Erralpha and Gabpa/b specify PGC-1alpha-dependent oxidative phosphorylation gene expression that is altered in diabetic muscle.

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Recent studies have shown that genes involved in oxidative phosphorylation (OXPHOS) exhibit reduced expression in skeletal muscle of diabetic and prediabetic humans. Moreover, these changes may be mediated by the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator-1alpha (PGC-1alpha). By combining PGC-1alpha-induced genome-wide transcriptional profiles with a computational strategy to detect cis-regulatory motifs, we identified estrogen-related receptor alpha (Erralpha) and GA repeat-binding protein alpha as key transcription factors regulating the OXPHOS pathway. Interestingly, the genes encoding these two transcription factors are themselves PGC-1alpha-inducible and contain variants of both motifs near their promoters. Cellular assays confirmed that Erralpha and GA-binding protein a partner with PGC-1alpha in muscle to form a double-positive-feedback loop that drives the expression of many OXPHOS genes. By using a synthetic inhibitor of Erralpha, we demonstrated its key role in PGC-1alpha-mediated effects on gene regulation and cellular respiration. These results illustrate the dissection of gene regulatory networks in a complex mammalian system, elucidate the mechanism of PGC-1alpha action in the OXPHOS pathway, and suggest that Erralpha agonists may ameliorate insulin-resistance in individuals with type 2 diabetes mellitus.
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