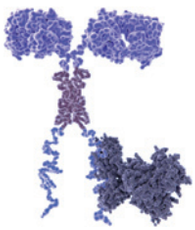
July 15, 2020 | Volume 80 | Number 14

CANCER RESEARCH

BREAKING INSIGHTS

Highlights from Recent Cancer Literature

CAR Therapies – Stop Driving Solo!

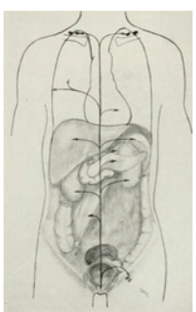


Chimeric antigen receptor (CAR)-directed immunotherapies are challenging in solid cancers. Lai and colleagues demonstrated that engineering CAR T cells to activate dendritic cells (DC) in tumors engaged an endogenous $CD8^+$ T-cell response that significantly improved control of solid tumors in mice. Engineered overexpression of Flt3L (a growth factor for DCs) in cancer cells themselves, in DCs, or in tumor-directed CAR T cells, all improved control of solid cancer models in mice. Mechanistically, Flt3L in the tumor microenvironment enhanced generation of $Batf3^+$ DCs known to activate antitumor $CD8^+$ T cells. Combining CAR T cells overexpressing Flt3L with the toll-like receptor 3 agonist poly(I:C) to activate the newly generated DCs, as well as an agonistic antibody against 4-1BB, because Flt3L-induced DCs promoted high 4-1BB on $CD8^+$ T cells, enhanced endogenous antitumor $CD8^+$ T cells, leading to potent and long-lasting tumor control.

Expert Commentary: CAR T-cell immunotherapies can be improved by engineering the cells to express Flt3L to support the function of dendritic cells that activate endogenous antitumor $CD8^+$ T-cell responses.

Lai J, Mardiana S, House IG, Sek K, Henderson MA, Guiffrida L, et al. Adoptive cellular therapy with T cells expressing the dendritic cell growth factor Flt3L drives epitope spreading and antitumor immunity. Nature Immunology; Published online May 18, 2020; doi:10.1038/s41590-020-0676-7.

Systemic Antitumor Effects of Stereotactic Ablative Radiation Therapy

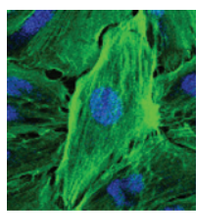


Local radiation therapy has been traditionally thought to have little influence on distant metastases. Recent studies have suggested that a low level oligometastatic state exists whereby local metastasis-directed therapy may alter the metastatic process. Preclinical studies have also suggested a possible systemic antitumor immune response after radiation. Phillips and colleagues conducted a randomized trial in low volume metastatic prostate cancer patients treated with stereotactic ablative radiation therapy metastasis-directed therapy to examine its potential systemic effects. Disease progression and new metastases were delayed significantly and stereotactic ablative radiation therapy invoked a systemic adaptive immune response.

Expert Commentary: This hypothesis-generating trial suggests that further study into the potential systemic immunologic effects of stereotactic ablative radiation therapy is warranted. *(Image courtesy of Wikimedia Commons.)*

Phillips R, Shi WY, Deek M, Radwan N, Lim SJ, Antonarakis ES, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE phase 2 randomized clinical trial. JAMA Oncol 2020;6:650–9.

Mechanosignaling Loop Confers Resistance in Melanoma

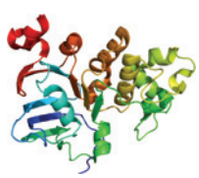


While response of *BRAF*-mutant melanoma patients to inhibitors of MEK or BRAF (BRAFi) is robust, most patients relapse. This resistance is driven by both genetic and nongenetic mechanisms, the latter dependent on transcriptional reprogramming of a subset of dedifferentiated mesenchymal cells. Comparing isogenic BRAFi-sensitive and -resistant melanoma cells, Girard and colleagues identified autocrine upregulation of numerous components of the extracellular matrix (ECM), collagen stiffness, and mechanosensory force–mediated ECM remodeling. Interestingly, the BRAFi-resistant remodeled ECM was sufficient to desensitize untreated melanoma cells to BRAFi. The mechanosensory properties of the BRAFi-resistant melanoma cells required a YAP and myocardin-related transcription factor (MRTF)–driven transcriptional program. Similar ECM remodeling was also found during melanoma growth *in vivo* following treatment with BRAFi. Remodeling was attenuated when mice were cotreated with a YAP inhibitor, increasing the efficacy of the BRAFi.

Expert Commentary: The efficacy of BRAFi against melanoma might be improved if cotreated with a drug that attenuates ECM/mechanosensory signaling. *(Image from cited article courtesy of publisher.)*

Girard CA, Lecacheur M., Ben Jouira R., Berestjuk I., Diazzi S, Prod'homme V, et al. A feed-forward mechanosignaling loop confers resistance to therapies targeting the MAPK pathway in BRAF-mutant melanoma. Cancer Res 2020;80:1927–41.

Turning Cold Pediatric Brain Tumors Hot



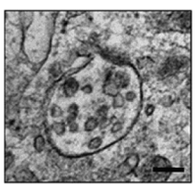
Garancher and colleagues transplanted a syngeneic MYC-driven Group 3 murine medulloblastoma model co-expressing either dominant negative p53 (MP) or Gfi1 (MG). Strikingly, only MP tumors engrafted. Both depletion of T cells and inactivation of p53 allowed MG tumors to engraft. A dramatic decrease of MHC-I was observed on the surface of p53-inactivated MG tumors, also observed in other *TP53* mutant human and murine medulloblastomas, as well as *TP53* mutant diffuse intrinsic pontine glioma (DIPG). The authors showed that

p53 directly regulated trafficking of MHC-I to the cell membrane through direct binding to Erap1 and Tap1. Knockdown of Erap1 resulted in engraftment of MG tumors. Finally, TNF and lymphotoxin-β receptor agonists rescued MHC-I expression *in vitro* and *in vivo*. TNF sensitized both MP and DIPG tumors to anti-PD-1 therapy.

Expert Commentary: *TP53* mutations are hallmarks of both DIPG and very high-risk Sonic hedgehog medulloblastoma, highly fatal cancers. Because p53 regulates immune cell evasion, combining anti-PD-1 therapy with TNF has potential in otherwise incurable tumors. *(Image courtesy of Wikimedia Commons.)*

Garancher A, Suzuki H, Haricharan S, Chau LQ, Masihi MB, Rusert JM, et al. Tumor necrosis factor overcomes immune evasion in p53-mutant medulloblastoma. Nature Neuroscience; Published online May 18, 2020; DOI: 10.1038/s41593-020-0628-4.

Senescent Stromal Cells Drive Resistance via Extracellular Vesicles

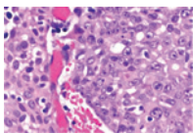


Mutual interaction between cancer cells and the surrounding tumor microenvironment (TME) is crucial for malignant progression. Extracellular vesicles (EV), which can be secreted from various cell types, have recently emerged as a mechanism mediating cell-cell interactions. Cellular senescence is a potent tumor-suppressive program that prevents neoplastic events. Senescent cells synthesize and secrete a plethora of extracellular proteins, a phenomenon referred to as the senescence-associated secretory phenotype. Han and colleagues presented evidence that senescent human stromal cells drive progression by producing small extracellular vesicles (sEV). Once released, senescent stromal sEVs significantly altered the expression profile of recipient cancer cells and enhanced their aggressiveness, specifically promoting resistance mediated by expression of ABCB4.

Expert Commentary: Senescent stromal cells produce sEVs, promoting cancer resistance in therapeutic settings, a process driven by SIRT1 decline in stromal cells and ABCB4 augmentation in cancer cells. A combination of a conventional chemotherapy to target cancer cells with a SIRT1 activator significantly improved outcome by restraining sEV biogenesis in senescent stromal cells. *(Image from cited article courtesy of publisher.)*

Liu Han, Qilai Long, Shenjun Li, Qixia Xu, Boyi Zhang, Dou X, et al. Senescent stromal cells promote cancer resistance through SIRT1 loss-potentiated overproduction of small extracellular vesicles. Cancer Research; Published first on May 4, 2020; DOI: 10.1158/0008-5472.CAN-20-0506.

Targeting Replication Stress in Renal Medullary Carcinoma



Renal medullary carcinoma (RMC) is a rare and very malignant tumor that affects adolescents of African background. RMC is resistant to tailored therapies against other renal cell carcinomas, suggesting that it has distinct molecular traits. Msaouel and colleagues found that the molecular profile of RMC indeed was different from other renal tumors. The authors showed that RMC contains markers for high replication stress and a high number of focal copy-number alterations. Notably, the cells showed an immune profile with increased expression of the cyclic GMP-AMP synthase interferon genes (cGAS-STING) pathway.

Expert Commentary: The presentation of the molecular landscape of RMC exposes new possibilities to target replication stress in the treatment of this deadly cancer. *(Image courtesy of Wikimedia Commons.)*

Msaouel P, Malouf GG, Su X, Yao H, Tripathi DN, Soeung M, et al. Comprehensive molecular characterization identifies distinct genomic and immune hallmarks of renal medullary carcinoma. Cancer Cell 2020;37:720–734.e13.

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.