Hypoxia is a common feature of tumors and an important contributor to malignancy and treatment resistance. We and others have shown that a lysosomal degradation pathway, autophagy, which enables cells to recycle and redirect nutrients to adapt to metabolic stresses, is required for the survival of hypoxic cells. Consequently, autophagy inhibition sensitized tumors to irradiation as determined by tumor growth delay experiments.

Our research focuses on unraveling the molecular mechanisms that are required for the activation of autophagy during hypoxia and to exploit these for therapeutic purposes. During this presentation, I will describe some of our recent findings and how we think that we can use autophagy targeting to improve tumor treatment. For example, we identified a radioresistant subset of glioblastoma that, when metabolically challenged, is highly dependent on autophagy for survival. Its dependency on autophagy provides a novel opportunity to delay recurrence of the tumors after treatment.

Hypoxia promotes EMT and stemness through suppression of Dicer
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Tumor hypoxia is associated with aggressive disease and poor clinical outcome in many types of cancer. This is due in large part to the ability of hypoxia to influence important signalling pathways that augment metabolism, angiogenesis, genetic instability, and metastasis. Recent data suggests that hypoxia may also promote stemness in normal stem cell microenvironments, and in the oxygen deprived microenvironments of some solid tumors. We have discovered a novel potential mechanism that may underlie these observations. We found that hypoxia causes a rapid loss of the enzyme Dicer, an essential component in the miRNA biogenesis pathway. This occurs through an epigenetic mechanism that results in transcriptional silencing of the Dicer1 gene. Loss of Dicer during hypoxia or following genetic knockdown results in a defect in the creation of mature and functional miRNA, and a corresponding increase in miRNA precursor forms. However, loss of Dicer has a differential effect on individual miRNAs and resulted in a particular loss of members of the miR200 family. We observed knockdown results in derepression of its target ZEB1 and induces an epithelial-mesenchymal transition (EMT) characterized by an altered cell morphology, loss of E-cadherin, and acquisition of N-cadherin and vimentin. In human mammary epithelial cells transformed with dominant oncogenes, exposure to hypoxia or knockdown of Dicer1 induces EMT and acquisition of stem cell properties including increased sphere formation, and expression of the cell surface markers CD24+/CD44+/CD133 which have been shown to enrich in tumor initiating cells. Importantly, both EMT and acquisition of stem cell properties are prevented during hypoxia by overexpression of miR200b. Dicer1 and hypoxia were also found to be negatively correlated in a large clinical series of breast cancer gene expression studies and both low Dicer expression and high hypoxia were associated with poor outcome. Collectively, these data indicate that hypoxic suppression of Dicer leads to increased stemness through repression of the miR200 family and suggest this effect may contribute to the known association of hypoxia with metastasis and poor outcome in patients.