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Cancer-Immune Microenvironment: A Review

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ABSTRACT

Malignant growth cells, stromal tissue, and extracellular network make up the tumor microenvironment. The tumor microenvironment is significantly influenced by the immune system. Malignant tumors are not a collection of altered cells, but rather an additional organ made up of non-cancerous cells that make up a large portion of the tumor mass and have turned bad and lost the ability to maintain the communication necessary for maintaining the tissue's homeostasis. The tumor microenvironment is made up of a variety of important components, such as tumor parenchyma cells, fibroblasts, mesenchymal cells, blood, and lymphatic arteries, as well as tumor-invading immune cells, chemokines, and cytokines. Another fundamental reason for linking the tumor genotype to the participating immune cells is the release of tumor-inferred chemokines, which are controlled by certain oncogenes. According to ongoing research using a BRAFV600E and Pten-deficient mouse model of melanoma, constitutive tumor-inborn WNT/-catenin signaling is associated with poor immunological penetration and insufficient anticancer T cells, largely because CD103+ DC recruitment and recurrence are decreased. Even before dispersed malignant tumor cells reach a secondary organ, immunological alterations brought on by the tumor have an impact on the development of metastatic infection. Systemic immune tolerance and alterations in the characteristics of surrounding myeloid cells can favorably influence a tumor's capacity to develop a metastatic location. Currently, it is widely believed that the immunological circumstances in the tumor microenvironment play a fundamentally important role in the anticipation, development, and progression of tumors. Studies on a variety of malignant tumors have provided compelling evidence that the state of the tumor microenvironment is closely related to the course of the disease. The review's objective is to provide an overview of the impact of host immunological factors on the development of the tumor microenvironment and subsequent illness.

Keywords: Cancer; Microenvironment; Prognosis; Therapy; Tumor

Abbreviations: TME: Tumor Microenvironment; VEGF: Vascular Endothelial Growth Factor; PDGF: Platelet-Derived Growth Factor; MMPs; Matrix Metalloproteinase; MDSC: Myeloid-Derived Suppressor Cells; TLRs: Toll-Like Receptors; BCG: Bacillus Calmette-Guérin

Introduction

Malignant growth cells, stromal tissue, and extracellular network make up the tumor microenvironment. The tumor microenvironment is significantly influenced by the immune system. Certainly, extensive research has been done in the preceding few decades on the puzzling relationship between malignant development cells and the host immune response. Several immune deficits have been linked to accelerated tumor growth in both animal and human models [1,2]. It has been extensively documented [3-5] that transplant patients who receive long-term immunosuppressive medication have a greater tumor incidence.

Moreover, mice with weakened immune systems because of genetic modifications get cancer more frequently [6-9]. It is currently widely accepted that strong immune system tumor surveillance is necessary to maintain the host's homeostasis. The immune system's cancer reconnaissance may ultimately fail, although playing a crucial role in host defense. Prior to becoming clinically noticeable, the immune system first eliminates cancer cells. After there comes an equilibrium phase, during which less immunogenic tumor changes

are determined until the malignancy eventually «escapes» immune monitoring [10,11]. Yet, the persistent inflammation brought on by chronic conditions may also promote the emergence of new cancers [12].

Gastric, colorectal, hepatic, and cervical cancers are all closely linked to basic, ongoing provoking reactions [13,14]. This type of expression of several immunological gene products during ongoing inflammation appears to create an excellent milieu for the emergence and spread of cancer [10,14]. Interestingly, extensive genomes studies being conducted on cancer patients have revealed a link between the tumor microenvironment's characteristics—specifically, the level of host tissue inflammation—and a better prognosis for the patient [15-17]. An immunosuppressed microenvironment with a predominance of natural immune components routinely benefits the tumor. On the other hand, patients who maintain active, pro-inflammatory immune responses inside the tumor microenvironment have superior results [18,19]. The review's objective is to provide an overview of the impact of host immunological factors on the development of the tumor microenvironment and subsequent illness.

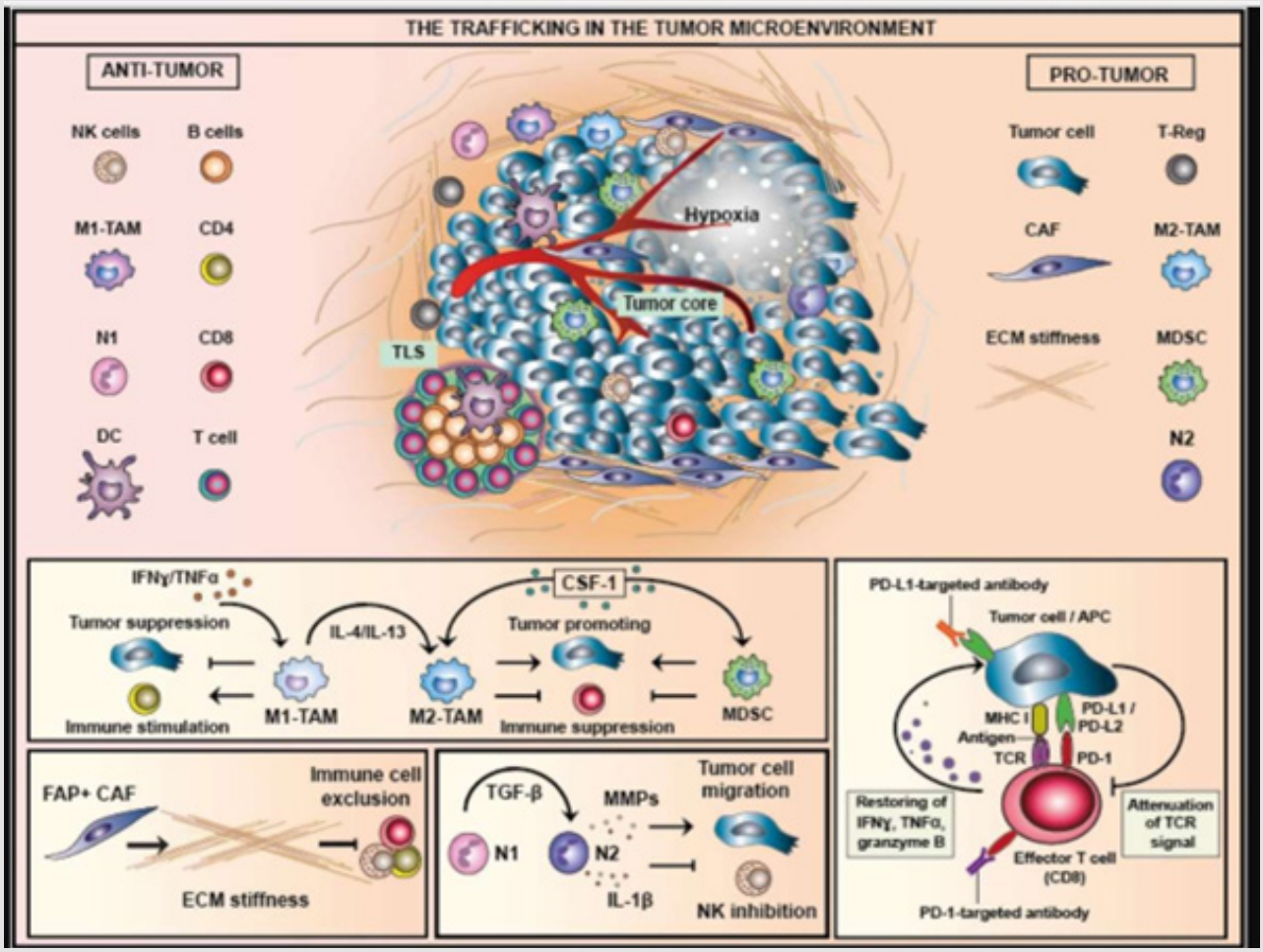

Figure 1: The trafficking in the tumor microenvironment [24].

The Tumor Microenvironment

Malignant tumors are not a collection of altered cells but rather an additional organ made up of non-cancerous cells that make up a large portion of the tumor mass but have turned bad and lost the ability to maintain a communication that would have enabled tissue homeostasis [20]. These cells include immunological cells as well as fibroblasts, adipocytes, pericytes, vascular endothelial cells, and others [21]. Comparatively to what occurs during organogenesis during development, tumor and stromal cells co-proliferate, and communication between the various segments results in a constant phenotypic and practical adaptability. Via junctions, receptors, and

a variety of indicators produced by the many cell types enclosed in a three- dimensional extracellular network, dynamic equal correspondence between cells and the surroundings is guided (ECM). This combines ECM-rebuilding enzymes with glycoproteins, proteoglycans, cytokines, and growth factors, providing both fundamental assistance and accurate information [22]. The ability of stromal and immune cells to digest cells and function alters dynamically when tissue homeostasis is disrupted [23]. The tumor microenvironment (TME) is made up of this intricate network (Figure 1) [24], and tumor research must make a substantial effort to create a multidimensional map that will make clear the highways and byways of the front line of malignant tumours.

Characteristics of the Tumor Microenvironment

The tumor microenvironment contains a variety of important components, such as tumor parenchyma cells, fibroblasts, mesenchymal cells, blood, and lymphatic arteries, as well as tumor-invading immune cells, chemokines, and cytokines [25]. These numerous and varied components meet the definition of a complex system, wherein the interdependence between the pieces is multilevel, multiscale, and nonlinear in nature [26]. Each of these components has the potential to significantly contribute to the development and spread of tumors. The construction and renovation of the extracellular network is the responsibility of these non-immune segments, and tumor associated fibroblasts are a major source of growth factors that promote the development of carcinoma cells [27]. While existing blood and lymphatic arteries may serve as routes for local assault and distant metastasis, the formation of new blood vessels is essential for tumor progression as the mass increases [28,29]. Many studies have demonstrated that the development of factors like vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and matrix metalloproteinase (MMPs), which stimulate vein development, contribute to the spread of tumor cells and predict poor patient endurance [29].

Other host cell lineages, like mesenchymal stem cells, can separate into the many cell types required to fuel angiogenesis as the disease progresses in addition to producing new cancer cells [30]. Yet, due to their fundamental role in the development of tumors and the management of cancer, the immunological components of the tumor microenvironment have gained attention in recent years. Malignant tumor outcomes are mostly determined by immune cells that penetrate tumors, including myeloid-derived suppressor cells (MDSC), tumor-related macrophages, and cytotoxic lymphocytes. Several studies have shown that increased MDSC and tumor-associated macrophage concentrations promote tumor growth via a variety of suppressive mechanisms [31,32]. On the other hand, different aggressive tumor cells have a good prognosis when cytotoxic lymphocytes are present in the tumor microenvironment [33-35].Chemokines and cytokines are two additional immunological components of the tumor microenvironment that may alter the local balance of proregulatory and anticancer immune responses [36,37].Innate immunity components, such as the toll-like receptors (TLRs), can identify risk signals in the microenvironment, such as heat shock proteins, nucleic acids, and HMGB1 transformed, dying, or dead tumor cells, and these signals can trigger anticancer immune responses [38,39].

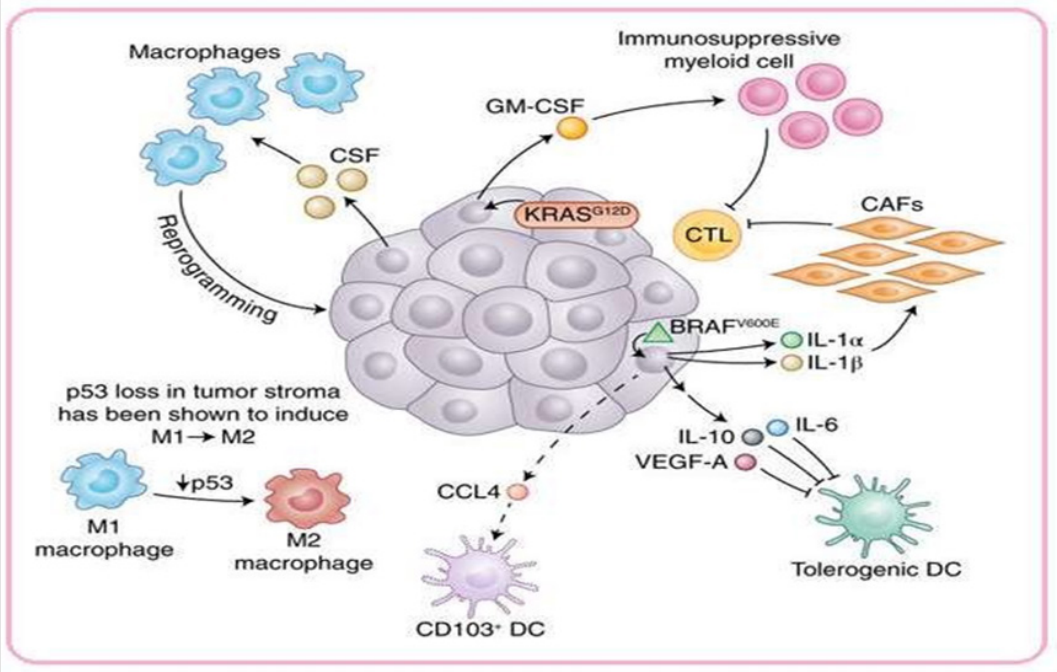

Figure 2: How tumor genotypes and phenotypes shape TIME [41].

Interconnectivity of Tumor Genotypes and Phenotypes and the Tumor Immune Microenvironment

It remains to be established how the composition of the tumor immune microenvironment is influenced by cytokines and chemokines released by cancer, cancer oncogenes, and mutation landscapes (TIME). Although there are many models that can demonstrate relationships between immunological configuration and cancer genotype/phenotype, these models are not sufficiently robust to allow this agreement to be immediately used toward therapeutic intervention [40,41] (Figure 2).

Tumor-Derived Chemokines

Another fundamental reason for linking the tumor genotype to the participating immune cells is the release of tumor-inferred chemokines, which are controlled by certain oncogenes. Current data from a BRAFV600E and Pten-deficient mouse model of melanoma suggest that constitutive tumor-inborn WNT/-catenin signaling is associated with poor immunological penetration and insufficient anticancer T cells, mostly because CD103+ DC recruitment and recurrence are reduced [42]. In vitro DC migration assays and transcriptional analysis of tumor cells have revealed that constitutive WNT/-catenin signaling causes reduced production of Ccl4, a potent chemo attractant for a variety of myeloid cells, including CD103+ DCs. This finding may help to explain why CD103+ DC recruitment is reduced and CD8+ T cell penetration into the tumor microenvironment is similarly poor. Several studies in mice have shown that tumor discharged CCL2 causes the enrollment of CCR2+ old-style monocytes in the tumor, where they split into TAMs, a protumoral myeloid population [43]. This is true even if the precise oncogenic determinant of expression is unclear.

The Immune Environment in Metastasis

Even before dispersed malignant tumor cells reach a secondary organ, immunological alterations brought on by the tumor have an impact on the development of metastatic infection. Systemic immune tolerance and alterations in the characteristics of surrounding myeloid cells can favorably influence a tumor's capacity to develop a metastatic location. Certain combinations of immune populaces that have the ability to both promote and suppress metastasis development quickly gather tumor cells as they spread to distant tissue locations [43,44]. An astonishing amount of evidence supports the pro-metastatic ability of both macrophages and classically inflammatory monocytes [45-47]. Mice lacking Csj-1, which is required for the development of CSF-1-subordinate cells, as well as monocytes and macrophages, demonstrate delayed progression of mammary cancer to metastasis, according to a novel study using the MMTV-PyMT breast cancer mouse model [44]. According to recent research, macrophages and their ancestors populations observed in pre-metastatic tumor locations greatly advance metastasis in addition to TAMs in the primary malignancy [47,48]. According to studies conducted on mice, CD4+ T cell-derived IL-4 indirectly promotes breast malignant tumor spread by regulating macrophage phenotype, so demonstrating a role for both the innate and adaptive immune systems in stifling beneficial anticancer effects [45].

Unusual waves of myeloid cells absorb tumor material as leading metastatic tumor cells arrive and die, delivering antigen to both pro- and antitumor immune compartments, according to a recent study using multiphoton intravital imaging of the lung pre-metastatic location in mice [48]. In any event, the majority of the tumor material is overpowered by monocytes, which may sequester significant tumor antigen from stimulatory DC populations. Moreover, a decline in monocytes results in increased antigen loads in those DCs.Non-classical or «watching» monocytes have been shown to exhibit anti-metastatic capabilities, despite the fact that classical inflammatory monocytes have a proven capability for metastatic advancing [49]. Neutrophils play fundamental roles in tumor improvement, just like monocytes and macrophages. Neutrophil levels are elevated in the blood and accumulate in peripheral organs during tumor growth, contrary to what several preclinical mouse cancer models have demonstrated [50-54]. Neutrophils' roles in metastasis, however, are still debatable. While some studies have focused on neutrophils' anti-metastatic activity [54,55], others have found that they have pro-metastatic characteristics [50,52,56-59]. By direct cytotoxicity against spreading malignant tumor cells, tumor-entrapped neutrophils have been shown to prevent lung metastasis in the 4T1 mouse breast cancer model [54]. Furthermore, according to a recent study, a subpopulation of neutrophils that communicate with the MET proto-oncogene protects against the growth of metastasis [56]. On the other hand, it has been discovered that neutrophils, in the MMTV-PyMT breast cancer model,

promote metastasis to the lung by increasing the number of metastasis-starting malignant tumor cells through the release of leukotrienes [50]. Neutrophils have also been discovered to promote metastasis by stymieing antitumor immunity in a model of lobular breast carcinoma [52]. Cancer-incited IL17-delivering T cells are responsible for the systemic growth and polarization of pro-metastatic neutrophils [52], demonstrating the close interaction between the innate and adaptive immune systems during metastasis. A growing body of evidence suggests that immunostimulatory myeloid cells can also enhance anticancer T cell responses, even though much of what is known about immunological organization at the metastatic location focuses on cells with immunosuppressive capabilities. Despite consuming the majority of tumor antigen, macrophages usually fail to successfully activate T cells in vitro [60], which is consistent with their recently reported pro-tumorigenic activity. In any case, CD103+ DCs are far superior T cell activators [60,61], and their absence leads to a crucial expansion in pneumonic metastasis [48], suggesting that even in the metastatic site, CD103+ DCs are important for inciting

potent antitumor CD8+ T cell responses. This is despite the fact that their presence in cancer and metastatic sores is sparse. Collectively, these data support the idea that treating myeloid cells to reduce immunosuppression and stimulate T cell responses may be a useful immunotherapeutic approach to treating patients with metastatic malignant tumor cells.

Cancer Immunotherapy

The host immune system is being strengthened by medications. The holy grail of tumor immunotherapy remains the ability of the host immune system to recognize and eradicate cancer cells with minimal systemic damage [62]. William B. (Coley's poison) pioneered the use of immunotherapy as the primary therapy for the management of lethal malignancies in 1891.In patients with delicate tissue sarcomas, Dr. Coley directly injected streptococcus bacteria into tumors, muscle tissue, or intravenously «to provoke erysipelas and the immune system» to attack the tumor [63]. Despite emerging clinical use of chemotherapy and radiation therapy, its use was eventually discontinued 40 years later [64] due to its extreme toxicity and lack of consistent results. Coley's original theories regarding tumor immunotherapy, which still hold true today, suggest that activating immunity can undoubtedly result in tumor dismissal. In the 1970s, Morales et al. established the viability of the bacterium Bacillus Calmette-Guérin (BCG) in the treatment of superficial bladder cancer, which was the first of the advanced applications of Coley's standard [65]. This clinical indication is supported by recent research by Old et al. that demonstrates the antitumor effects of BCG in a mouse model [66]. In addition to his work on BCG, Old also conducted extensive research and worked on the interpretation of tumor necrosis factor in 1975 [67]. However, the idea that the immune system might be crucial in the treatment of many malignant tumors remained outside the purview of conventional oncology [68]. The disclosure and depiction of dendritic cells by Ralph Steinman in 1973, the portrayal of MHC constraint in 1974 by Zinkernagel and Doherty's, the documentation of NK cell activity in 1975 by Eva Klein's, the concentrate in gigantic size of cytokines in breast malignant cells, renal cell cancer, glioblastoma, lymphoma, and melanoma during the 1980s, began the state-of-the-art safe based cancer treatment in clinical medication [68].

Conclusion

Currently, it is widely believed that the immunological circumstances in the tumor microenvironment play a fundamentally important role in the anticipation, development, and progression of tumors. Studies on a variety of malignant tumors have provided compelling evidence that the state of the tumor microenvironment is closely related to the course of the disease. Whether a pro-tumor or anti-tumor immune response predominates in the microenvironment depends on the presence of immune cell types or chemicals. For malignant tumor immunotherapies to be successful in the future, it is now widely accepted that the immune response must be altered from one that elevates tumors to one that damages them. Controlling the immunological borders that define the tumor microenvironment may work to affect the balance of host responses leading to effective immunization. Improved knowledge of the functions of immune cells and chemicals in the tumor microenvironment will be crucial for the development of more effective novel treatments.

Data Availability

All of the required data will be available upon request to the corresponding author.

Authors' Contributions

The author wrote the review article alone.

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Conflicts of Interest

There are no conflicts of interest.

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