Mitochondrial function and HIF-1-independent organismal survival under hypoxia

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ABSTRACT

Oxygen deficiency, referred to as hypoxia, entails substantial reprogramming of mitochondrial metabolism to meet energy requirements. As such, reduction of mitochondrial efficiency and enhancement of glycolytic metabolism are commonly observed in hypoxic cells. This adaptation is attributed mostly to the activity of hypoxia-inducible factor 1 (HIF-1), as our knowledge on HIF-1-independent responses remains obscure. Here, we show that mitochondrial function is more prevalent than or act in parallel to glycolysis even under conditions of hypoxia. Challenging the prevailing notion, we show that maintenance of mitochondrial function is sufficient to promote survival of hypoxic cells independently of HIF-1. Importantly, we uncover a noncanonical role of E2F/EFL-1 transcription factor in mitochondrial metabolism. Under hypoxia, EFL-1 overrides HIF-1 activity on mitochondria. Particularly, EFL-1 controls the expression of hypoxia-responsive genes involved in oxidative phosphorylation, TCA cycle and glycolysis. Interestingly, we found that loss of the EFL-1 target TRIAP1/MDMH-35, increases mitochondrial cardiolipin levels and mitochondrial bioenergetics in response to oxygen deprivation. We propose that the EFL-1/MDMH-35 axis controls mitochondrial cardiolipin biosynthesis independent of HIF-1 to determine hypoxic cell survival and/or death.