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Review

Organellar non-coding RNAs: Emerging regulation mechanisms

André Dietrich*, Clémentine Wallet, Rana Khalid Iqbal, José M. Gualberto, Frédérique Lotfi

Institut de biologie moléculaire des plantes, CNRS and Université de Strasbourg, 12 rue du Général Zimmer, 67084 Strasbourg, France

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ABSTRACT

Originally focused on the nuclear and cytosolic compartments, the concept of regulation driven by non-coding RNAs (ncRNAs) is extending to mitochondria and chloroplasts. These organelles have distinct genetic systems that need coordination with cellular demands. In mammals, nuclear-encoded microRNAs were found associated with the mitochondria. Some of these contribute to the regulation of mitochondrial transcription and translation. Others were proposed to be stored in the organelles and to be released for regulation of nuclear transcripts. Further ncRNAs of various sizes derive from the mitochondrial genome and it was speculated that organelles host antisense or RNA interference pathways. Long ncRNAs mapping to the mitochondrial DNA seem to operate in the nucleus. Altogether, the origin and trafficking of ncRNAs categorized as mitochondrial in mammals raise questions far beyond the current knowledge. In protozoa, hundreds of guide RNAs specify editing events needed to generate functional messenger RNAs. Only few ncRNAs have been reported in plant mitochondria, but editing sites were revealed in non-coding regions of the organellar genome, suggesting that the corresponding transcripts have a function. Conversely, numerous ncRNA candidates were identified in chloroplasts, essentially mapping to the plastid genome. A synthetic view of the data with their functional implications is given here.

1. Introduction

The accumulation of “omics” data established that genetic complexity scales not with gene number but with gene regulation [1]. At the same time, the dogma dictating that gene regulation is essentially mediated by protein factors fell apart with the non-coding RNA (ncRNA) revolution [2]. Small interfering RNAs (siRNAs) and microRNAs (miRNAs) were identified as major actors in depicting most biological functions. Beyond RNA interference processes involving these 18–25 nucleotide small RNAs, further technical advances in genome and transcriptome analyses identified thousands of long non-coding RNAs (lncRNAs) with a length over 200 nucleotides. These have a broad repertoire of functions in chromosomal dynamics, telomere biology, chromatin modification, transcription control, or metabolism regulation [3–6]. Large sets of lncRNAs can be conserved between different organisms [7]. Over the years, both miRNAs and lncRNAs were shown to be involved in disease [8], DNA damage repair [9,10], or plant stress responses [11].

Data on the nuclear and cytosolic RNA world has been accumulating. Short or long nuclear-encoded ncRNAs regulating mitochondrial functions or mitochondrial dynamics have been identified [12–14]. A number of miRNAs control nuclear genes involved in organelle functions and thus contribute to regulate mitochondrial metabolism and morphology, as well as mitophagy and mitochondrion-mediated apoptosis [13]. Conversely, information on ncRNAs in organellar genetic compartments, *i.e.* mitochondria and chloroplasts, has long remained limited. The question is of importance, as organelles are primary powerhouses and metabolic factories in the cell and thus need to be fully integrated into the regulation and coordination mechanisms ensuring cellular homeostasis. The field is now growing and challenges further dogmas on RNA compartmentation and trafficking. The present review addresses these different aspects with emphasis on organellar lncRNAs.

2. The potential of organelles to encode or acquire non-coding RNAs

Organellar genomes are seen as tiny, as compared to their nuclear counterparts. This is only partially true. The size of the

* Corresponding author.
E-mail addresses: andre.dietrich@ibmp-cnrs.unistra.fr (A. Dietrich), clementine.wallet@ibmp-cnrs.unistra.fr (C. Wallet), khalid.iqbal@ibmp-cnrs.unistra.fr (R.K. Iqbal), jose.gualberto@ibmp-cnrs.unistra.fr (J.M. Gualberto), lotfif@unistra.fr (F. Lotfi).

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mitochondrial DNA (mtDNA) varies to a large extent between different organisms. It is as small as 6 kb in the Apicomplexan parasite *Plasmodium* [15], but reaches over 11 Mb in some *Silene* plant lineages [16]. In model and crop plant species the mtDNA is in the range of 200–700 kb, containing less than 60 known genes for proteins, transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs) [17,18] (Fig. 1). Besides identified genes, part of which include introns, the plant mtDNA contains stretches of sequences of nuclear or plastid origin, whereas more than half of its content is of unidentified origin and function. Due to the presence of multiple promoters, most of the plant mtDNA sequences are nevertheless transcribed and the transcriptome is subsequently shaped by RNA processing and stability control [19,20]. Such a situation is compatible with the production of ncRNAs having a potential regulatory function.

Animal mitochondrial genomes are much more compact, with a size of 16.5 kb in mammals [21]. Nevertheless, whereas the so-called heavy strand of the mtDNA is fully packed with coding sequences (genes for 2 rRNAs, 12 proteins, 14 tRNAs), the opposite, light strand carries only 1 protein gene and 8 tRNA genes (Fig. 1). Still, both strands are entirely transcribed, yielding after processing of the transcripts a set of non-coding sequences that are antisense to the know genes [22].

Mitochondria do not only have the genomic potential to produce regulatory RNAs, they also possess pathways that enable RNA uptake from the cytosol. In many organisms, the set of mtDNA-encoded tRNAs is not sufficient to support protein synthesis and it is complemented with nuclear-encoded tRNAs that the organelles share with the cytosolic translation apparatus [23,24]. The number of imported tRNAs ranges from 1 to all mitochondrial tRNAs, depending on the organism and species, and their identity varies as well. In plants, one third to one half of the mitochondrial tRNAs are shared with the cytosol. The mammalian mtDNA has long been considered to encode all organellar tRNAs, but import of cytosolic $tRNA^{Gln}$ has been reported in rats and humans [25]. In marsupials, mitochondria take up a $tRNA^{Lys}$ from the cytosol [26]. Mammalian mitochondria also import the nuclear-encoded 5S rRNA [27,28]. Evidence for an association of this RNA with the mammalian organellar ribosomes has been reported [29,30], but recent crystal structure results appear to exclude a structural role of the 5S rRNA in the mitoribosome [31,32]. Mitochondrial import of the nuclear-encoded catalytic RNA components of RNase P and RNase MRP has been reported upon early studies in mammals [33,34]. It has been alternatively denied or confirmed, and again claimed following functional analyses of the RNA uptake mechanism [35,36].

So far sequenced chloroplast genomes range in size from 59 to 521 kb (see for instance http://chloroplast.ocean.washington.edu/), with an average around 150 kb for a number of land plants. The chloroplast DNA (cpDNA) is generally divided into three regions, a large and a small single copy region separated by the two copies IRa and IRb of an inverted repeat. Chloroplast genomes contain more identified genetic information than their mitochondrial counterparts, with for instance 87 protein genes, 4 rRNA genes and 37 tRNA genes in the model plant *Arabidopsis thaliana* [37] (Fig. 1). As in plant mitochondria, transcription in chloroplasts is initiated at multiple specific promoters throughout the genome, including intergenic regions [38]. Processing of primary transcripts from both strands, especially polycistronic RNAs, might as well represent a source of sense and/or antisense non-coding sequences. As to the possibility to acquire ncRNAs, it has been implied that chloroplasts can also take up exogenous RNAs. In particular, the viroids belonging to the family *Avsunviroidae* are considered to migrate into chloroplasts, where they are efficiently replicated. Trafficking might involve a nuclear-dependent step [39]. In addition, transport of the mRNA coding for the eucaryotic translation initiation factor 4E into chloroplasts has been reported [40]. However, at the present stage, RNA import into the chloroplast seems to be restricted, in contrast to the many examples described for mitochondria.

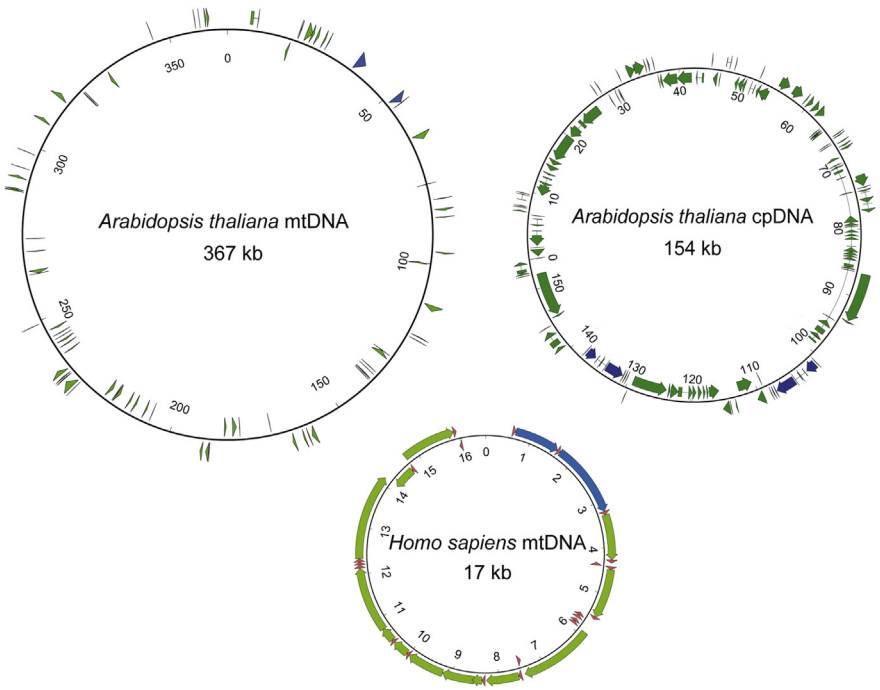

Fig. 1. Organellar genomes of *Arabidopsis thaliana* and *Homo sapiens*. Mitochondrial (mtDNA) and chloroplastic (cpDNA) genomes are represented in a circular form showing the respective gene densities. Genes are indicated outside or inside the circle according to their location on the (+) or (−) strand; protein genes are in green, rRNA genes are in blue, and tRNA genes are in red.

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