Hypoxia-inducible factor-1 α regulates energy fuel metabolism and mediates metabolic plasticity during ammonia stress response in ovarian cancer stem-like cells

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Ammonia is produced by cancer cells as a by-product of glutamine metabolism during rapid cell growth. Although the toxicity of ammonia has been well known, specific factors that deal with ammonia-induced cellular stress and regulate cell metabolism to survive have yet to be identified. We demonstrated that the hypoxia-inducible factor-1 α (HIF-1 α) is stabilised and activated during ammonia stress response. The ablation of HIF-1 α promoted apoptosis caused by high levels of ammonia. Moreover, we identified glutamine synthetase (GS) as a key driver of cancer cell proliferation under ammonia stress and glutamine-dependent metabolism in ovarian cancer stem-like cells marked by the expression of CD90. Interestingly, activated HIF-1 α counteracts GS function in glutamine metabolism by facilitating glycolysis leading to elevated glucose dependency. Our studies reveal the hitherto unknown functions of HIF-1 α that promote metabolic plasticity during ammonia stress response in the cancer stem-like cells where GS facilitates cell proliferation and HIF-1 α contributes to remodeling in energy fuel usage resulting in attenuated proliferation but conversely promoting cell survival.