https://doi.org/10.1038/s41590-023-01704-w

Cancer immunology leads the way

Cancer immunology research is diverse, uses cutting-edge technologies and continues to excite with its constantly evolving contribution to new therapeutic options, and not just for patients with cancer.

Cancer immunology and immunotherapy is at the forefront of biomedical research. Early adoption of the latest technologies has enabled researchers to explore in intricate detail how the tumor microenvironment is structured and functions, and how this information is being used to direct therapeutic strategies, control metastases or design cancer vaccines. CRISPR technologies, engineering cells for immunotherapy, spatial omics and the application of artificial intelligence systems to make sense of big data are driving this field in a way that also contributes to a better general understanding of fundamental immunology; for example, through the characterization of interferon signatures or immune cell stemness, exhaustion and dysfunction, and how this information can be used to interfere with cellular metabolism and boost the effector function of immune cells.

"Early adoption of the latest technologies has enabled researchers to explore in intricate detail how the tumor microenvironment is structured and functions…"

To provide an overview of these important advances, we have commissioned a series of Reviews on cancer immunology and immunotherapy, the first three of which are now published in the current issue of *Nature Immunology*.

Logan Walsh and Daniela Quail review the explosion of omics methods that depict granular and spatial features of the tumor microenvironment, and how immune, vascular, stromal and cancer cells interact to contribute to tumor immune and therapy responses. One of the difficulties with these emergent technologies is in the analysis and integration of vast datasets. Machine learning and artificial intelligence systems are set to become essential partners in mapping and understanding the tumor microenvironment, and in helping to identify tumor and immune signatures that can direct personalized treatments to avoid non-responsiveness and adverse effects.

"Machine learning and artificial intelligence systems are set to become essential partners…"

Excitement around chimeric antigen receptor (CAR) T cell research continues to gather pace with applications beyond cancer, as CAR technology is applied to other immune cells such as macrophages and natural killer (NK) cells. In their Review, Oula Dagher and Avery Posey Jr compare engineering methods and the therapeutic potential of CAR T and CAR NK cells. NK cells are natural tumor cell killers that recognize 'missing self' signals or cellular stress ligands, but unlike T cells, they are not MHC restricted and can use innate CAR-independent cytotoxicity. CAR NK cell therapies also seem to be less likely to result in a damaging cytokine release syndrome and could be a powerful method to combat solid tumors that are not responsive to CAR T cells.

Glenn Bantung and Christoph Hess review immunometabolism in the tumor microenvironment. Competition for nutrients between cancer cells, stromal cells and immune cells in the tumor microenvironment, as well as the underlying intracellular metabolism of these cells, is a crucial determinant of the cancer immune and therapeutic response. Some of the latest potential anticancer drugs target mitochondrial enzymes with the aim of altering the balance in favor of effector immune cell functions and to limit cancer cell proliferation. However, clinical trial failures suggest that the available inhibitors and their metabolic targets are not specific to cancer cells or immune cells and altering their metabolism can have opposing therapeutic outcomes. As such, more tailored therapeutics that can be precisely delivered are needed to move this field forward.

In future Reviews, Caitlin C. Zebley, Dietmar Zehn, Stephen Gottshalk and Hongbo Chi cover immune cell dysfunction in the tumor, looking at epigenetic and metabolic processes of immune suppression and T cell exhaustion and strategies to mitigate these processes during immunotherapy. They will also explain the regulation of T cell stemness and strategies to enhance T cell durability for cellular therapy. Martin Roelsgaard Jakobsen deciphers the complicated and sometimes confusing literature of tissue-specific and cell-specific anti-cancer and pro-cancer STING and type 1 interferon functions. Belinda Parker and Nicole Haynes discuss evidence for the immunological control of metastasis. Modeling metastasis and dissecting the cancer interactome have refined our understanding of the metastatic cascade in which anti-tumor immunity controls cancer dissemination, dormancy and outgrowth. Understanding the mechanisms of immune control and escape, including the effect of cells in the metastatic microenvironment, is leading to the discovery of new immunotherapeutic targets. Samir Khleif reviews the field of cancer vaccination. The rollout of the COVID-19 mRNA vaccine has revitalized interest in the field and the hope that vaccination can prevent some cancers or support immunotherapies that target them.

These Reviews and more cancer immunology and immunotherapy content can be found at https://www.nature.com/collections/aadbcbjffa and in future issues of *Nature Immunology*.

Published online: 27 November 2023