Pancreatic Cancer

Major finding: MiT/TFE-driven transcriptional induction of autophagy–lysosome genes is required for PDA growth.

Mechanism: Constitutive MiT/TFE activity enhances lysosomal scavenging to maintain intracellular amino acid pools.

Impact: Increased lysosomal activity is critical for PDA metabolic homeostasis and a potential therapeutic target.

MiT/TFE PROTEINS MEDIATE METABOLIC REPROGRAMMING IN PANCREATIC CANCER

Pancreatic ductal adenocarcinoma (PDA) is characterized by a hypoxic, nutrient-poor microenvironment and relies on scavenging pathways to obtain macromolecular substrates required for tumor growth. These pathways, autophagy and macropinocytosis, converge on the lysosome, where degradation and recycling of nutrient building blocks occurs. However, the mechanism by which autophagy is activated and whether autophagy and macropinocytosis are functionally integrated are unknown. Perera and colleagues found that, in addition to increased autophagosomes, PDA cells exhibited elevated lysosomal biogenesis and increased expression of an autophagy–lysosome gene program, suggesting that autophagy and lysosomal function may be coordinately regulated at the transcriptional level. Consistent with this idea, the MiT/TFE family of transcription factors, microphthalmia-associated transcription factor (MITF), transcription factor binding to IGHM enhancer 3 (TFE3), and transcription factor EB (TFEB), which regulate autophagosome and lysosome biogenesis under nutrient stress, were highly expressed in PDA cells. Knockdown of MiT/TFE proteins in PDA cells repressed the autophagy–lysosome gene signature, leading to defects in lysosome activity and impairments in both autophagy and macropinocytosis. PDA cells displayed constitutive MiT/TFE nuclear localization and activation independent of nutrient status and despite intact mTOR complex 1 (mTORC1) signaling, which normally induces cytoplasmic retention of MiT/TFE proteins. This escape from mTORC1-mediated inhibition was dependent on the nuclear import protein importin 8 (IPO8), which interacted with TFE3, was highly expressed in human PDA cells, and was required for MiT/TFE nuclear accumulation and stabilization in PDA cells. Global metabolite profiling revealed that elevated autophagosome–lysosome function in PDA cells was necessary to maintain intracellular amino acid levels and enable cell survival. In support of this finding, MiT/TFE depletion decreased the growth of PDA cell lines and suppressed xenograft tumor growth, whereas MITF overexpression enhanced tumor formation. These results identify MiT/TFE proteins as central regulators of metabolic reprogramming in PDA and define autophagy–lysosome activation as a hallmark and potential therapeutic target of PDA. ■

Perera RM, Stoykova S, Nicolay BN, Ross KN, Fitamant J, Boukhali M, et al. Transcriptional control of autophagy–lysosome function drives pancreatic cancer metabolism. Nature 2015 Jul 13 [Epub ahead of print].

Clinical Trials

Major finding: The BTK inhibitor ibrutinib is preferentially effective in patients with the ABC subtype of DLBCL.

Clinical relevance: Chronic active BCR signaling confers sensitivity to ibrutinib even in the absence of BCR mutations.

Impact: The ABC DLBCL gene expression signature may select patients most likely to respond to ibrutinib.

THE ABC SUBTYPE OF DIFFUSE LARGE B-CELL LYMPHOMA IS RESPONSIVE TO IBRUTINIB

Diffuse large B-cell lymphoma (DLBCL) is categorized into two distinct molecular subtypes, activated B cell-like (ABC) and germinal center B cell–like (GCB). The ABC subtype is characterized by chronic active B-cell receptor (BCR) signaling, which stimulates NF-κB activity via Bruton tyrosine kinase (BTK), suggesting that inhibition of BTK may be preferentially effective in ABC DLBCL. To test this hypothesis, Wilson and colleagues assessed the activity of the selective covalent BTK inhibitor ibrutinib in 80 patients with relapsed or refractory *de novo* DLBCL in a phase I/II clinical trial. Indeed, the response rate to ibrutinib was greater in patients with ABC DLBCL (14 of 38; 37%), including a 16% rate of complete responses, than in patients with GCB DLBCL (1 of 20; 5%). The response rate was high among patients with a mutation in the BCR subunit gene *CD79B* (5 of 9; 55.5%), and was even higher among patients with both *CD79B* and myeloid differentiation primary response 88 (*MYD88*) mutations (4 of 5; 80%), consistent with *in vitro* evidence of cooperation between the BCR and MYD88 pathways. Importantly, the majority of ibrutinib responders (67%) had wild-type *CD79A* and *CD79B*, providing evidence that nongenetic influences may also drive chronic active BCR signaling in DLBCL. In contrast, tumors with *MYD88* mutations but wild-type *CD79B* did not respond to treatment, suggesting that MYD88 can promote ABC DLBCL independent of BCR signaling. In addition, ibrutinib was ineffective in tumors with mutations that activated CARD11, which acts downstream of BTK, and in tumors with mutations that inactivated TNFAIP3, which negatively regulates NF-κB. Together, these findings suggest that ABC DLBCL may arise via BCR-dependent and BCR-independent mechanisms and support the use of the ABC DLBCL gene expression signature to select patients likely to respond to ibrutinib in ongoing phase III DLBCL clinical trials. ■

Wilson WH, Young RM, Schmitz R, Yang Y, Pittaluga S, Wright G, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. Nat Med 2015;21:922–6.