Cellular Immunology 343 (2019) 103967

Contents lists available at ScienceDirect

Cellular Immunology

journal homepage: www.elsevier.com/locate/ycimm

Editorial

An ever-increasing body of research has established the importance of the tumor microenvironment (TME) in contributing to the initiation, growth, and progression of cancer [1]. The recent clinical success of cancer immunotherapy, most notably the development of checkpoint inhibitor antibodies targeting the programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) receptors, has brought the immune cells in the TME to the forefront of cancer research and therapeutic development [2]. In this Special Issue, we have assembled reviews from various experts across the fields of cancer and immunology that characterize the phenotypes and functions of cells in the TME, with a special focus on immune cells.

The immune cells in the TME can be broadly characterized into the categories of inflammatory cells with potential anti-tumor function that are undergoing suppression and immunosuppressive cells which inhibit anti-tumor immunity and can promote tumor growth. Tumor infiltrating lymphocytes (TIL) are a key inflammatory cell population in the TME that directly respond to checkpoint blockade immunotherapy and have also shown promise as agents for adoptive cell therapy [3,4]. Badalamenti et al. describe the role of TIL in the TME and their potential use as a biomarker of patient prognosis undergoing standard treatments and as a predictor for response to immunotherapy [5]. A review by Massa et al. also focuses on effector T cells in the TME, detailing the multitudes of obstacles that limit their anti-tumor reactivity including suppressive immune cells, molecular modulators, and metabolites [6]. Myeloid cells are among the most abundant immune cells in the TME, including tumor-associated macrophages (TAMs), dendritic cells (DCs), myeloid-derived suppressor cells (MDSCs), and neutrophils. Schupp et al. review how these cells lead to immunosuppression and detail current therapeutic approaches to attempt to re-direct their activity [7]. Stromal cells also promote tumorigenesis directly through interactions with tumor cells and indirectly though interactions with immune cells in the TME. A review by Liao et al. describes cancer associated fibroblasts (CAFs) and their role in promoting tumorigenesis and suppressing anti-tumor immunity [8].

The immune cell composition can vary greatly across different tumor types (as well as across patients within a cancer type), and the proper the application of immunotherapies to different cancers will require thorough understanding of this composition. Heymann et al. describe the TME of a rare primary bone-cancer, osteosarcoma, that is characterized the presence of T lymphocytes, macrophages, B cells and neutrophils and review the latest immunotherapy approaches being employed to treat osteosarcoma in the clinic [9].

Another important role for the immune system in cancer is in the process of transformation. Chronic inflammation can be a precursor to cancer, and Hashash et al. review the immune cell composition of patients who have inflammatory bowel disease (IBD), a premalignant condition [10].

The cells in the TME largely exert their influence through various intercellular signaling pathways. A review by Binder describes the role of heat shock protein chaperones (HSPs) in initiating and regulating immune responses to tumors via receptors on DCs, ultimately leading to the recruitment and activation of effector T cells [11]. In a primary research paper, Gao et al. present evidence for an inflammatory feed-forward signaling loop between immune cells and lung cancer cells. In this positive feedback loop, high mobility group protein B1 (HMGB1) signals to enhance DC maturation and recruitment, consequently leading to increased IFNγ production in intratumoral T cells. This IFNγ production then leads to additional HMGB1 and other DC recruiting factors being produced by the tumor cells [12]. A review by Akimoto et al. details insights into the role of another key signaling pathway indicated in chronic inflammation, the IL-33/ST2L signaling axis. This pathway has been shown to regulate immune activity in ulcerative colitis, and there are some reports suggesting that it impacts colorectal cancer development as well [13]. Finally, Gallo et al. review the impact of viruses on cells in the TME and the tumor, specifically in the context of patients who are recipients of solid organ transplants. These patients are immunocompromised and are more susceptible to viral infections and virally-induced cancers [14].

Understanding the cross talk and mutual influence of tumor cells and immune cells in the TME will be integral to the future of cancer research. Characterizing the cell subsets and signaling pathways operating in the TME will both help to inform current treatments and ultimately lead to the development of new cancer therapies that can remodel the pro-tumor microenvironment to favor anti-tumor immunity.

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