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CORRESPONDENCE

PTEN deficiency permits the formation of pancreatic cancer in the absence of autophagy

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Dear Editor,

Macroautophagy (hereafter, autophagy) is a membrane-trafficking process that delivers cargos to lysosomes for degradation.[1] The process preserves cellular integrity by facilitating removal of damaged proteins and organelles, thereby protecting against various forms of disease. The involvement of autophagy in cancer, however, is context-specific.[2] For example, work by ourselves and others has shown that progression of certain KRAS-driven cancers, including pancreatic ductal adenocarcinoma (PDAC), requires autophagy for full development of disease.[3–5] However, in tumors driven by oncogenic KRAS and deletion of p53, loss of autophagy does not block pancreatic tumor development and even accelerates the disease.[5]

This caused us to question if autophagy's contribution to PDAC development is specifically controlled by p53 or if other genetic lesions can also modulate autophagy's role in this disease. To test this hypothesis, we examined the impact of autophagy loss in a different model of PDAC driven by oncogenic KRAS (G12D) combined with deficiency of the tumor suppressor, Phosphatase and Tensin Homolog (PTEN)—a factor lost in PDAC, albeit with a relatively low frequency.[6] Four cohorts of mice were generated with the following genotypes: (1) Pdx1-Cre $KRas^{G12D/wt}$ $Pten^{wt/-}$ $Atg7^{wt/wt}$; (2) Pdx1-Cre $KRas^{G12D/wt}$ $Pten^{wt/-}$ $Atg7^{-/-}$; (3) Pdx1-Cre $KRas^{G12D/wt}$ $Pten^{-/-}$ $Atg7^{wt/wt}$; and (4) Pdx1-Cre $KRas^{G12D/wt}$ $Pten^{-/-}$ $Atg7^{-/-}$ (Supplementary Figure 1a).

Consistent with previous studies, tumors formed in Pdx1-Cre $KRas^{G12D/wt}$ $Pten^{wt/-}$ $Atg7^{wt/wt}$ mice (Supplementary Figure 1b).[6] However, in contrast to what we and others have observed in tumors containing mutant *KRas* as the only genetic lesion,[3–5] deletion of the critical autophagy regulator *Atg7* did not block formation of PDAC in animals that were also hemizygous for *Pten* in their pancreas (Supplementary Figure 1b). In fact, *Pten* hemizygosity not only permitted tumor formation in the absence of *Atg7*, but loss of autophagy in this context caused earlier death associated with pancreatic tumor formation when compared with autophagy-competent animals (Supplementary Figure 1b). Importantly, as is routinely undertaken to diagnose PDAC,[7] we performed histological analysis of tissue morphology, which showed that both autophagy-competent and -deficient animals developed PDAC and that tumors from Pdx1-Cre $KRas^{G12D/wt}$ $Pten^{wt/-}$ $Atg7^{-/-}$ mice lacked ATG7 expression, were deficient in LC3 puncta formation, had a strong diffuse LC3 stain indicative of accumulation of the LC3-I form of the protein,[5] and had high levels of the adapter protein p62/SQSTM1—all signs that these tumors were indeed autophagy-deficient. In line with previous studies,[8] these tumors were also negative for PTEN (Supplementary Figure 1b) and importantly were also wild-type for p53 (data not shown).

We also examined the impact of deleting both alleles of *Pten* on pancreatic tumor formation driven by oncogenic KRAS in either the absence or presence of Atg7. This revealed that autophagy-deficient tumors (which lack LC3 puncta and accumulate p62) can also form in the total absence of PTEN (Supplementary Figure 1c), but loss of Atg7 did not accelerate tumor onset in this context. It is possible, however, that the extremely rapid onset of tumor formation caused by oncogenic KRAS and loss of PTEN (median = 13 days) does not permit the detection of further accelerating events.

When taken together, our findings show that autophagy's contribution to tumor development can be determined by the status of either *Pten*, *p53* or other as yet unidentified factors. In these contexts, loss of autophagy can then promote tumor development probably through changes in metabolism, accumulation of oxidative stress, DNA damage and increased inflammation.[2] It should be stated, however, that our findings give no indication that the genetic status of *p53* or *Pten* would determine the response of an established tumor to a modulator of autophagy. This is a completely different context when compared with loss of autophagy during tumor development and is undoubtedly an area worthy of further investigation.

Conflict of Interest

The authors declare no conflict of interest.

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