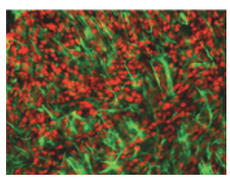
Cancer Research
Breaking Insights
Highlights from Recent Cancer Literature
AACR American Association for Cancer Research

Astrocytes Promote Progression in Medulloblastoma

Astrocytes are abundant in the microenvironment of many types of brain tumors, where they provide factors important for tumor growth. Liu and colleagues demonstrate that tumor-associated astrocytes play an important role in the progression of Sonic Hedgehog (SHH) subgroup medulloblastoma. They show that unlike normal astrocytes, tumor-associated astrocytes produce and secrete SHH that promotes growth of medulloblastoma cells *in vitro*. *In vivo*, ablation of tumor-associated astrocytes attenuated medulloblastoma progression. SHH stimulated expression of the type VI intermediate filament Nestin in medulloblastoma cells via a noncanonical signaling pathway. As they previously showed that Nestin contributed to medulloblastoma progression by attenuating Gli3 repressor activity, they suggest attenuation of Gli3 as a mechanism by which tumor-associated astrocytes potentiate medulloblastoma growth.

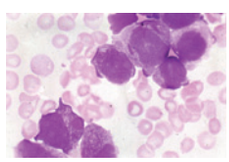


Expert Commentary: Tumor-associated astrocytes play an important role in medulloblastoma progression by regulating expression of Nestin via the production and secretion of SHH. (*Image from cited article courtesy of the publisher.*)

Liu Y, Yuelling LW, Wang Y, Du F, Gordon RE, O'Brien JA, et al. Astrocytes promote medulloblastoma progression through hedgehog secretion. Cancer Res 2017;77:6692–6703.

Apoptosis-Inducing Combination Therapy in AML

BCL-2 inhibitors have shown significant promise; however, development of resistance occurs with overexpression of Mcl-1. Pan and colleagues exploit observations that MDM2 inhibitors suppress p53 function to reactivate its apoptotic effect. In acute myeloid leukemia (AML) cells lacking p53 mutations, an MDM2 inhibitor reversed resistance to Bcl-2 inhibition by driving degradation of Mcl-1. Similarly, Bcl-2 inhibition reversed the resistance of AML cells to p53 activation by switching the cellular response of p53 activation from G_1 arrest to apoptosis. The combination of the two agents, moreover, was able to mitigate the resistance to each agent alone, leading to impressive synergy in multiple murine and patient-derived xenograft models of AML.

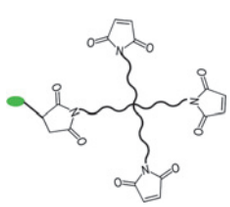


Expert Commentary: These findings delineate mechanisms of resistance to targeted agents and strategies to overcome such resistance. They also caution that in administering single agent Bcl-2 or MDM2 inhibitors clinically, the possibility of reciprocal Mcl-1 or Bcl-2 upregulation should be considered. (*Image courtesy of Wikimedia Commons.*)

Pan R, Ruvolo V, Mu H, Leverson JD, Nichols G, Reed JC, et al. Synthetic lethality of combined Bcl-2 inhibition and p53 activation in AML: mechanisms and superior antileukemic efficacy. Cancer Cell 2017;32:748–60.

Glioblastoma Drug Resistance in 3D Cultures

Therapeutic resistance plays a critical role in the lethality of glioblastoma (GBM). Xiao and colleagues developed a brain-mimetic biomaterial extracellular matrix (ECM) platform for 3D culturing of patient-derived GBM cells. Using this hydrogel platform, 3D-cultured GBM cells developed rapid resistance to erlotinib—a clinical small-molecule EGFR inhibitor. Unlike patient-matched gliomasphere cultures, biomaterial-cultured GBM cells maintained expression of ECM receptors and showed resistance kinetics similar to orthotopic xenografts in mice.

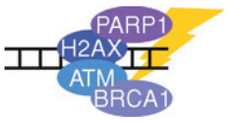


Expert Commentary: This study shows how specific interactions between GBM cell receptors and scaffold components contribute significantly to therapeutic resistance. This *ex vivo* model of GBM is fast and provides a more controlled experimental context than animal models. This biomimetic scaffold with orthogonal control over ECM parameters provides a unique tool to understand the complex microenvironment in GBM tumors that fuels treatment resistance and cancer progression. (*Image from cited article courtesy of the publisher.*)

Xiao W, Zhang R, Sohrabi A, Ehsanipour A, Sun S, Liang J, et al. Brain-mimetic 3D culture platforms allow investigation of cooperative effects of extracellular matrix features on therapeutic resistance in glioblastoma. Cancer Research; Published OnlineFirst December 27, 2017; doi: 10.1158/0008-5472.CAN-17-2429.

Breaking Insights

Targeting Drug Addiction in MAPKi-Resistant Melanoma

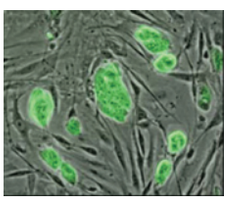


Upon withdrawal of MAPK inhibitors (MAPKi) in MAPKi-resistant BRAF mutant ($BRAF^{MUT}$) or $NRAS^{MUT}$ melanoma, a transient decrease in fitness occurs due to drug addiction. Hong and colleagues demonstrate that MAPKi withdrawal resulted in increased levels of phosphorylated ERK (pERK) and that the magnitude of increase in the abundance of pERK determined whether cells showed transient cell cycle arrest or irreversible cell-death secondary to increased DNA damage. Remarkably, in tumors that showed transient cell cycle arrest after MAPKi withdrawal, treatment with either a BRAFi (which increased the abundance of pERK) or a PARPi (which increased DNA damage after MAPKi withdrawal) led to irreversible cell-death.

Expert Commentary: These studies provide insight into how drug addiction at time of MAPKi resistance can be leveraged upon MAPKi withdrawal. These resistant cells can be targeted using agents that increase ERK activity and/or DNA damage. (*Image from cited article courtesy of the publisher.*)

Hong A, Moriceau G, Sun L, Lomeli S, Piva M, Damoiseaux R, et al. Exploiting drug addiction mechanisms to select against MAPKi-resistant melanoma. Cancer Discovery 2018;8:74–93.

Senescence and Cancer Stemness: A Complex Interplay

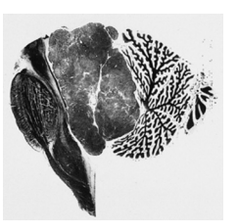


Senescence is a form of cell cycle arrest induced by stress such as chemotherapeutic DNA damage. Milanovic and colleagues investigated the impact of chemotherapy-induced senescence on stem cell-related properties of malignant cells. Gene expression profiles and functions of senescent and nonsenescent B-cell lymphomas derived from Eμ-*Myc* mice were compared. A genetically switchable model of senescence targeting p53 to mimic escape from cell cycle arrest was also used. They show that cells released from senescence re-entered the cell cycle with higher Wnt-dependent clonogenic growth potential, compared with cells that had never been senescent. *In vivo*, these previously senescent cells had higher tumor-initiation potential than never senescent cells. Notably, short-term activation of senescence in p53-regulated models of acute lymphoblastic leukemia and acute myeloid leukemia resulted in reprogramming of non-stem leukemia cells into self-renewing stem cells.

Expert Commentary: These data provide novel mechanistic insights into the plasticity of cancer cells, with implications for cancer therapy. They also offer an explanation for the high aggressiveness observed in relapsed hematological malignancies. (*Image courtesy of Wikimedia Commons.*)

Milanovic M, Fan DNY, Belenki D, Däbritz JHM, Zhao Z, Yu Y, et al. Senescence-associated reprogramming promotes cancer stemness. Nature 2018;553:96–100.

No Mutations? No Problem!



Profiling 44 primary ependymoma's across two nonoverlapping cohorts, Mack and colleagues identified superenhancers specific to high-risk posterior fossa group A (PFA) and RELA-fused subgroups. Functional validation was performed by shRNA in cell lines, and in developing zebrafish and mouse brains, resulting in a novel trispecies analysis. Overlaying RNA-sequencing, ATAC-sequencing with the functional validation, and probing of curated drug interaction database revealed subgroup-restricted therapeutic targets, specifically HDAC7, EPHA2, FGFR1, and CACNA1H. Targeted treatment resulted in potent and clinically applicable antitumor activity against cell lines representing PFA and RELA-fused ependymoma.

Expert Commentary: Ependymoma treatment is restricted to surgery and radiation. Next- generation sequencing in ependymoma revealed no clinically available drug targets. Through enhancer profiling, this study identified clear biological differences between the different subgroups of ependymoma and provides new targets for therapy. (*Image courtesy of Wikimedia Commons.*)

Mack SC, Pajtler KW, Chavez L, Okonechnikov K, Bertrand KC, Wang X, et al. Therapeutic targeting of ependymoma as informed by oncogenic enhancer profiling. Nature 2017;553:101–5.

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.

Highlights from Recent Cancer Literature

Cancer Res 2018;78:843-844.