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Review

Dynamic regulation of mitochondrial transcription as a mechanism of cellular adaptation ☆

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ABSTRACT

Eukaryotes control nearly every cellular process in part by modulating the transcription of genes encoded by their nuclear genome. However, these cells are faced with the added complexity of possessing a second genome, within the mitochondria, which encodes critical components of several essential processes, including energy metabolism and macromolecule biosynthesis. As these cellular processes require gene products encoded by both genomes, cells have adopted strategies for linking mitochondrial gene expression to nuclear gene expression and other dynamic cellular events. Here we discuss examples of several mechanisms that have been identified, by which eukaryotic cells link extramitochondrial signals to dynamic alterations in mitochondrial transcription. This article is part of a Special Issue entitled: Mitochondrial Gene Expression.

1. Introduction

Mitochondria are involved in many diverse metabolic processes. While they possess their own genome, emerging evidence suggests that cellular events outside the mitochondria are tightly coupled to gene expression patterns within the organelle. Coupled with recent pre-clinical success using strategies that modulate mitochondrial translation to inhibit cancer cell growth [1], it has become clear that understanding the mechanisms by which cellular signaling pathways impinge on mitochondrial gene expression will be of significant benefit. Perhaps the best characterized of the mitochondrial functions is the participation in oxidative phosphorylation via the electron transport chain. Each organelle can contain several copies of the mitochondrial genome, which comprises a circular unit of dsDNA approximately 16,600 base pairs in length [2]. This double stranded molecule contains a heavy strand and a light strand, which are distinguished by their relative sedimentation density (Fig. 1).

Functionally, the mitochondrial genome encodes 37 known genes: 22 tRNA, 2 rRNA and 13 polypeptides that are part of the oxidative phosphorylation system [2]. The remaining protein components of the mitochondria are encoded and transcribed from the nuclear genome and subsequently imported into the mitochondria [3]. In addition to its transcribed regions, the mitochondrial genome possesses a non-coding control region approximately 1.1 kb in length [2]. The function of this region is not completely characterized, but it contains the origin of replication and transcriptional promoter regions [4,5]. Transcription begins at one of two promoter sites in the heavy strand (HSP1 and HSP2) and one promoter in the light strand (LSP) [6].

Like the majority of mitochondrial components, the proteins necessary for transcription and replication of the mitochondrial genome are not encoded within the organelle itself, but rather are encoded in the nucleus. Mitochondrial transcription is carried out by the single subunit polymerase POLRMT/mtRNAP, which displays high sequence similarity to the polymerases of T-odd lineages of bacteriophages [4,7,8]. Additionally, at least three critical transcription factors have been identified—TFAM, mTERF and TFB1M (or its paralog TFB2M) [9,10]. TFAM contains two DNA-binding HMG-boxes separated by a linker region and a C-terminal tail involved in promoter-specific transcription [11,12]. There are several TFAM binding sites in the control region of the mitochondrial genome upstream of transcriptional initiation sites [13]. Functionally, recent work has shown that TFAM introduces a “U-turn” in mtDNA at the LSP, which mediates transcriptional activation [14,15]. TFB1M and TFB2M are transcription factors that are similar to rRNA methyltransferases [16]. Although TFB2M is two orders of magnitude more efficient than TFB1M, both are able to form heterodimers with POLRMT/mtRNAP and activate transcription [9]. However there is significant evidence since their discovery to support non-redundant functions for TFB1M and TFB2M [17–19]. While TFB2M is required for transcription as a transcription factor, TFB1M has been shown to be involved in translation through its role in rRNA modification via methyltransferase activity. Furthermore, the loss of TFB1M does not lead to a decrease in mitochondrial transcription. Additionally, despite its negative results, it has been shown multiple times that TFB1M did not support mitochondrial transcription in highly purified *in vitro* systems. mTERF, a transcriptional termination

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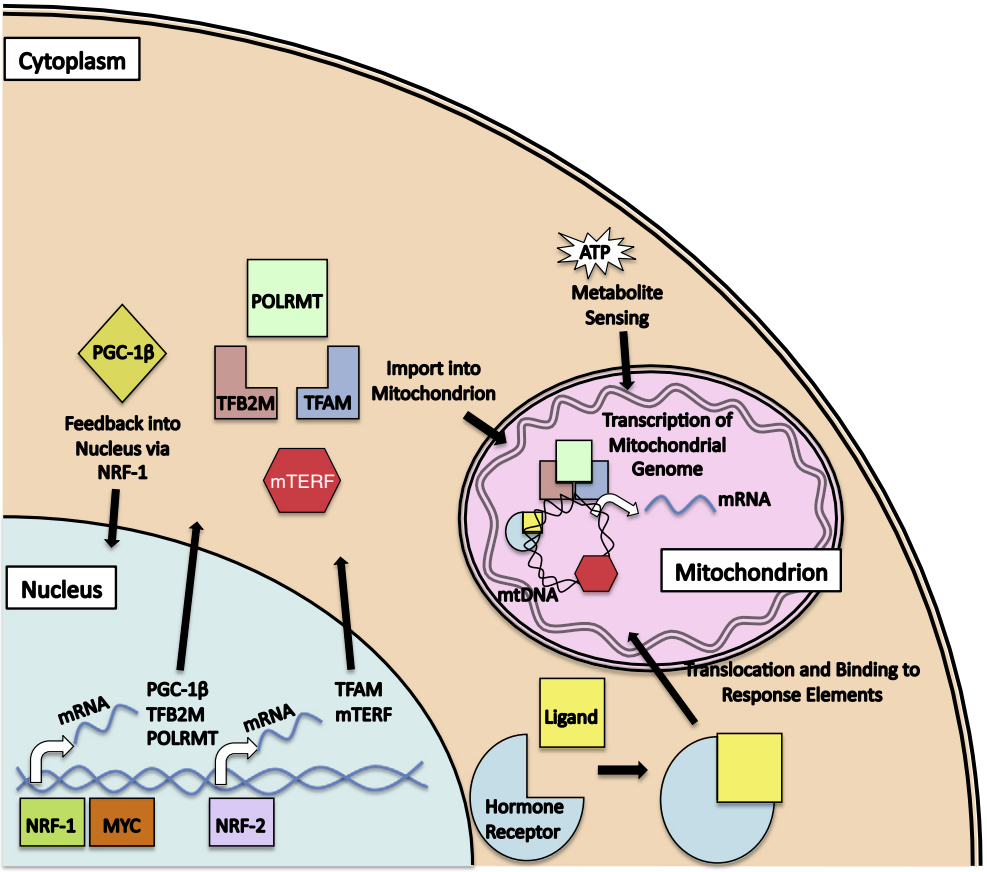

Fig. 1. Mechanisms for dynamic regulation of mitochondrial transcription. Mitochondrial transcription can be modulated by nuclear events, cytoplasmic signals or direct sensing of metabolites, among other mechanisms. Nuclear events include activation by the MYC and NRF-2 transcription factors of broad programs of nuclear genes encoding mitochondrial proteins. For MYC, part of this regulation is due to its ability to control the expression and/or function of other transcriptional regulators, such as PGC-1β and NRF-1. As part of this process, the nuclear encoded component of the mitochondrial transcription apparatus is induced (e.g. TFAM, TFB2M, POLRMT and mTERF). For the nuclear hormone receptor family of transcription factors, control of mitochondrial gene expression is more complicated. Members of this family implicated in mitochondrial gene expression include the Glucocorticoid Receptor, Thyroid Hormone Receptor, Androgen Receptor and Estrogen Receptor. These receptors not only perform their well-characterized role in binding and regulating genes in the nuclear genome, but recent evidence suggests also enter mitochondria and bind and regulate response elements in the mitochondrial genome. As a more direct mechanism for dynamic regulation of mitochondrial gene expression, the mitochondrial transcriptional machinery is responsive to cellular levels of ATP, thus coupling metabolic status with transcriptional regulation. Taken together, these and other mechanisms cooperate to provide the cell with a variety of strategies for dynamically regulating mitochondrial function in response to changes in the cellular environment.

factor, is structurally composed of three leucine zippers and two separate basic DNA binding domains [10,20,21]. Interestingly, mTERF binding sites on the mitochondrial genome are both upstream and downstream from transcriptional units. This has led to the proposal that transcriptional termination and initiation are functionally linked, with mTERF facilitating the transfer of POLRMT/mtRNAP from the terminated site to the initiation site [22].

The fact that these vital components of mitochondrial transcription are encoded in the nucleus provides an opportunity for regulation and synchronization with other important aspects of cellular physiology. For example, nuclear regulation of mitochondrial transcription may allow the cell to coordinate the production of the mitochondrial and nuclear-encoded subunits of the oxidative phosphorylation system at levels that achieve the appropriate stoichiometry. Another example might include increased biosynthetic reactions in the mitochondria to provide the cell with the building blocks needed for increased cell cycle progression. Here we explore several examples in which nuclear-encoded factors and other extra-mitochondrial aspects of cellular physiology influence mitochondrial transcription. Ultimately we discuss how these factors allow the cell to maintain a tight link between metabolic/biosynthetic demands and mitochondrial function.

Accepting the principle that individual cells might rely on altered mitochondrial transcription as a mechanism for adapting to a changing environment, we are left with the question of how a cell might accomplish this. Among the seemingly simplest mechanisms might be the utilization of nuclear signaling pathways to regulate the expression of genes encoding essential, rate-limiting components of the mitochondrial transcription apparatus. Alternatively, components of the mitochondrial transcriptional apparatus might respond directly to signaling pathways. For example, phosphorylation of the mitochondrial RNA polymerase POLRMT/mtRNAP by growth factor activated kinases could alter its catalytic activity, as it does for RNA pol-II within the nucleus [23,24]. Another potential mechanism for the dynamic regulation of mitochondrial transcription could be the ability of transcriptional regulators that normally function on the nuclear genome, to transiently translocate into the mitochondria to regulate transcription there. Examples of many of these types of dynamic regulatory mechanisms have come to light in recent years. Here we will provide a handful of examples to illustrate these phenomena.

2. Control of mitochondrial transcription by the MYC and NRF transcription factors

As discussed above, transcription of the mitochondrial genome must respond in a dynamic fashion to changes in the cellular requirement for mitochondrial function and actual numbers of mitochondria, as energy and biosynthetic demands change with alterations in cell cycle progression and other events [25,26]. For example, as cells receive signals to