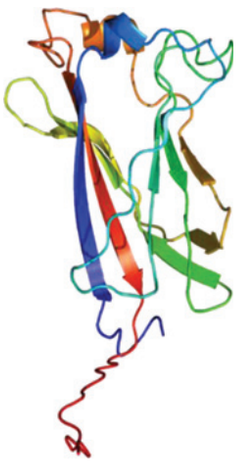
Cancer Research
Breaking Advances
Highlights from Recent Cancer Literature

American Association for Cancer Research

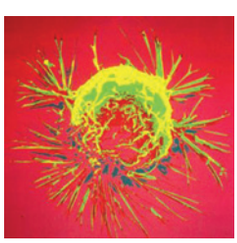
SPOP, Ubiquitination, and Renal Cell Carcinoma



The von Hippel-Lindau (VHL) tumor suppressor gene promotes ubiquitination and degradation of HIFα and is lost in clear cell renal cell carcinoma (ccRCC). Li and colleagues show that HIF regulates *SPOP* expression. Interestingly, SPOP was expressed in the nuclei of normal kidney but was cytoplasmic in ccRCCs, suggesting that cytoplasmic localization contributes to malignancy. An "SPOP-cyto" allele deleted for nuclear localization enhanced cell proliferation and promoted tumorigenesis in a xenograft model. An E3 ligase, SPOP promoted the degradation of cytoplasmic proteins with SPOP-binding motifs, including PTEN, DUSP7, GLI2, and DAXX. These data suggest that loss of VHL in ccRCC leads to elevated HIF and HIF targets, including SPOP. Cytoplasmic SPOP prevents degradation of tumor suppressors, thus promoting ccRCC. (*Image courtesy of Wikimedia Commons.*)

Li G, Ci W, Karmakar S, Chen K4, Dhar R, Fan Z, Guo Z, et al. SPOP promotes tumorigenesis by acting as a key regulatory hub in kidney cancer. Cancer Cell 2014;25:455–68.

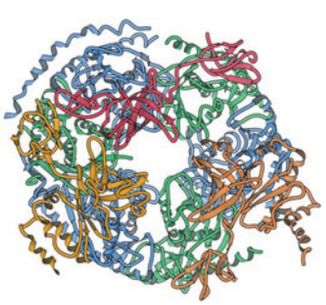
Cancer Progression Is Regulated via Stiffness-Induced miRNAs



Mouw and colleagues report that increased extracellular matrix (ECM) stiffness induces expression of the protumorigenic miR18a in breast tissue. In turn, miR18a targets the PTEN and HOXA9, activating downstream oncogenic signals. The authors detected increased MYC expression, known to stimulate miR18a, in stiffer tissue and reduced miR18a in response to MYC inhibition. MYC is downstream of β-catenin, and active β-catenin was increased in mammary epithelial cells grown on stiff substrates. Expression of miR18a was higher in breast cancer samples compared with nonmalignant samples and was increased in luminal B breast cancers relative to luminal A. Tumor stiffness was correlated with increased miR18a and decreased PTEN and HOXA9 expression. These findings suggest a prognostic role for tumor stiffness and miR18a levels in patients with breast cancer. (*Image courtesy of Wikimedia Commons.*)

Mouw JK, Yui Y, Damiano L, Bainer RO, Lakins JN, Acerbi I, et al. Tissue mechanics modulate microRNA-dependent PTEN expression to regulate malignant progression. Nat Med 2014;20:360–7.

Exosome-Delivered miRNA Abets Endothelial Cells



Zhou and colleagues demonstrate that miR105, produced by tumor cells and packaged into exosomes, promotes metastasis. Among more than 200 small RNAs differentially expressed between metastatic MDA-MB-231 and nonmetastatic MCF-10A cells, miR105 was studied based on its predicted targeting of tight junction protein 1 (TJP1) and expression in other metastatic lines. Exosomes purified from MDA-MB-231 conditioned media stimulated endothelial cell migration and could transfer miR105 to endothelial cells. Inhibition of miR105 in mammary fat pad xenografts decreased local invasion and metastatic tumor burden. High levels of miR105 in exosomes derived from sera of patients with stage II or stage III breast cancer correlated with later development of metastases. These data suggest that tumor growth and metastasis depend on tumor-microenvironment cross-talk, and that this cross-talk may be amenable to therapeutic targeting and use as a predictive biomarker. (*Image courtesy of Wikimedia Commons.*)

Zhou W, Fong MY, Min Y, Somlo G, Liu L, Palomares MR, et al. Cancer-secreted miR-105 destroys vascular endothelial barriers to promote metastasis. Cancer Cell 2014;25:501–15.

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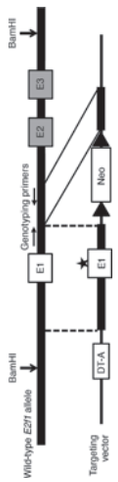
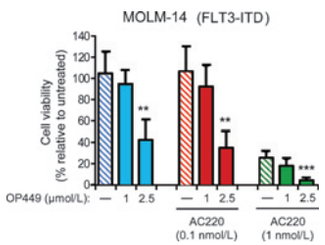


E2F1 Stimulates DNA Repair in Response to UV Radiation

Phosphorylation of E2F1 (following DNA damage) promotes stabilization of this transcription factor, aiding DNA repair through recruitment to sites of DNA damage. To analyze phosphorylation of E2F1 *in vivo*, Biswas and colleagues generated a knock-in mouse in which serine 29 was mutated to alanine. In response to UV radiation and doxorubicin, the S29A mutation impaired stabilization of E2F1 without affecting expression of E2F target genes. Wild-type and S29A knock-in mice also showed similar apoptotic and proliferative responses to acute UV radiation. The S29A mutation prevented E2F1 association with damaged DNA and reduced DNA repair efficiency. Knock-in mice showed increased sensitivity to UV-induced skin carcinogenesis. These investigators link the ability of E2F1 to directly promote DNA repair with the suppression of tumor development. (*Image from cited article courtesy of publisher.*)

Biswas AK, Mitchell DL, Johnson DG. E2F1 responds to ultraviolet radiation by directly stimulating DNA repair and suppressing carcinogenesis. Cancer Res; Published OnlineFirst April 16, 2014; doi:10.1158/0008-5472.CAN-13-3216.

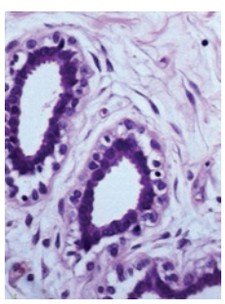
Targeting Phosphatases in Refractory Leukemia



The SET oncoprotein, an endogenous inhibitor of the PP2A phosphatase, is a therapeutic target in leukemia. Agarwal and colleagues previously described OP449, a peptide antagonist of SET, and here evaluate its ability to inhibit growth of chronic myeloid leukemia (CML) and acute myeloid leukemia (AML) cells. SET antagonism was PP2A dependent, reduced oncoprotein levels and led to growth inhibition, enhanced apoptosis, and impaired clonogenicity of both AML and CML cells, including cells harboring drug-resistant BCR–ABL1 compound kinase-domain mutations. Combined targeting with specific kinase inhibitors or genotoxic agents was synergistic and selective for leukemia cells, including primary patient cells with blastic CML, AML with FLT3-ITD, JAK3, or RAS mutations. Combined targeting of phosphatase and tyrosine kinase signaling pathways warrants further exploration for genetically heterogeneous AML. (*Image from cited article courtesy of publisher.*)

Agarwal A, Mackenzie RJ, Pippa R, Eide CA, Oddo J, Tyner JW, et al. Antagonism of SET using OP449 enhances the efficacy of tyrosine kinase inhibitors and overcomes drug resistance in myeloid leukemia. Clin Cancer Res 2014;20:2092–103.

Clones Share the Effort during Breast Cancer Growth



Cleary and colleagues show that approximately half of Wnt-driven mouse mammary tumors harbor biclonal populations of basal $Hras^{mut}/Wnt1^{low}$ and luminal $Hras^{wt}/Wnt1^{high}$ subclones. Within these tumors, $Hras^{mut}/Wnt1^{low}$ clones depend on Wnt producing luminal cells for growth. Upon elimination of the $Hras^{wt}/Wnt1^{high}$ subclones, $Hras^{mut}/Wnt1^{low}$ clones either generated mutations in the β-catenin pathway (among others) or recruited heterologous cells that produced Wnt1. These results suggest that tumors may not organize following normal stem cell hierarchies, instead utilizing clonal structures that cooperate for growth. These ideas challenge the common assumption derived from cancer genome sequencing that low allelic fractions are late events. Instead, these may be early clones that allow for interclonal cooperation. (*Image courtesy of Wikimedia Commons.*)

Cleary AS, Leonard TL, Gestl SA, Gunther EJ. Tumour cell heterogeneity maintained by cooperating subclones in Wnt-driven mammary cancers. Nature 2014;508:113–7.

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 2014;74:2905-2906.