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The effects of mitochondria-associated long noncoding RNAs in cancer mitochondria: New players in an old arena

Yijing Zhao[a,b], Lemeng Sun[a,b], Rachel R. Wang[c], Ji-Fan Hu[a,b,**], Jiuwei Cui[a,*]

[a] Cancer Center, The First Hospital of Jilin University, Changchun, 130021, China
[b] VA Palo Alto Health Care System and Stanford University Medical School, Palo Alto, CA 94304, USA
[c] Department of Microbiology, University of Manitoba, Winnipeg, Manitoba, R3Y 0G1, Canada

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ABSTRACT

LncRNAs, as new players in the old battle against cancer, are significant components of gene regulatory networks. Mitochondria-associated lncRNAs have newly been discovered to work in concert with transcription factors and epigenetic regulators to modulate mitochondrial gene expression and mitochondrial function. Many mitochondria-associated lncRNAs regulate mitochondrial biosynthesis, bioenergetics, apoptosis and possibly govern the cross-talk of mitochondria with nuclei. The complexity of mitochondria-associated lncRNAs is now just starting to envisage. In this review, we collected available evidence that reinforces the importance of mitochondria-associated lncRNA in cancer metabolism, apoptosis, and cell senescence. For the non-exhaustive list of mitochondria-associated lncRNAs, we identified 18 lncRNAs in total (mitochondria-encoded lncRNAs or nuclei encoded mitochondria function associated lncRNAs) as emerging new players in cancer mitochondrial function. As lncRNAs exhibit cancer-type-specific expression patterns, they are attractive targets for selective therapeutic interventions. Manipulation of their function may thus represent a valuable strategy for future cancer treatment.

1. Introduction

1.1. Old arena: cancer mitochondria

Mitochondrion, as an essential multifunction organelle, has been an old arena in the study of biology. Their functions in energy generation, calcium signaling, and apoptotic factors have guaranteed their core status in cancer, especially in the transformation from normal cells into cancer cells (Corbet and Feron, 2017; Singh and Costello, 2009). Decades ago, Otto Warburg observed that glucose fermentation occurs in the presence of oxygen in cancers, suggesting that the mitochondria respiratory defect may be the significant underlying cause of cancer. This effect became known as aerobic glycolysis or the 'Warburg effect', which he interpreted as mitochondrial dysfunction (Warburg et al., 1927). However, with the advance of mitochondria knowledge, it has become known that mitochondrial dysfunction in cancer cells is not only limited to metabolism, but is prevalent in other mitochondria activity, such as mitochondrial calcium signaling, and mitochondrial apoptosis, replicative senescence and so on (Danese et al., 2017; Scatena, 2012). These mitochondria activities facilitated or adapt to the cancer formation, metastasis, invasion, survival, which in the long term reveal cancer patients diagnosis, prognosis and therapeutics. In this paper, we will focus on the transformation of mitochondria function in cancer cells to envisage the possibility of targeting the mitochondria in cancer therapy.

1.2. New players: long noncoding RNAs

The discovery that cytosolic tRNAs are transferred into the mitochondria was made in 1967 but the research of non-coding RNAs still

Abbreviations: ANRIL, Antisense non-coding RNA in the INK4 locus; ASO, Antisense oligonucleotides; CRM1, Chromosome region maintenance 1; GAS5, Growth arrest-specific transcript 5; HOTAIR, Hox Transcript Antisense Intergenic RNA; mtDNAs, Mitochondrial DNAs; mtlncRNAs, Mitochondrial-encoded lncRNAs lncRNA; ntmtlncRNAs, Nuclear-transported mitochondria-associated lncRNAs; MAC, Mitochondria apoptosis induced channel; lncRNAs, Long noncoding RNAs; RS, Replicative senescence; SIPS, Stress-induced premature senescence

* Corresponding author at: Cancer Center, The First Hospital of Jilin University, No. 71. Xinmin Street, Changchun 130021, China.
** Corresponding author at: VA Palo Alto Health Care System and Stanford University Medical School, Palo Alto, CA 94304, USA.
E-mail addresses: yijing16@mails.jlu.edu.cn (Y. Zhao), sunlm15@mails.jlu.edu.cn (L. Sun), Wangr322@myumanitoba.ca (R.R. Wang), jifan@stanford.edu (J.-F. Hu), cuijw@jlu.edu.cn (J. Cui).

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remained untouched for a long period of time (Suyama, 1967). Information about mitochondrial noncoding RNA started to accumulate only in recent years (Kim et al., 2017). In 2011, the human mitochondria transcriptome was first provided by near-exhaustive deep sequencing of long and short RNA fractions from purified mitochondria (Mercer et al., 2011). Until now, a total of 18 lncRNAs including mitochondria-encoded lncRNAs (mtlncRNAs) or nuclei encoded mitochondria function associated lncRNAs (ntmtlncRNAs) have been discovered to play a critical role in manipulating the mitochondrial function in cancer cells. Their function in mitochondria are not only restricted in metabolism reprogramming, but also in mitochondrial genome expression manipulating, stress signal transmission, and mitochondria-associated apoptosis. Now, time is ripe to further classify and define the mitochondria-related lncRNAs and we will discuss these lncRNAs regarding their classification and function in cancer mitochondria.

1.3. New games: the interplay of lncRNAs and mitochondria function in cancer

Long noncoding RNAs, as new classes of regulatory non-coding RNAs, are suspected to manage cancer mitochondria reprogramming. The mitochondrial genome shows different characteristics compared with the nuclear counterpart. The main differences include: the use of divergent genetic codes, transmission by maternal inheritance, a higher mutation rate, polyploidy status and a more compact organization (Ro et al., 2013). In human cells, mitochondria also contain genomes, that produce mitochondrial-unique 37 nucleic acids and 13 proteins. The mitochondrial genome encodes protein components of the respiratory chain and ATP synthase complexes, but hundreds of other nuclear-encoded proteins involved in respiration and in different functions must be synthesized in the rough endoplasmic reticulum and then imported into mitochondria. In this way, the mitochondrion, a semi-autonomous organelle, is under the control of a framework of cellular signaling that culminates in the coordinated expression of the two cellular genomes: nuclear DNA and mitochondrial DNA (Neupert and Herrmann, 2007; Scatena et al., 2012), where, long noncoding RNAs are one of the important new players in this game. However, there are seldom of reports in our knowledge discussing whether cancer biology behavior transformation signal comes from the mitochondria itself or the nuclei. Thus it is time for us to explore whether long noncoding RNA components are involved in this coordinate system.

2. Classification and location of mitochondria-associated lncRNAs

As mitochondria are autonomous organelles, they contain their own genetic materials known as mitochondrial DNA (mtDNA). Mitochondria-associated lncRNAs can be encoded by both the mitochondria genome and the nuclear genome, which are then transported into mitochondria (Table1). The mitochondria genome transcript lncRNAs are referred to as mitochondria-encoded lncRNAs (mtlncRNAs) (Fig. 1), while the lncRNAs generated by nuclear genome but transported to mitochondria are referred as nuclear-transported mitochondria-associated lncRNAs (ntmtlncRNAs).

mtlncRNAs are lncRNAs transcribed from the mitochondrial genome. These lncRNAs are also known as retrograde signals as they could report the mitochondrial activity and state to the host nucleus, which may finally trigger cell signal pathway and lead to the cell adaptation (Vendramin et al., 2017). Moreover, these lncRNAs could be further divided into two categories according to the post-translated processing. For example, lncND5, lncND6, lncCybt are the antisenses of the mitochondria genes ND5, ND6, and Cybt. Those lncRNAs are continuous and complementary of the original gene, which are categorized into “simple antisense mitochondrial DNA-encoded lncRNAs”. On the other hand, there are mtlncRNAs separated by the mitochondria gene, such as LIPCAR and SncmtRNA. These RNA splicings belong to the category of mitochondria lncRNAs called “Chimeric mitochondrial DNA-encoded lncRNAs”(Dong et al., 2017). There are two newly discovered mtlncRNAs; MDL1 and MDL1AS where MDL1 covers the tRNA Pro antisense gene and all of the human D-loop region, and MDL1AS being the antisense transcript of MDL1 (Gao et al., 2017).They both belong into the first category of “simple antisense mitochondrial DNA-encoded lncRNAs”. In all of the mtlncRNAs, the most common are SncmtRNA and ASncmtRNA, which are found outside the organelle and especially localized in the nucleus associated with heterochromatin. Their distant nuclear localization reveals the presence of the mitochondrial-nuclear communication pathway or retrograde signaling, which is considered as an important step in neoplastic transformation and cancer progression (Landerer et al., 2011).

There are bunches of nuclear-encoded lncRNAs (ntmtlncRNAs) transported into the mitochondria or to the outer membrane of mitochondria that function to monitor and fine-tune mitochondria copy number, status, morphology, and function. These nuclear-encoded lncRNAs are so-called anterograde signals (Vendramin et al., 2017). Among those ntmtlncRNAs, RMRP is the best-known example. RMRP is encoded by the nuclear genome, but binds to RNA protein HuR in the nucleus and mediates its CRM1 (chromosome region maintenance 1)-dependent export to the cytosol. After RMRP is imported into mitochondria, GRSF1 binds to RMRP and increases its abundance in the matrix (Noh et al., 2016). It has been reported that ntmtlncRNAs shuttles between the nuclei and mitochondria, which creates a new marker of nuclei transcript lncRNA in the organization of the cell organelle.

From the whole picture of the nuclei and mitochondria, it can be seen that lncRNAs shuttle between the nuclear genome and the mitochondria genome, thereby maintaining their function as communication signals (Wang and Chang, 2011). Moreover, considering that there is a fair amount of mitochondrial genome inserted in the nuclear genome, lncRNAs need to be excluded if this particular transcript could be derived from the nuclear genome (Vendramin et al., 2017).

3. The function of mitochondria-associated lncRNAs in cancer

3.1. LncRNAs manipulate mitochondria metabolism

For a long period of time, reprogramming of energy metabolism in cancer mitochondria seemed counterintuitive, in that cancer cells must compensate for the 18-fold lower efficiency of ATP production afforded by glycolysis relative to mitochondrial oxidative phosphorylation. Recently, this counterintuitive energy reprogramming is thought to increase glycolysis, which allows the diversion of glycolytic intermediates into various biosynthetic pathways, including those generating nucleosides and amino acids. This metabolism pattern reprogramming in turn facilitates the biosynthesis of the macromolecules and organelles required for assembling new cells (Zong et al., 2016). In other words, metabolites themselves can be oncogenic by altering cell signaling and blocking cellular differentiation (Ward and Thompson, 2012). This reprogramming of energy metabolism (reduced bioenergetic pathway and increased biosynthetic pathway) has been added in the next generation indicators of cancer (Hanahan and Weinberg, 2011), suggesting that targeting cancer cell mitochondria may be crucial for the advancement of emerging cancer therapies.

Recent results have proven that ntmtlncRNAs may play a key role in manipulating mitochondria metabolism (De Paepe et al., 2018). These ntmtlncRNAs are mainly involved in mitochondrial bioenergetics and biosynthesis and may interact with proteins implicated in mitochondrial metabolism and translation of mitochondrial encoded peptides. Through the manipulation of those proteins and peptides, ntmtlncRNAs can affect mitochondria metabolism and apoptosis (Goding, 2016). SAMMSON, a typical example of this working model, is especially expressed in > 90% of invasive vertical growth phase melanoma and migratory melanoblasts. SAMMSON is found to interact with P32, a