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Tumor microenvironment: recent advances in various cancer treatments

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Abstract. – This is a review regarding different types of cancer treatments. We aimed at analyzing the tumor microenvironment and the recent trends for the therapeutic applications and effectiveness for several kinds of cancers.

Traditionally the cancer treatment was based on the neoplastic cells. Methods such as surgery, radiation, chemotherapy, and immunotherapy, which were targeted on the highly proliferating mutated tumor cells, have been investigated. The tumor microenvironment describes the non-cancerous cells in the tumor and has enabled to investigate the behavior and response of the cancer cells to a treatment process; it consists in a tissue that may have a predictive significance for tumor behavior and response to therapy. These include fibroblasts, immune cells and cells that comprise the blood vessels. It also includes the proteins produced by all of the cells present in the tumor that support the growth of the cancer cells.

By monitoring changes in the tumor microenvironment using its molecular and cellular profiles as the tumor progresses will be vital for identifying cell or protein targets for the cancer prevention and its therapeutic purposes.

Key Words:
Cancer, Tumor, Tissue microenvironment, Therapeutic applications.

Introduction

Cancer is one of the major causes of death globally. More than 11 million people are diagnosed with cancer and this rate has been estimated to increase to 16 million by 2020. In 2017, nearly 13% of all cancers diagnosed in adults ageing 20 and older were rare cancers, defined in this report as cancers with fewer than 6 cases per 100,000 people per year[1]. An early detection and treatment of the cancer for a better health management are needed. The cancer evaluation is carried out covering the nature of cancer, risk assessment, prevention, and health management[2]. A tumor is an abnormal growth of cells that have no functional purposes and the potential to spread to the adjoining cells or organs or other parts of the body. Not all tumors are cancerous; indeed, benign tumors do not spread to other parts of the body[3-5]. There are many types of cancers that affect the humans[6] and the cancer cells show no signs or symptoms at an early stage of development. The causes of the benign tumor are not very clear and they may be due to reasons such as genetic disorders, unhealthy food habits, occupational stress, exposure to radiations and/or intake of toxins, may be caused by infections or inflammations, etc.. Generally benign tumors do not require treatment or removal. If there is a recommended treatment, the tumor is removed by surgical procedures. The surgical procedure to remove the tumor should not damage the surrounding healthy cells or tissues. The non-surgical procedure commonly followed is medication or by a measured quantity of radiation. Tumor shows signs of symptoms as it starts to grow in mass. Symptoms of the growth of the tumor are related to the location where they are growing. The common types of benign tumors are adenomas, fibroids, hemangiomas, lipomas, meningiomas, myomas, nevi or moles, neuromas, osteochondromas, papilloma, etc.[7]. The common local symptoms of cancer may be due to the growth of the mass of the tumor or its process of ulceration. The growth of the mass in the brain may affect the normal functioning of the brain, the growth of a mass in the lungs can

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cause blocks in the bronchus, leading to various respiratory disorders. The growth of a mass in the breast tissues can lead to breast cancer and the lump can be easily felt. The ulceration of the mass leads to bleeding of the tumor and based on the location shows up various symptoms at various stages of the abnormalities. The growth of the masses with the ulcerations may be painless at times and the individual may feel the pain at the advanced stage of cancer[8]. The systemic symptoms of the tumor occur due to the effects that are unrelated to direct or metastatic spread. The commonly observed symptoms are unexplained weight loss; fever, feeling fatigue, skin condition changes, etc.. The metastasis form of cancer spreads from its original growth position to the near by locations by spreading to the adjoining cells or tissues, lymphatic spread to regional lymph nodes or by hematogenous spread via the blood to the various parts of the body[9].

Treatment for Cancer

There are many types of cancer treatment methods depending on the type of cancer and at what stage it is advanced. There is no particular method or technique foe treatment for cancer. Treatment options can be chemotherapy, surgery, radiation therapy, hormonal therapy, targeted therapy including immunotherapy, etc.. In some cases the treatment plan may use a combination of the treatment methods to have maximum effectives for the treatment. Each of the treatments has its own side effects to the patient; then, it is always necessary for the doctor to discuss the treatment plans with the patient and their family and obtain their concurrence before proceeding with the treatment plan. In some cases, it is always safe for the patient and the doctor to go in for a second opinion for proceeding with any treatment plan. A complete removal of the cancer tissues without causing damages to the adjoining tissues is the required goal for any treatment plan. The complete of removal of the cancer tissues is limited by property of the cancer tissues to spread to the adjoining tissues or spread to distant sites by microscopic metastasis. Treatment procedures such as chemotherapy and radiotherapy have negative side effects on the normal healthy tissues. The basic purpose of a cancer treatment plan is to have cure for the cancer and, when a complete cure is not possible, the treatment plan should be to suppress the cancer to a subclinical state and maintaining the normal state for the subject to lead a normal quality of life.

Types of Cancer Treatments

With the technological advances the cancer treatments have undergone tremendous changes and the understanding of the underlying biological processes have increased. Various cancer treatment methods have been practiced in the past and many innovative methods, such as targeted therapy, are being practiced currently. Since new information and understanding of biological process of cancer tissues are emerging regularly, new treatment procedures and plans are being developed and modified to have increased effectiveness and precision of the treatment, thereby enabling the survivability of the patients and improving their quality of life. Cancer can be treated by surgery, chemotherapy, ionizing radiation therapy, hormonal therapy, targeted therapy etc.

Surgery

Treatment of cancer by surgical procedure is commonly practiced for non-hematological cancers. By surgical method, the surgeon removes the cancer tissues from the body. The surgical procedure can give a complete or partial cure for the cancer. There may be side effects of the surgical procedure depending on the type of cancer and the health condition of the individual. If the cancer has metastasized to other parts of the body, then removal of cancer completely by surgical process is not possible. The growth of the cancer cells follows the Halstedian model of cancer progression[10] where the tumors start growing locally and spreading to the lymph nodes and to the rest of the body. The treatment of cancer by surgical procedure can be done to cancers that are localized and the tumor is of small size.

Some of the cancer treatments by surgical procedures are mastectomy of breast cancer, brain tumor by neurosurgery, prostatectomy for prostate cancer, kidney cancer, lung cancer, liver cancer etc.. Surgically, the aim is to remove the locally grown tumor or removal of the entire organ if fully spread to the organ. Cancer cells cannot be completely removed by the surgical procedure, and even a presence of a single cancer cell that is invisible can regrow into a new tumor and spread to other parts of the body. The chances of reoccurrence of the cancer can be assessed by carrying out biopsy by the pathologist; the surgically removed tissues is analyzed for the presence of healthy tissues. Evaluating the presence of healthy or cancerous tissues, the amount of cancerous tissues left in the patient can be analyzed, which is useful to investigate the staging

of cancer[11,12]. Other treatment procedures, such as chemotherapy, can be done before or after that the surgical procedure is carried out to remove the affected tissues.

Chemotherapy

The method of chemotherapy is carried out through the use of drugs, usually known as anticancer drugs, to kill or destroy the cancer cells. These drugs interfere with the growth of tumors and even destroy the cancer cells. The chemotherapy is generally considered as an effective method of treatment of cancer; however it can cause severe side effects as they can destroy either healthy cells or tissues. The side effects caused by the chemotherapy treatment depend upon the type of drugs being used for treatment and the type of the cancer, its locations and also on the individual's response to the particular chemotherapy treatment. The side effect on the cancer patient is not related to the effectiveness of the treatment and it vanishes once the treatment process is completed. Generally the chemotherapy treatments are prescribed to a subject in measured quantity or in a specific number of intervals over a period of time. Sometimes the chemotherapy is administered as two or more drugs at the same time; this method of treatment is known as combination chemotherapy[13].

Radiation Therapy

Radiation therapy method of cancer treatments makes use of high doses of radiation generally ionizing radiation to kill cancer cells and destroy the tumor tissues. This treatment is commonly used in conjunction with the surgery to remove or reduce the size of the tumors. The radiation therapy is commonly delivered externally or internally to the desired location. The radiation therapy given both internally or externally can also damage the normal cells and induce the side effects of the normal cells due to these ionizing radiations[14].

The radiation therapy is commonly used to treat most of the types of tumor such as cancers of the brain, breast, cervix, larynx, liver, lung, pancreas, prostate, skin, stomach, uterus, etc.. Radiation therapy is also used to treat cancers like leukemia and lymphoma[15]. The radiation dose to be delivered to the cancer or tumor site depends upon various factors such as age of the person, type of the tumor, location of the tumor, and possible side effects on the radiation source on the nearby tissues and organs. The radiation therapy is not used if the cancer is at the advanced stages or if the tumor is located at highly vulnerable locations. The cancer cells grow and divide faster than the normal cells. The radiation therapy uses a specialized equipment to deliver measured doses of radiation to the cancer cells. The radiation therapy kills tumor cells by damaging their DNA either directly or by creating free radicals within the cells that can in turn damage the DNA. This treatment uses high-energy ionizing radiation such as x-rays. These treatments are commonly practiced only on adults and in children they have significant side effects.

Immunotherapy

Immunotherapy is a method of cancer treatment that helps the immune system to fight cancer. This is also known as biologic therapy, which stimulates the disease fighting mechanism within the patient's body to fight the cancer. A high number of researches have been carried out to treat the cancer by immunotherapy, such as monoclonal antibodies that block specific protein function by binding to cancer cells, which train the immune system to recognize and attack the cancer cells. This method of treatment is safe and does not have any major side effects.

Hormone Therapy

The hormone therapy fights cancer by changing the amount of hormones in the body to treat certain types of cancer that depend on these chemicals to grow and spread. This treatment method is used for treating cancers of breast, reproductive system and prostrate. The side effects depend on the type of cancer, age, sex and the type of drug used in the treatment.

Targeted Therapy

The targeted treatment of cancer targets the cancel cells that re-enable the cells to grow, divide and spread. Targeted treatment uses specific agents for the deregulated proteins of cancer cells. The small molecule targeted therapy drugs are generally inhibitors of enzymatic domains on the mutated, overexpressed, or otherwise critical proteins within the cancer cells.

Tumor Microenvironment

Tumor Microenvironment (TME) is the cellular environment in which the tumor exists in the human system. It includes the blood vessels, fibroblast, cells that contribute to the immunity, bone marrow-derived inflammatory cells, lymphocytes, signaling and the extracellular matrix

(ECM)[16,17]. The tumor existing can interact with the surrounding microenvironment leading to different effects. The tumor can interact with the microenvironment by releasing extracellular signals, can promote tumor angiogenesis and induce peripheral immunity tolerance. The immune cells in the microenvironment can also affect the growth and evolution of the cancerous cells[18]. The tumor microenvironment contributes to the tumor heterogeneity. Tumor microenvironments are recognized as key-contributing factors for studying the cancer progression and drug resistance to the cancer treatment. Figure 1 illustrates tumor microenvironment showing the cell-cell interactions that contribute to cancer cell progression, invasion and metastasis. The cancer is not isolated in the environment; instead, it is due to the collaboration of different types of the uncontrolled growth of the cells. The cancer cells also exhibit a characteristic features that are different from that of the healthy tissues, which enables for pharmacological targeting. The cancer cells are malignant cell masses that can damage the adjoining cells. The interactions between the malignant and normal cells create the tumor microenvironment. The non-malignant cells of the tumor microenvironment have a dynamic and often tumor-promoting function at all stages of carcinogenesis[19]. The condition within the tumor microenvironment has also varying the levels of metabolic characteristics of tumors and can be used for planning the treatment[20]. The common features of tumor microenvironments suggest that targeting the nonmalignant cells, or mediators of their communication, have applications across different tumor types that could complement other treatment options[21]. The tumor – to progress and develop into a life-threatening entity –has to develop four characteristic features: (a) ability to move; (b) capability to degrade the extra cellular matrix (ECM); (c) capability to survive in blood; (d) capability of establishing itself in a new tissue environment. The tissue microenvironment is of critical importance to study the tumor progress and its development within the tissues[22]. The role of cancer tissue microenvironment during the growth and the progress stage is of critical importance for studying and understanding the cancer tissue biology and will be useful for diagnostics and therapeutic purposes. The following sections investigate the tumor associated stroma at the primary sites enable to support the tumor growths, with a role of vasculature, fibroblasts, macrophages, immune suppressor cells

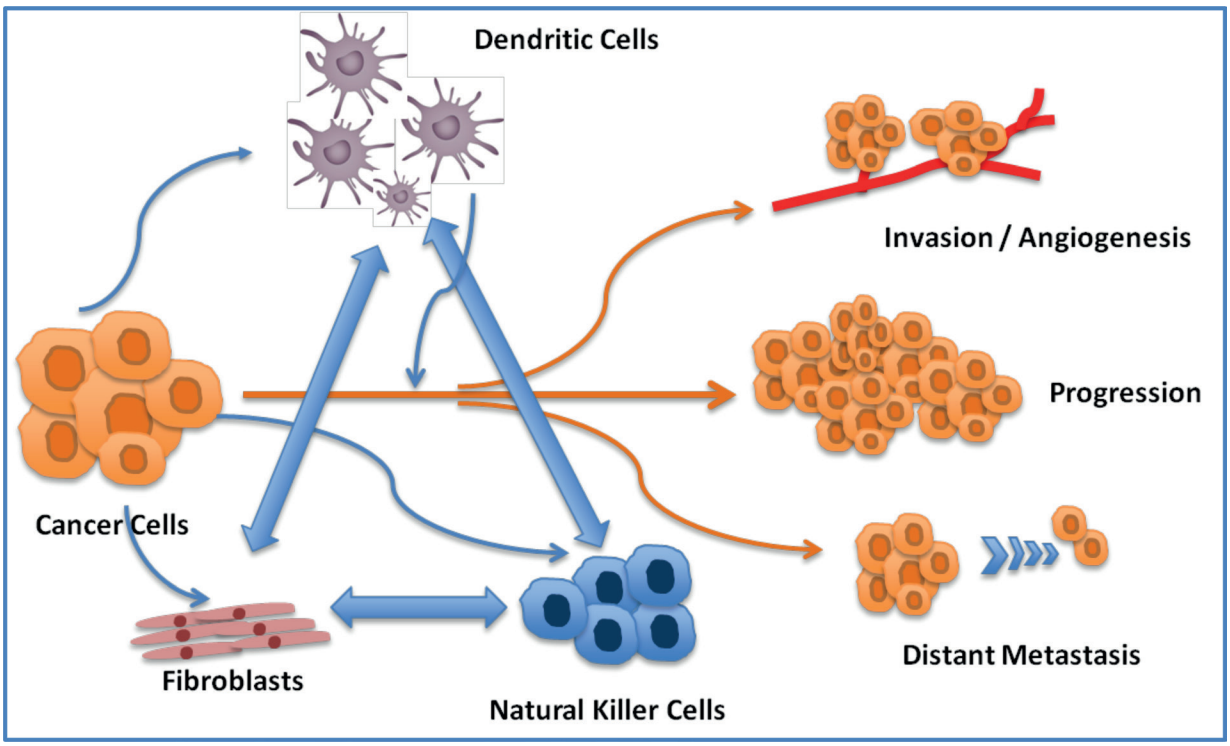

Figure 1. Tumor microenvironment shows the cell-cell interactions, which contribute to cancer cell progression, invasion, and metastasis.

and various other components of the tumor that are supportive to the tumor microenvironment. Most of the cancers are carcinomas or cancers commonly grow in the epithelial tissues that are not vascularized[23]. The vascular structures of the tumors are leaky and they accumulate molecules in the blood stream to a greater extent as compared to that of the normal tissues. These have enhanced permeability and retention effect, and the vasculature of the tumor is generally leaky, accumulating the molecules in the blood stream instead of the normal tissues. The tumor microenvironment is generally hypoxic; since the tumor mass increases and grows further away from the blood vessels leading to genetic disability, the lack of oxygen can also cause glycolytic behavior in cells, inducing the greater cell migration *in-vivo* and *in-vitro*. This may also lead to degradation of the extra cellular matrix (ECM)[24,25]. The reactive stroma cells of a carcinoma are the connective tissues located below the basal lamina, such as fibroblasts, ECM, cells that are responsible for immunity and other molecules and cells. The stroma surrounding the tumor often reacts to the intrusion through the inflammation, similar to the ways they respond to wounds[26]. The inflammation can enhance the angiogenesis and drastically increase the cell cycle and prevent cell death and augment tumor growth[27]. Carcinoma associated fibroblasts (CAFs) are a heterogeneous group of fibroblasts whose functionality is taken away by the cancer cells and is redirected towards carcinogenesis[28]. CAFs are derived from normal fibroblasts in the surrounding stroma, but can also come from pericytes, fibrocytes, mesenchymal cells, smooth muscle cells, epithelial mesenchymal transition (EMT) or endothelial mesenchymal transition (EndMT)[29-31]. CAFs *in vitro* do not retard the cancer growth and perform several functions that support the tumor growth[32]. CAFs also secrete a vascular endothelial growth factor (VEGF), fibroblast growth factor (FGFs), platelet derived growth factor (PGGF) and other pro-angiogenic signals that will induce the angiogenesis[33]. CAFs also secrete a transforming growth factor beta (TGF-β) that is associated with EMT and – by this process – the cancer cells metastasize and inhibit the cytotoxic T cells and natural killer T cells[34,35]. CAFs restrict the cell distribution by physically excluding them as medicated by their cellular matrix and also excluding them via biosynthesis of CXXL12.

Recent Advances in Tumor Microenvironment

The conventional cancer therapy treatments are effective to the cancer cells but they are also cause of damage to the healthy tissues and cells. New treatment methods of cancer treatments are being practiced for the treatment of cancer and its molecular mechanisms are well characterized. The slow or rapid growth of the tumors cells results in the inability of the blood vessels to provide oxygenation and nutrients to the tumor cells, leading to oxygen deficient or hypoxic regions within the tumor. Tumor microenvironment will enable to investigate the clinical trials tests, many types of treatment such as new drugs, new approaches to treatment method using surgery or a radiation therapy or a new combination of treatments.

Tumor microenvironment is considered important for the cancer therapy due to the varying levels of the influence of the different treatments methods used. The various drawbacks of the conventional methods of tumor treatments are that the tumor vascular structures are leaky and highly disoriented; they lack of oxygenation to the tumor core, making it immune to radiation treatments, since to be delivered, the cells far from blood vessels required – and not receive – the necessary nutrients or any chemotherapy substances. Due to these drawbacks, tumor microenvironment and an effective therapeutic method for cancer prognosis and treatment are needed.

Current researches on tumor treatments are focusing on microenvironment as the treatment efficiency of the anticancer therapies differs significantly in comparison of those found in the normal tissues. Then, investigations are now focusing on the tumor microenvironment as a separate cancer associated entity that may be targeted. New methodologies are identified and are effective through specific targeting of the tumor microenvironment. The tumor microenvironments are extensively exploited in the tumor vasculature, as the oxygen deprives cancer cells, which are effective to the radiation therapy.

The melanoma patients develop resistance to both chemotherapy and targeted-therapy drugs. The chemotherapy and targeted therapies, immune checkpoint blockade treatment methods commonly practiced, are not effective to all the melanoma patients. A number of contributing factors such as gene mutations, the physiology of the cell functionality and tumor heterogeneity, contribute to the resistance of the tumor cells

to the treatment provided. Recent investigations carried out have shown the role of inflammatory tumor microenvironment. Furthermore, it has been proven that the multi-modal approach for targeting the microenvironment, in addition to malignant cells, is necessary for a better therapy response[36].

Angiogenesis is a formation of new blood vessels involving the migration, growth and differentiation of endothelial cells that line the inside wall of the blood vessels, which are controlled by the chemical signals in the body. Controlling the angiogenesis is a critical step in the cancer progression and its potential therapy. The role of tumor microenvironment in the control of angiogenesis and the method of dissection of the molecular interactions enhances the prognostic and facilitates the targeted therapy[37].

Understanding of the tumor stroma in advancing cancer is improved by the scaffolding and matrix-based 3D systems. The drug delivery systems made from synthetic and natural biomaterials deliver drugs to kill stromal cells or reprogram the microenvironment for tumor inhibition. 3D models have been used to understand the tumorigenesis. Also, the effects of tumor stroma for cancer treatment for different drug delivery systems were analyzed[38].

Chemoprevention is the use of pharmacologic or natural agents that inhibit the development of invasive cancer either by blocking the DNA damage that initiates carcinogenesis or by arresting or reversing the progression of premalignant cells, in which such damage has already occurred. Studies[39] of primary dysfunction in the tumor microenvironment and the epithelial dysfunction are critical for the carcinogenesis, especially for the cancer chemoprevention.

Hypoxia tumor cells are resistant to the cancer therapies and the reasons may be due to the advanced stages of malignancy. These cells inhibit tumor cell differentiation and play a direct role in the maintenance of the cancer stem cells. They were found to have profound impact on the evolution of the tumor stromal microenvironment. The hypoxia may enable to create a microenvironment to differentiate the tumor cells and the stromal cells, suggesting that targeting hypoxic stem cells may be a key to successful tumor management[40].

Tumor cells retain a range of dependence on interactions with the non-malignant cells and the stromal elements that constitute the tumor microenvironment. By understanding the interactions, the pathogenesis of most B Cell lymphomas, and their potential therapeutic opportunities for targeting oncogenic pathways, is possible now and in the future[41].

Studies were carried out to analyze the temporal changes in gene expression when breast cancer cells survive and grow on brain, bone marrow, and lung tissue maintained in an *in vivo* culture system, as models of the metastatic colonization of these tissues. It was observed that the transient activation of the genes associated with homeostasis and stress, later by the elaboration of cell morphology and cell division, lead the cells adapted to thrive in the host tissue microenvironment[42].

Breast cancer treatment using the microenvironment by targeting the generation of DNA intercalation inhibits topoisomerase II and interferes with the DNA replication. The chemotherapeutic agents kill cancer cells and the treatment triggers a stromal reaction leading to TNF-**α** production by endothelial and other stromal cells. The network of the endothelial-carcinoma myeloid signaling interactions provides a mechanism linking chemo-resistance and metastasis with possibility for intervention[43].

Development of the prostrate cancer is not only confined to the cancer epithelial cell, but also involves the tumor microenvironment. Prostate cancers metastasize to the skeleton, and there is considerable research being carried out to analyze the interaction between prostate cancer epithelial cells and the bone microenvironment. The signaling pathways do exist between epithelial cells, stromal cells and the extracellular matrix to support tumor progression from the primary site to regional lymph nodes and the distant metastases. The prostate cancers metastasize to the skeleton and research is being carried out to study the interactions between prostrate cancer epithelial cells and the bone microenvironment. The signaling pathways that are involved in normal prostate and bone development lead to dysregulation in cancer, thereby simulating excessive cell growth and neovascularization and leading to invasive properties to the epithelial cells, weakening of the antitumor immunity and castrate-resistant disease. This study regarding the relationship between cancer epithelial cells and the organ specific microenvironment enables the development of novel therapeutic techniques[44].

Acquired resistance to anticancer treatments is an essential barrier to reduce the morbidity and mortality of the malignant tumors. Tissue

microenvironments have been found to influence cellular phonotypes and to have susceptibility to toxic insults. The expression of WNT16B in the prostate tumor microenvironment attenuated the effects of cytotoxic chemotherapy *in vivo*, thereby promoting tumor cell survival and disease progression. These results delineate a mechanism by which genotoxic therapies given in a cyclical manner can enhance subsequent treatment resistance through cell nonautonomous effects that are contributed by the tumor microenvironment[45].

The bone marrow microenvironment enables the survival, differentiation, and proliferation of hematopoietic cells, which are supported by fibroblast-like bone marrow stromal cells, osteoblasts, and osteoclasts, that secrete soluble factors and extracellular matrix proteins that mediate these functions. This makes the normal hematopoietic cells and epithelial tumor cells that metastasize to bone, protect from the chemotherapeutic agents. Due to this drug resistance, tumor cells are protected from apoptosis induced by both chemotherapy and physiologic mediators of cell death, thereby allowing them to survive and lead to minimal residual disease, increasing the probability for development of acquired drug resistance[46-48].

Pancreatic cancer is one of the major causes of cancer death in the world. The structural proteins in the microenvironment of pancreatic cancer can be modified or targeted, including the hyaluronan, collagen and secreted protein, acidic and rich in cysteine. Current methods are being exploiting rather than targeting/destroying the microenvironment by normalizing the structural proteins, reversing epithelial-to-mesenchymal transition. The results have shown beneficial results that can be clinically evaluated[49,50].

There are three methods commonly used to detect the lung cancers: (1) measurement of partial oxygen pressure (pO2) with needle electrodes; (2) detection of hypoxia-induced proteins in tumor or blood; (3) imaging hypoxia and tumor vasculature[49]. Presently, there are several promising modalities to image hypoxia and the tumor vasculature; these include dynamic perfusion imaging and positron emission tomography scanning with radiolabeled nitroimidazoles. To evaluate the effects of these agents, a non-invasive mean of imaging the TME is critical. To date, there are several promising modalities to image hypoxia and the tumor vasculature; these include dynamic perfusion imaging and positron emission tomography (PET) scanning with radiolabeled nitroimidazoles.

Though there are many therapeutic advances for the cancer treatments, most of the mature B-cell malignancies remain incurable. Evidence suggests that crosstalk with accessory stromal cells in specialized tissue microenvironments, such as the bone marrow and secondary lymphoid organs, favors disease progression by promoting malignant B-cell growth and drug resistance. There is a paradigm shift in the treatment of selected B-cell malignancies, moving from targeting primarily the malignant cells toward combining cytotoxic drugs with agents that interfere with the microenvironment's proactive role. Such approaches hopefully will help eliminating residual disease, thereby improving our current therapeutic efforts[51-53].

Future Drug Development Regarding the Importance of Tumor Microenvironment

The study of tumor microenvironment, its cellular and molecular components, and how they affect tumor progression, are emerging topics in cancer research. The factors released by the tumor cells themselves, in particular pro/anti-inflammatory molecules or pro/anti-angiogenic mediators that contribute in creating an environment, mostly affect or not the tumor. The events and molecules involved in this cross talk within the tumor microenvironment have emerged as attractive targets in anticancer therapeutic treatments. The stroma surrounding the cancer cells plays an important role to study the development, progression and the behavior of the tumor. It has been reported[54] that the interactions between the stroma and the neoplastic cells are a major factor to study the cancer growth and its progression. Tumor microenvironments have contributed greatly to the study of the tumor development and progress. The new treatments process for the tumor cells by tumor microenvironment is going to offer promising treatment, moreover helping in the drug discovery and development for cancer treatment[55,56]. The tumors growth and progression in human is a very complex topic to understand as their functionality is multifaceted, for which they rely upon their growth, invasion and metastasis. The microenvironment of a tumor is an integral part of its physiology, structure and functioning, and it is an essential aspect of the tumor property as it supplies the required nutrient environment

for the malignant process. A fundamental deranged relationship between tumor and stromal cells is essential for tumor cell growth, progression, and development of life threatening metastasis. The stromal cells within the tumor microenvironment are genetically stable and are suitable for therapeutic purposes with minimal risk of any side effects or reoccurrence of the tumor. Improved understanding of this interaction may provide new and valuable clinical targets for cancer management, as well as risk assessment and prevention. Non-malignant cells and secreted proteins from tumor and stromal cells are active participants in the cancer progression.

Conclusions

By monitoring the changes in the tumor microenvironment using their molecular and cellular profiles, as the tumor progresses, will be pivotal for identifying cell or protein targets for the cancer prevention and for their therapeutic purposes.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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