CANCER IMMUNOLOGY RESEARCH

WHAT WE'RE READING

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

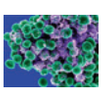
CRISPR screens reveal cBAF complex regulation of T-cell differentiation and function

CRISPR-based screening can enhance understanding of T-cell biology (from marius walter via Wikimedia Commons)

Using CRISPR-based screening, two groups have identified canonical BRG1/BRM-associated factor (cBAF) complex components as regulators of T-cell differentiation and function that are important for antitumor immunity. Guo et al. find cBAF levels influence the fate of activated $CD8^+$ T cells: high levels promote effector T-cell differentiation and low levels promote memory T-cell differentiation. Belk et al. show cBAF complex components, including Arid1a, promote T-cell acquisition of epigenetic features of exhaustion and limit T-cell persistence. Reducing cBAF activity, either pharmacologically (Guo et al.) or genetically (Belk et al.), improves tumor control in mouse models. The two studies suggest modulating the cBAF complex may improve T cell–based cancer immunotherapy.

Guo A, . . ., Green DR. ***Nature*** *2022 June 22;607:135–141.*
Belk JA, . . ., Satpathy AT. ***Cancer Cell*** *2022 July 11;40:768–86.E7.*

Immune checkpoint inhibitors unleash pathogenic immune responses against the microbiota



S. epidermis-specific T-cell responses can drive skin irAEs (from NIAID via NIH Flickr)

Increasing our understanding of the mechanisms underlying immune-related adverse events (irAEs) is important for optimizing the use of immune checkpoint inhibitors (ICI). Using a mouse model of skin irAEs, Hu et al. find that exposure to *Staphylococcus epidermis* at the time of anti-CTLA4 treatment induces an inflammatory response resembling skin irAEs in patients treated with ICIs. The response is driven by *S. epidermis*–specific T cells that produce IL17 and leads to the emergence of *S. epidermis*–specific memory T cells. Further analysis will determine whether modulating cross-talk between the host immune system and microbiota can alleviate skin irAEs.

Hu ZI, . . ., Belkaid Y. ***PNAS*** *2022 June 21;119:e2200348119.*

Sotigalimab and/or nivolumab with chemotherapy in first-line metastatic pancreatic cancer: clinical and immunologic analyses from the randomized phase 2 PRINCE trial

Phase II clinical trial results testing chemoimmunotherapy in PDAC (via Rawpixel)

Immunotherapy has so far been ineffective in the treatment of pancreatic ductal adenocarcinoma (PDAC). Padrón et al. report results from a phase II clinical trial evaluating chemotherapy combined with the anti–PD-1 nivolumab or the CD40-agonist sotigalimab, or with both together. The only group of patients among whom the 1-year overall survival rate was significantly greater than a historical control rate of 35% was the group assigned nivolumab/chemotherapy. Analysis of circulating and tumor biomarkers identified distinct immune signatures of improved outcome for patients receiving nivolumab/chemotherapy or sotigalimab/chemotherapy that could be used for patient selection in future clinical trials.

Padrón LJ, . . ., Vonderheide RH. ***Nat Med*** *2022 June 3;28:1167–77.*

"To be or not to be" . . . regulatory

B cells can promote or suppress tumors depending on the TME (Carsten Tolk mit via Flickr)

The role of B cells in the suppression or promotion of tumors remains unclear. In colorectal cancer (CRC), Wang et al. discover a specific regulatory B-cell subset expressing leucine-tRNA-synthase-2 (LARS2) and TGFβ1 that contributes to CRC progression by altering metabolic processes in the tumor microenvironment (TME). In a second study, Sagiv-Barfi et al. demonstrate that B-cell activation and antigen presentation are key to inducing antitumor T-cell responses, and both B and T cells are needed for efficacy of combination therapy with IL12, anti-OX40, and CpG in breast cancer. The two studies highlight how B-cell responses in the TME not only depend on cancer type, but also on B-cell phenotype and regulatory function.

Wang Z, . . ., Chu Y. ***Immunity*** *2022 June 14;55:1067–81.E8.*
Sagiv-Barfi I, . . ., Levy R. ***Sci Immunol*** *2022 May 27;7:eabn5859.*

Deciphering the immunopeptidome *in vivo* reveals new tumour antigens

Profiling the diversity of tumor antigens (Andy Mitchell via Wikimedia Commons)

A greater understanding of *in vivo* cancer-specific patterns of peptide presentation by MHC class I complexes is needed to improve the development of antigen-specific immunotherapies. Jaeger et al. develop and use a new genetically engineered mouse model to profile the cancer immunopeptidome from autochthonous pancreatic ductal adenocarcinoma and lung adenocarcinomas. The authors find little correlation between mRNA abundance and peptide detection, suggesting significant posttranslational regulation of tumor-specific peptide presentation. Dendritic cell vaccines loaded with lung adenocarcinoma peptides uniquely identified by the assay induce antigen-specific T-cell responses *ex vivo*, highlighting the model's ability to capture the cancer immunopeptidome.

Jaeger AM, . . ., Jacks T. ***Nature*** *2022 June 15;607:149–55.*

Mapping the developing human immune system across organs

A new map of human immune cell development (tzunghaor via openclipart)

Understanding how and where the immune system develops can provide a better understanding of cancer origin and facilitate the development of novel immunotherapies. Through single-cell profiling and spatial transcriptomics of nine prenatal tissues, Suo et al. have generated a comprehensive atlas of the developing human immune system. Highlights of the findings include the discovery that human immune development occurs across multiple tissue sites, including sites not considered primary hematopoietic organs; the identification of a population of prenatal B1 cells; and the demonstration that unconventional T cells are selected on thymocytes. This road map provides a resource for advancing immune-based science and medicine.

Suo C, . . ., Teichmann SA. ***Science*** *2022 May 12;376:eabo0510.*

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