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Reprogramming in cancer

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Immune Cell Lineage Reprogramming in Cancer

Immune evasion in cancer is a key impediment to effective anti-tumor immunity and immunotherapy, as a result of widespread immunosuppression. In cancer, both adaptive and innate immune cells have demonstrated phenotypic and functional instability by reprogramming into distinct cell subsets or states that influence tumor development, progression, and metastasis. Our findings painted a rather full picture of our present understanding of immune cell reprogramming and related processes in cancer, both with and without therapeutic intervention.

Reprogramming Innate Immune Cells in Cancer

Components of the innate immune system, in addition to the adaptive immune system, have a role in tumour development, progression, and immunotherapy response. Innate immune cells come in a variety of shapes and sizes. Some have tumor-killing properties, while others have anti-tumor properties. Innate killer (NK) cells are important in the fight against cancer because of their natural cytotoxicity. Intense myeloid cells, such as Myeloid-Derived Suppressor Cells (MDSC) and Tumor-Associated Macrophages (TAMs) accumulate in many types of cancers, just as suppressive lymphocytes. MDSC differentiation and function have been linked to a number of transcription factors, including C/EBP and c-Rel. Researchers proposed a c-Rel-C/EBP enhanceosome in myeloid precursors containing these known transcription factors as a unified mechanism for the regulation of MDSC signature genes during differentiation in response to aberrant inflammatory cytokine signals, implying potential therapeutic strategies by targeting MDSC specifically [1]. The former has also raised some intriguing proactive questions, pointing out that the in vitro M1/M2 experimental model cannot accurately represent intra-tumoral TAM heterogeneity, and that new technologies, such as single-cell RNA sequencing and spatial localization, could help us better understand TAMs. Although the studies do not give an exhaustive list of innate immune cells, they do emphasize the relevance of innate tumor immunity control and the possibility to harness the flexibility of these innate immune cells for cancer treatment.

Reprogramming Adaptive Immune Cells in Cancer

CD8+ T-cells, as one of the most important anti-tumor cytotoxic T lymphocytes (CTLs), are usually found in the tumor in fatigued and malfunctioning forms. CD8+ T-cell fatigue is a divisive issue in cancer research, with two hypotheses offered to explain its formation: one, effector cell attrition in response to persistent antigen stimulation, and the other, early bifurcation of an exhausted lineage during carcinogenesis [2]. Researchers demonstrated that while both tumor-specific and tumor-nonspecific bystander CD8+ T cells traffic to solid tumors via the chemokine receptor CXCR3, the former cells are exhausted, while the latter cells within the same tumor microenvironment retain memory and functional activity, supporting the notion that chronic TCR stimulation is the central driver of T-cell exhaustion. Early priming without CD4+ T-cells, on the other hand, helps develop CD8+ T-cells into a pre-dysfunctional state, allowing them to produce the transcription factor TCF-1 and co-inhibitory receptors like PD-1, according to some studies. Antigen stimulation causes them to differentiate into TCF-1 terminally exhausted cells, which are controlled by the transcription factor TOX. Importantly, PD-1 inhibition in combination with CD27 co-stimulation and various alternative techniques that mimic CD4+ T-cell assistance might entirely restore the pre-dysfunctional condition, implying novel cancer immunotherapy tactics. Memory bystander CD8+ T-cells, on the other hand, does not express large amounts of PD-1. It's unclear if these cells react to PD-1 inhibition as well as CD8+ T-cells that are pre-dysfunctional [3].

Reprogramming the Tumor Microenvironment

Cancer is increasingly being thought of as a "tumor ecosystem," in which tumor cells interact with other tumor cells, stromal cells, and other immune cells to form an immunosuppressive TME that is a key impediment to efficient anti-cancer immunity. Instead of focusing on a single type of immune cell, researchers looked at

the epigenetic regulation of tumor cells, intratumoral immune cells, tumor-immune crosstalk, and TME heterogeneity from a systemic perspective, suggesting that combining epi-drugs and immunotherapy is an effective cancer treatment strategy. This also touched on how micro biota-derived signals or metabolites may epigenetically control the TME, which is an area that needs to be explored more [4]. The TME provides an environment that is detrimental to immune effector cell nutrition intake and metabolism. Tumor-infiltrating immune cells are controlled by genetic and epigenetic variables, including noncoding RNAs, internally or extrinsically from tumor cells, according to a review of ovarian cancer TME. This study also looks at cytokine signaling and components like JAK-STATs that influence tumor-immune interactions in the TME. The genetic heterogeneity of tumor cells influences the complexity and adaptability of TME, which may be measured by targeted next-generation sequencing. The geographical heterogeneity of numerous tumors of resected multifocal hepatocellular carcinoma can be determined using this method [5]. Furthermore, circulating-free DNA from matched preoperative peripheral blood successfully captures these genetic modifications, making it a viable tool for predicting cancer progression and perhaps guiding the selection of the best treatments for cancer patients, including immunotherapies.

Reprogramming Immune Cells and TME in Response to Cancer Therapy

Due to its reversibility, cancer treatments that attempt to transform the TME from immunosuppressive to immune-supportive are likely to trigger immune cell lineage reprogramming, which might be a target for future therapeutic strategies. Various cancer immunotherapeutic approaches are currently being used in the clinic, with immune checkpoint inhibitors (ICIs) targeting PD-1, PD-L1, and CTLA4 showing the most promising results, despite the fact that overall response rates in many types of cancer remain low, particularly in cancers with high levels of immunosuppressive cells in the TME or insufficient infiltration of effector cells into tumor.

Based on this putative molecular relationship, combining ICIs with angiogenesis inhibitors to minimize immunosuppression while increasing effector cell penetration into the tumor to reprogram the TME might improves the result of ICI-based therapy [6]. A thorough review of the mechanisms of vascular endothelial growth factor signaling in tumor immune evasion and progression, as well as preclinical and clinical trials of employing the combined strategy for the treatment of advanced non-small cell lung cancer. Immune-related side effects, in contrast to the positive outcomes, are a key concern for ICI-based treatment.

Conclusion

Updates on the effects of immune cell lineage reprogramming on tumor genesis, progression, and treatment results are provided in this article. Despite the fact that cancer immunotherapy has emerged as a viable treatment option for cancer patients, there is still much to learn about TME control, which is hampered by the flexibility and heterogeneity of immune and tumor cells. We are certain that each publication published under this Research Topic will contribute to the discovery of novel cellular and molecular candidates or pathways that may be used to build cancer-fighting therapies.

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