Rewiring lipid metabolism by hypoxia-inducible factor-1 in tumor microenvironment: New targets for cancer therapy?

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Cancer cells rewire metabolic processes to adapt to the nutrient- and oxygen-deprived tumor microenvironment, promoting their proliferation and metastasis. Studies of the Warburg effect have shown that glycolytic cancer cells are more invasive and aggressive. Lipid metabolism is important because lipids function as energy sources, in cell membranes, and as signaling molecules. Obesity is also a risk factor for various cancer types; therefore, targeting lipid metabolism shows promise for cancer therapy. Here we review the lipid metabolic reprogramming in cancer cells mediated by hypoxia-inducible factor-1 (HIF-1). HIF-1 is the master transcription factor for tumor growth and metastasis and transactivates genes related to proliferation, survival, angiogenesis, invasion, and metabolism. The glucose metabolic shift (Warburg effect) is mediated mainly by HIF-1. HIF-1 modifies lipid accumulation, -oxidation, and lipolysis in cancer, triggering its progression. We found that the lipid/HIF-1 axis promoted tumor metastasis in a colon cancer xenograft mouse model. In addition, lipid-enhanced HIF-1 triggers 3D cell growth of hepatocellular cellular carcinoma (HCC) cells. Mechanistically, HIF-1 regulated lipid metabolism in hepatocellular carcinoma through fatty acid binding protein 5 (FABP5) that identified as a driver for HIF-1 synthesis and a disrupter for FIH/HIF-1 interaction at the same time. Our results show an in vitro model of a biomimetic TME and provide new mechanistic insights into the effects of ADSC-released fatty acids on cancer cells as oncometabolites. Therefore, targeting lipid metabolic alterations by HIF-1 has therapeutic potential for cancer.