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EDITORIAL

Beyond Kras: MYC Rules in Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) most often arises from advanced pancreatic intraepithelial neoplasia harboring mutated *KRAS*. Pancreatic intraepithelial neoplasia derive from foci of acinar–ductal metaplasia in which acinar cells have transdifferentiated into ductal-like cells, underscoring the potential acinar cell origin of PDAC. E47 is a basic helix-loop-helix transcription factor that binds to an enhancer box sequence, hence the designation of *E*. E proteins heterodimerize with tissue-specific class II basic helix-loop-helix proteins, thereby promoting cell differentiation in a tissue-specific manner. It previously was shown that inducible expression of E47 in human pancreatic cancer cells leads to the induction of genes associated with acinar cells, up-regulation of p53-inducible nuclear protein 1 and cyclin-dependent kinase inhibitor p21, and inhibition of proliferation.[1]

In the article by Scully et al[2] in this issue of *Cellular and Molecular Gastroenterology and Hepatology*, the authors show that E47 exerts additional beneficial effects in PDAC. Thus, E47 also increases Cyclin-dependent kinase inhibitor 1B (p27) levels in pancreatic cancer cells by up-regulating p27 messenger RNA levels and attenuating p27 protein degradation, while concomitantly lowering myelocytomatosis (MYC) messenger RNA levels and enhancing MYC protein degradation. Appropriately, the authors used 2 recently established patient-derived pancreatic cancer cells, 1 from a primary tumor and the other from a hepatic metastasis, in addition to 3 pancreatic cancer cell lines that have been in long-term culture. Despite differences in mutation status among the 5 cell lines, there were remarkable similarities in the E47-induced alterations in their transcriptomes, and Gene Ontology analysis showed that genes implicated in cell division were commonly regulated by E47 in these pancreatic cancer cells.

The antiproliferative actions of E47 were mediated through several pathways. First, cell-cycle progression was inhibited by the up-regulation of p21[1] and p27, the latter confirmed by the finding of enhanced proliferation in E47-overexpressing cells after small interfering RNA–mediated knockdown of p27. Second, cell proliferation was inhibited by the down-regulation of MYC protein, an effect that was prevented by lentiviral-mediated expression of the T58A mutant form of MYC that is resistant to proteosomal degradation and thereby prevents E47 from down-regulating MYC. Third, E47 decreased the expression of E2F target genes that promote cell proliferation resulting from activation of the retinoblastoma protein (pRb), as evidenced by E47-mediated pRb hypophosphorylation. This effect was prevented by short hairpin RNA–induced knockdown of human pRB, and was rescued by the expression of murine pRb. Fourth, E47 induced an increase in senescence-associated β-galactosidase, caused the appearance of large pancreatic cancer cells with variable size, and down-regulated the expression of certain proteins such as lamin B1 and centromere protein A. These alterations are consistent with induction of cell senescence, which is known to attenuate proliferation and induce cell-cycle arrest.

Mutated *KRAS* is the major driver mutation in PDAC, but it may be associated with oncogene-induced senescence, a phenomenon originally shown to be owing to increased expression of wild-type p16 and p53 and to be associated with an enduring G1 arrest.[3] Oncogene-induced senescence also can be induced by other mechanisms such as activation of mitogen-activated protein kinase and DNA damage response pathways, p21 and p27 up-regulation, pRB activation, and MYC inactivation. Scully et al[2] excluded p16, p53, mitogen-activated protein kinase, or DNA damage response activation as contributors to E47-mediated senescence. Instead, their findings suggest that E47 induces cell-cycle arrest and senescence-like alterations in pancreatic cancer cells by the combined actions of up-regulated p27, down-regulated MYC, and activated pRB.

Senescent cells have the capacity to express proinflammatory cytokines, a phenomenon termed *senescence associated secretory phenotype* (SASP), and the released cytokines can exert beneficial effects by orchestrating the destruction of damaged cells. However, SASP also can induce a chronic inflammatory state that promotes malignant transformation. Moreover, in the presence of mutated *KRAS*, loss of pRB has been associated with expression of senescence markers and an intense SASP that enhances PCC proliferation, a phenomenon termed *senescence bypass*.[4] As a consequence of excessive mitogenic signaling driven by Kras and occurring in conjunction with loss of p16 and overexpression of tyrosine kinase receptors and cyclin D1, pRB often is dysfunctional in PDAC. It may be difficult, therefore, to completely restore pRB functions in PDAC.

In contrast with difficulties inherent in targeting mutated Kras or dysfunctional pRB therapeutically, an increasing number of pharmacologic approaches are becoming available to antagonize MYC's actions. Given MYC's important role in enhancing cell proliferation, ability to protect pancreatic cancer cells from undergoing senescence, and capacity to suppress differentiation, the current findings support the concept that MYC is a crucially important therapeutic target in PDAC, and raise the possibility that targeting MYC could restore the balance toward

E47-mediated inhibition of proliferation and promotion of differentiation.

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Conflicts of interest
The author discloses no conflicts.

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