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Nuclear transcription factor STAT6 regulates mitochondrial biogenesis through decrease of mitoribosome assembly factor MTG1.

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Mitonuclear communication is controlled by key factors and classified as anterograde and retrograde responses. Although it is reported that the key molecules are dually localized in nucleus and mitochondria regulate mitochondrial processes, mitochondrial mechanisms regulated by these factors are largely unknown. Among these dually distributed transcription factors (TFs), the roles of Signal Transducer and Activators of Transcriptions (STATs) are partially known.

We reported previously that STAT6 in mitochondrial outer membrane impairs mitochondrial fusion by inhibiting MFN2 dimerization. Here, we describe that STAT6 induces decrease of mitochondrial membrane potential (Ψm), release of cytochrome C, and activation/oligomerization of BAX/BAK under hypoxic condition, leading to cell death. We also reveal that STAT6 as TFs decreases mitochondrial mass, suggesting another role of STAT6 in mitochondrial mechanisms. Using RNA-seq analysis, our data showed that STAT6 regulates nuclear-encoded mitochondrial gene expressions as well as glycolysis-related genes. Among the lists of mitochondrial gene changed by STAT6, it was found reduction of MTG1 (a key factor in mitoribosome assembly), suggesting translation attenuation through inhibition of mitochondrial ribosome assembly. These findings reveal that STAT6 is a regulator of mitochondrial biogenesis as well as mitochondrial dynamics.