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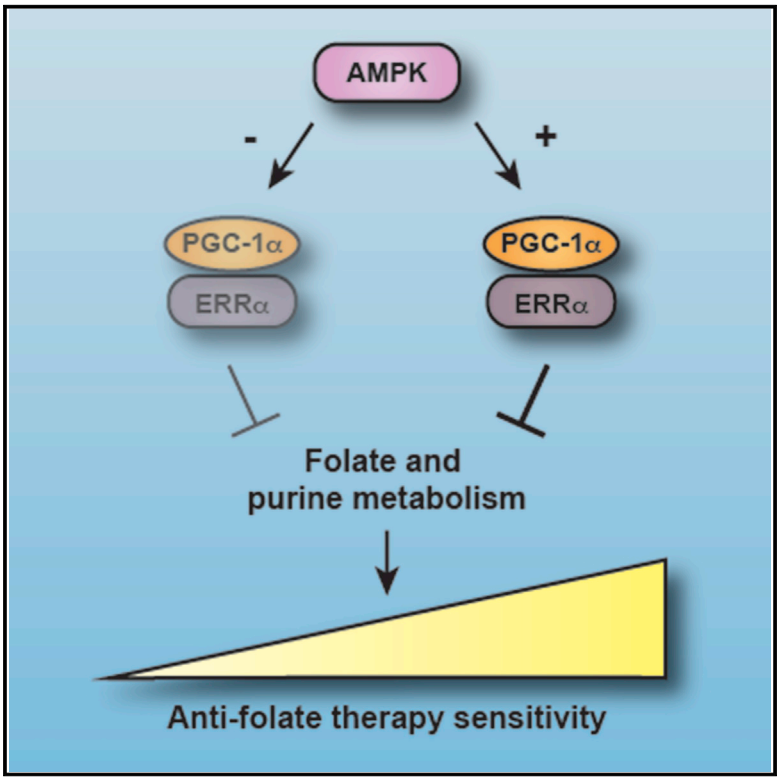
The PGC-1α/ERRα Axis Represses One-Carbon Metabolism and Promotes Sensitivity to Anti-folate Therapy in Breast Cancer

Graphical Abstract



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In Brief

Audet-Walsh et al. demonstrate that PGC-1α, in concert with ERRα, is a key downstream mediator of AMPK metabolic reprogramming in cancer cells. They also uncover that the PGC-1α/ERRα axis acts as a repressor of folate cycle metabolism and purine biosynthesis, sensitizing breast cancer cells to anti-folate therapy.

Highlights

- The PGC-1α/ERRα axis is a key effector of AMPK metabolic reprogramming in cancer
- The PGC-1α/ERRα axis represses folate cycle metabolism
- The PGC-1α/ERRα axis decreases purine biosynthesis
- The PGC-1α/ERRα axis sensitizes cells and tumors to anti-folate therapy

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The PGC-1α/ERRα Axis Represses One-Carbon Metabolism and Promotes Sensitivity to Anti-folate Therapy in Breast Cancer

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SUMMARY

Reprogramming of cellular metabolism plays a central role in fueling malignant transformation, and AMPK and the PGC-1α/ERRα axis are key regulators of this process. The intersection of gene-expression and binding-event datasets for breast cancer cells shows that activation of AMPK significantly increases the expression of PGC-1α/ERRα and promotes the binding of ERRα to its cognate sites. Unexpectedly, the data also reveal that ERRα, in concert with PGC-1α, negatively regulates the expression of several one-carbon metabolism genes, resulting in substantial perturbations in purine biosynthesis. This PGC-1α/ERRα-mediated repression of one-carbon metabolism promotes the sensitivity of breast cancer cells and tumors to the anti-folate drug methotrexate. These data implicate the PGC-1α/ERRα axis as a core regulatory node of folate cycle metabolism and further suggest that activators of AMPK could be used to modulate this pathway in cancer.

INTRODUCTION

The orphan nuclear receptor known as estrogen-related receptor α (ERRα, NR3B1) and the peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α) act together as a transcriptional regulatory node important for the expression of metabolic genes (Deblois et al., 2013; Giguère, 2008; Mootha et al., 2004; Villena and Kralli, 2008). Indeed, the PGC-1α/ERRα axis is now well established as a central regulator of energy metabolism that induces the global expression of genes involved in mitochondrial biogenesis and functions (Eichner and Giguère, 2011; Giguère, 2008; Handschin and Spiegelman, 2006). Specifically, gene expression and genome-wide binding analyses demonstrated that PGC-1α and ERRα share a functional relationship in controlling the expression of vast metabolic gene networks in numerous tissues (Chang et al., 2011; Deblois et al., 2010; Laganière et al., 2004; Schreiber et al., 2004; Wende et al., 2005). ERRα binds to the promoters of all genes encoding enzymes of glycolysis and many nuclear-encoded mitochondrial genes involved in energy metabolism (Charest-Marcotte et al., 2010; Dufour et al., 2007; Eichner and Giguère, 2011). Moreover, PGC-1α and ERRα exploit auto-regulatory feedforward loops to promote the expression of metabolic genes and mitochondrial activity (Handschin et al., 2003; Laganière et al., 2004; Mootha et al., 2004; Schreiber et al., 2004).

The expression and activity of ERRα and PGC-1α are highly adaptable and can respond to various physiological and pathological cues. In support of this point, PGC-1α is a key effector of the energy-sensing signaling cascade orchestrated by AMP-activated protein kinase (AMPK) (Jäger et al., 2007). AMPK occupies a central position in the reprogramming of cells to adapt to metabolic stress by promoting catabolism and inhibiting anabolism in order to restore the pool of cellular ATP (Hardie et al., 2012). Specifically, AMPK promotes catabolic reactions, such as lipid oxidation and cellular respiration, and inhibits anabolic processes, such as lipid and protein synthesis (Hardie et al., 2012). AMPK activation induces the expression of PGC-1α, and the AMPK-mediated increase in mitochondrial respiration has been shown to be dependent on PGC-1α in muscle cells (Jäger et al., 2007). In addition, AMPK phosphorylates PGC-1α, which potentiates its activity (Jäger et al., 2007). Clearly, PGC-1α is a significant downstream effector of AMPK-dependent metabolic effects, but which specific pathways are regulated by the AMPK/PGC-1α/ERRα partnership are yet to be identified.

The PGC-1α/ERRα axis is a central regulator of metabolism in cancer, notably breast cancer (Deblois and Giguère, 2013; Deblois et al., 2013). The expression of PGC-1α is reduced in breast tumors compared with normal tissues (Deblois et al., 2013). However, within the various breast cancer subtypes, the levels