Presentation:
Mouse Models of Apoptosis, Autophagy, Necrosis, and Cancer

Speaker:
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Abstract:
Role of Autophagy in Promoting Survival, Limiting Necrosis, and Preventing Chromosome Instability as a Tumor Suppression Mechanism

Autophagy is a bulk degradation process that promotes survival under metabolic stress, but can also be a means of cell death if executed to completion. Monoallelic loss of the essential autophagy gene *beclin1* causes susceptibility to metabolic stress, but also promotes tumorigenesis. This raises the paradox that the loss of a survival pathway enhances tumor growth where the exact mechanism is not known. We have found that autophagy is a survival pathway utilized by tumor cells to survive metabolic stress. Tumor cells with defect in apoptosis survive long-term metabolic deprivation through autophagy that when inhibited by allelic loss of the *beclin1*, *atg5* deficiency or PI-3 kinase pathway activation, promotes necrotic cell death due to metabolic catastrophe. In vivo tumor necrosis brought about by defects in apoptosis and autophagy under conditions of metabolic stress is associated with inflammation and accelerated tumor growth. Thus autophagy can function as a tumor suppression mechanism by limiting necrosis and inflammation. Failure to sustain metabolism through autophagy is also associated with increased DNA damage, gene amplification and aneuploidy, and this genomic instability may promote tumorigenesis. Thus autophagy maintains metabolism and survival during metabolic stress that serves to protect the genome and prevent chronic inflammation, explaining the paradox that the loss of a survival pathway leads to tumor progression. Identification of this novel role of autophagy may be important for rational chemotherapy and therapeutic exploitation of autophagy inducers as potential chemopreventive agents.