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CELL BIOLOGY

Choreography of protein synthesis

Both nuclear genes and genes in organelles called mitochondria are involved in the assembly of the cellular energy-producing machinery. RNA-translation programs that coordinate the two systems have now been identified.

MARTIN OTT

In cells, organelles known as mitochondria convert chemical energy from food into ATP, a molecule that fuels most of the reactions of life. Energy conversion relies on a series of macromolecular machines collectively called the oxidative phosphorylation system, which consists of protein complexes of the respiratory chain and the large enzyme ATP synthase. These complexes are composed of protein subunits that are encoded by either nuclear or mitochondrial DNA. In a paper online in *Nature*, Couvillion *et al.*[1] provide insight into how these two genetic systems are coordinated in time, despite being separated physically by cellular membranes.

The two distinct genetic systems in eukaryotic cells (cells that are characterized by membrane-bounded compartments) have their origin in an endosymbiotic event that occurred roughly 1.5 billion years ago — when a bacterial cell and an archaeal cell merged. This resulted in combining the efficient energy-conversion system of mitochondria (the former bacterial cells) with the greater complexity of the original archaeal cell. During evolution, most of the former bacterial genes were transferred to the nuclear genome[2]. This in turn created the need for systems to import nuclear-encoded proteins into mitochondria[3].

Mitochondria still contain a vestigial genome that encodes a limited set of proteins, including key subunits of the oxidative phosphorylation system. These proteins are synthesized by mitochondrion-specific ribosomes (RNA–protein complexes that mediate protein synthesis), which have developed from the endosymbiont's bacterial ribosome into a particle that differs in structure and composition from the ribosomes in the cytoplasm[4,5]. The dual genetic origin of subunits of the oxidative phosphorylation complexes necessitates tight coordination between mitochondrial- and nuclear-gene expression to supply similar quantities of subunits for the assembly process (Fig. 1).

Couvillion and colleagues performed their analyses in yeast. When yeast cells switch from obtaining their energy through the anaerobic fermentation of glucose to oxygen-requiring respiration, dramatic reprogramming of gene expression occurs. This phenomenon has been studied extensively in the context of alterations in the expression of nuclear genes. Couvillion and colleagues' study, however, sets a new standard by including analyses of mitochondrial-gene expression, revealing previously unrecognized complexities and levels of regulation.

The classical view of gene reprogramming is that changes in metabolism and its accompanying stress activate the transcription of specific genes and so provide increased amounts of the associated messenger RNAs. Couvillion *et al.* combined analyses of transcription with quantification of the efficiency with which these mRNAs are translated into proteins, using an approach called ribosome profiling. Specifically, they performed profiling on the cytoplasmic and mitochondrial translation machineries in parallel.

The authors found that the metabolic shift from fermentation to respiration in yeast resulted in a rapid accumulation of all of the nuclear-transcribed mRNAs that encode subunits of the oxidative phosphorylation system. Surprisingly, however, the translation of these mRNAs did not increase equally for all transcripts. Transcripts that encode subunits constituting respiratory-chain complexes (such as complexes III and IV) were preferentially translated, whereas translation of those encoding ATP-synthase subunits was repressed.

Another unexpected finding was that mitochondrial protein synthesis followed the same translational program as its cytoplasmic counterpart, with subunits of the respiratory chain gaining translational efficiency at the expense of ATP synthase subunits. In essence,

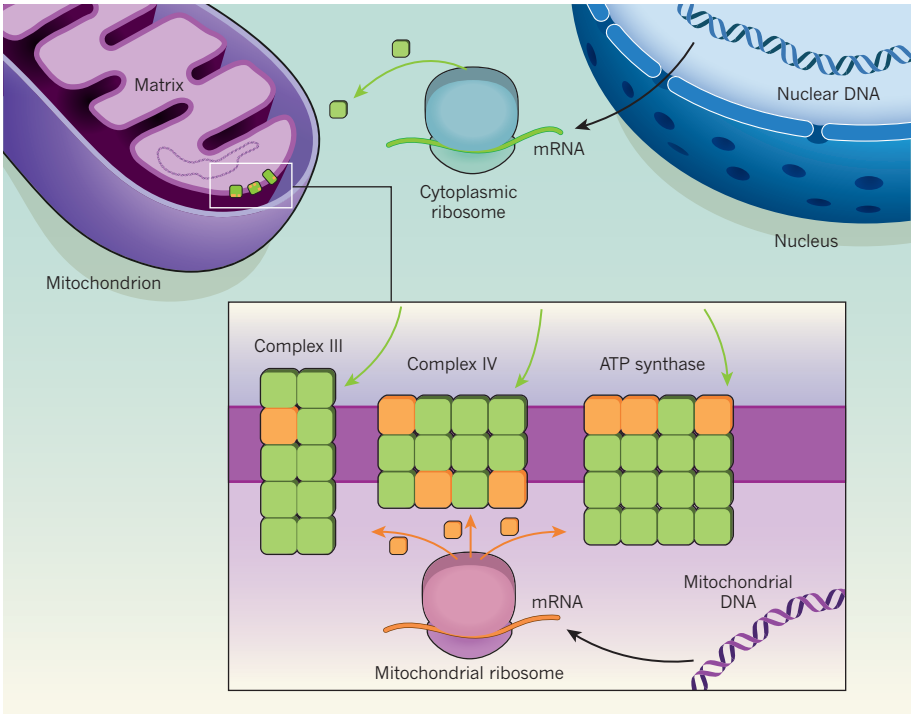

Figure 1 | Composite protein assembly in mitochondria. The mitochondrial oxidative phosphorylation system consists of a series of large complexes (such as complexes III and IV and ATP synthase), each containing many subunits. The subunits are encoded by mitochondrial or nuclear genes. Messenger RNAs that encode subunits with a nuclear origin are translated by ribosomes in the cytoplasm, and the resulting proteins are imported into mitochondria. By contrast, mRNAs of the subunits encoded by mitochondrial genes are translated by mitochondrial ribosomes in the organelle's matrix. Couvillion *et al.*[1] report that the translation, but not the transcription, of nuclear and mitochondrial mRNAs is synchronized.

therefore, the two genetic systems respond identically, despite being located in different compartments.

The authors also found that changes in the translation of nuclear-encoded mRNAs in the cytoplasm were independent of mitochondrial translation. By contrast, inhibition of cytoplasmic ribosomes not only induced the translation of many mitochondrial transcripts, but also specifically reduced the synthesis of some proteins. The latter observation is in line with previously identified feedback mechanisms[6–8] that adjust the synthesis of a subset of mitochondrial proteins to levels that can be assembled into oxidative phosphorylation complexes.

Although the reprogramming of cytoplasmic translation during stress is well documented[9], how mitochondrial translation is adjusted in response to stress and altered metabolic needs is largely unknown. The expression of individual mitochondrial mRNAs is controlled by translational activators[10] — a diverse family of nuclear-encoded RNA-binding proteins with ill-defined molecular functions. Future challenges therefore include unravelling the exact molecular functions of these translational activators and how they cooperate with other factors involved in translation initiation, to explain how metabolic cues modulate protein synthesis in mitochondria. An equally exciting challenge will be to extend this research from yeast to more-complex eukaryotic cells, such as those of mammals. ■

Martin Ott *is at the Center for Biomembrane Research, Department of Biochemistry and Biophysics, Stockholm University, SE-106 91 Stockholm, Sweden.*

e-mail: martin.ott@dbb.su.se

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