (117-121). Indeed, most lncRNAs transcribed from nuclear DNA form lncRNA-protein complexes (lncRNPs) that are essential for their function in both the nucleus and the cytoplasm.

We reviewed mitochondrial lncRNAs derived from the mitochondrial genome (*lncND5*, *lncND6*, *lncCyt b*, *SncmtRNA*, *ASncmtRNA1/2*, and *LIPCAR*) and the nuclear genome (tRNAs, *5S* rRNA, MRP RNA, and RNase P RNA). For many lncRNAs examined in molecular detail, the interacting protein partners (RBPs) (122, 123) have been associated with their function. Future studies should examine whether specific RBPs associated with lncRNAs function as import/export factors. Besides specialized RBPs, there might be a basic machinery that controls RNA mobilization. This machinery employs ATP and appears to rely on factors located in the mitochondrial outer membrane (OM) as well as on core components of the protein import pathway, the TOM/TIM complex (60). An earlier study in yeast suggested that the yeast Tom20 and Tim44 complexes were involved in translocating the cytoplasmic $tRNA^{Lys}$ into mitochondria (59). VDAC (voltage-dependent anion channel), an abundant structural protein in the OM, appeared to contribute to mitochondrial tRNA import in plants (124). It will be important to test in the near future if VDAC and/or other OM-associated proteins can recognize and capture cytosolic RNAs at the surface of mammalian mitochondria.

### Composition and function of the mitoribosome (mitochondrial ribosome)

The mitochondrial ribosome (mitoribosome) has been identified in organisms from yeast to mammalian cells (125, 126), and was found to be poorly conserved in structure and composition among species. The mitoribosome is associated with the mitochondrial inner membrane, facing the matrix side, which enables it to insert highly hydrophobic nascent polypeptides easily upon translation (22, 127-130). Smirnov *et al*. proposed a model whereby the imported *5S* rRNA associated with the mitoribosomal large subunit (LSU), affecting mitochondrial translation efficiency (18) and helping to explain the high abundance of *5S* rRNAs found in mammalian mitochondria. However, a more recent study using cryo-EM provided alternative molecular evidence that mitoribosomal LSU has negligible or no *5S* rRNA (131). Considering its vital roles for maintaining mitochondrial biogenesis and functions, the structural and functional RNA component of the mitoribosome also deserves in-depth investigation.

### Impact of mitochondrial RNA mobilization on cellular homeostasis and disease

Optimal mitochondrial activity is necessary for cell homeostasis. Accordingly, mitochondrial dysfunction has been linked to chronic neurodegenerative disorders including Alzheimer's disease (AD), associated with the deposition of toxic Aβ peptide and DNA damage caused by defective base excision repair (132-134), and Parkinson's disease, caused by genetic alterations of PINK1, Parkin, DJ-1, and α-Synuclein (135-138). In addition, increasing evidence suggests that mitochondrial dysfunction contributes to cardiovascular disease (139, 140), muscle atrophy (141), insulin resistance (142), chronic obstructive pulmonary disease (143), cancer cachexia (144), and neuromuscular disorders (145). Mitochondrial dysfunction associated with damage and mutations of the mitochondrial DNA has been linked to accelerated aging and age-related disease (146, 147).

As previously hypothesized, mitochondria-directed RNA can be used as an endogenous vector that is effectively mobilized into mitochondria, carrying inserted heterologous sequences. Theoretically, it seems possible to introduce a particular RNA sequence which is complementary to the mutated region of mitochondrial DNA, thereby lowering the replication efficiency and clearing the 'bad' mitochondria from cells (148). In fact, interventions devised to eliminate pathogenic mitochondrial DNA, involving the creation of a chimeric RNA bearing a mitochondrial import signal and a sequence proximal to the mitochondrial DNA mutation site, were recently reported (149). These and other strategies are under consideration as we develop molecular and pharmacological methods to intervene in disease processes linked to aberrant mitochondrial function.

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## CONFLICTS OF INTEREST

The authors have no conflicting financial interests.

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