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Review Article

The critical role of tumor microenvironment in cancer evolution and metastasis

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Abstract

Tumor microenvironment (TME) is the indispensable module that hosts the tumor and fuels the development of cancer, the reason of death of nearly 8.8 million people in the year 2015. It is the source of nutrients and nurturing environment that supports tumor growth, progression as well as metastasis. TME acts as the platform to escape immune response by cancer cells and contribute towards drug resistance. Therefore, TME has become the immense interest of researchers across the world in order to develop novel anticancer agents, especially in terms of manipulation of its components. TME plays a key role cancer initiation, invasion, angiogenesis, metastasis, dysfunction of immune response and drug resistance and the importance of studying its components one-at-a-time cannot be stressed enough. The purpose of this review is to (1) delineate the role of various components of TME including extracellular matrix, cancer associated fibroblasts, tumor associated macrophages, tumor associated neutrophils, myeloid derived suppressor cells, natural killer cells, dendritic cells, B lymphocytes, T lymphocytes, pericytes and adipocytes and relate it to cancer pathogenesis, (2) outline the roles of these components in cancer evolution starting from initiation to metastasis (3) and discuss some recent strategies for the continued development of anticancer agents. Furthermore, recent identifications of novel therapeutic targets as well as new pharmacological intervention strategies will also be discussed accordingly.

Keywords: Cancer, Tumor, Tumor microenvironment, TME, Cancer metastasis, Anticancer Therapies, Tumorigenesis.

1. Introduction

Tumor microenvironment is the heterogeneous inhabitants of numerous types and subtypes of cells that accommodate the tumor within to facilitate cancer evolution which is the second leading death causing disease [1]. Nearly 8.8 million people died of cancer in the year 2015 and researchers predicts 12 million people will die in 2020 which posits us against economic challenge as well costing 1.16 trillion dollar in 2010[1, 2]. Therefore, researchers are trying to understand every aspect of cancer evolution patterns starting from tumor growth to cancer metastasis. Malignancy of cancer depends largely on the formation, invasion and metastasis of the tumor which are the benchmarks that transform locally formed tumor into a systemic, metastatic and life-threatening disease [3, 4]. Primarily, cancer invasion occurs as a result of controlled cytoskeletal dynamics by the tumors and followed by the migration to adjacent tissues and leads to metastasis when tumor colonize at distant organ [4-6]. Researchers have understood almost all the characteristics of cancer including cancer cells multiplication, invasion, metastasis, resisting apoptosis, evade from growth suppression, angiogenesis, eliminating cell energy, evading immune system, gene mutation, tumor associated inflammation etc. however, the characteristic behind the formation of cancer is still unknown [7-9]. Recent studies suggest that malignant properties of cancer is not only the result of formation of tumor due to genetic mutation but also interactions between the cancer cells and its surrounding cellular and non-cellular components that promotes the proliferation, metastasis and progression of cancer[10-13]. Collectively these cellular and non-cellular components are collectively named as tumor microenvironment (TME) which resemble the seed and soil theory proposed by Stephen Paget in 1889

where primary tumor is the seed and surrounding microenvironment is the soil and outcomes from the seed depends on the fertility of the soil[14]. Therefore, TME is marked as the vibrant ecosystem that promotes cancer progression at all stages of carcinogenesis by recruiting other stromal cells surrounding it [10, 15, 16]. The knowledge of TME has changed the perception regarding cancer evolution and its treatment strategies from tumor centered view to tumor ecosystem since negligible change in any components of any ecosystem drastically affect the stable environs [10, 17-20]. Since Traditional therapies of cancer are not always effective since many cancer cells recur after therapies therefore Pienta *et al* suggest the 'Ecological Therapy' that targets the ecosystem surrounding the primary tumor which will interfere with any of the components of the tumor ecosystem to bring down the cancer evolution[17, 21, 22]. The goal of this review is to summarize the components of the tumor microenvironment and their role during various stages of tumor progression as well as to discuss the strategies and therapeutic agents to target the tumor microenvironment to counteract the cancer progression.

2. The role of tumor microenvironment and its key components in cancer

Cancers are not only the result of malignant cells but also a complex combination of malignant cells and collaboration of different types of malcontrolled cells around cancer that creates the microenvironment. The tumor microenvironment is decisive for invasion, metastasis and maintenance of tumorigenesis which is considered as a key contributor for cancer progression and drug resistance [10, 13]. The components of the TME include endothelial cells, and pericytes, platelets, mast cells, neutrophils, inflammatory monocytes, activated adipocytes, a-smooth muscle actin, myofibroblasts, mesenchymal stem cells, myeloid-derived suppressor cells (MDSCs), macrophages, CD8 T-cells, NK T-cells, CD4 T-cells, and B cells, and tissue fibroblasts [23-25]. All of these components of the TME together develop an ecosystem during cancer progression and engage with different hallmarks including proliferation of cancer cells, avoiding of apoptosis, angiogenesis, inhibiting hypoxia, impeding the immune system, and activating immune cells to support invasion and metastasis [26-30]. Throughout the tumorigenesis, microenvironment is changed in molecular as well as cellular level due to the interaction between incipient cancer cells, host structural cells as well as adaptive and innate immune cells while incipient neoplastic cells recruit and activate some stromal cells to permit cancer cells to invade surrounding normal tissue and to metastasize in distant organ [31]. Though these cells are not malignant themselves but due to their environment and interactions with each other as well as with cancers cells, they acquire an altered dynamic function of cancer promotion during all stages of carcinogenesis [32].

2.1 Extracellular Matrix

Extracellular matrix (ECM) is the blend of different proteins with some other molecules, which is one of the dominant components of TME that provides support to the cancer cells and play a vital role in cancer evolution [33-35]. During tumor progression, all the conformations and components available in ECM and altered by ECM remodeling in causes change in structure, composition and properties of the ECM that is deliberated as the prerequisite for cancer cells invasion from initial tumor cells [36, 37]. ECM remodeling also facilitates other incompetent cells to invade and contribute to TME. Researcher found that MMPs (Matrix metalloproteases) triggered by CAFs (Cancer Associated Fibroblasts), tumor cells, TAMs (Tumor Associated Macrophages), are responsible for ECM remodeling by degrading ECM proteins [5]. Moreover, HIF-1(hypoxia-inducible factors) also activates gene encoding protease which are responsible for degradation (MMP2, MMP9, MMP14) and remodeling (LOX, LOXL2, LOXL4) of ECM [38]. ECM consists of different components including collagen, elastin, fibronectin (FN), laminin, cytokines, growth factors, proteolytic enzymes, proteoglycans and other molecules [39]. Among all the components collagen, elastin, laminin, fibronectin and proteoglycans make up the basement membrane and responsible for the stiffness of tissues [40]. Though all the components of ECM contribute to cancer invasion however, fibronectin (FN) and collagens are the major determinants of tumor microenvironment [41]. Fibronectin regulates the spatial orientation and solidity of cells but when it is overexpressed in tumor cells, it promotes cancer propagation, invasion and metastasis [39]. Moreover, fibronectin acts as a port in ECM, while assembling with laminin it creates a meshwork that performs like a tract for cancer cells metastasis [42]. Relatedly, collagens are considered as the highway for the invasion of cancer cells through ECM. Collagens are generously present all over the ECM and determine the foremost attributes of it since various subtypes of collagen modifies the morphology and cytoskeletal properties of the cells present in TME [41]. Studies reported that peripheral cells were exposed in collagen demonstrated over growth of cells and collective migration. ECM are found to provide elasticity, ductility and compressive strength to cells in TME interacting with different types of growth factors like chemokines and angiogenic factors present in ECM[37]. Basically tumor heterogeneity and complexity depends on the biochemical and mechanical properties of the ECM. Mechanical parameters of ECM including matrix thickness, stiffness, porosity and density provide the diversity of tumor phenotypes that scaffolds the cancer cells proliferation, migration as well as mode of direction [43]. These

mechanical characteristics of ECM undergoes intense changes during cancer evolution what regulates cancer cells behavior and functions. For example, local tumor cells invasion is facilitated by the increase of ECM stiffness during tumor progression through cells adhesion and generation of high traction force due to formation of stress fibers [44]. Another research found that epithelial cells migration swiftness increases due to increase of the matrix stiffness due to the alteration of cellular contractility [44]. In addition, density and porosity of ECM also have significant effect on the rate of cancer cells invasion and mode of invasion. With the increase of porosity, cancer cells invasion mode switch from collective invasion to single cell invasion whereas one more study found accumulation of cells due to the high density of ECM which eventually promotes of speed of cell migration [45].

2.2 Cancer Associated Fibroblasts

Cancer associated fibroblasts (CAF) are the one of the principal heterogeneous cells in tumor microenvironment and play dynamic role in cancer prognosis. CAFs are the irreversibly activated form of fibroblasts from stromal cells [35]. Fibroblasts are responsible for wound healing process with the production of various types of collagens and basement membrane proteins which are the key components of extracellular matrix [46]. CAFs are the important elements for cancer that increase the ability of tumor proliferation, invasion and metastasis by releasing different types of cytokines, growth factors and metalloprotein[35, 47]. Cancer is characterized as the wound that do not heal. During natural wound healing process, activated fibroblasts named as myofibroblasts remain functional for a time being but in tumor microenvironment they remain active perpetually. Activation of CAFs depends on several factors including, communication between neoplastic and fibroblast cells, adhesion of molecules, leukocytes, reactive oxygen species, microRNA and several growth factors e.g. TGF-b1, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and interleukin-6 (IL-6) [48]. All these factors specifically interacts with their receptor to facilitate epithelial to mesenchymal cell transition (EMT) which is responsible for affecting firmness of the core tumor, boosting metastasis, esteeming cancer invasion and immunosuppression [49]. Studies show that CXCL12 [Chemokine (C–X–C motif) ligand 12 (CXCL12)] and MMP-2 (matrix metallopeptidase 2) proteins are significantly present in CAFs that provoke EMT to enhance the cancer invasion and metastasis [50, 51]. MMP-2 are very much uttered in cancer cells and promotes EMT by degrading ECM and releasing various cytokines [50]. SMADs proteins are also abundantly present in CAFs promoting cancer invasion [52]. Researchers found that CAFs promote and metastasize tumor through HGF, TGF-β, platelet-derived growth factor (PDGF) and promote angiogenesis via fibroblast growth factor 2 (FGF2), VEGF that eventually leads to cancer invasion [49, 53]. On the other hand, Interleukin-22 (IL-22) and HCT116 cells exposed to have invasive phenotypes that advances cancer progression. Overexpression of Galectin-1 protein present in tumor microenvironment also spreads cancer development in neighboring cells and are responsible for various types of cancer like laryngeal cancer, breast cancer, prostate cancer etc. [54]. On the other hand, growth factors released in CAFs activates SRC, the growth factor receptor-bound protein 2 (GRB2) and phosphoinositide-3-kinase (PI3K) by means of phosphorylation of tyrosine residues of the receptors and regulates the expression of genes like activating protein 1 (AP-1) and erythroblast transformation specific (ETS) protein [55-58]. ETS are found to phosphorylate transcription factors that support EMT and results in tumor cells progression with ensuing proliferation [56]. CAFs also regulate immune system, interacting with neuroendocrine cells and immune-inflammatory cells by expressing PDL-1, PDL-2, and ICAM-1 that suppress immune response and mutually promotes initiation, invasion, progression and metastasis of cancer [59]. Therefore CAFs are considered essential for cancer development since they remodel the extracellular matrix (ECM), recruits inflammatory cells in cancer progression, initiates angiogenesis and most importantly stimulate cancer cells proliferation straight away.

2.3 Tumor Associated Macrophages

Tumor associated macrophages (TAM) are one of the most numerous inflammatory cells present in TME and perform as the regulator of hypoxia, angiogenesis, tumor fibrosis as well as helps to immune escape[16]. They are considered as the requisite collaborator of cancer cells invasion, migration and metastasis. Basically, their interference with TME decides their phenotypes and response and function to the cancer progression [60]. These cells are stemmed from monocyte precursors, as well as converted to M2 phenotype from M1 due to the activities of various chemokines such as IL-4, IL-10 and TGF-b [31]. M2 phenotype promotes the cancer progression whereas M1 phenotypes exert antitumor capabilities at the early stage before M2 become dominant [61]. TAM cells mount up in the hypoxic and necrotic zones of TME because of the upregulation of HIF-1 dependent CXCR4, release of VEGF, EMAP2 etc. [62]. Unfortunately, TAMs have pro-tumorigenic activities that makes tumor prognosis difficult [63]. Cancer cells in the TME prolongs the survival of TAM releasing VEGF and M-CSF (macrophage colony-stimulating factor) [64, 65]. TAMs are accountable for the ECM remodeling and dissolution owing to the release of MMPs, plasmin and uPA (urokinase-type plasminogen activator) which empowers cancer cells migration as well [66]. In addition, researchers found TAMs exceedingly

accumulated with oligonucleotide transcripts that encodes for angiogenic factors making TAMs prime contributor of angiogenesis [67]. One of the significant functions of TAMs is secretion of higher level of TGF (transforming growth factor) cytokine that ominously diminishes capabilities of T cells and helps cancer cells to attain stem cells like features and stimulates cancer cells fibrosis [68]. TAMs are also shown to take part in tumorigenesis as well as supporting the growth of cancer cells via releasing TNF, EGF and IL-6 [16]. Lastly, TAMs help cancer cells to escape immune system by suppressing Th1 adaptive immunity caused by poor presentation of antigens as well as by releasing immunosuppressive agents like TGF-b, IL-10 etc. [69].

2.4 Tumor Associated Neutrophils

Neutrophils are the indispensable components for antimicrobial and anti-inflammatory activities in the body and contribute 50-70% of circulating leukocytes. Recent studies elucidated functions of neutrophil in cancer environment beyond their defense mechanism. In cancer patients, phenotypic changes in monocytes take place that generates myeloid-derived suppressor cells (MDSCs) and differentiated into tumor-associated neutrophils (TANs) in tumor microenvironment which are functionally and epigenetically diverse from normal neutrophils [35]. Moreover, the phenotypic change induces CD11b+, CD33+, CD66+ expression and secretion of cytokines and chemokines in higher amount from TANs that promotes tumor growth, angiogenesis and metastasis [70]. Different types of cytokines, chemokines invites neutrophils in the tumor microenvironment along with genomic instability and tumor cell lysis. TANs are categorized into two subtypes based on their function to tumor microenvironment N1 and N2 where N1 demonstrate anti-tumor properties and N2 is a pro-tumor phenotype [71]. N2 is the culprit for cancer cell proliferation, angiogenesis and metastasis [72]. First of all, TANs reduces the CD8+ and T-cells response against tumor as well as reduces the conversion of arginine to ornithine and urea that increases cellular proliferation and dampen immune response [70]. In addition, TANs are observed to contain proteins like matrix metalloprotease (MMP-9), neutrophil elastase (NE), serine proteases which are found to unswervingly uplift cancer cell proliferation [73]. Secondly, TANs induces angiogenesis in tumor microenvironment by releasing NE and MMP-9, as well as upholds cancer invasion. MMP-9 decomposes the ECM whereas NE degrades the basement membrane prompts the discharge of VEGFα that is responsible for angiogenesis [74]. Recent studies suggest that, CXCL6 and CXCL1 chemokines contribute to angiogenesis through CXCR2 chemokine receptor [75]. Along with other factors, hepatocyte growth factor (HGF) controls angiogenesis through direct action on cellular complex and indirectly elevating VEGF and IL-8 secretion. Lastly, several studies found association of TANs in tumor metastasis through diverse mechanism. According to Welch *et al* TANs secret basement membrane decomposing enzymes including collagenase-IV and heparanase that assist metastasis [76]. TANs in association with TAMs revealed to promote cancer cells extravasation through IL-8 induced ICAM- integrin signaling that form cluster on tumor cells, activates cellular passage pathways, induce cell-cell aggregation and aids tumor cell survival from immune surveillance [77]. In addition, NE in higher amount decomposes the extracellular matrix and aids in cancer cells invasion as well as metastasis [73]. Besides, according to Huh *et al* circulating tumor cells expedites the endothelium migration to cancer cells by direct anchoring to vascular endothelium that initiates formation of further metastases [78].

2.5 Myeloid derived Suppressor Cells

Myeloid-derived suppressor cells (MDSCs) are defined as the myeloid cells which are unlikely the mature myeloid cells but pathologically active and demonstrate immunosuppressive competences [79]. MDSCs are elucidated to upkeep tumor growth and metastasis by means of different mechanisms including tumor microenvironment altering, preventing immune-mediated destruction of cancer cells, inducing cancer cells “stemness”, formation of a premetastatic niche, and transition of epithelial to mesenchymal (EMT) [80]. Numerous constituents of MDSCs include two broad classes but small group of myeloid precursor, undeveloped mononuclear monocytic cells phenotypically similar to monocytes (M-MDSCs) and undeveloped granulocytic polymorphnuclear (PMN) cells phenotypically similar to neutrophils (PMN-MDSCs) [81]. CD11b+, CD14+, CD33+, CD15− HLA-DR−/lo are the cells of M-MDSCs [82]whereas CD14−, CD15+ HLA-DR−/lo CD66b+ are the PMN-MDSCs cells present in TME[83]. All the cells in MDSCs are responsible for the suppression of immune response as a result of TGF-β, IL-10, COX2, iNOS, and ARG1 expression as well as reduced presence of T cells, presence of T_{reg} among other cells and cysteine sequestration [80]. In addition, MDSCs cells generate various mediators like MMP-9, VEGF, bFGF which reconciles angiogenesis and metastasis of cancer [84]. Activated MDSCs along with mediators including VEGF, Tumor-derived hypoxia-induced lysyl oxidase, IL-6, IL-10 and S100A8/A9 altogether establishes pre-metastatic niche for cancer cells which is depicted as the preparation of remote organ for cancer cells entrance [85]. Moreover, recent studies have found engagement of MDSCs in EMT depending on CD11b+ cells which is component of M-MDSCs [85]. Lastly, myeloid derived IL-6 were found with stem cell phenotypic property in a mouse model which is deliberated as the main reason of MDSCs induction to EMT [86].

2.6 Natural Killer Cells

Natural killer cells are the subsections of lymphocytes that demonstrates substantial anti-tumor phenotypic capabilities because of malignant cells killing and rendering cancer metastasis [87]. NK cells receive signals from several receptors regarding any kind of phenotypic changes in their surrounding environment and initiates cytotoxic activity to kill those infected cells [23]. Numerous types of receptors expressed include CD94:NKG2A, KIR, NKp44, NKp30, NKp46, NKG2D, DNAM-1 which are not only involved in cytolytic activities but also regulates the secretion of cytokines and chemokines like TNF-α, GM-CSF, IFN-γ, RANTES and MIP1-[88]. Interestingly, NK cells can increase their cytokines secretion using different TLRs e.g. TLR-2, TLR-3, TLR-7 in response to a number of PAMPs (Pathogen Associated Molecular Patterns) [89]. Cytolytic activation of NK cells depend on some factors including stimulation of cytokines like IL-2, IL-15, IL-12 etc. and ligation of receptor e.g. NCRS which is a current interest to develop immunotherapy against cancer [90, 91]. Few recent studies have found the correlation between NK cells with EMT that mediates NK dependent cellular response in cancer during EMT due to the upregulation of NKG2D activating ligands and downregulation of HLA-I expression which promotes immunogenicity[92]. In recent times, Glasner et al. discovered anti-metastatic capabilities of NK cells engaging NKp46 receptor. According to him, fibronectin 1 (FN1) is expressed due to the signals generated by IFN-g (secreted by NK cells) as a result of ligation of NKp46 receptor that shrinks cancer cells metastasis [93]. Additionally, NK cells present in TME is a good prediction of cancer prognosis. However, several studies stated that NK cells in TME might not kill the tumor cells appropriately due to their anergic phenotype generated by cancer cell facilitated transforming growth factor beta (TGF-b) [94]. NK cells also upregulate HLA-I and make cancer resistant against NK cell interceded killing [95]. Furthermore, several studies found modification of immunogenicity due to the modulation of tumor cells phenotypes by NK cells that confer resistance to NK cells and T cells [96]. NK cells are also found to upregulate PD-L1 which is a ligand that aids cancer cells to escape host immune system [97].

2.7 Dendritic Cells

Dendritic cells are the immune cells present in body with dendrites like projection which functions as an operational link between innate and adaptive immunity of the immune system [98]. DCs are the most prominent antigen presenting cells in the body that proceed antigens to activate T lymphocytes assist in growth and proliferation of B lymphocytes. Dendritic cells are developed from bone marrow and upon maturation with activation migrate to lymphoid tissues [98]. Next to activation, DCs can lengthen the patient survival from different carcinomas as well as reduces metastasis in oral, head, neck tumors when are in primary lesions [99]. DCs can adjourn cancer progression as well as lymph node metastasis as well. In addition, they expose significant prognostic phenotypes and correlates with pathologic grade during tumor diagnosis [16, 100, 101]. However, cancer at advanced stage accelerates dendritic cells apoptosis in the tumor microenvironment that diminishes functionality of DCs and lead to dysfunction at times. Numerous factors are responsible for tumor associated apoptosis of dendritic cells including neuropeptides, nitric oxide, gangliosides and some other molecules [102]. In addition, deposition of excessive lipid layer on DCs contributes to DCs dysfunction. Adenosine deposition, decreased pH, lactate upsurge and hypoxia blight the functions of DCs in TME [103]. DC with altered functionality and impaired antigen presentation in TME supports the tumor progression [104]. Additionally, tumor associated DCs are found to be a feeble stimulator of immune response attributable to their faulty activation and differentiation. Along with poor stimulation, tumor associated DCs divert anti-tumor DCs into immunosuppressive cells that assist to evade immune system. Inf-DCs demonstrate suppressive phenotype along with exudation of tumor promoting IL-6 [105]. Then again, IL-10 in TME impedes CD103+CD11b DCs to produce IL-12 that amends antigen specific T cell responses [106]. Last but not the least, pDCs a subtype of DCs in several studies elucidated to have tumorigenic properties that stimulate tumor progression and poor prognosis [105].

2.8 B Lymphocytes

In recent times, B lymphocytes are explicated as an impending contributor to TME that shape up the activities of other immune cells, secrets cytokines along with production of antibody [107]. Typically B cells were believed to only secret antibodies and stimulate T cells activation, however recent studies have found various phenotypic expressions with contribution of 25% cell mass in some cancers [108, 109]. These cells are the crucial player in the TME with distinctive subsets including germinal B cells, naïve B cells, memory B cells, plasma cells and recent advancement in cancer research has found existence of another type of B cells coined as regulatory B cells B_{reg} as similar as T_{reg} cells [110]. Therefore, based on the different actions of different subtypes, B cells are discovered to exhibit both pro and antitumor immune action. Moreover, B cells expression facilitates better prognosis for different types of cancer. To begin with, let's talk about the antitumor response of B cells due to antigen presenting properties, secretion of antibodies and production of inflammatory molecules [16]. First of all, antibodies are produced (e.g. TIL B cell derived antibodies, antibody against p53, IgG) in TME generates antitumor response and cause complement dependent breakdown of cancer cells. These antibodies furthermore makes complex

with antigens and initiate complement system to influence T cell infiltration in TME [111]. Then again, B lymphocytes perform as immunomodulatory cells owing to the secretion of numerous cytokines and chemokines, accountable for antitumor response [112]. Lymphotoxin a cytokine produced by B cells aids the formation of TLOs (tertiary lymphoid organs) that confers improved prognosis and longer patient survival [113]. Moreover, B cells exhibits their antigens presenting capabilities too using B cells receptor which is the basically one of prime mechanism of memory response from this cells in addition to T cells expansion accumulation in TME[114, 115]. Several studies in mouse models have found association of B cells for stimulation of CD4+ and CD8+ T cells [116]. However, apart from these antitumor responses, B cells are discovered to suppress the antitumor responses in cancer patients to facilitate cancer growth and progression via production of tumorigenic factors, antibody dependent immune response and secretion of cytokines [117]. First of all, some of the antitumor antibodies produce CICs (circulating immune complexes) that triggers activation of Fcγ receptors; remodel ECM, initiates pro-angiogenic functions results in cancer cells proliferation and progression [118-120]. On the other hand, B cells produce lymphotoxin, a factor that initiates lymph angiogenesis via canonical and non-canonical NF-kB signaling to expedite tumor progression [121, 122]. B cells in TME modify androgen receptors via upregulation of IL-8 level to boost cancer metastasis [123]. Lastly, B cells secret numerous types of cytokines proficient to suppress antitumor immunity by inhibiting T cells, DCs and NK cells. To be more specific, like T_{reg} cells, B_{reg} cells upholds antitumor immunity suppression by secreting IL-10, IL-35, and TGF-b etc. that supports cancer growth [111]. TGF-b secreted by B_{reg} transform CD4+ T cells into T_{reg} cells that blocks the functions of NK cells and cytotoxic T cells to promote cancer metastasis when B_{reg} in MZP (for marginal zone precursors) amplify immunosuppressive atmosphere. These cells are also observed liable for inhibition of cancer cell clearance [124, 125].

2.9 T Lymphocytes

T cells are one of the most obvious cells present in TME also known as TIL (tumor infiltrating lymphocytes) with increasing number in cancer patients, among them only one type reveals anti-cancer property [126, 127]. In broad spectrum, T cells include two major types of immune cells known as CD4+ and CD8+ inhibits tumor metastasis though there is controversy that T cells helps in tumor growth [128]. CD4+ cells are known as helper T lymphocytes whereas CD8+ cells are known as cytotoxic T lymphocytes (CTL). CD8+ cells disrupts cancer cells with the help of perforin, IFN-γ, granzyme B and factors provided by other components of TME [129, 130]. In addition, CD8+CD45RO+ cytotoxic memory T cells are concomitant with high prognosis capabilities of carcinoma [131]. Besides CTL, helper T cells CD4+ are subdivided into 4 major categories TH_1, TH_2, TH_{17} and T_{reg} which modulate the cytotoxic activities of CD8+ cells [132, 133]. TH_1 and TH_2 cells mostly controls the anticancer properties with discharge of TGF-β, IFN-γ, IL-2 from TH_1 cells and IL-4, IL-5, IL-6 from TH_2 cells that accelerates the activation of CD8+ cells as well as macrophages[132, 134, 135]. These cytokines and chemokines also uphold the production of nitric oxide, activation of dendritic cells and recruitment of eosinophils results in anticancer properties [136, 137]. On the other hand, TH_{17} cells are the most exceptional T lymphocytes since they can either inhibit cancer or promote based on their activation due to signals generated in TME [138]. TH_{17} cells are differentiated into TH_1 cells that secrets various cytokines e.g. IFN-γ, TNF-α, IL-2 to mediates the anticancer regulations on the other hand, they can promotes the cancer cells survival as well by amending immune response [138, 139]. TGF-β in the TME precedes to TH_{17} cells conversion into TH_{17}/T_{reg} cells for obstruction of CD8+ T cells cytotoxic activity and facilitates cancer progression [135]. T_{reg} cells are basically the suppressive T cells characterized by CD25 and FOXP3 [140] transcription factor and derived from naive T cells in presence of IL-6 and TGF-β [133]. T_{reg} cells produce IL-10, IL-17, TGF-b, and CTLA4 along with adenosine which performs as an immunosuppressive agent in favor of cancer [141]. Last of all, T_{reg} cells worsen cancer prognosis when they are present in high volume in TME [12, 141].

2.10 Pericytes

Pericytes are the contractile and vigorous cells found in interaction with blood vessel to wrap them and concomitant to vasculature. Pericytes alleviates growing vasculature, modifies embryonic vasculatures, inhibits vascular leakiness and reduces unnecessary sprouting [142]. These functions of pericytes are thought to prevent cancer invasion and metastasis since they stabilize micro vessel walls lining [12, 16, 127]. Research found angiogenesis due to the deficiency of pericytes in TME [143]. Pericytes in TME are considered as important components capable of causing tumor homing and an emerging target to cancer therapies associated with vascular normalization [144]. On the other hand, pericytes dysfunctions at advanced stage of tumor are found guilty for angiogenesis, and metastasis along with avoidance of immune system [145, 146]. Pericytes releases growth factors in TME that stimulate the endothelial cells which in turn generates signaling molecules like TGF-β, PDGFR-β etc. to recruit supplementary pericytes for stabilization [147]. Since cancer proliferates rapidly, vascular maturation does not take place and make basement membrane spasmodic which proceeds to abnormal functions. Therefore, tumor associated blood vessels become unevenly shaped, messy, disproportionately branched, convoluted, leaky and loosely

bound with pericytes that results in angiogenesis [143, 147, 148]. Whereas, reduced number of pericytes causes tumor growth, invasion and metastasis but augmented pericytes are responsible for drug resistant against cancer [144]. Then again, stemness is one of the major wickedest sides of pericytes in TME [144]. These cells are found to differentiate into diverse cells including adipocytes, vascular smooth muscle cells, chondrocytes, neural cell lineages and myofibroblast[149]. Therefore, pericytes are deliberated as the precursor of mesenchymal stem cells (SMCs) that spectacles bimolecular markers as similar as SMCs and participate in tumor development, self- renewal of cancer cells as well as cancer aggressiveness [84, 150]. Cheng *et al* has found a significant and reciprocal connection between pericytes and cancer stem cells that aids in cancer development [151]. Pericytes are furthermore accountable for the evasion of immune system by cancer cells due to upregulation of Rgs5 and PDL-1[152]. PDL-1 prevents the activities of CD8+ T cells to evade immune system whereas Rgs5 enhances the tumor cell persistence [153, 154]. In addition, CD90, CD248, PDGFR-β are expressed in pericytes which also demonstrates immunosuppressive capabilities [155]. Last of all, due to the abnormal functionalities in TME, decreased pericytes coverage to micro vessels spread the tumor cells at distant organs [144].

2.11 Adipocytes

According to WHO 600M people were obese in the year 2014 which is one of the reasons for intensifying numerous types of cancer including colorectal, breast, endometrial etc. and poor prognosis of them[156]. Adipocytes are the main culprit for fat accumulation in the body which is one of the key components of tumor microenvironment. Adipocytes constitute 18–25% and 25–31% of body masses for man and woman respectively, classified into two categories named white adipocytes and brown adipocytes [157]. These adipocytes secrets adipokines like leptin, adiponectin, hormones, chemokines, cytokines and more than 400 types of factors intensifying tumor growth, invasion, metastasis and drug resistance[158]. First of all, adipocytes in close contact with tumor cells are responsible for tumor growth and promotion. Several studies have discovered, adipocytes in TME release numerous types of adipokines that promotes the cancer progression. For example, IGF-1R released in TME from adipocytes triggers MAPK and PI3K/Akt pathway for cancer growth and survival [159]. Leptin: Adiponectin ratio is another critical parameter for cancer cells since leptin upsurges cancer proliferation via ERK1/2 pathway whereas, adiponectin decreases cancer cells via activation of AMPK pathway, and inhibition of PI3K/Akt, NF-κB, Wnt/β-catenin and ERK1/2 pathways [160]. Adipocytes also supports the tumor growth with sufficient supply of energy that cancer cells use throughout the progression. Adipocytes secret free fatty acids (FAA) which are stored in the form of lipids that generates ATP through fatty acid β-oxidation and serve as the power bank for carcinogenesis [157, 161]. Secondly, adipocytes are active component for angiogenic process that forms uncontrolled blood vessels. VEGFA an angiogenic growth factor is secreted by adipocytes and leptin is found to upregulate VEGF using NF-κB and HIF-1[146, 162]. Thirdly, adipocytes are imperative component for cancer cell invasion and metastasis. Adipocytes secret and express IL-6, IL-18 and exosomes which participate as a cancer promoter as well as migration and invasion [163]. Moreover, several MMP (matrix metalloproteinases) that remodel the ECM and initiate cancer cell invasion and migration are from adipocytes [157, 158]. In addition to all these factors, adipocytes can cause tumor homing for metastasis via secretion of diverse chemokines and cytokines comprising MCP-1, IL-6, IL-8 and TIMP-1 (tissue inhibitor of metalloproteinase-1) [164]. Furthermore, cancer cells protection is another feature of these cells through aggregating the adhesion of ECM, secretion of adipokines and exosomes [157, 165]. Lastly, and endocrine therapies do not perform as much good as in obese people like lean people therefore, adipocytes develop resistance against the endocrine drugs and chemotherapies [157, 166].

3. Anticancer therapy focused on TME

Tumor microenvironment ismade up of abundant heterogeneous cells and mediators which communicate with each other and demonstrates both pro and antitumor activities. This cancer associated feature of TME opens up a new window for developing new anticancer therapies targeting the components of TME that will inhibit cancer cells growth, invasion and metastasis [13, 167]. For example, targeting ECM remodeling can provide easier access of chemotherapy agents to the cancer cells [168]. Diverse enzymes e.g. FAK, SHH inhibitors are providing promising clinical outcomes for cancer therapies [169, 170]. We have seen the compassionate engagements of CAFs in cancer advancement what make these cells a tempting target for cancer treatment. The most convenient approach is to block the feedback interaction between CAFs and cancer cells. Researchers now a days focusing on blockage of different pathways including HGF/MET signaling pathway, TGF-β signaling, PDGF/PDGFR signaling pathway [146, 171]. Moreover, MMP inhibitors are revealed as a good therapeutic target in addition to fibroblast markers like FAP [172]. There are strong manifestation of cancer evolution due to the presence of TAMs in cancer which is a novel target for cancer therapies. Targeting TAMs include reduction of monocyte recruit in TME targeting CCL2-CCR2 pathway, inhibition of CSF1/CSF1R signaling pathway to obstruct TAMs activation and reprograming the TAMs using various

components like Thymosin-α, β-glucan [173-175]. Moreover, therapies targeting TGF-β and IFN-β has turn out to be a good approach for targeting TANs. Disrupting the cancer homing abilities with anti-CXCR2 antibodies, pointing on chemokines and cytokines from TANs are recent therapeutic strategies that inhibits cancer progression [176, 177]. MDSCs in TME are another target for the cancer treatment since they are accountable for tumor growth [79]. These cells can be eliminated from TME using mild chemotherapies, can be inactivated in TME by up regulation of NRF2 [178]. In addition, ATRA (all-trans-retinoic acid) is found to divert myelopoiesis from generating MDSCs results in less MDSCs cells in TME [179]. Furthermore, NK cells are other potent constituents in TME that can be used to cancer therapies. For example, clinical data indicates the safety of autologous and allogeneic natural killer cells in different types of malignancies [180]. NK cells in TME has opened a vast platform to work on for developing anticancer therapies like production of genetically modified NK cells, monoclonal antibodies, Bi- and Trispecific Antibodies, designing CARs and immunomodulatory drugs that shows better therapeutic actions than conventional therapies[91, 181]. Dendritic cells are the neglected components in TME are the major source of CXCL9 and CXCL10 chemokines responsible for cancer promotion [182]. CD103+ DCs are the target of interest to inhibit cancer promotion whereas DC based vaccines are the point of interest to improve cancer patients [183, 184]. Then again, Pericytes present vascular endothelium layer create a protective layer and hinders the insertion of chemotherapeutic agents. As a result cancer treatment targeting pericytes is basically focused on its inhibition to endothelium [145]. VEGF secreted from Pericytes and PDGFR from EC generates the shield, therefore therapies target to reduce the capabilities of VEGF and PDGFR in order to ease the entrance of chemotherapeutic agents [185-187]. Furthermore, adipocytes are discovered to have protumorigenic functions, as a result targeting various factors regarding adipocytes accumulation is a recent area of cancer treatment. The factors include targeting adipocyte differentiation, insulin resistance, PPARγ agonists, dysfunctional adiposity, estrogen synthesis/ aromatase inhibitors and tumor metabolism [157, 188]. Additionally, immunotherapies based on T lymphocytes has demonstrated unprecedented outcomes in clinical trial. These therapies include ACT Immunotherapy known as transfer of potential transfer of T cells to TME, Block immune checkpoint and production of T cells dependent vaccines such as MAGE-A3, gp100, MART-1[189-191]. Last of all, BCRs (B cells receptors) are another emerging approach for developing anticancer therapies, targeting B lymphocytes along with B_{reg} cells to prevent cancer progression[125, 192-194].

4. Conclusion

Cancer cells are highly adaptable and elastic to all the therapies available as well as the modifications due to the presence of contiguous heterogeneous TME components and results in poor prognosis. Since the TME components are responsible for numerous pathways of cancer evolution, therefore the question arise, can TME components be a better target to prevent cancer progression? Numerous studies have uncovered several TME based anticancer strategies however all the pathways are not revealed yet. Therefore, this is the time to decipher all the possible pathways to develop novel anticancer drugs.[195-196] For instance, targeting the adipocytes to diminish storage of lipids which are the power bank of carcinogenesis. Immunomodulation can be a prodigious pathway since suppressive immunity is one of the main reasons behind cancer evolution that help to escape host immune system. In addition, inhibition of non-malignant cells present is TME are liable for drug resistance as well as cancer progression could be another source to emerge anticancer therapies. Then again, the interaction between cancer cells and host cells play key roles in malignancy through signaling molecules that open up a new hole-in-the-wall for cancer treatment. Last but not the least, modification of the B cells present in TME to produce specific antibodies against the cancer cells can resist cancer progression. However, targeting any single molecular pathway will instigate drug resistance, therefore targeting different aspects of TME e.g. combination of antiangiogenic agents to stop growth, cytotoxic agents to eradicate the tumor, low dose chemotherapies to maintain the leftover of cancer cells, immunomodulation of TME to lessens immune suppression possibly will aid us grasp the inclining peak where tumor promotion is incapacitated, chaotic blood vessels are repaired with normal blood supply and malignant cells are shattered along with the production of new antigens which could be used for the production of cancer cells specific monoclonal antibodies, a current interest of research for potential anticancer therapies. Since this novel approach to develop anticancer drugs is focused on components of tumor microenvironment, further studies are warranted for better understanding of the mechanisms of tumor microenvironment modulation that will assist us to develop the long awaited anticancer therapies to rule over the second leading cause of death, cancer.

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