Review

Multi-tasking: nuclear transcription factors with novel roles in the mitochondria

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Coordinated responses between the nucleus and mitochondria are essential for the maintenance of homeostasis. For over 15 years, pools of nuclear transcription factors (TFs), such as p53 and nuclear hormone receptors, have been observed in the mitochondria. The contribution of the mitochondrial pool of these TFs to their well-defined biological actions is in some cases clear and in others not well understood. Recently, a small mitochondrial pool of the TF signal transducer and activator of transcription factor 3 (STAT3) was shown to modulate the activity of the electron transport chain (ETC). The mitochondrial function of STAT3 encompasses both its biological actions in the heart as well as its oncogenic effects. This review highlights advances in our understanding of how mitochondrial pools of nuclear TFs may influence the function of this organelle.

Nuclear TFs in the mitochondria

Several reports have shown that pools of nuclear TFs with well-characterized functions in the nucleus are also present in the mitochondria (mitoTFs) [1–11]. MitoTFs comprise those of the nuclear hormone receptor family as well as TFs (e.g., p53, NF-κB and the STATs) that are activated downstream of the binding of growth hormones and cytokines to cell-surface receptors. The mitochondrial function of nuclear hormone receptors has been recently reviewed [4,6] and will not be discussed here. Instead, we will summarize our understanding of the actions of mitoTFs whose activities are mediated by hormones and cytokines that bind cell-surface receptors.

In general, the fraction of TFs in the mitochondria is very small compared to the levels in the cytosol or nucleus (5–10%). The potential functional effects of mitoTFs are varied and include apoptosis, respiration, and mitochondrial gene expression (Figure 1). Interestingly, most TFs that reside in the mitochondria (including NF-κB, p53, CREB and MEF2D) are reported to regulate mitochondrial respiration or biogenesis [7,12–15]. Often, defects in the function or expression of these mitoTFs result in altered susceptibility to the opening of the mitochondrial membrane transition pore (MMTP) and/or increased generation of reactive oxygen species (ROS), presumably through electron leakage from complexes I and III of the ETC.

The biological effects of mitoTFs are likely to be both immediate and long-term, whereas their actions in the nucleus are predominantly long-term (hours to days). Interestingly, in $p53^{-/-}$ murine embryonic fibroblasts (MEFs) activation of NF-κB is enhanced and glycolysis is increased [16], suggesting that these TFs can regulate mitochondrial function. However, there was no attempt to examine whether the actions of p53 were mediated by its localization in the mitochondria or by nuclear gene expression.

Owing to the small amount of these mitoTFs, however, their role in mitochondrial function is controversial. One of the major hurdles in the dissection of mitoTF function is the design of experimental models that allow separation of their mitochondrial actions from their nuclear function. For example, disrupted expression of STAT3 in the heart results in cardiomyopathy and decreased ETC activity [17–19]. However, it remains unclear what unique contributions the mitochondrial versus nuclear STAT3 make to the maintenance of cardiac homeostasis. By contrast, it is clear that the ability of Ras to transform $Stat3^{-/-}$ mouse embryonic fibroblasts (MEFs) depends on STAT3 expression in the mitochondria without any requirement for its nuclear presence [3]. These results, as well as extensive studies of the role of mitochondria-localized p53 discussed further below, are examples where the actions of a TF in the mitochondria contribute to its physiological functions.

There is also limited information concerning the mechanisms by which TFs are transported into the mitochondria; for the most part they do not contain defined mitochondrial targeting sequences. Mitochondrial heat-shock proteins 70 (mtHSP70) or 90 (mtHSP90) appear to be involved in the transport of several mitoTFs [5,8,20,21] and additional mechanisms of mitochondrial translocation exist for some of the mitoTFs (Table 1). Once transported, the mitoTFs can be divided into those that are localized within the mitochondria (e.g., STAT3, NF-κB, CREB, and MEF2D) and those that are associated with the outer mitochondrial membrane (e.g., p53 and IRF3).

In this review we provide an overview of how the mitochondrial fraction of these TFs contributes to their overall biological function, and discuss what is known

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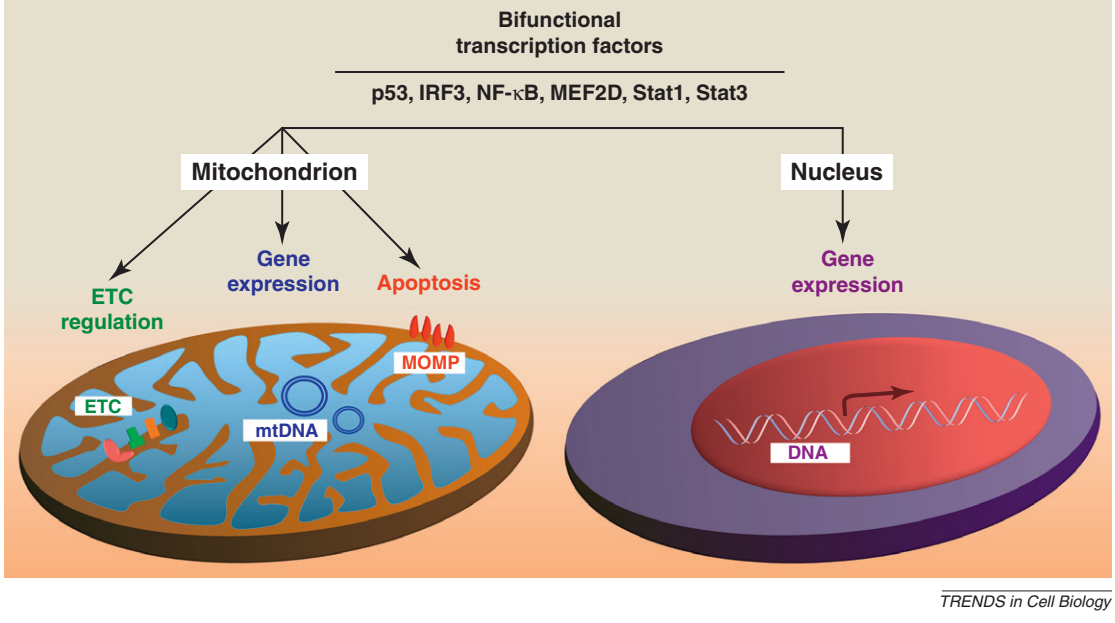

Figure 1. Nuclear transcription factors (TFs) that play distinct roles in the mitochondria. In the nucleus, TFs regulate gene expression, whereas in the mitochondria they directly affect activity of the ETC (e.g., STAT3 [9]), interact with the apoptotic machinery (e.g., p53 [70], IRF3 [22]), and modulate the expression of mtRNAs (e.g., CREB [7], NF-κB [5], MEF2D [8] and STAT1). ETC, electron transport chain; MOMP, mitochondrial outer-membrane permeabilization; mtRNA, mitochondrial RNA; mtDNA, mitochondrial DNA.

about their mechanism of translocation and action within the mitochondria. We first discuss those mitoTFs that associate with the outer mitochondrial membrane (OMM), and then summarize what is known about the intramitochondrial TFs.

TFs associated with the outer mitochondrial membrane

p53 and IRF3 exert their proapoptotic effects within the mitochondria by regulating the actions of Bcl-2 family members [21,22]. The association of p53 with the OMM is induced by a variety of stress signals. Stress-induced translocation of p53 to the mitochondria following exposure to γ radiation, hypoxia, or numerous other proapoptotic signals involves mono-ubiquitination of a distinct cytoplasmic pool of p53 by the E3 ligase Mdm2. At the outer mitochondrial membrane, p53 is de-ubiquitinated, permitting it to interact with Bcl2 proteins and induce apoptosis [23]. RNA viruses or synthetic double-stranded RNA, poly(I:C), induce IRF3 translocation to the mitochondria [22]. Both p53- and IRF3-mediated apoptosis correlate with their translocation to the mitochondria. The proapoptotic actions of IRF3 do not require its binding to DNA and are independent of nuclear gene expression. Both IRF3 and p53 bind to the Bcl-2 family proteins, resulting in activation of the mitochondrial apoptotic pathway through facilitation of mitochondrial outer-membrane permeabilization (MOMP) (Figure 2) [22,23]. IRF3 binds to BAK, which is a transmembrane protein localized at the OMM, leading to BAK oligomerization, MOMP formation, and release of proapoptotic factors from the intermembrane space into the cytosol (Figure 2a) [22]. Under stress conditions, formation of the proapoptotic p53–BAK complex is correlated with the disruption of the anti-apoptotic Mcl1–BAK complex (Figure 2b) [24]. p53 also interacts with another proapoptotic Bcl-2 family member, BAX, which results in disruption of the anti-apoptotic sequestration of BAX by Bcl-xL (Figure 2c) [25]. Activated BAX is then inserted into the OMM, where it oligomerizes and facilitates MOMP formation.

Although it is unknown whether p53 and IRF3 influence the actions of each other in the mitochondria, IRF3 potentiates the growth-inhibitory actions of p53 [26]. The fact that similar types of stress induce both IRF3 and p53 translocation to the mitochondria suggests the possibility of crosstalk between these mitoTFs.

p53 has diverse actions within the cell and the mitochondrial fraction contributes to several of these. Radiation of mice stimulates accumulation of p53 in the

Table 1. Mechanisms of mitochondrial translocation and functions of the nuclear TFs

TF	Function in the mitochondria	Import into the mitochondria	Refs
p53	- Binds to Bcl-2 family members and induces apoptosis - Inactivates MnSOD	Mono-ubiquitination, mtHSP60 and mtHSP70	[23,32,70]
IRF3	- Interacts with Bax	TOM70/HSP90	[20,22]
CREB	- Increases the expression of mtRNAs and complex I activity	mtHSP70	[7,11]
NF-κB	- Inhibits mtRNA expression and mitochondrial respiration	mtHSP70	[2,5]
MEF2D	- Regulates the expression of ND6 and complex I activity	N-terminal domain of MEF2D and mtHSP70	[8]
STAT3	- Facilitates the activities of complex I, II and V of the ETC - Attenuates ROS release from the ETC - Regulates MPTP	GRIM-19, TOM/TIM/HSP90?	[3,9,19,46,54,71]