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The missing link between lipid droplets and autophagy in ovarian cancer

Viji Shridhar[1], Debarshi Roy[1], Susmita Mondal[1], Xiaoping He[1], Ashwani Khurana[1], Chen Wang[1], Ann Oberg[1] and Thomas Dierks[2]
[1]Mayo Clinic, USA
[2]University of Bielefeld, Germany

It is increasingly being recognized that altered lipid metabolism is an early event in carcinogenesis and a central hallmark of many cancers. Under nutrient deprived conditions, excess free fatty acids are stored as triglycerides in lipid droplets (LD) to be used for energy. A second cellular response to starvation is autophagy, in which the cell digests its own components to provide nutrients. Microarray and Metabolomics profiling identified the lipid pathway as one the major pathways modulated by loss of HSulf-1 in OVCA. HSulf-1deficient cells (OV202 Sh1/sh2, OV2223 and Sulf-1 KO MEFs) possess high levels of lipid droplets (LD) that are absent in the HSulf-1 proficient isogenic cells (TOV21G and SKOV3). More importantly, TEM analysis showed that all HSulf-1 proficient cells displayed increased number of autophagic vesicles compared to isogenic HSulf-1 deficient cells. Pharmacological inhibition and ShRNA downregulation of cPLA2 activity, a protein involved in LD biogenesis resulted in decreasing the number of LDs and promoted autophagy in OV202 Sh1cells and elevated the autophagy inducing protein DAPK and autophagy related markers including LC3BII levels suggesting a novel cross-talk between LD biogenesis and autophagy in ovarian cancer cells. HS mimetic PG545, a tumor microenvironment targeting drug that mimics the action of HSulf-1, reduced LDs and promoted autophagy in Sh1 and Sh2 cells. Collectively, these results identify the critical role of HSulf-1, a major regulator of growth factor mediated signaling in the tumor microenvironment as the missing link in regulating both autophagy and LDs in OVCA.

Biography

Viji Shridhar laboratory is focused on genetic, molecular and functional analysis on altered genes in ovarian cancer involved in chemoresistance and metastatic phenotype. He has a broad background in genetic, epigenetic, molecular and functional analysis of known and novel genes (identified using state of the art high throughput screening techniques) that may play important roles in the progression of ovarian and breast cancer. A major focus of my program is to understand the metabolic derangement in promoting ovarian carcinogenesis and therapeutically target pathways altered in ovarian cancer with novel therapeutics. He has previously shown that metformin, (an antidiabetic drug) treatment inhibits ovarian cancer cell growth both in vitro and in vivo and sensitizes cells to cisplatin induced cytotoxicity (hyperlinked). As PI or co-Investigator on several previous and currently funded NIH and Foundation-grants on the roles of HSulf-1 and HtrA1 in ovarian cancer, he has laid the groundwork for successfully completing the proposed research by developing resources and establishing productive collaborations. In addition, He has successfully administered the projects (e.g. staffing, research protections, budget), collaborated with other researchers, and produced several peer-reviewed publications from each project. He has a demonstrated record of successful and productive research projects in an area of high relevance and National interest. Over the past 15 years Viji Shridhar has mentored 22 postdoctoral fellows and 14 Clinical Fellows in my laboratory.

Shridhar.Vijayalakshmi@mayo.edu