Telomerase

**Major finding:** TERT promoter mutations may induce early and late tumorgenesis by separate mechanisms.

**Mechanism:** The mutations first upregulate TERT to promote immortalization but later promote genomic instability.

**Impact:** The findings reveal a complex two-step mechanism by which TERT promoter mutations promote tumorigenesis.

**TERT PROMOTER MUTATIONS PROMOTE IMMORTALIZATION AND GENOMIC INSTABILITY**

Mutations in the promoter of TERT, which encodes the reverse transcriptase component of telomerase, occur commonly in cancer, including in the majority of cutaneous melanomas, and are associated with a poor prognosis and shortened telomeres despite enhanced telomerase expression. Conversely, patients with constitutionally shorter telomeres have a reduced risk of cancer. These seemingly contradictory observations illustrate that the role of TERT promoter mutations is incompletely understood. Chiba, Lorbeer, and colleagues investigated the role of acquired TERT promoter mutations in four human melanomas arising from adjacent preneoplastic nevi. The telomeres were shorter in melanomas with TERT promoter mutations compared with the associated nevus, indicating that promoter mutations were not sufficient to promote TERT expression to counteract telomere shortening. However, TERT promoter mutations did promote proliferation of fibroblasts and support cellular immortalization. In wild-type fibroblasts, telomeres shortened progressively, whereas in fibroblasts with TERT promoter mutations, telomeres initially shortened but stabilized after approximately 70 population doublings, resulting in preferential maintenance of short telomeres and indicating that TERT promoter mutations do not protect against telomere shortening. In cells with TERT promoter mutations, when telomeres were critically shortened telomerase expression increased, preventing further telomere shortening and promoting immortalization. Further, telomerase activity became rate-limiting when the number of critically short telomeres increased, resulting in an increase in genomic instability that may promote tumorigenesis in cells with TERT promoter mutations. These findings elucidate mechanisms by which TERT promoter mutations may promote tumorigenesis, suggesting that in early tumorigenesis TERT promoter mutations may prevent critical telomere shortening to delay replicative senescence and promote cancer cell immortalization, and later in tumorigenesis may promote genomic instability.


Pancreatic Cancer

**Major finding:** PON2 promotes GLUT1-mediated glucose transport, is upregulated in PDAC, and is required for PDAC growth.

**Mechanism:** PON2 depletion promotes anoikis via AMPK-mediated FOXO3A activation and PUMA upregulation.

**Impact:** Activation of the AMPK–FOXO3A–PUMA pathway may suppress PDAC growth and metastasis.

**PON2 PROMOTES GLUCOSE UPTAKE TO SUPPORT PDAC GROWTH AND METASTASIS**

The glycolytic and glutamine metabolic pathways are deregulated in pancreatic ductal adenocarcinoma (PDAC), but the mechanisms underlying this deregulation are not well understood. Nagarajan and colleagues performed an siRNA screen of metabolic genes overexpressed in patients with PDAC to identify those essential for PDAC tumor growth. Paraoxonase 2 (PON2) was found to be required for the growth of PDAC cells in vitro and in vivo, and cooperated with KRAS to accelerate tumor progression. Further, PON2 expression prevented anoikis, to allow enhanced PDAC metastasis. Transcription of PON2 was directly repressed by the tumor suppressor p53; thus, p53 inactivation resulted in PON2 upregulation. Mechanistically, PON2 loss activated the cellular starvation response, leading to AMPK-mediated activation of the tumor suppressive transcription factor FOXO3A, and upregulation of its proapoptotic target gene PUMA, to promote anoikis and suppress PDAC growth and metastasis. Conversely, PON2 overexpression promoted glucose uptake by binding to the glucose transporter GLUT1 and blocking its interaction with the inhibitory protein STOM, thereby supporting PDAC growth and metastasis. Consistent with these findings, depletion of FOXO3A or suppression of AMPK activation could promote tumor growth in PON2-deficient cells and suppress anoikis. In a mouse model of PDAC lung metastasis, PON2 depletion could suppress the growth of established lung tumors. Moreover, the AMPK agonist metformin or AICAR inhibited PDAC colony formation and suppressed tumorigenesis in vivo. Thus, AMPK activation and PON2 inhibition have similar effects in suppressing PDAC tumor growth. The identification of PON2 as an essential regulator of GLUT1-mediated glucose transport for PDAC growth and metastasis suggests that pharmacologic activation of the AMPK–FOXO3A–PUMA pathway may be a therapeutic approach to suppress PDAC growth.

PON2 Promotes Glucose Uptake to Support PDAC Growth and Metastasis

Cancer Discov 2017;7:1058. Published OnlineFirst August 18, 2017.

Updated version

Access the most recent version of this article at:
doi:10.1158/2159-8290.CD-RW2017-157

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