**Metabolism**

**Major finding:** Impairment of host autophagy reduces circulating arginine and suppresses growth of some tumors.

**Concept:** Tumors are arginine auxotrophs, which renders them sensitive to reduction of circulating arginine.

**Impact:** Autophagy provides tumors with essential nutrients that may represent a targetable vulnerability.

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**AUTOPHAGY SUSTAINS TUMORS BY MAINTAINING SERUM ARGININE LEVELS**

Autophagy maintains cellular homeostasis by degrading and recycling intracellular components to support the metabolic demands of proliferating cancer cells, as tumor-specific inhibition of autophagy suppresses tumor growth. Poillet-Perez and colleagues observed that host-specific inhibition of autophagy through deletion of Atg7 or Atg5 also suppressed the growth and proliferation of multiple allografted tumors. Serum metabolite profiling revealed a marked decrease in circulating arginine levels upon host autophagy loss, suggesting that host autophagy sustains tumor growth by providing tumor cells with arginine. Not every tumor model evaluated was dependent on host autophagy, but most tumors that could not synthesize arginine due to loss of argininosuccinate synthase 1 (ASS1) expression were dependent on host autophagy, and the presence of circulating arginine. Circulating arginine was depleted upon loss of host autophagy due to increased serum levels of the arginine-degrading enzyme arginase 1 (ARG1), which was released from damaged liver hepatocytes into the circulation. Dietary supplementation of autophagy-deficient hosts with arginine partially restored serum arginine levels and promoted growth of arginine-auxotrophic tumors, further suggesting that sufficient circulating arginine is necessary to support tumor growth. These findings establish that host autophagy can sustain tumor growth by maintaining circulating levels of required nutrients and raise the possibility that limiting essential tumor nutrients in circulation may be an effective way to exploit metabolic vulnerabilities of tumors and suppress tumor growth.


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**Drug Resistance**

**Major finding:** Biomarker analysis of a phase II trial reveals mechanisms of resistance to BTK and BCL2 inhibition.

**Mechanism:** SWI/SNF mutations led to upregulation of BCL-xL, which promoted resistance to ibrutinib and venetoclax.

**Impact:** Targeting BCL-xL may be beneficial in the subset of patients with MCL who are resistant to ibrutinib and venetoclax.

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**SWI/SNF MUTATIONS CONFER RESISTANCE TO IBRUTINIB PLUS VENETOCLAX IN MCL**

Mantle cell lymphoma (MCL) is a B-cell malignancy that is generally refractory to conventional chemotherapy, but a recent phase II study showed that combined targeting of constitutive B-cell receptor signaling with the Bruton tyrosine kinase (BTK) inhibitor ibrutinib and antiapoptotic signaling with the BCL2 inhibitor venetoclax leads to complete responses in approximately 70% of patients with relapsed or refractory MCL. However, 20% of patients were intrinsically resistant to this regimen and an additional 10% of patients relapsed following an initial response. Agarwal, Chan, and colleagues sought to evaluate the genomic determinants of response and resistance to ibrutinib plus venetoclax in patients enrolled in this trial as well as to establish improved methods to monitor these genomic features in the clinic with the ultimate goal of predicting response or emerging resistance. Whole-exome sequencing of the 24 patients enrolled in the trial revealed that the 5 nonresponders each harbored mutations or chromosomal losses affecting genes encoding subunits of the SWI/SNF chromatin remodeling complex. Knockdown of the SWI/SNF ATPase SMARCA4 in MCL cells conferred resistance to combined ibrutinib plus venetoclax and was associated with reduced chromatin accessibility and expression of the transcription factor gene ATF3, which resulted in increased expression of the ATF3 antiapoptotic target gene BCL-xL to confer resistance to the combination of ibrutinib and venetoclax. Of note, inhibition of BCL-xL restored sensitivity to ibrutinib and venetoclax in MCL cells. These genomic alterations were monitorable in real time through detection of circulating tumor DNA (ctDNA) levels, and patients with detectable SWI/SNF gene mutations and/or loss of chromosome 9p21.1-24.3 (harboring the other SWI/SNF ATPase gene, SMARCA2) had significantly shorter progression-free survival. Intrinsic and secondary resistance could also be tracked longitudinally by monitoring ctDNA levels. These findings provide initial insight into mechanisms underlying resistance to combined BTK and BCL2 inhibition and show the feasibility of monitoring response to MCL therapy with ctDNA testing.


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