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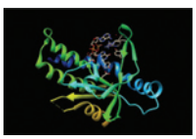
CANCER IMMUNOLOGY RESEARCH

WHAT WE'RE READING

A Sampling of Highlights from the Literature
Article Recommendations from Our Deputy and Senior Editors

Effective activation of STING



Mimicking STING–cGAMP binding can activate signaling (by Kissiovd via Wikimedia Commons)

How to effectively induce STING activation in the tumor microenvironment has not yet been determined. Lu et al. developed microparticles that can release an encapsulated STING agonist in waves, allowing for timed release into the tumor microenvironment (TME) without having to perform multiple intratumoral injections. Treatment of tumor-bearing mice reduces tumor growth and metastases. Chin et al. identified SR-717, a non-nucleotide small-molecule STING agonist, that mimics cGAMP and can confer the active conformation of STING to promote antitumor responses by $CD8^+$ T cells and NK cells. Pan et al. identified MSA-2, which binds and activates human and mouse STING preferentially in the acidified TME, can be given safely as a subcutaneous and oral treatment, induces clearance of tumors, and generates long-lasting antitumor immunity. These studies highlight the potential utility of new classes of STING agonists.

Lu X, . . ., Jaklenec A. ***Sci Transl Med*** *2020 Aug 12;12:eaaz6606.*
Chin EN, . . ., Lairson LL. ***Science*** *2020 Aug 21;369:993–9.*
Pan B-S, . . ., Addona GH. ***Science*** *2020 Aug 21;369:eaba6098.*

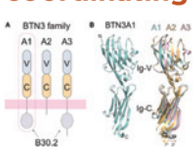
The role of TREM2 in protumoral immune responses

scRNA-seeking for TREM2 effects (by Mohamed Hassan via PxHere)

Immune-suppressive cells support tumor growth, thus identification and targeting of these cells are crucial to induce antitumor immunity. Katzenelenbogen et al. use a novel technology that integrates scRNA sequencing with intracellular protein activity (INs-seq) to establish that TREM2 expression positively correlates with arginase-1^+ myeloid cells in tumors. Knockout of TREM2 decreases myeloid cells and improves T-cell function in tumors, delaying tumor growth. Molgora et al. demonstrate that TREM2 knockout or blockade delays tumor growth in a T cell–mediated manner and improves checkpoint blockade efficacy. Thus, $TREM2^+$ tumor-infiltrating myeloid cells inhibit antitumor immunity and are targetable.

Katzenelenbogen Y, . . ., Amit I. ***Cell*** *2020 Aug 20;182;872–85.E19.*
Molgora M, . . ., Colonna M. ***Cell*** *2020 Aug 20;182:886–900.E17.*

BTN3A1 governs antitumor responses by coordinating αβ and γδ T cells



BTN3A1 can be overexpressed in cancer (from Fig. 2 of Gu et al., Front Immunol 2015)

Butyrophilins (BTNs) have a structure comparable to some B7 family inhibitory members but regulate T-cell responses through unclear mechanisms. Payne et al. show that BTN3A1 is overexpressed in high-grade ovarian cancer and disrupts αβ T-cell activation by preventing segregation of the phosphatase, CD45, from the immunologic synapse. Stabilizing BTN3A1's extracellular domain with CD277 antibodies or BTN3A1 blockade reversed this, unleashing both αβ and γδ T-cell responses. Thus, targeting inhibitory BTNs could be a potential strategy to boost antitumor responses and increase efficacy of immunotherapy.

Payne KK, . . ., Conejo-Garcia JR. ***Science*** *2020 Aug 21;369:942–9.*

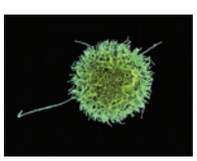
Chimeric antigen receptor designed to prevent ubiquitination and downregulation showed durable antitumor efficacy

Altering CARs to inhibit ubiquitination (image from PickPik)

Despite the efficacy of chimeric antigen receptor (CAR) T-cell therapies, many cancer patients do not respond or eventually fail with poor CAR T-cell persistence. Upon antigen binding, CARs are ubiquitinated and downregulated from the surface of T cells, and subsequently degraded intracellularly. Ubiquitination-blocking mutations in CARs reverse degradation, and lead to enhanced signaling and recycling with increased CAR surface expression. These effects improve tumor control, increase the persistence of CAR T cells in mice, and promote differentiation to central memory cells. Thus, inhibiting the ubiquitination of CARs improves the efficacy and longevity of CAR T-cell therapy.

Li W, . . ., Wang H. ***Immunity*** *2020 Aug 18;53:456–70.E6.*

Cancer cells educate natural killer cells to a metastasis-promoting cell state



Activating NK cells can reduce tumor spread (by NIAID via Wikimedia Commons)

How tumors evade NK-cell surveillance is not yet fully elucidated. With exposure to tumor cells, NK cells acquire a resting, rather than active, phenotype and not only lose cytotoxic ability but promote metastasis. Sequencing and receptor–ligand analysis show tumor-exposed NK cells upregulate inhibitory receptors, as well as DNA methyltransferases (DNMTs), and bind tumor cells via KLRG1 or TIGIT. Blocking tumor interaction through TIGIT or KLRG1, or inhibiting DNMTs, reduces tumor cell spread.

Chan IS, . . ., Ewald AJ. ***J Cell Biol*** *2020 Jul 9;219:e202001134.*

CD47 ligation repositions the inhibitory receptor SIRPA to suppress integrin activation and phagocytosis

Don't eat me! (adapted from "Children Eating and Enjoying Watermelon Fruit" via Wannapik Studio)

CD47 is a "don't eat me" signal used by tumor cells to avoid being phagocytosed by macrophages via CD47 ligation of SIRPA. The biochemical basis of this "don't eat me" signal remains unclear. CD47 ligation re-localizes SIRPA to the phagocytic synapse, where it interferes with macrophage cell spreading by inhibiting inside-out activation of integrin signaling. Reactivating integrins via manganese re-induces engulfment and phagocytosis of targets with or without CD47 conjugation. Thus, activating integrins may hold utility in reversing the protective impact of tumor expression of CD47.

Morrissey MA, . . ., Vale RD. ***Immunity*** *2020 Aug 18;53:290–302.E6.*

Cancer Immunology Research

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Cancer Immunol Res 2020;8:1229.