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Editorial

Introduction to the Special Issue: The tumor microenvironment and molecular regulation of innate immune cells

This special issue was designed to highlight emerging knowledge centered on the roles of innate immune populations in the tumor microenvironment. A great deal of research effort has been directed at delineating the functions of adaptive immune subsets, primarily T lymphocytes, in tumor immunity. This has led to impressive advances in knowledge and, more importantly, powerful new immunotherapies. Nonetheless, major hurdles remain in the quest to eliminate cancer. Understanding how innate immune cells contribute to tumor growth and anti-tumor immune responses will continue to improve understanding of functional interactions between tumors and the immune system, and may yield novel therapies that improve cancer outcomes.

The ability of the immune response to control tumor growth was recognized over a century ago, with striking cancer regression elicited by injection of live bacteria or bacterial products into tumors. The advent of the modern era of immunotherapy was only made possible, however, through fundamental studies of the immune system, the development and study of mouse models of human cancers, and the effective translation of immune modulating factors or immune cell therapies into clinical practice. Immunotherapy is now viewed as a major approach in cancer treatment, and options for its use are expanding rapidly. Immunotherapies are employed along with classical cancer treatments such as radiation, chemotherapy, or targeted therapeutics. In many cases, however, established therapies have limited efficacy, as tumors escape or evolve, often to reoccur as metastatic lesions that greatly diminish survival outcomes. By contrast, immunotherapy has yielded durable responses, with patients demonstrating undetectable or manageable tumor burden after treatment. Immunotherapy has therefore significantly enhanced the quality of life and lifespan of many cancer patients, underscoring its power and continued potential as a cancer treatment.

A majority of immunotherapies target or utilize T lymphocytes, which comprise a major arm of the adaptive immune response. Immunotherapies such as adoptive T cell therapy using ex vivo expanded T cells from a patient's tumor, or engineered T cells expressing a chimeric antigen receptor (CAR-T), rely on T cell effector populations, which have the ability to directly kill tumor cells. Additional immunotherapeutic approaches use antibodies that block inhibitory molecules that dampen T cell function, thus unleashing potent T cell-mediated tumor immune responses. Despite these successes, it is increasingly clear that a significant fraction of cancer patients do not respond to immunotherapy, and therefore novel approaches are needed in the clinic. Alongside, it has been recognized that T lymphocytes are only one of many immune populations that infiltrate tumors; in fact, the representation of immune lineages within specific tumors varies significantly among cancer types. Tumors contain an abundance of innate immune cells including myeloid lineage cells, which are often found in greater amounts relative to T lymphocytes, as well as other potent innate effectors such as natural killer (NK) cells. Hence, exciting new angles of study center on understanding the function of innate immune cells in tumors. Important questions include whether and how innate immune cells interact functionally with the tumor or tumor-infiltrating T lymphocytes, and whether targeting innate subsets will enhance current immunotherapies, conventional cancer treatment, or lead to novel single agent cancer therapies.

We have drawn on the expertise of investigators studying innate immune cells in cancer for this issue, with articles that cover roles of myeloid- or lymphoid-origin innate immune cells. Beatty et al. review the activities of tumor-infiltrating macrophages in cancer. Macrophages can be an abundant population in tumors, and have been associated with both pro- or anti-tumor immune responses. Here, Beatty et al. significantly extend our understanding of tumor-infiltrating macrophages, highlight their interplay with cancer treatment as well as their effects on therapeutic resistance, and point to new strategies to target macrophages in cancer therapy. Two additional reviews focus on dendritic cells (DCs), which are considered the "professional" antigen presenting population of the immune system yet comprise a relatively rare immune population in tumors. Vatner and Janssen discuss exciting advances in understanding roles for DCs as bridges between innate immune activation signals from cancer and induction of adaptive T cell immunity. Vatner and Janssen also highlight recent work implicating the intracellular DNA sensor STING in the ability of DCs to sense dying tumor cells and activate potent anti-tumor T cell responses. The review by Chrisikos et al. covers mechanisms by which DCs are regulated by cytokines developmentally and in tumors, and highlights emerging information supporting important roles for the cDC1 population in eliciting tumor immunity. Nicholson and colleagues present recent findings centered on the importance of innate lymphocyte subsets in cancer, including tumor-associated innate lymphoid cells (ILCs) and NK cells. Moreover, Nicholson et al. cover exciting recent data revealing a novel NK cell checkpoint that may be exploited for new cancer treatments. The discussion of innate lymphoid cells is continued by Putoczki and colleagues who examine the role of ILC3's and Th17-producing cells in the initiation and progression of gastrointestinal tumors.

Owen and Parker review our knowledge of the unique exchange that happens in the bone marrow niche between bone marrow cells, innate immune cells and disseminated tumor cells. There is much to learn about this fascinating area of research, particularly given that the majority of cancer patients succumb to metastatic disease. Leach, Sansom and Morton discuss the complex role of neutrophils and the mechanisms by which they promote metastatic disease, including the

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secretion of proteases and suppression of NK and CD8 T cell activity. The importance and inherent plasticity of myeloid cells in the context of chronic lymphocytic leukemia is discussed by Hanna et al., who highlight the pathogenic role of various myeloid subsets and the potential for therapies that target these cells.

It is clear that each of the different immune subsets can impact on cancer progression in a multitude of ways. However, it is important to consider the tumor environment as the sum of a complex interplay between different immune subtypes, stroma and the extracellular matrix, set amidst a milieu of cytokines, chemokines and proteases. Careful experimental dissection is required not only at a cellular and protein level, but using appropriate in vivo models that let us examine the impact of changing one aspect of the cellular response amidst a complex multi-cellular environment. By taking this approach, studies reviewed herein and future work offers hope for novel intervention strategies that enhance anti-tumor immunity.

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