Review of: "Hypoxia-induced macropinocytosis represents a metabolic route for liver cancer"

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When cancer cells need food and oxygen – Drink it up!

Hypoxia is a common challenge of the microenvironment in solid tumors, and cancer cells often adapt to oxygen deprivation by the upregulation of hypoxia-inducible factor-1 alpha (HIF-1α). HIF-1α is the major transcriptional regulator for cell responding to changes in oxygen concentration, activating the transcription of genes that are involved in angiogenesis, cell survival, glucose metabolism and invasion. Therefore, HIF-1α could promote tumor survival and cancer metastasis by several overlapping mechanisms. On the other hand, macropinocytosis, the evolutionary conserved endocytic route that takes up large amount of extracellular fluids and proteins, is well-known as a scavenging strategy for cancer cells to obtain nutrients for rapid growth. However, correlation between these two pathways has never been reported.

In this work, Zhang et al. thoroughly and clearly demonstrate that hypoxia could induce macropinocytosis in hepatocellular carcinoma (HCC), but not normal liver cells, through the HIF/EHD2 pathway. Importantly, the macropinocytosis induced by hypoxia is required for HCC cell growth both *in vitro* under hypoxic condition and *in vivo* as a xenograft in mouse, without affecting their death. Mechanistically, the hypoxia-induced macropinocytosis is mediated by an actin and membrane remodeling ATPase, EHD2, that is upregulated by HIF-1α. Consistent with these evidences, knockout out of EHD2 significantly reduced proliferation of HCC cells *in vitro* and *in vivo*.

Together, Wong and colleagues uncover a previously uncharacterized mechanism between tumor-microenvironment and macropinocytosis. Intriguingly, the way that normal liver cells and cancer cells respond to the hypoxic environment is different and the differential effect on these cells provide an opportunity to develop efficient and effective strategy to eradicate hepatocellular carcinoma. The response to hypoxic environment of cancer cells are therefore worthy for further investigation to understand in-depth and develop potential strategy to treat cancers other than HCC.