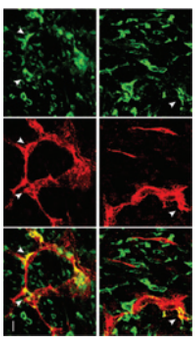
Cancer Research
Breaking Advances
Highlights from Recent Cancer Literature
AACR American Association for Cancer Research

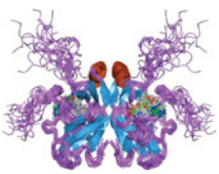
Macrophage Tie2 Expression in Tumor Relapse



Chen and colleagues used animal models to identify a molecular mechanism by which tumors relapse after chemotherapy. Treatment with chemotherapeutic drugs leaves behind resistant tumor cells and affects the tumor microenvironment. Chen and colleagues showed that elevated expression of Tie2 on macrophages in tumors correlated closely with relapse following chemotherapy. Further, tumor regrowth could be inhibited by conditionally deleting Tie2 expression in macrophages. Hypoxic conditions in the tumor allowed for Tie expression in tumor-infiltrating Tie2-CD11b^{+} cells, from which Tie2^{+} macrophages were derived. Addressing molecular mechanisms of action, the authors found that Tie2 expression inhibited apoptosis in macrophages under stressed conditions via AKT-dependent signaling. Thus, this paper identifies a novel mechanism by which Tie2 expression in macrophages allows for tumor relapse following chemotherapy and might serve as a novel strategy to target tumor relapse. *(Image from cited article courtesy of the publisher.)*

Chen L, Li J, Wang F, Dai C, Wu F, Liu X, et al. Tie2 expression on macrophages is required for blood vessel reconstruction and tumor relapse after chemotherapy. Cancer Res 2016;76:6828–38.

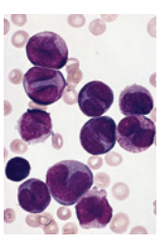
Methylation Status Defines High-Risk Ependymomas



Posterior fossa ependymoma, a unique malignancy, has no recurrent somatic nucleotide variants and is defined by altered DNA methylation. To further characterize epigenetic alterations, Bayliss and colleagues performed mass spectrometry on a cohort of ependymomas. A group of posterior fossa ependymoma had DNA hypomethylation, markedly reduced H3K27me3, and increased H3K27ac. H3K27me analysis and genome-wide DNA methylation profiling resembled that of H3K27M-mutated pediatric high-grade glioma. Cross species analysis revealed radial glial cells from P6/P30 murine cerebellum had a transcriptional program similar to these posterior fossa ependymomas, consistent with previous observations that radial glial cells represent cells of origin for posterior fossa ependymoma. Finally, reduced immunoreactivity for H3K27me3 correlated with poor outcome in a multivariable model, suggesting the use of epigenetic profiling to select patients expected to benefit from epigenetic modifier therapy. *(Image courtesy of Wikimedia Commons.)*

Bayliss J, Mukherjee P, Lu C, Jain SU, Chung C, Martinez D, et al. Lowered H3K27me3 and DNA hypomethylation define poorly prognostic pediatric posterior fossa ependymomas. Sci Transl Med 2016;8:366ra161. doi 10.1126/scitranslmed.aah6904.

Hypomethylating Agents in Ultra High-Risk AML

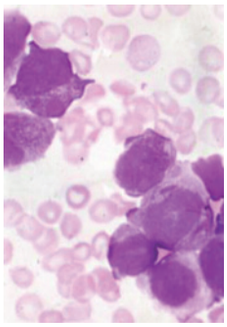


Patients whose acute myeloid leukemia (AML) or myelodysplastic syndrome harbors a TP53 mutation have an especially poor outcome. Welch and colleagues performed exome and gene panel sequencing to determine how specific mutations impact treatment with the hypomethylating agent decitabine. A prospective trial enrolled 84 patients treated with two cycles of decitabine, extended to 32 additional patients. Clinical response correlated robustly with high-risk cytogenetic profiles and TP53 mutations, in stark contrast to response failures typical with standard AML induction chemotherapy. Clearance of bone marrow blasts tended to precede mutation clearance. Responses were transient; decitabine failed to eliminate all leukemia-specific driver mutations. No methylation signature was identified among responders to suggest epigenetic priming for decitabine response. Pre-existing subclones influenced response, expanding clonally at relapse. This pilot study suggests sensitivity to decitabine therapy in ultra-high risk AML patients. *(Image courtesy of Wikimedia Commons.)*

Welch JS, Petti AA, Miller CA, Fronick CC, O'Laughlin M, Fulton RS, et al. TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. N Engl J Med 2016;375:2023–36.

Breaking Advances

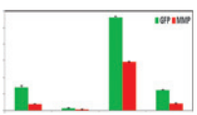
Gene Stemness Score for Risk Determination in AML



Resistance to induction chemotherapy, or relapse subsequent to a patient's initial response, is a clinically important problem. Ng and colleagues set about to identify biomarkers of high-risk acute myeloid leukemia (AML) patients, specifically analyzing drug resistance in leukemia stem cells (LSC). They identified genes differentially expressed in LSC^{+} and LSC^{-} populations derived from AML patients, the bulk of which were also found in hematopoietic stem cells. Correlating these differentially expressed genes with survival, they identified a 17-gene LSC signature associated with outcome. Using an additional cohort of diverse AML subtypes, they further showed that this signature accurately identified patients who were resistant to induction therapy. This minimal gene signature could be used to identify high-risk AML patients, who could then be stratified into more aggressive treatment regimens. *(Image courtesy of Wikimedia Commons.)*

Ng SW, Mitchell A, Kennedy JA, Chen WC, McLeod J, Ibrahimova N, et al. A 17-gene stemness score for rapid determination of risk in acute leukemia. Nature 2016;540:433–7.

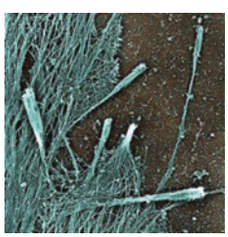
Calcium-Binding Protein S100A4 Aids Metastasis



Ismail and colleagues performed genetic studies in *Drosophila* to assess relevance of the calcium-binding protein S100A4 in metastatic dissemination of mutant Ras-induced tumors in the developing nervous system. Activation of the stress kinase JNK and production of the matrix metalloproteinase MMP1 were significantly increased in flies that overexpressed mutant Ras^{Val12} and S100A4. Metastatic dissemination associated with S100A4 overexpression could be suppressed genetically or chemically by blocking JNK and MMP1. Interestingly, elevated expression of mammalian paralogs MMP2, MMP9, and MMP13 in breast cancer patient specimens correlated with decreased patient survival. Levels of MMP2 and MMP13 correlated with levels of S100A4, while levels of MMP9 levels correlated with S100P within individual tumors. The authors identify an evolutionarily conserved pathway used by S100A4 to aid metastatic dissemination, with implications for cancers in which metastases track along nerves. *(Image from cited article courtesy of the publisher.)*

Ismail TM, Bennett D, Platt-Higgins A, Al-Medhity M, Barraclough R, Rudland RS. S100A4 elevation empowers expression of metastasis effector molecules in human breast cancer. Cancer Research; Published OnlineFirst November 10, 2016; doi: 10.1158/0008-5472.CAN-16-1802.

Hypertension Drugs Block Cancer Invasion



Jacquemet and colleagues highlight the potential for repurposing antihypertensive L-type calcium channel blockers (CCB) to target cancer. Using a high-throughput microscopy-based drug screen, a surprising discovery was made that CCBs inhibited filopodia formation in cancer cells. Filopodia are actin-rich finger-like protrusions used by cancer cells during invasion. The authors demonstrate that L-type calcium channels are expressed in different cancers and alterations in genes encoding these channels are associated with poor patient survival. L-type calcium channels promote cell invasion by positively regulating filopodia formation and stability, and subsequent maturation into talin-rich integrin-signaling nodes (focal adhesions). Thus, uncovering an underappreciated role for L-type calcium channel signaling, previously thought to be confined to excitable cells, in cancer cell migration and invasion, and show that CCBs may be valuable drugs to combat these processes. *(Image by Lubov Czech, Tatyana Svitkina, and Changsong Yang courtesy of Wikimedia Commons.)*

Jacquemet G, Baghirov H, Georgiadou M, Sihto H, Peuhu E, Cettour-Janet P, et al. L-type calcium channels regulate filopodia stability and cancer cell invasion downstream of integrin signalling. Nat Commun 2016;7:13297. doi: 10.1038/ncomms13297.

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 2017;77:219-220.