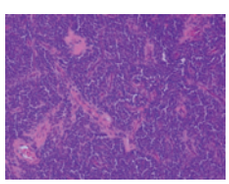
Cancer Research
Breaking Advances
Highlights from Recent Cancer Literature
AACR American Association for Cancer Research

Inhibiting Aggregation Restores p53 Function

In some cancers, mutant p53 protein accumulates in a self-aggregated amyloid-like state. Studying p53-mutant high-grade, serous ovarian carcinoma (HGSOC), Soragni and colleagues demonstrate that a cell-penetrating peptide (ReACp53) inhibits p53 amyloid formation. Peptide treatment switched the balance from nonfunctional p53 aggregates to soluble functional protein. The resolubilized p53 relocated to the nucleus and regulated target genes. Like wild-type p53, it halted cell proliferation and triggered apoptosis in cell lines and HGSOC patient-derived organoids. Intraperitoneal administration of the peptide decreased tumor proliferation, shrank HGSOC xenografts, and was effective against even intraperitoneally disseminated tumors. Given the prevalence of p53 mutations, ReACp53 could be effective in many different cancer types, although it remains to be determined which of the thousands of described p53 mutants, other than the well-established aggregation-prone ones, will respond. *(Image courtesy of Wikimedia Commons.)*

Soragni A, Janzen DM, Johnson LM, Lindgren AG, Thai-Quynh Nguyen A, Tiourin E, et al. A designed inhibitor of p53 aggregation rescues p53 tumor suppression in ovarian carcinomas. Cancer Cell 2016;29:90–103.

Notch Signaling in Glioma



Neural stem cells (NSC) depend on Notch signaling, which involves receptor activation, release of the intracellular domain, interaction with the nuclear CSL (RBP-Jκ in mice) transcription complex, and expression of target genes such as *HES5*. Using a PDGF-B-driven, p53 mutant model for glioma, Giachino and colleagues observed that HES5-positive cells could initiate tumors and that only a minority of tumor cells was HES5-positive. Moreover, inactivation of Notch signaling via ablation of RBP-Jκ resulted in increased tumor aggressiveness, increased cell proliferation, and decreased survival. Blocking RBP-Jκ and p53 in HES5-positive progenitors *in vivo* resulted in hyperplastic lethal neoplasms composed of primitive neuroectodermal cells. In human glioma, increased *HES5* expression was associated with longer overall survival. Thus the authors add a cautionary note regarding Notch inhibitors in glioma and suggest the ability of Notch to maintain NSCs may contribute to its tumor suppressive functions in some gliomas. *(Image courtesy of Wikimedia Commons.)*

Giachino C, Boulay JL, Ivanek R, Alvarado A, Tostado C, Lugert S, et al. A tumor suppressor function for Notch signaling in forebrain tumor subtypes. Cancer Cell 2015;28:730–42.

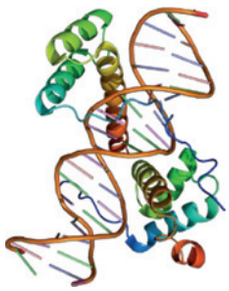
Targeting R-spondin Attenuates Colorectal Tumor Growth

Recurrent translocations of R-spondin (RSPO) genes, *RSPO2* and *RSPO3*, are proposed to drive colorectal cancer. R-spondins are secreted proteins that bind to LGR5 and amplify WNT activity to maintain intestinal stem cell function. Storm and colleagues hypothesized that *RSPO3* translocation-driven colorectal cancer would also be WNT dependent. They developed blocking antibodies against RSPO2 or RSPO3 to treat mice harboring two distinct patient-derived *RSPO3* translocation-driven colorectal cancer xenografts. Anti-RSPO3 inhibited growth, and resulted in differentiated cells and mucus production. Effects were limited to the *RSPO2* and *RSPO3* translocation-driven colorectal cancers, with no impact on *APC*-mutant driven patient-derived xenografts. Treated tumors exhibited reduced engraftment and reduced levels of cancer stem cell biomarkers, CD144 and CD133, consistent with anti-RSPO3 targeting cancer stem cells driving the growth of the *RSPO3* translocation-driven tumors. *(Image by Brian Gratwicke courtesy of Wikimedia Commons.)*

Storm EE, Durinck S, de Sousa e Melo F, Tremayne J, Kljavin N, Tan C et al. Targeting PTPRK-RSPO3 colon tumours promotes differentiation and loss of stem-cell function. Nature 2016;529:97–100.

Breaking Advances

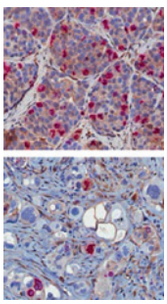
Leukemias Sensitized to PARP Inhibitors



Using primary transformed mouse hematopoietic cells and human leukemic cell lines *in vitro* and *in vivo*, Esposito and colleagues found that PARP inhibitor (PARPi) sensitivity could be attributed to repressive transcription factors such as AML1-ETO and PML-RARα blunting the DNA damage response (DDR). In contrast, the key downstream MLL-AF9–transactivated target *HOXA9* activated key DDR transcriptional programs, resulting in PARPi resistance. HOXA9 alone was sufficient to convert PARPi-sensitive AML1-ETO and PML-RARα leukemic cells to a PARPi-resistant DDR-proficient state, with genetic or pharmacologic inhibition of HOXA9 in MLL-AF9 leukemic cells sensitizing to PARPi. These findings suggest that therapies being developed to target the DDR might be used either alone or in combination with HOXA9 inhibitors against many of the AML molecular subtypes. *(Image courtesy of Wikimedia Commons.)*

Esposito MT, Zhao L, Fung TK, Rane JK, Wilson A, Martin N, et al. Synthetic lethal targeting of oncogenic transcription factors in acute leukemia by PARP inhibitors. Nat Med 2015;21:1481–90.

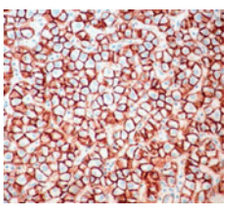
Targeting R-Spondin Slows Growth of Multiple Cancers



While intracellular components of WNT signaling, Axin, APC, and β-catenin, are mutated in several cancers, overexpression of WNT ligand has not been associated with human disease. Using a reporter-based screen in multiple human tumors, Chartier and colleagues identified four R-spondin family members (RSPO) as secreted factors that work with WNT proteins to activate β-catenin signaling. The authors developed monoclonal antibody antagonists of the RSPO family members. Anti-RSPO treatment inhibited tumor growth in patient-derived tumor xenograft models as a single agent and in combination with chemotherapy. Blocking RSPO signaling also inhibited tumorigenesis. Further, anti-RSPO treatment in responsive tumors strongly inhibited β-catenin downstream target genes. Thus, RSPO is a tumor-derived activator of WNT signaling in human cancer and represents a therapeutic target. *(Image from cited article courtesy of the publisher.)*

Chartier C, Raval J, Axelrod F, Bond C, Cain J, Dee-Hoskins C, et al. Therapeutic targeting of tumor-derived R-Spondin attenuates β-catenin signaling and tumorigenesis in multiple cancer types. Cancer Res 2016;76:713–23.

Imaging EMT *In Vivo*



Loss of E-cadherin junctions, a hallmark of epithelial-to-mesenchymal transition, is associated with increased grade and poor prognosis in many cancers. Erami and colleagues generated an E-cadherin-GFP mouse, enabling fluorescence recovery after photo bleaching–based *in situ* quantification of E-cadherin during progression. They crossed E-cadherin-GFP mice with a $Kras^{G12D}/p53^{WT}$ mouse model of noninvasive pancreatic ductal adenocarcinoma (PDAC); E-cadherin junctions were unaltered in noninvasive tumors. In contrast, invasive/metastatic PDAC driven by $Kras^{G12D}/p53^{R172H}$ mobilized E-cadherin junctions *in vivo*. *In vivo* monitoring of E-cadherin mobility was also applicable to assessing the efficacy of anti-invasive drug treatment, with SRC inhibitor reversing the E-cadherin junctional mobility. Thus, E-cadherin junctional mobility correlates with increased invasion and metastasis *in vivo*, and monitoring E-cadherin junctions could be valuable in preclinical efforts to target cancer invasion. *(Image by Ed Uthman courtesy of Wikimedia Commons.)*

Erami Z, Herrmann D, Warren SC, Nobis M, McGhee EJ, Lucas MC, et al. Intravital FRAP imaging using an E-cadherin-GFP mouse reveals disease- and drug-dependent dynamic regulation of cell-cell junctions in live tissue. Cell Rep 2016;14:152–67.

Note: Breaking Advances 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.

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Cancer Res 2016;76:987-988.