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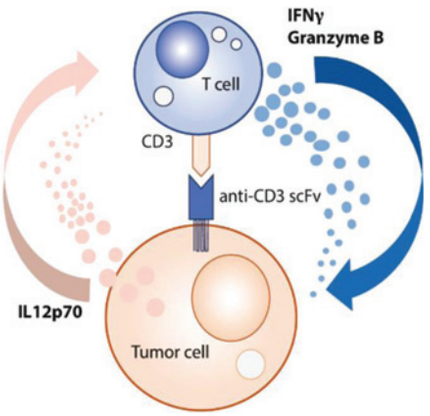
MOLECULAR CANCER RESEARCH
HIGHLIGHTS

Selected Articles from This Issue

Intratumoral IL12 + Anti-CD3 Increases Antitumor Immunity



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Intratumoral electroporation of IL12-encoding plasmids (IT-pIL12-EP) enhances antitumor immunity in treated and distant tumors. However, IT-pIL12-EP outcomes are in part dictated by infiltrating T-cell composition, where higher proportions of cytotoxic T cells as opposed to more immunosuppressive immune cells predicts enhanced IT-pIL12-EP responsiveness. In an effort to increase proportions of activated cytotoxic T cells in IT-pIL12-EP-treated tumors, Han and colleagues supplemented IT-pIL12-EP with electroporation of plasmids encoding membrane-anchored anti-CD3 single-chain variable fragments (scFv). The authors found that including anti-CD3 scFv with IL12 enhances proliferation and interferon-γ (IFNγ) secretion in both $CD8^+$ cytotoxic T cells and $CD4^+$ T regulatory (Treg) cells, and that costimulation with membrane-bound anti-CD3 with IL12 reduces Treg suppression. Supplementing IT-pIL12-EP with plasmids encoding anti-CD3 scFv *in vivo* enhances proliferation and cytotoxicity of tumor antigen-specific T cells, leading to augmented antitumor immunity against B16-F10 melanoma and 4T1 mammary tumor cells. Treating human melanoma-infiltrating T cells with IL12 and anti-CD3 scFv enhances cytotoxic $CD8^+$ expansion, IFNγ secretion, and PD-1 expression *in vitro*, suggesting IT-pIL12-EP and anti-CD3 scFv could augment PD-1 immune checkpoint inhibition responsiveness in melanoma patients.

WEE1 Inhibition Sensitizes HNSCC to TNFα

Hu *et al.* | Page 867

Tumor necrosis factor alpha (TNFα)-mediated cytotoxicity can be resisted via NF-κB activation and downstream survival signals in head and neck squamous cell carcinoma (HNSCC). Toxicities accompanying NF-κB signaling inhibition necessitate other methods of targeting the pathway. To search for novel targets affecting NF-κB signaling, Hu and colleagues performed a RNAi screen targeting the kinome and druggable genomic targets in a HNSCC cell line expressing NF-κB promoter response elements in tandem with a β-lactamase reporter gene. The screen revealed that G2/M checkpoint kinases WEE1 and cyclin dependent kinase 1 (CDK1) promote NF-κB signaling. WEE1 inhibition using AZD1775 disrupts WEE1 interactions with IκB kinase (IKK)α/β and RELA, reducing IKKα/β and RELA phosphorylation and NF-κB signaling. Correspondingly, AZD1775 augments TNFα-mediated HNSCC cell death, including in HNSCC radiotherapy *in vivo*. WEE1 and CDK1 expression levels and disease outcome correlations are dependent on human papillomavirus (HPV) infection status, suggesting HPV influences the signaling pathway. In addition to unveiling a novel signaling axis, this study presents a new potential way in which NF-κB can be therapeutically targeted in HNSCC.

miR-183 Promotes Breast Cancer Metastasis by Reducing SIN3A

Davenport *et al.* | Page 883

Decreased SIN3A expression in human breast cancer cell lines enhances tumorigenic phenotypes *in vitro* and tumor progression *in vivo*. However, how SIN3A abundance in breast tumors compares to its abundance in normal breast tissue is unknown, as is how SIN3A expression is regulated in breast tumors. To address these questions, Davenport and colleagues assessed SIN3A mRNA and corresponding protein levels in patients and validated these findings using public data sets (TCGA and METABRIC). The authors found that the SIN3A mRNA 3′ untranslated region harbors a sequence complementary to that of oncogenic miR-183, and that miR-183 silences SIN3A expression and enhances expression of genes that SIN3A transcriptionally represses. Accordingly, miR-183 expression negatively correlates with breast cancer patient survival and induces breast cancer cell migration and invasion *in vitro* and pulmonary metastasis *in vivo* through SIN3A downregulation. Overall, the novel miR-183-mediated regulation of SIN3A expression uncovered in this study could be used to inform metastatic breast cancer intervention strategies moving forward.

BCL-XL Inhibitors Ablate Senescent GBM Cells

Rahman *et al.* | Page 938

Radiation and temozolomide (TMZ), the standard treatments for glioblastoma (GBM), are known to induce a non-proliferative, senescent phenotype in surviving GBM cells. However, GBM cells often eventually escape treatment-induced senescence, leading to residual tumor outgrowth and GBM recurrence. To assess whether recently discovered senolytic drugs can eliminate senescent GBM cells, Rahman and colleagues tested the effects of 10 senolytic drugs on 12 human GBM cell lines treated with radiation or TMZ. The authors found that senolytic drugs targeting BCL-XL, as well as siRNA-mediated BCL-XL abrogation, enhance senescent GBM cell death. The results of the study suggest that pharmacological BCL-XL inhibition could augment antitumor effects of radiation and TMZ treatment, and potentially inhibit residual GBM cell outgrowth and disease recurrence.

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