Leveraging Metabolism to Treat Primary and Metastatic Kidney Cancer

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Clear cell renal cell carcinoma (ccRCC) is the most common kidney cancer with excessive neutral lipid uptake and storage as a defining feature. We previously demonstrated that ccRCC cell survival depends on exogenous cholesterol obtained from high density lipoprotein (HDL) particles imported through scavenger receptor class B type 1 (SCARB1), a surface protein universally overexpressed in human ccRCC tumors. Polyunsaturated ether phospholipid-enriched ccRCC cells are exquisitely sensitive to ferroptotic stimuli. We reveal here an unexpected role for HDL in suppressing ccRCC ferroptosis at multiple stages of disease progression. Using genetic and pharmacological approaches, we determined that triglycerides (TGs) derived from SCARB1-imported HDL are used to replace ferroptosis initiating oxidized phospholipid acyl chains. This occurs via the Lands Cycle, a dynamic lipid remodeling process previously unexplored for pro-ferroptotic ether lipids. Inhibiting either HDL import or Lands Cycle lipases results in significant ferroptotic ccRCC cell death. SCARB1-mediated opposition to ferroptosis is critical for circulating ccRCC cell survival in blood, the prevalent route for ccRCC metastasis and a naturally oxidizing environment. Primary patient samples and patient derived xenografts confirm that HDL is actively imported in developing tumors, based on apolipoprotein A1 (APOA1, a prominent HDL component) accumulation and increased circulating APOA1 levels in sera obtained from ccRCC patients following nephrectomy. Our studies demonstrate that HDL particles obtained via SCARB1 promote ccRCC cell survival and disease progression by suppressing ferroptosis and identify SCARB1 as an attractive target for treatment of both primary tumors and hematogenous metastases.