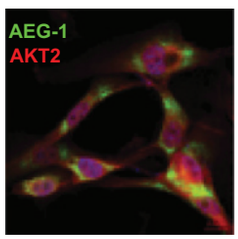
Cancer Research
Breaking Advances
Highlights from Recent Cancer Literature
American Association for Cancer Research

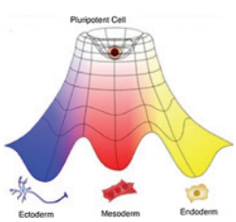
AEG-1 Chooses AKT2 as Its Partner in Glioma



Astrocyte elevated gene-1 (AEG-1 or *MTDH*) expression is elevated in glioblastoma brain tumors, enhancing invasion, metastasis, angiogenesis, and therapy resistance via the Akt signaling pathway, where a positive feedback loop between AEG-1 and Akt drives tumorigenesis. Hu and colleagues show that the interaction between AEG-1 and AKT2 drives glioblastoma. Expression of both AEG-1 and AKT2 is elevated in glioblastoma. The presence of AEG-1 and AKT2 in patient samples was correlated directly with progression and inversely with survival. The authors determined that the AEG-1–AKT2 interaction stabilized AKT2 phosphorylation at S474, which enhanced downstream signaling, increasing cell proliferation and survival. Disrupting the AEG-1–AKT2 interaction caused reduced cell viability and invasion. Thus, targeting AEG-1–AKT2 signaling might serve as a novel therapeutic option. (*Image from cited article courtesy of publisher.*)

Hu B, Emdad L, Bacolod MD, Kegelman TP, Shen X-N, Alzubi MA, et al. Astrocyte elevated gene-1 (AEG-1) interacts with Akt isoform 2 to control glioma growth, survival and pathogenesis. Cancer Res; Published OnlineFirst October 10, 2014; doi:10.1158/0008-5472.CAN-13-2978.

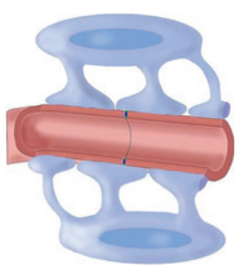
Lose Your Tail and Become Senescent



Oncogene-induced and replicative senescence are processes thought to curtail transformation and to be associated with a repressive chromatin state. However, oncogene-triggered signals that activate a stable, possibly irreversible epigenetic state of chromatin repression remain unknown. Duarte and colleagues show that during senescence, the tail of Histone H3.3 is cleaved by Cathepsin L, leading to cleaved H3.3cs1. Overexpression of H3.3cs1 lacking the first 21 amino acids from the tail was sufficient to induce senescence. H3.3cs1 was incorporated into the nucleosomes by the histone chaperone complex HUCA and regulated transcriptional silencing of RB/E2F genes due to permanent removal of H3K4me activation marks. These findings identify a novel mechanism of histone H3 posttranslational modifications other than methylation/acetylation that ensures a stable program of senescence. (*Image from StemBook courtesy of Wikimedia Commons.*)

Duarte LF, Young AR, Wang Z, Wu HA, Panda T, Kou Y, et al. Histone H3.3 and its proteolytically processed form drive a cellular senescence programme. Nat Commun 2014;5:5210.

Finding a Way across the Blood–Brain Barrier



Yu and colleagues used a humanized transferrin receptor (TfR, TFRC) bispecific antibody to deliver therapeutic antibody across the blood–brain barrier in primates. Antibodies targeting TfR increase brain delivery via receptor-mediated transcytosis. β-secretase (BACE1) cleaves amyloid precursor protein to amyloid-β peptides (Aβ), enabling delivery estimates of BACE1 blocking antibody based on Aβ levels. Maximal delivery to the brain was achieved using an antibody with optimal TfR affinity. In primates, unlike mice, there was no significant impact on the hematopoietic system following treatment with the anti-TfR/BACE1 bispecific antibody, potentially due to decreased levels of TfR-positive circulating reticulocytes in primates. Treatment with bispecific anti-TfR/BACE antibody resulted in a robust reduction in Aβ levels in the brains of nonhuman primates, suggesting the utility of humanized bispecific antibodies to treat brain cancer. (*Image from Sykepleiepluss.com courtesy of Wikimedia Commons.*)

Yu YJ, Atwal JK, Zhang Y, Tong RK, Wildsmith KR, Tan C, et al. Therapeutic bispecific antibodies cross the blood-brain barrier in nonhuman primates. Sci Transl Med 2014;6:261ra154.

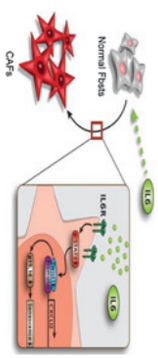
Breaking Advances

Cell-to-Cell Exosome Transfer Promotes Tumorigenesis

Exosomes are protein, mRNA, and microRNA (miRNA) containing nanovesicles secreted by cells, including cancer cells. Melo and colleagues show that breast cancer exosomes carry miRNAs and components for processing pre-miRNAs. Breast cancer–derived exosomes induced profound transcriptome changes in nontransformed mammary epithelial cells. For example miR-21 and miR-10b have established roles in breast cancer and were upregulated in normal cells upon cancer exosome uptake. Strikingly, normal cells exposed to cancer exosomes became tumorigenic in mice. Serum isolated from breast cancer patients was found to be enriched in exosomes compared with serum of healthy donors and induced transcriptional changes analogous to exosomes derived from cultured cancer cells. This study suggests a mechanism whereby cancer exosomes "infect" normal cells adjacent to the tumor and drive progression. (*NASA image in public domain courtesy of Wikimedia Commons.*)

Melo SA, Sugimoto H, O'Connell JT, Kato N, Villanueva A, Vidal A, et al. Cancer exosomes perform cell-independent microRNA biogenesis and promote tumorigenesis. Cancer Cell 2014;26:707–21.

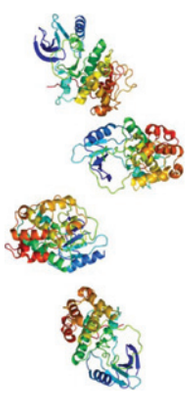
A New Twist in Cancer-Associated Fibroblasts



Lee and colleagues show that the transcription factor TWIST1 causes transdifferentiation of normal quiescent fibroblasts into cancer-associated fibroblasts (CAF). Treating normal human fibroblasts with IL6 and other proinflammatory cytokines *in vitro* resulted in induction of TWIST1 expression and caused transdifferentiation of normal fibroblasts into CAFs via STAT3 phosphorylation. *In vivo*, ectopic expression of IL6 enhanced tumor infiltration of TWIST1-expressing CAFs. Overexpressing TWIST1 in normal fibroblasts caused expression of CAF markers and malignant characteristics. Conversely, silencing TWIST1 expression in CAF abrogated tumor-promoting properties. Expression of TWIST1 correlated with expression of CXCL12, a transcriptional target of TWIST1 in patient tumors. Finally, overexpressing TWIST1 in normal fibroblasts suppressed premature senescence, while TWIST1 attenuation accelerated senescence in CAFs. Thus, TWIST1 is a potential target that regulates tumor progression enhanced by the tumor microenvironment. (*Image from cited article courtesy of publisher.*)

Lee KW, Yeo SY, Sung CO, Kim SH. Twist1 is a key regulator of cancer-associated fibroblasts. Cancer Res; Published OnlineFirst November 3, 2014; doi:10.1158/0008-5472.CAN-14-0350.

Inhibitors Suppress MYCN-Driven Cancer



A subset of cyclin-dependent kinases (CDK) regulates the expression of *MYC*. Chipumuro and colleagues knocked down transcriptional CDKs in a *MYCN*-amplified neuroblastoma cell line, demonstrating decreased expression of *MYCN*. They next screened and identified the CDK7 inhibitor THZ1 as the most potent attenuator of *MYCN* expression. THZ1 treatment of *MYCN*-amplified neuroblastoma resulted in decreased proliferation and increased apoptosis *in vitro* and tumor regression *in vivo*. THZ1 exhibited global effects on transcription. Interestingly, these effects on global transcription, as well as THZ1's cytotoxicity on neuroblastoma cells, could be phenocopied by knockdown of *MYCN*. The authors conclude that the cytotoxicity of THZ1 on *MYCN*-driven neuroblastoma was due both to direct effects on *MYCN* expression through inhibition of CDK7, and indirect effects due to attenuation of MYCN's activity on super enhancers. (*Image by EMW courtesy of Wikimedia Commons.*)

Chipumuro E, Marco E, Christensen CL, Kwiatkowski N, Zhang T, Hatheway CM. CDK7 inhibition suppresses super-enhancer-linked oncogenic transcription in MYCN-driven cancer. Cell 2014; http://dx.doi.org/10.1016/j.cell.2014.10.024.

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;74:7159-7160.