Preface: Tumor-Associated Macrophages and Tumorigenesis: Therapeutic Targeting Strategies

This special issue of Critical Reviews™ in Oncogenesis (CRO), titled “Tumor-Associated Macrophages and Tumorigenesis: Therapeutic Targeting Strategies,” is a timely subject in the current field of immunotherapy in cancer. Cancer immunotherapy has experienced new milestones in the treatment of a subset of patients with cancers resistant to conventional chemo- and radiotherapies. Such milestones include the application of checkpoint inhibitors, chimeric antigen receptor (CAR)-T cells, engineered CD8 T cells, and other modalities. However, there remain large subsets of cancer patients who are not responsive to such modalities and are in need of new therapies. The resistance encountered is the result of various mechanisms that are clearly not the same for different cancers and different cancer patients and creates difficulties and challenges for developing the appropriate new immunotherapy approaches. Nevertheless, new investigations are being undertaken with novel approaches aimed at overcoming immune resistance.

It has been well documented in the literature that the tumor microenvironment (TME) is immunosuppressive for the majority of cancers and results in cancer immune evasion from the anti-tumor immune response, leading to tumor growth and metastasis. In the TME, tumor-associated macrophages (TAMs) are found at high frequency and exert their immunosuppressive activities via both cell-cell interactions and the secretion of immunosuppressive factors. TAMs are polarized from the anti-tumor M1 phenotype to the immunosuppressive M2 phenotype. Therefore, TAMs have been considered an important therapeutic target to inhibit its immunosuppressive properties and role in immune evasion. Accordingly, such an intervention, alone or in combination with checkpoint inhibitors, should lead to restoring the anti-tumor immune response and inhibition of tumor growth.

In this issue, several chapters deal with different approaches to targeting TAMs in cancer. The article by Jung and Bonavida titled “The Role of TAMs in the Regulation of Immune Resistance in Cancer” reviews the role of TAM infiltration in the TME and their immunosuppressive effects. The role of TAMs in the modulation of CD8 T cell checkpoint expression and TAM-induced signaling pathways responsible for the immune evasion are discussed. Also explored are the means by which one may prevent the polarization of the M1 phenotype to the immunosuppressive M2 phenotype. In addition, a review is briefly presented on various biomarkers associated with TAM immune resistance. Likewise, various pharmacological agents and targeting immunotherapeutic approaches are discussed critically with an emphasis on the use of combinational approaches to enhance their anti-tumor effects.

The article by Priyadarshini et al. titled “Particulate Matter and Its Impact on Macrophages: Unraveling the Cellular Response to Environmental Health” reviews the role of macrophage dysfunction through the inhalation of particulate matter (PM). Macrophage malfunction will likely result in their inability to fight microbes, viruses, and diseases such as cancer. The authors describe the mechanisms by which the PM affects the function of macrophages, such as by triggering inflammation, oxidative stress, and tissue damage. In addition, the authors review the various underlying mechanisms by which the PM affects phagocytosis, intracellular cascades, and the release of pro-inflammatory mediators. Various potential therapeutic strategies are also discussed. The influence of PM exposure to macrophages and their role in the TME is an area that requires further investigation.

The article by McWhorter and Bonavida titled “The Role of TAMs in the Regulation of Tumor Cell Resistance to Chemotherapy” focuses on an area of clinical relevance underlying one of the major mechanisms by which TAMs influence the response of cancer to cytotoxic chemotherapies. There have been reports in cancer patients of a correlation between the level of TAMs in the TME and chemoresistance. The authors review the various mechanisms that
have been postulated by which TAMs may regulate the response to chemotherapy. Several of such mechanisms are briefly discussed and include enhancing drug efflux, facilitating drug detoxification, enhancing cancer stem cell resistance, enhancing angiogenesis, and causing poor penetration of the drug into the TME, thus enhancing the cancer anti-apoptotic pathway. The authors also discuss the various strategies that can target TAMs and reverse chemoresistance.

The article by Festekdjian and Bonavida titled “Targeting the Depletion of M2 Macrophages: Implication in Cancer Immunotherapy” reviews the various approaches that have been considered to deplete the immunosuppressive M2 macrophages as a strategy to restore the anti-tumor immune response in the TMA. Such approaches include the use of microRNAs, targeting specific transcription factors, chemokines and cytokines, and the pivotal CSF-1/CSF-1R signaling pathway that induces M2 macrophages and the use of nanotechnologies to directly target the M2 macrophages. Also discussed are various ongoing clinical trials targeting M2 macrophages, directly or indirectly, and the new challenges faced with these approaches.

The article by Bui and Bonavida titled “Polarization of M2 Tumor-Associated Macrophages (TAMs) in Cancer Immunotherapy” reviews the potential therapeutic approach of polarizing the immunosuppressive TAMs into the anti-cancer M1 phenotype and restoring the anti-tumor immune response. The authors review the various signaling pathways that are involved in this polarization and the approaches that have been reported for targeting the M2 into the M1 macrophage phenotype. Such approaches include the application of HDACs, PI3K inhibitors, TLR agonists, and metabolic reprogramming. The authors also discuss the challenges to be faced with the heterogeneity of different types of cancer.

Overall, this special issue of CRO covered a timely topic in cancer immunotherapy and provided updated scientific investigations of an important approach to restore the anti-tumor immune response via targeting the immunosuppressive TAMs.

Guest Editor:

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