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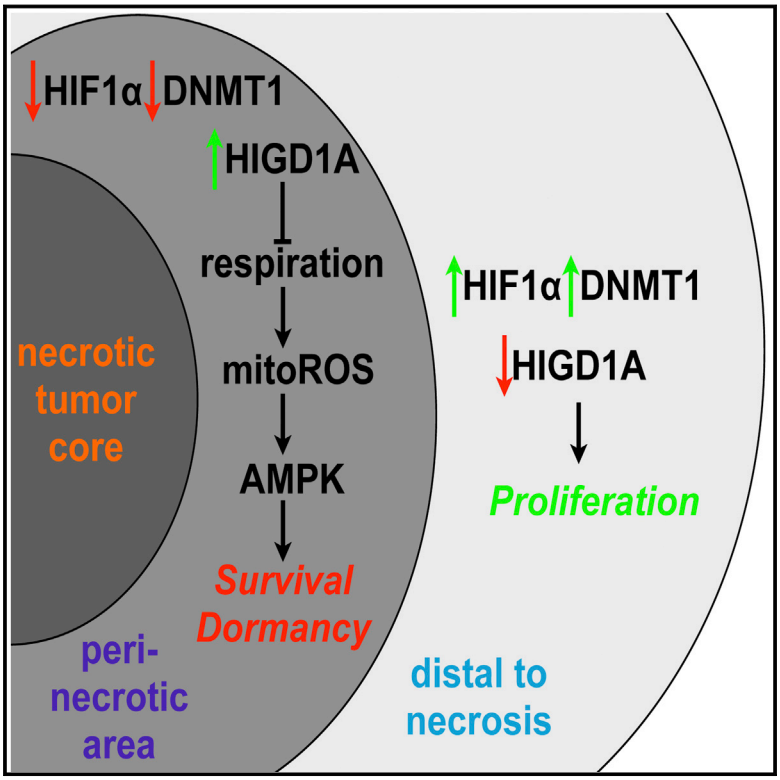
Report

HIGD1A Regulates Oxygen Consumption, ROS Production, and AMPK Activity during Glucose Deprivation to Modulate Cell Survival and Tumor Growth

Graphical Abstract



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In Brief

Hypoxia-inducible gene domain family member 1A (HIGD1A) is a hypoxia-inducible factor 1 (HIF-1) target found in perinecrotic tumor regions lacking HIF-1 expression. Ameri et al. now find it interacts with the electron transport chain to trigger mitochondrial ROS-dependent AMPK activation and reduces respiration and total ROS to promote survival and suppress growth.

Highlights

- HIGD1A protects from glucose deprivation but suppresses tumor growth
- HIGD1A interacts with the electron transport chain to decrease respiration
- HIGD1A can be induced independent of HIF-1 via differential methylation
- HIGD1A may play roles in metabolic regulation of tumor dormancy

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HIGD1A Regulates Oxygen Consumption, ROS Production, and AMPK Activity during Glucose Deprivation to Modulate Cell Survival and Tumor Growth

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SUMMARY

Hypoxia-inducible gene domain family member 1A (HIGD1A) is a survival factor induced by hypoxia-inducible factor 1 (HIF-1). HIF-1 regulates many responses to oxygen deprivation, but viable cells within hypoxic perinecrotic solid tumor regions frequently lack HIF-1α. HIGD1A is induced in these HIF-deficient extreme environments and interacts with the mitochondrial electron transport chain to repress oxygen consumption, enhance AMPK activity, and lower cellular ROS levels. Importantly, HIGD1A decreases tumor growth but promotes tumor cell survival in vivo. The human *Higd1a* gene is located on chromosome 3p22.1, where many tumor suppressor genes reside. Consistent with this, the *Higd1a* gene promoter is differentially methylated in human cancers, preventing its hypoxic induction. However, when hypoxic tumor cells are confronted with glucose deprivation, DNA methyltransferase activity is inhibited, enabling HIGD1A expression, metabolic adaptation, and possible dormancy induction. Our findings therefore reveal important new roles for this family of mitochondrial proteins in cancer biology.

INTRODUCTION

Heart disease, stroke, and cancer are associated with hypoxia (Semenza, 2014) and nutrient deprivation (Hardie et al., 2012). Hypoxia inducible factor 1 (HIF-1) is a widely expressed transcription factor that regulates the survival of cells during oxygen and glucose deprivation (Iyer et al., 1998; Maltepe et al., 1997; Ochiai et al., 2011; Ryan et al., 1998). HIF can also regulate tumor metabolism by repressing respiration (Kim et al., 2006; Papandreou et al., 2006) while promoting glycolysis, which enables rapid tumor cell proliferation (Vander Heiden et al., 2009). When severe, cancer cells can survive hypoxia and/or nutrient deprivation by entering a dormant state, which suppresses their growth (Bragado et al., 2012; Sosa et al., 2013). Since most cancer therapies target proliferating cells, oxygen/nutrient-deprived tumor regions frequently become resistant and contribute to tumor recurrence. New agents are therefore being developed to target these regions (Harada et al., 2012; Zhang et al., 2014). Paradoxically, chronically oxygen-starved tumor regions frequently lack HIF-1α expression (Ameri et al., 2010; Sobhanifar et al., 2005), likely due to simultaneous glucose deprivation (Catrina et al., 2004; Osada-Oka et al., 2010). However, some HIF-1 target genes such as CAIX remain either due to greater protein stability (Sobhanifar et al., 2005) or HIF-1-independent pathways (van den Beucken et al., 2009).

Oxygen or glucose deprivation promotes reactive oxygen species (ROS) production, which can trigger adaptive responses such as HIF induction (Sena and Chandel, 2012) or can induce apoptosis (Malhotra et al., 2008). Therefore, cells need to modulate both oxygen consumption and ROS production in order to survive oxygen/glucose deprivation. One pathway that cells utilize to achieve this relies on AMP-dependent protein kinase (AMPK) activation (Jeon et al., 2012). AMPK can activate multiple adaptive pathways, including antioxidant mechanisms. Interestingly, the effects of AMPK on tumor growth are complex, acting as oncogene or tumor suppressor depending on context (Hardie and Alessi, 2013).

Hypoxia-Inducible Gene Domain Family Member 1A (HIGD1A) is a survival factor regulated by HIF-1 (Wang et al., 2006). We previously demonstrated that HIGD1A is expressed in regions of severe ischemia in vivo (Ameri et al., 2013) that frequently