Nuclear transcriptional regulation by mitochondrial-encoded MOTS-c

Changhan Lee

Leonard Davis School of Gerontology, University of Southern California, Los Angeles, CA, USA; USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; Biomedical Science, Graduate School, Ajou University, Suwon, Korea

ABSTRACT

Cellular stress response is coordinated through the communication between mitochondria and the nucleus. However, whereas mitochondria are regulated by nuclear-encoded proteins, the nucleus was considered ungoverned by mitochondrial-encoded factors. We recently reported that a mitochondrial-encoded peptide directly regulates the nuclear genome upon cellular stress, indicating an integrated bi-genomic cross-communication mechanism.

Eukaryotic cells are multi-genomic systems, whereby each unique genome is compartmentalized in the nucleus, mitochondria and, in the case of plants, chloroplasts. The non-nuclear genomes evidently originate from endosymbiotic bacteria, which are thought to have provided several advantages, including bioenergetics, that allowed for eukaryotic evolution. For the past 1–2 billion years, the mitochondrial and nuclear genomes have co-evolved as the ancestral cells became functionally more complex. A lingering question remains on how the progress from an endosymbiotic relationship, which is not uncommon even today, to their establishment as a key organelle was coordinated. Of the many requisites, communication must have been key in fine-tuning the merger and consequent evolution of eukaryotic life. The ‘language’ that was used to mediate such communication presumably derived from mechanisms encoded in the original genomes of both parties, thus providing a foundation for eukaryotic cellular regulation. This notion is supported by the fact that more than 1,000 proteins encoded in the nuclear genome translocate to mitochondria to regulate various mitochondrial functions. On the contrary, mitochondrial DNA (mtDNA) has been traditionally known to host 13 protein coding genes, all of which are components of the electron transport chain (ETC) with no evident signaling roles. However, recent identification of short open reading frames (sORFs) encoded in mtDNA that yield bioactive peptides with regulatory roles, collectively categorized as mitochondrial-derived peptides (MDPs), provides another layer of mitochondrial communication. There are now eight published MDPs, including humanin, SHLPI–6 (small humanin-like peptide 1–6), and MOTS-c (mitochondrial open reading frame of the twelve S rRNA type-c), that have unique and overlapping biological significance.

In a recent report, we have shown that MOTS-c can dynamically translocate to the nucleus in response to cellular stress in an adenine monophosphate (AMP)-activated protein kinase (AMPK)-dependent manner. Within the nucleus, MOTS-c interacted with multiple stress-responsive transcription factors, including nuclear factor erythroid 2-related factor 2 (NFE2L2/NRF2), activating transcription factor 1 and 7 (ATF1/ATF7), and others (unpublished data from our lab). MOTS-c was associated with purified chromatin fractions, indicating interaction with DNA. Indeed, MOTS-c could bind to the promoter regions of NRF2-target genes that generally possess antioxidant response element (ARE) sequences, which required its hydrophobic core and cationic tail residues, and regulate downstream gene expression. A global profile of MOTS-c-dependent nuclear gene expression in response to glucose restriction, using RNA-seq, revealed that a broad range of genes, including bona fide NRF2-target genes, were involved. In addition, several transcription factor (TF)-binding motifs were enriched in the promoters of MOTS-c-regulated genes, such as ATF1/ATF7 and JUND (also known as JunD proto-oncogene, AP-1 transcription factor subunit), which are also related to NRF2. MOTS-c, but not nuclear-null mutants, significantly improved cellular survival under metabolic stress MOTS-c.

In summary, MOTS-c (i) is largely extra-nuclear and translocates to the nucleus upon cellular stress, (ii) requires the activation of AMPK, a master regulator of metabolic homeostasis, for nuclear transport, (iii) interacts with stress-responsive TFs and their target genes in the nucleus, and (iv) increases survival under metabolic deprivation. Together, these data demonstrate that MOTS-c is a mitochondrial-encoded regulator of the nuclear genome, the first of its kind to be reported, whose genetic message to the nucleus is to promote an adaptive stress
response to maintain cellular homeostasis under deprived conditions. From a conceptual perspective, these findings indicate that the co-evolved mitonuclear genomes cross-regulate each other, providing evidence of the integrated genetic basis of bidirectional mitonuclear communication.

Our findings may also have considerable implications in cancer, which is a product of constant evolution and adaption with strong genetic and metabolic drivers (Figure 1). Cancer is a genetic disease, but the current approach in both basic research and translation development is largely focused on the nuclear genome, leaving the mitochondrial genome is the blind spot. Further, cancer is also considered a metabolic disease, in which mitochondria generally assume an altered metabolic role (i.e. Warburg effect) and exhibit altered communication to other cellular compartments\(^1\) to support the rampant growth. Notably, we previously reported that MOTS-c is an AMPK-dependent regulator of cellular metabolism and can not only retard the proliferation of the immortalized HEK293 cells, but also prevent diet-induced obesity and insulin-resistance and age-dependent insulin resistance in mice. Although there is much unveiled about the metabolic rewiring in cancer, how mitochondria communicate to other organelles in cancer is a critical question that remains largely enigmatic. This question is of special significance, again, for a major disease with strong metabolic and genetic bases. Thus, a large knowledge-gap currently exists on how the genetic network weaved by the two genomes are altered in cancers to provide evolutionary advantage for survival and growth.

We believe we have just only begun to unravel an archaic communication system that existed throughout eukaryotic evolution. As with any unexplored territory, there are more questions remaining than answers provided. Some fundamental questions that will advance our knowledge base on MDPs include the regulatory mechanisms of their expression, mode of intra- and extra-cellular transport, and their impact on the nuclear gene regulation in aging and age-dependent chronic diseases, such as cancer.

**Disclosure of Potential Conflicts of Interest**

C.L. is a consultant for and a shareholder of CohBar, Inc.

**ORCID**

Changhan Lee http://orcid.org/0000-0003-0327-4712

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