Cancer Research
Breaking Insights
Highlights from Recent Cancer Literature
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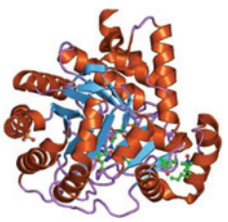
Activating p53

Therapies that activate the tumor suppressor p53 have significant potential therapeutic utility. Using a phenotypic screen for wild-type p53 transcription, Ladds and colleagues identified over 100 small molecules that activated p53 in cells. A series of tetrahydroindazoles (HZ00) inhibitors of dihydroorotate dehydrogenase (DHODH) blocked *de novo* pyrimidine nucleotide synthesis. Through crystallization of DHODH with a more potent analog, HZ05, they demonstrated that (R)-HZ05 was the active enantiomer. DHODH was a frequent target for structurally diverse compounds, as they also identified twelve other DHODH inhibitor chemotypes. Treatment with HZ compounds resulted in cells accumulating in S-phase, increasing p53 synthesis, and synergizing with inhibitors of p53 degradation to reduce tumor growth *in vivo*. The authors propose a novel strategy to promote cancer killing by p53, instead of its reversible effect on cell-cycle arrest.



Expert Commentary: This work uncovers the therapeutic implications of DHODH inhibition in potentiating blockade of p53 degradation. (*Image courtesy of Wikimedia Commons.*)

Ladds MJGW, van Leeuwen IMM, Drummond CJ, Chu S, Healy AR, Popova G, et al. A DHODH inhibitor increases p53 synthesis and enhances tumor cell killing by p53 degradation blockage. Nat Commun 2018;9:1107. doi: 10.1038/s41467-018-03441-3.

Casein Kinase 1α Promotes Autophagy in Lung Cancer

CK1α acts as a tumor suppressor in some cancers, often in cooperation with *p53*. Cai and colleagues show that *CK1α* induced autophagic flux in non-small cell lung cancer (NSCLC) cells. Silencing of *CK1α* attenuated expression of autophagy genes. Reciprocally, induction of autophagy increased expression of *CK1α*, whereas inhibition of autophagy decreased levels of *CK1α*. CK1α regulates autophagy by associating with the carboxyl-terminal domain of PTEN, which displaces the ubiquitin ligase NEDD4-1, increasing the stability of PTEN. Stabilized PTEN in turn attenuates AKT activity, increasing FOXO3a-induced transcription of the autophagy regulator *ATG7*. Blocking this CK1α-driven accumulation of ATG7 cooperated with oncogenic *HRAS* to promote tumorigenesis in lung epithelial cells. Thus, CK1α promotes autophagy and suppresses NSCLC growth in a PTEN-dependent manner, as loss of PTEN attenuates this activity.

Expert Commentary: *CK1α* functions as a tumor suppressor in NSCLC, where it functions as a potent regulator of autophagy. (*Image courtesy of Wikimedia Commons.*)

Cai J, Li R, Xu X, Zhang L, Lian R, Fang L, et al. CK1α suppresses lung tumor growth by stabilizing PTEN and inducing autophagy. Nat Cell Biol 2018;20:465–78.

Tumor Suppressor LncRNAs in Neuroblastoma

The lncRNA *CASC15* and its antisense counterpart *NBAT1* at the ch 6p22.3 locus house neuroblastoma risk-associated single-nucleotide polymorphisms. Mondal and colleagues show that reduced expression of these lncRNAs is associated with a poor outcome in patients and that knockdown inhibits differentiation. CASC15 overexpression promotes neuronal differentiation by destabilizing CHD7, a transcriptional activator of *SOX9*, via ubiquitin-mediated degradation. CASC15-003/NBAT1 act in trans and compensate for each other, recruiting USP36 from the nucleolus, destabilizing CHD7, and downregulating *SOX9* expression.

Expert Commentary: This study identifies two sense/antisense lncRNAs at the neuroblastoma risk-associated 6p22.3 locus to be tumor suppressors. Although they act in trans with no overlapping sequence, these lncRNAs promote retinoic acid–induced differentiation of neuroblastoma cells through ubiquitin-mediated degradation of transcriptional regulators of dedifferentiation genes. These studies help elucidate the functional significance of neuroblastoma risk-associated loci and identify mechanisms of therapy resistance. (*Image courtesy of Wikimedia Commons.*)

Mondal T, Juvvuna PK, Kirkeby A, Mitra S, Kosalai ST, Traxler L, et al. Sense-antisense lncRNA pair encoded by locus 6p22.3 determines neuroblastoma susceptibility via the USP36-CHD7-SOX9 regulatory axis. Cancer Cell 2018;33:417–34.

Breaking Insights

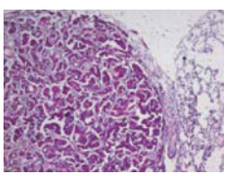
The TRAIL to Success Leads to NK Cells

Efforts to develop an activator of the TRAIL pathway to inhibit tumor growth have spanned two decades. Wagner and colleagues rediscovered a previously known but underexplored antitumor activity of TRAIL—suppression of metastases through natural killer (NK) cell regulation. They found that treatment with the TRAIL inducer, ONC201, resulted in tumor regression and prevented metastases *in vivo*. ONC201 treatment led to increased PD-L1-positive T cells and NK cells in the mouse tumor microenvironment, and increased circulating TRAIL-secreting NK cells in patient samples. NK cells were necessary for antitumor response. Finally, they demonstrated that the combination of ONC201 and an anti-PD-1 agent was more efficacious than anti-PD-1 monotherapy.

Expert Commentary: These studies describe a novel mechanism of action for ONC201, which is already in clinical trials. Thus, the combination of anti-PD-1 and ONC201 could rapidly be investigated in the clinic. (*Image by Matt Wright courtesy of Wikimedia Commons.*)

Wagner J, Kline CL, Zhou L, Campbell KS, Macfarlane AW, Olszanski AJ, et al. Dose intensification of TRAIL-inducing ONC201 inhibits metastasis and promotes intratumoral NK cell recruitment. The Journal of Clinical Investigation; Published online March 13, 2018; doi: 10.1172/JCI96711.

NFκB in KRAS Mutant Lung Cancer

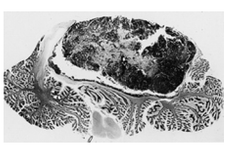


Approximately 30 to 40% of lung adenocarcinomas (LADC) diagnosed in Europe and North America harbor *KRAS* mutations. Mutant *KRAS* was recently shown to interact with IKKs, key intermediates in NFκB signaling, to promote survival, stemness, and drug resistance in LADC. Vreka and colleagues scrutinized the role of IKKα and IKKβ in *KRAS*-mutant LADCs induced by urethane in combination with respiratory epithelial expression of oncogenic $KRAS^{G12D}$. In mouse models of tobacco carcinogen- and oncogenic $KRAS^{G12D}$-generated LADC, IKKα was essential for disease initiation and progression. Moreover, IKKα selectively advanced cellular proliferation in the context of mutant KRAS and was also highly expressed in human LADC.

Expert Commentary: The authors confirm a requirement for IKKα in *KRAS*-driven LADC, implicate IKKα as a *KRAS* nononcogene addiction partner, and show that targeting IKKα may block LADC, an aggressive and therapeutically resistant cancer. (*Image from cited article courtesy of the publisher.*)

Vreka M, Lillis I, Papageorgopoulou M, Giotopoulou GA, Lianou M, Giopanou I, et al. IκB kinase α is required for development and progression of KRAS-mutant lung adenocarcinoma. Cancer Research; Published first March 27, 2018; doi: 10.1158/0008-5472.CAN-17-1944.

Phosphoprotein Signaling across Medulloblastoma Subgroups



To discern protein signaling effectors, Zomerman and colleagues profiled phosphorylation of 285 synthetic peptides from 50 primary medulloblastomas. They observed a MYC-like cluster enriched for responses to DNA damage and external stimuli, and p53, apoptotic, and neuronal signaling. A second cluster was enriched for cell-cycle transition and G-protein-coupled receptor signaling. The MYC-like cluster consisted of SHH and half of Group 3 tumors with high MYC levels, while cluster 2 comprised the remaining Group 3s with lower MYC and Group 4s. In immortalized epithelial cells, MYC/MYCN overexpression and a TP53 mutant/null had protein signaling states similar to the MYC-like cluster. Finally, the DNA-damage response/p53 signaling abnormalities in the MYC-like cluster may respond to WEE1 and ATR inhibition that exacerbate DNA replication stress.

Expert Commentary: This study shows that the two highest risk groups of medulloblastoma (TP53 mutant SHH and MYC-amplified Group 3s) share similar signaling networks, suggesting a common approach of targeting replication stress. (*Image courtesy of Wikimedia Commons.*)

Zomerman WW, Plasschaert SLA, Conroy S, Scherpen FJ, Meeuwsen-de Boer TGJ, Lourens HJ, et al. Identification of two protein-signaling states delineating transcriptionally heterogeneous human medulloblastoma. Cell Rep 2018;22:3206–16.

Note: Breaking Insights are written by *Cancer Research* editors. Readers are encouraged to consult the articles referred to in each item for full details on the findings described.