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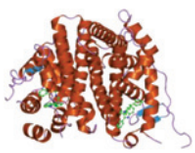
CANCER RESEARCH

BREAKING INSIGHTS

Highlights from Recent Cancer Literature

RNA Binding by Estrogen Receptor Alpha

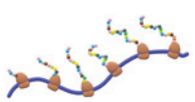


Estrogen receptor α (ERα) has been studied exhaustively in the past in regard to its role in regulating gene transcription in breast cancer and for its potential as a druggable target to improve breast cancer therapy. Despite this, Xu and colleagues were able to uncover a novel function of ERα as an RNA-binding protein, which they demonstrated is required for cancer progression independent of transcriptional regulation. ERα binds to an extensive network of mRNAs to post-translationally regulate numerous cancer-associated processes, including stress responses. A genetic screen revealed stress response proteins including XBP1, eIF4G2, and MCL1 were regulated by ERα via this newly discovered process and had implications in cell survival and resistance to ER-targeted chemotherapy.

Expert Commentary: The discovery that the RNA-binding activity of the ERα transcription factor is crucial for breast cancer development shows that we still have much to find regarding well-studied proteins in order to understand cancer progression and development of novel cancer drugs. *(Image courtesy of Wikimedia Commons.)*

Xu Y, Huangyang P, Wang Y, Xue L, Devericks E, Nguyen HG, et al. ERα is an RNA-binding protein sustaining tumor cell survival and drug resistance. Cell 1842021;184:5215-29.e17.

Getting Sloppy with the MAPK Pathway



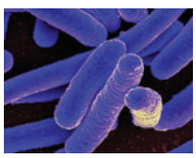
Dysregulated mRNA translation is critical for tumorigenesis; however, amino acid deficiency can induce ribosomal frameshifting, resulting in aberrant protein expression. Champagne and colleagues demonstrated that oncogene-driven ribosomal frameshifting, which they termed "sloppiness" occurs globally across cancer types and may make tumor cells susceptible to T-cell–dependent killing. Tryptophan deficiency induced sloppiness across tumor types, however, this was not observed in noncancerous cells. Sloppiness required MAPK pathway activation and led to aberrant peptide expression on the cell surface in a MAPK pathway–dependent manner. In the setting of MAPK pathway inhibitor resistance, sloppiness was restored and enhanced T-cell killing was observed.

Expert Commentary: The authors describe a novel oncogene-driven ribosomal frameshifting, which may result in a therapeutic vulnerability to immunotherapy after targeted therapy resistance. *(Image courtesy of Wikimedia Commons.)*

doi: 10.1158/0008-5472.CAN-81-22-BI

Champagne J, Pataskar A, Blommaert N, Nagel R, Wernaart D, Ramalho S, et al. Oncogene-dependent sloppiness in mRNA translation. Molecular Cell; Published online September 21, 2021; DOI: 10.1016/j.molcel.2021.09.002.

Engineered Bacteria Fuel T Cells to Fight Cancer

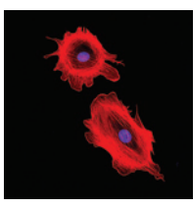


L-Arginine (L-arg) is a critical component of T-cell metabolism, which helps to activate their antitumor properties, but the availability of L-arg within tumors is often limited. Canale and colleagues demonstrated that engineering *Escherichia coli* to hyperproduce L-arg within tumors enhances the effectiveness of checkpoint blockade immunotherapy. After showing that oral supplementation with L-arg significantly improved survival of mice treated with anti-PD-L1, they aimed to develop a targeted approach to deliver L-arg to tumors. An engineered strain of *E. coli*, which disrupted an L-arg repressive feedback circuit, hyperproduced arginine. When injected directly into mouse tumors, the *E. coli* persisted and drastically elevated L-arg within the tumor. Increased L-arg was associated with increased infiltration of effector T cells ($CD4^+$ and $CD8^+$) and reduced regulatory T cells. Intravenous injection of *E. coli* also led to the colonization and persistence of bacteria in tumors, indicating that a systemic treatment for metastatic disease would be feasible.

Expert Commentary: Bacteria engineered to hyperproduce L-arginine colonized tumors and enhanced the effectiveness of checkpoint blockade immunotherapy. *(Image courtesy of Wikimedia Commons.)*

Canale FP, Basso C, Antonini G, Perotti M, Li N, Sokolovska A, et al. Metabolic modulation of tumours with engineered bacteria for immunotherapy. Nature; Published online October 6, 2021; DOI: 10.1038/s41586-021-04003-2.

Stromal Priming with Focal Adhesion Kinase Inhibitors



Focal adhesion kinase (FAK) inhibitors are currently under clinical investigation, but there is as yet no clear indication of how they can best be used in the clinical setting. Therapeutically targeting FAK is also complicated by the importance of FAK in both epithelial tumor cells and stromal cells, as it is not well understood how FAK inhibition in these two populations impacts disease progression. Using an impressive collection of *in vitro* and *in vivo* model systems, Murphy and colleagues showed that inhibition of FAK in stromal cells led to alterations in matrix deposition and alignment, which disrupted the collective migration of tumor cells. In

contrast to previous attempts to use chronic FAK inhibitor treatment, the authors demonstrated stromal priming with a FAK inhibitor was sufficient to impair tumor cell invasion and sensitized pancreatic ductal adenocarcinoma (PDAC) to chemotherapy, which was dependent on changes in matrix stiffness. They also identified Merlin, the product of the neurofibromatosis type 2 tumor suppressor gene, as a potential biomarker in PDAC that predicted sensitivity to FAK inhibitor stromal priming.

Expert Commentary: This study provides much needed insight into the complex effects of FAK inhibition in both stomal and epithelial tumor cells and offers the potential to tailor treatments based on individual tumor characteristics.

Murphy KJ, Reed DA, Vennin C, Conway JRW, Nobis M, Yin JX, et al. Intravital imaging technology guides FAK-mediated priming in pancreatic cancer precision medicine according to Merlin status. Sci Adv 2021;7:eabh0363. DOI: 10.1126/sciadv.abh0363.

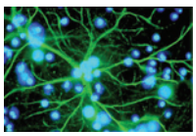
Targeting Creatine to Limit Tumor Cell Energy

Creatine kinase brain type (CKB) phosphorylates and converts the metabolite creatine into its high energy form, phosphocreatine. Phosphocreatine uptake, via the creatine transporter SLC6A8, promotes increased ATP levels, and hence survival, in tumor cells. Kurth and colleagues showed that the creatine mimetic, RGX-202, can attenuate growth of a number of colorectal cancer models *in vivo* regardless of mutational subtype. Further, metabolic profiling indicated that RGX-202 functioned in an on-target manner in such tumors. CKB levels served as a predictive biomarker of RGX-202 response in colorectal cancer mouse models. Importantly, RGX-202 suppressed liver metastases in these models. RGX-202 significantly reduced levels of creatine in the blood and urine of gastrointestinal cancer patients in a phase I clinical trial, consistent with RGX-202 acting in an on-target manner in cancer patients.

Expert Commentary: Reduction of phosphocreatine levels using a creatine transporter inhibitor reduced growth and metastases of colorectal cancer.

Kurth I, Yamaguchi N, Andreu-Agullo C, Tian HS, Sridhar S, Takeda S, et al. Therapeutic targeting of SLC6A8 creatine transporter suppresses colon cancer progression. Sci Adv 2021;7:eabi7511. DOI: 10.1126/sciadv.abi7511.

Radiation-Induced Senescence Drives GBM Recurrence



Glioblastoma (GBM) is invariably fatal despite surgical resection, radiation, and chemotherapy (temozolomide). One side effect of radiation therapy is the induction of senescence and release of senescence-associated secretory phenotype (SASP) factors, which can promote the survival of residual tumor cells. In an effort to understand the contributions of senescent cells in GBM progression following radiation, Fletcher-Sananikone and colleagues observed that irradiation of mouse brains before implantation of tumor cells promoted tumor growth and triggered widespread senescence, particularly in astrocytes marked by upregulated p21 expression. Senescent astrocytes secreted multiple SASP factors including HGF, which activated Met in tumor cells, promoting their growth and invasion. Implantation of glioma cells with senescent astrocytes in mouse brains promoted tumor growth. Interestingly, treatment with the senolytic drug ABT-263 (navitoclax) preferentially killed senescent astrocytes *in vivo* in pre-irradiated brain, resulting in significant attenuation of glioma growth.

Expert Commentary: Radiation-induced senescence in the glioma microenvironment can drive tumor growth and indicates the potential of using senolytic drugs as an adjuvant therapy to mitigate recurrence of GBM after radiotherapy. *(Image courtesy of Wikimedia Commons)*

Fletcher-Sananikone E, Kanji S, Tomimatsu N, Macedo Di Cristofaro LF, Kollipara RK, Saha D, et al. Elimination of radiation-induced senescence in the brain tumor microenvironment attenuates glioblastoma recurrence. Cancer Research; Published OnlineFirst September 27, 2021; DOI: 10.1158/0008-5472.CAN-21-0752.

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.