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Mitochondria cripple without Krüppel

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Abstract

Proper mitochondrial biogenesis and removal is crucial in maintaining a healthy heart. Liao et al now show key roles for cardiac KLF4 in mitochondrial homeostasis via its interaction with the ERR/PGC-1 module, and mitochondrial clearance via regulation of mitophagy. Disruption of KLF4 leads to profoundly injured mitochondria and cardiac failure.

In 1950, Gloor first described mutants of the fruit fly *drosophila* that appeared crippled, or "krüppel" in German[1]. Fast-forward half a century, past the discovery of DNA and a molecular biology revolution, and we now know these fruit flies bore mutations in a gene called *Kruppel*, whose mammalian orthologs encode a family of zinc finger transcription factors known as Kruppel-like factors (KLFs). The KLF family is large. The 17 siblings (KLF1-17) act as transcriptional repressors or activators, and show different expression patterns among different tissues. They regulate numerous biologic programs in numerous contexts, including cell growth, differentiation, apoptosis, cell signaling and metabolism[2]. And now, a role is emerging for KLFs in the regulation of mitochondria.

Mitochondria are cellular power plants that generate ATP, the currency of energy in the cell. Mitochondria are most abundant in tissues that are most energetically active, such as heart, kidney, and retina. One third of heart mass is in fact mitochondria. Liao and colleagues[3] now show that KLF4, is critically required for mitochondrial biogenesis and homeostasis in the heart. The authors first genetically deleted KLF4 in postnatal hearts of mice, and then challenged these hearts by surgical placement of a constricting suture around the aorta. This procedure, called transverse aortic constriction (TAC), acutely increases the pressure against which the heart must pump, and thus also acutely increases the metabolic demands placed on the heart. The outcome was dramatic: profoundly injured mitochondria, loss of ATP balance, and cardiac failure. Deletion of KLF4 in prenatal hearts was even more impactful, preventing the normal post-natal mitochondrial proliferation, and leading to cardiac failure and death within weeks after birth. KLF4 thus critically regulates cardiac mitochondrial health.

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How does KLF4 regulate mitochondria? Mitochondria are complex organelles, the components of which are encoded by 100s of genes that must be coordinately regulated. The vast majority of mitochondrial proteins are encoded on the nuclear genome – only 13 are encoded on the mitochondrial genome itself. Well-established transcription factor networks coordinate this nuclear program in the heart and elsewhere (figure 1), including nuclear respiratory factors (NRF1 and 2), nuclear receptors such as estrogen-related receptors (ERRs) and Peroxisome proliferator-activated receptors (PPARs), and PPARγ co-activators 1α and β (PGC-1α and β) [4]. Liao et al. now show in some detail that the transcription factor KLF4 interacts with ERRα, likely forming a tri-protein complex with PGC-1α, and that this complex binds on evolutionary conserved DNA sites in promoter regions of numerous genes encoding mitochondrial proteins. Knockdown of KLF4 in cardiac cells prevented the induction of almost all of these genes by PGC-1α. The data thus neatly incorporate KLF4 into the already well-described regulatory network of mitochondrial biogenesis.

Are these observations unique to the heart and to KLF4? Probably not: Mallipattu and colleagues[5] recently reported that mice lacking KLF6 in kidney podocytes, another highly energetic cell, develop profoundly dysmorphic mitochondria and kidney failure in response to renal toxins. The authors show binding of KLF6 to the promoter of at least one key mitochondrial gene, *SCO2*. And Loft and colleagues[6] recently identified KLF11 as a novel regulator of mitochondrial function in adipose tissue, required for “browning” of white fat cells into mitochondria-rich and energy-dissipating cells. Here, the authors provide genome-wide data to show that KLF11 likely cooperates with PPARγ to activate and maintain brown-selective genes. Thus also outside the heart, mitochondria cripple without Krüppel.

Why are these reports important? First, they introduce a new class of players in the complex transcriptional regulatory networks of mitochondrial biogenesis and homeostasis. The components of these networks (NRFs, ERRs, PGC-1s, myc, etc) have been much studied, but no new major transcription factor has been added to the pantheon in a decade[7]. The arrival of KLFs thus potentially adds a layer of complexity that will fuel research for another decade or more. Second, somewhat surprisingly, KLFs have not been implicated in regulating mitochondrial biogenesis thus far, despite their wide and pleiotropic roles[2]. A key question now arises: in which of these numerous roles does regulation of mitochondrial homeostasis by KLFs matter?

Third, the study by Liao et al. also delves into the other side of the mitochondrial yin-yang: removal of sick (or crippled) mitochondria. A delicate balance between expansion and attrition of the mitochondrial network normally maintains mitochondrial health in the heart and elsewhere. In an illuminating final set of data, Liao et al. show that KLF4 not only regulates genes of mitochondrial biogenesis, but also regulates genes required for autophagy, a critical step in the controlled process of mitochondrial removal (mitophagy). KLF4 thus likely regulates both ends of the mitochondrial life cycle, and the balance between the two (figure 1).

These are still early days in the KLF/mitochondria story and many question remain. What is the precise relationship between KLFs and ERRs, NRFs, etc? How do KLFs interact with

the PGC-1 co-activators? Do KLFs regulate a unique subset of mitochondrial genes, and if so, are they different in different tissues, with different effects on mitochondrial biology? How many of the 17 KLFs can regulate mitochondrial programs, and are they redundant or interact with each other? The observation that deletion of KLF4 in the heart has a profound phenotype does support a unique role of KLF4, but co-deletion of other KLFs may uncover even more (analogous to co-deletion of PGC-1α and β in heart[8]). Answering these questions will require comprehensive genomic and epigenetic analyses, including effects on chromatin modifications, in various cell contexts, and in the presence and absence of various KLFs – no small task.

It is also interesting to note that the phenotypes seen in the absence of KLFs were largely provoked in response to physiological or pathological stressors, such as TAC and neonatal growth in the heart, or adriamycin in the kidney. What molecular pathways upstream of KLF4 and other KLFs modify their regulation of mitochondrial programs? For instance, how is KLF4 in the heart so strongly induced (10-fold) in the immediately post-natal period? And what would the response of KLF4 cardiac KO mice be to qualitatively different stresses, for example ischemia-reperfusion? An underlying question, unanswered thus far, is to what extent KLFs represent novel “nodes” that are, or can be, targeted to modulate mitochondrial biology, rather than more simply having a necessary role. Gain-of-function experiments will help answer this question.

Lastly, the other prominent “face” of Klf4 is its role as a pluripotent factor[9]. What is the relationship of pluripotency to mitochondrial homeostasis? For example, resetting human pluripotent stem cells to a more complete ground state involves re-expression of KLF4, a naïve marker, and concomitant activation of mitochondrial respiration[10]. And, tantalizingly, could KLF4 play a role in heart regeneration, a process of immense translational potential? There are clearly many questions raised by these new findings. There’s a new family on the block, and that can only mean more work, more complexity, and more fun.

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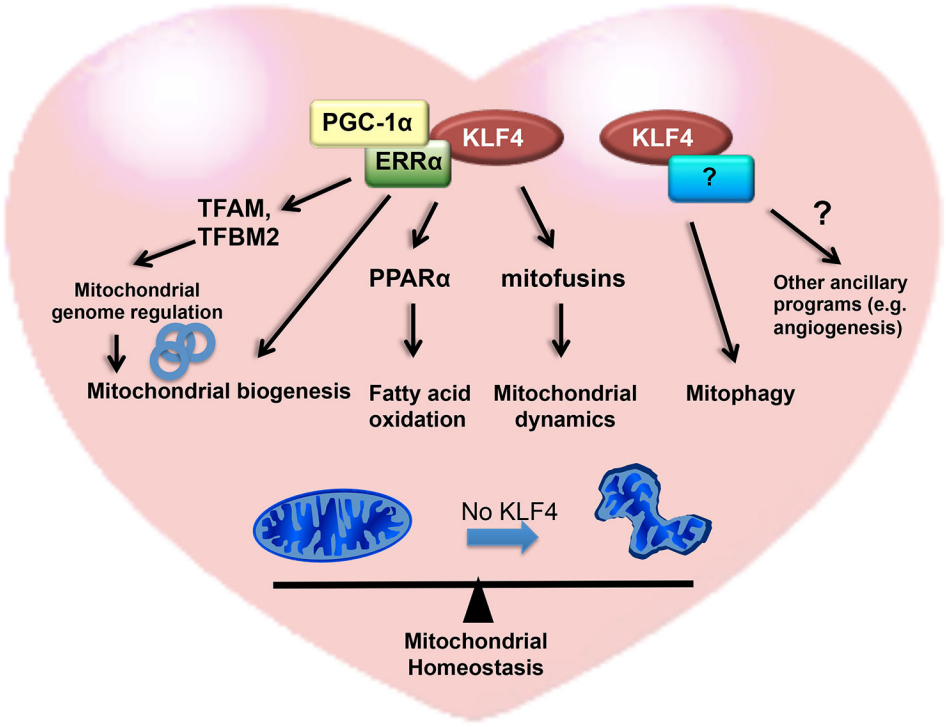

Figure 1. Key functions of KLF4 in cardiomyocytes

KLF4 forms a complex with ERRα and PGC-1α to drive expression of nuclear genes critical for mitochondrial biology. Among these gene products, TFAM and TFBM2 in turn co-regulate the mitochondrial genome, PPARα drives genes of fatty acid oxidation, and mitofusins regulate mitochondrial dynamics. In a still poorly defined protein complex, KLF4 also drives expression of genes likely involved in mitophagy, the removal of damaged mitochondria. Ultimately, KLF4 plays a crucial role in maintaining mitochondrial homeostasis, as evidence by “crippled” mitochondria in the absence of KLF4.