Autophagy

Major finding: Autophagic cell death during replicative crisis prevents further accumulation of genomic instability.

Mechanism: Telomere damage generates cytosolic DNA that activates the cGAS–STING pathway and stimulates autophagy.

Impact: Autophagy may be required to eliminate precancerous cells and prevent oncogenic transformation.

AUTOPHAGY PREVENTS BYPASS OF REPLICATIVE CRISIS

Cells with dysfunctional cell-cycle checkpoints continue to undergo cell division until their telomeres become critically short, at which point telomeres become deprotected and fuse and cells undergo cell death in a process known as replicative crisis. Individual cells that escape replicative crisis accumulate increasing levels of chromosomal instability and can potentially acquire properties of transformed cells, suggesting that cell death during replicative crisis is tumor-suppressive, but the underlying mechanisms of cell death in this process are unclear. Nassour and colleagues disrupted p53- and RB1-dependent cell cycle checkpoints in human fibroblasts and epithelial cells and observed that cell death during replicative crisis was associated with hallmarks of autophagy and not apoptosis. Moreover, knockdown of essential autophagy proteins allowed cells to continue proliferating and bypass crisis in association with reduced cell death. Autophagy-deficient cells that had bypassed replicative crisis developed high levels of telomere damage and chromosomal alterations, suggesting that autophagic cell death during replicative crisis prevents genomic instability. Telomere dysfunction–induced damage specifically induced autophagy, as it generated cytosolic DNA that activated the DNA-sensing cGAS–STING pathway, which was required for both replicative crisis and autophagic cell death. Although further work is needed to confirm whether bypass of replicative crisis in non-transformed cells caused by loss of autophagy drives genome instability and tumorigenesis *in vivo*, this and other studies showing that autophagy can play tumor-suppressive roles in certain contexts suggest that patients receiving autophagy inhibitors as cancer therapies may have an increased risk of secondary malignancies. ■

Nassour J, Radford R, Correia A, Fusté JM, Schoell B, Jauch A, et al. Autophagic cell death restricts chromosomal instability during replicative crisis. Nature 2019;565:659–63.

Oncogenes

Major finding: MYC and KRAS^{G12D} exhibit distinct roles in the post-transcriptional regulation of immune checkpoints.

Concept: MYC drives eIF2-driven bypass of KRAS^{G12D}-mediated suppression of the translation of PD-L1.

Impact: Clinically targeting translational control may enhance the efficacy of immunotherapy.

MYC-MEDIATED TRANSLATION OF PD-L1 PROMOTES LIVER CANCER IMMUNE ESCAPE

Oncogenes promote tumorigenesis by driving tumor growth and transcriptionally regulating the expression of immune checkpoints to promote immune escape, but it is unclear whether oncogenes also post-transcriptionally regulate immune checkpoint expression. To ascertain how oncogenes cooperate to control immune checkpoint expression, Xu, Poggio, and colleagues generated genetic mouse models of hepatocellular carcinoma with liver-targeted MYC overexpression (*Myc*^{Tg}) and/or expression of *Kras*^{G12D}. Only *Myc*^{Tg};*Kras*^{G12D} mice developed aggressive, highly metastatic and inflamed tumors: *Kras*^{G12D} mice developed tumors that were less inflamed and metastatic, and *Myc*^{Tg} mice failed to develop liver tumors. *Myc*^{Tg};*Kras*^{G12D} tumors were found to be transcriptionally, but not translationally, similar to *Kras*^{G12D} tumors, although there was no difference in global protein synthesis rates. Further, although both *Myc*^{Tg};*Kras*^{G12D} and *Kras*^{G12D} tumors exhibited increased expression of *Cd274* (the mouse ortholog of PD-L1), only *Myc*^{Tg};*Kras*^{G12D} tumors exhibited upregulation of PD-L1 ribosome footprints and expression of PD-L1 protein. Ribosomes in *Kras*^{G12D} tumors translate two upstream open reading frames (uORF) with uAUG and uCUG start sites, respectively, in the PD-L1 5′-UTR and do not translate the main PD-L1 ORF, suggesting that these uORFs prevent PD-L1 protein translation, while ribosomes engage the canonical AUG start site and synthetize PD-L1 in *Myc*^{Tg};*Kras*^{G12D} tumors. Mutation of uAUG or uCUG resulted in increased luciferase reporter activity, and CRISPR/Cas9-mediated editing of uAUG or uCUG in *Kras*^{G12D} tumor–derived cell lines resulted in increased PD-L1 protein levels *in vitro* and increased metastasis *in vivo*. *Myc*^{Tg};*Kras*^{G12D} tumors exhibited increased phosphorylation of eIF2α, a component of the eIF2 translation initiation complex, that allows ribosomes to bypass the uORF translational barrier resulting in PD-L1 protein expression. Treating *Myc*^{Tg};*Kras*^{G12D} tumors *in vivo* with eFT508, a new clinical compound that targets the phosphorylation of the major cap binding protein, eIF4E, decreased PD-L1 translation, increased immune activity, and decreased tumor burden. These findings characterize the post-transcriptional role of oncogenes in immunosurveillance and identify a potential immunotherapy strategy. ■

Xu Y, Poggio M, Jin HY, Shi Z, Forester CM, Wang Y, et al. Translation control of the immune checkpoint in cancer and its therapeutic targeting. Nature Med 2019;25:301–11.