ABSTRACT

Ovarian cancer remains a deadly disease. This is due to a combination of late stage discovery and marginally effective therapy, resulting from both inherent and acquired treatment resistance. Failure of conventional approaches to provide effective treatment for this ovarian cancer suggests that new ways of thinking are required. Our preliminary observations show that ovarian tumor cells acquire and retain more iron than their non-malignant counterparts. Evidence of enhanced iron utilization is evident in ovarian tumor tissue and in ovarian tumor progenitor cells. We hypothesize that ovarian cancer cells become dependent on maintaining supra-normal levels of metabolically available intracellular iron to support their growth and viability. We propose the term "iron addiction" to characterize this state. Altered iron metabolism may represent a new targetable hallmark of cancer. We propose three specific aims to test this hypothesis. In Aim 1, key differences in iron metabolism between normal ovarian stem cells and ovarian tumor progenitor cells derived from patient samples will be characterized using RNAseq and proteomics. The roles of these proteins in pathways essential to cancer cell iron metabolism will be determined. In Aim 2, alterations in oncogenic signaling that drive critical differences in iron metabolism in ovarian tumor progenitor cells will be assessed by interrogating the role of c-myc. Analysis of patient databases will be used to assess prevalence of c-myc-driven changes in iron metabolism and association with prognosis. Aim 3, we will use systems biology to identify key iron regulatory nodes and mechanisms through which other oncogenic drivers target iron. The overall goal of this proposal is to understand mechanisms underlying iron addiction in ovarian cancer and how changes in iron metabolism link to oncogenic signaling. This may provide insights into new and novel targets for ovarian cancer therapy.