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REVIEW

T cells in tumor microenvironment

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Abstract Tumors progress in a specific area, which supports its development, spreading or shrinking in time with the presence of different factors that effect the fate of the cancer cells. This specialized site is called "tumor microenvironment" and has a composition of heterogenous materials. The immune cells are also residents of this stromal, cancerous, and inflammatory environment, and their types, densities, or functional differences are one of the key factors that mediate the fate of a tumor. T cells as a vital part of the immune system also are a component of tumor microenvironment, and their roles have been elucidated in many studies. In this review, we focused on the immune system components by focusing on T cells and detailed T helper cell subsets in tumor microenvironment and how their behaviors affect either the tumor or the patient's outcome.

Keywords T cells · T helper cells · Th17 cells · Cancer immunology · Tumor microenvironment

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Tumor microenvironment

The development and propagation of cancer depend on not only cancer cells and cancer stem cells within tissue but also other necessary components, which can be named as cancer microenvironment that is regarded as cancer bed and involves many kinds of resident and non-resident constituents [1, 2]. Cancer as a very complex disease includes both the transformed cells and non-transformed cells as host stromal cells that involve endothelial cells, fibroblasts, immune cells, and complex extracellular matrix [3]. Cancer microenvironment that is composed of resident components as stromal cells and non-resident components as various kinds of immune cell populations is the major factor that determines the fate of cancer such as the prevention or encouraging the cancer initiation, metastasis and invasion, and angiogenesis [4]. It can be definitely said that any change that happens in the epithelial cells which also would result in changes in the stromal cell integrity affects and alters the characteristics and initiation of cancer in the way of it can promote invasion and metastasis [5]. As it is expected, those changes can be resulted from the abnormalities in the blood vessels that feed up the tumor cells. It also affects the amount of molecules, which are necessary for the normal metabolic reactions, and normal host cells that are found close to tumors, which begin to malignant tumors and gain the ability to spread among tissues. So, there is a reciprocal relationship between tumor microenvironment and malignant tumor cells as tumor cells can change its microenvironment and determine its characteristics. Additionally, tumor microenvironment can promote or prevent the initiation and propagation of cancer within tissues and body. The composition and characteristics of the tumor microenvironment can be different between the different kinds of cancer or between patients that have same type or even subtype of cancer. For example, as expectedly, solid tumors have different

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microenvironment components from the hematologic malignancies. Besides, there can be observable difference in the composition of immune cell types as T and B cells for the same cancer type [6]. In this review, after brief explanation about the general properties of tumor microenvironment, the composition of this tumor microenvironment will be focused and considered in details. Majority of T cells and their subsets on the cancer will be evaluated in details in addition to their action mechanisms against different types of tumors. As a part of their dual-face phenomenon in tumors, T_H17 cells as well as T_{reg} cells will be considered as main players of immune system attack or failure against cancer. This review will be helpful to the researchers who study on tumor microenvironment and are interested in the roles of immune system cells on cancer-specific niche.

Immune cells in tumor microenvironment

As mentioned before, there are different kinds of non-transformed components of tumor microenvironment as the stromal cells. As it is expected, carcinogenesis is affected not only by the epithelial cells but also by the other types of cells such as inflammatory cells, fibroblasts, and immune cells such as dendritic cells and macrophages [1, 7]. Angiogenesis, which is an essential phenomenon for the initiation of cancer and propagation as metastasis, provides the transportation of necessary molecules for the growth of cancer cells such as oxygen and nutrients between normal blood vessels and tumor cells by the formation of special vessel for cancer cells. For this reason, the formation of angiogenesis depends on the existence of endothelial cells in the tumor microenvironment [1, 8].

Cancer-associated fibroblasts (CAFs) are another important component of tumor microenvironment and in this environment; those fibroblasts are specific for the cancer cells. In this environment, they act as a regulatory component of tumor cells' specific phenomena such as metastasis, carcinogenesis, and therapy resistance and they can include mesenchymal cells, endothelial cells, and epithelial cells as a heterogeneous population [1, 9–11]. Those CAFs as prominent regulatory components are also regulated by cancer cells in terms of with some activator molecules [4]. In addition to those resident components of tumor microenvironment, there are also non-resident components that specify the characteristics of this microenvironment as dendritic cells, cancer-associated macrophages, T lymphocytes, B lymphocytes, and natural killer cells [3]. As it is known, many kinds of immune cells are responsible for the formation of immune response that can prevent or inhibit the initiation of cancer or propagation. The immune cells also play roles on invasion and metastasis within the different tissues, and those immune cells are carried to related site by cancer-related blood vessels and/or extravasation [12]. In many cases, this response can be achieved by host immune system when the cancer development is at early stage and while it cannot control its microenvironment effectively. However, when the tumor growth reaches the specific late stages, immune system cannot achieve the effective immune responses because of the immunosuppressive mechanisms of cancer cells and the high ability to control their microenvironment [3].

For many years, it was expected that all types of macrophages are responsible for fighting with cancerous cells; however, it is understood that some kinds of them can promote the initiation and propagation of cancer cells by forming specific cancer-associated macrophages [13]. Besides, they can produce immunosuppressive cytokines to prevent the necessary immune response and promote the angiogenesis by producing some necessary molecules [14]. On the other hand, dendritic cells which are the known best antigen-presenting cells in the immune system with their capability of present peptides through both MHC class I and MHC class II molecules are also involved in the regulation of immune response against tumor cells [3, 15]. The most advantageous feature of dendritic cells is the cross presentation system that leads to the activation of immune cells by two different paths: those of one, through the presentation of antigens to cytotoxic T cells by MHC class I molecules and thepresentation of the antigens by MHC class II at the same time, in order to get an efficient response from the immune system against the tumor [3]. In addition, there is another cell type as natural killer cells that belong to immune system and they share similar surface receptors with macrophages. However, there are additional kinds of surface receptors for natural killer cells and those cells have essential responsibilities to fight against tumor cell growth by some special surface receptor on natural killer cells [16, 17]. Those receptors are very important to sustain host cancer immune response against tumor initiation [18]. Furthermore, natural killer cells are accepted as dendritic editing cells to destroy partially immature dendritic cells (DCs) and inhibit their un-preferable functions inside the cells as inhibiting the activity of tolerogenic DCs and facilitating to maintain anti-tumor response [19–21]. In addition, extracellular matrix (ECM) can affect the fate of tumor. ECM establishes the direct contact with newly forming cancer cells and it can promote the conversion to malignant tumor and metastasis by majorly supporting the secretion of different cytokines [1, 22] (Fig. 1).

T lymphocytes in tumor microenvironment

T lymphocytes are abundant components of tumor microenvironment, and they are named as tumor-infiltrating lymphocytes in terms of existing close to growing tumor cells and forming special lymphocytes for cancer cell microenvironment [23]. In the microenvironment of all kinds of cancer,

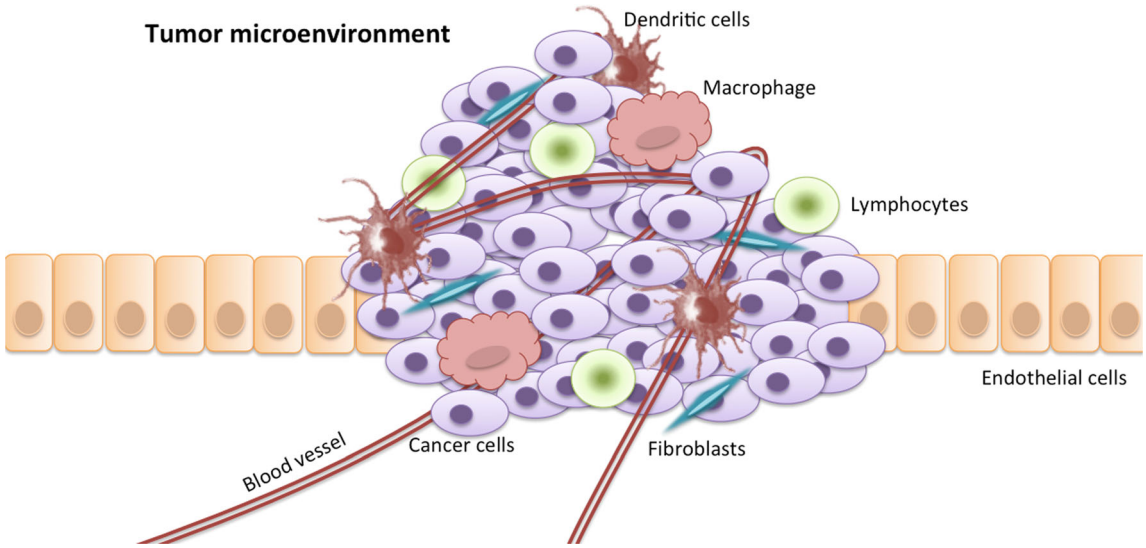

Fig. 1 Different cell types such as dendritic cells, macrophages, fibroblasts, and lymphocytes are found in a typical tumor microenvironment. The tumor mass is also feed by vascularization also known as angiogenesis in a malign way. The composition of each cell differs in each cancer types or between patients. The density of different cells also affects the outcome of the disease that was also detailed in the text

there are an increasing number of related tumor-infiltrating lymphocytes (TILs) in patients while only one kind of TIL cells can exhibit the necessary response against cancer cells as anti-cancer activity [3, 12]. As it is known, malignant cells are antigenic and produce specific antigens that are recognized and identified by immune cells (antigen-presenting cells) and introduced to host T cells (T lymphocytes) that can be defined as a part of cell-mediated immune system [24]. Although those antigens are used to activate host immune system to disrupt cancer cells or inhibit metastasis by activity of T cells, there can be a controversy as immune cells can promote the growth or propagation of cancerous cells [12]. T cells involve two main classes of immune cells as CD4+ and CD8+ [25]. Those cells are both responsible for the performance of anti-cancer activity. However, the type of CD8+ cells is named as cytotoxic T cells and they have the capability to kill and disrupt the target cells by the help of granzyme B and perforin which endow cytotoxic and apoptotic activity for those cells [3, 12]. In addition to them, there is a supporter molecule type for the activity of CD8+ as interferon gamma (IFN-γ), which is also produced by themselves [3]. The general principles and role of CD8+ in the tumor microenvironment have been worked with UV-induced skin cancer mouse models, chemically induced papilloma, and *ret*oncogene transgenic model of spontaneous melanoma to figure out the importance of CD8+ cells for the immunosurveillance as the response for the growing tumor and metastasis [3, 26–28]. The high amounts of CD8+ in the circulating system signify the existence of an abnormality/foreign material that should be eliminated in a host system. This situation is clearly promoted by the researches in patients with metastatic melanoma [3, 29]. After cancer cells are induced to be exposed to apoptosis, they constitute apoptotic bodies, which have the capabilities to induce tumor-infiltrating DCs to convert naive T cells to active/mature state. This tumor-specific immunosurveillance is achieved with those apoptotic bodies by moving them through lymph nodes and other different lymphoid organs and introducing the tumor-specific antigens to the other T cells [30–32] (Fig. 2).

Furthermore, the patients having the higher amount of tumor-infiltrated T cells were shown that they tend to exhibit good prognosis compared to the rest of the patients in various types of cancer including breast, lung, or colon [33, 34]. Tumor microenvironment generally provides suitable conditions for the cytotoxic activity of cytotoxic T lymphocytes (CTLs). Though, the activity of CTLs is affected by some factors, which are specified by different sources as tumor microenvironment by itself or tumor cells. These factors can be summarized as follows: (i) the amount of cytokines or chemokines which are released by the cells found in tumor microenvironment, (ii) the ability of tumor cells to escape from the cytotoxic activity of T cells by molecular plasticity, and (iii) behavior of the interactions between TCR and MHC molecule which can be exemplified by the situation of melanoma cells which are shown as having the reduced level of MHC-1 molecule expression on the surface of APC. Therefore, this situation prevents the recognition of specific antigens by DCs, introduces them to T cells, and lowers the further immune response [3, 35].

T_H1 and T_H2 cells in tumor microenvironment

In addition to cytotoxic T cells, there is another class of T cells as CD4+, which acts as helper cells and modulates the

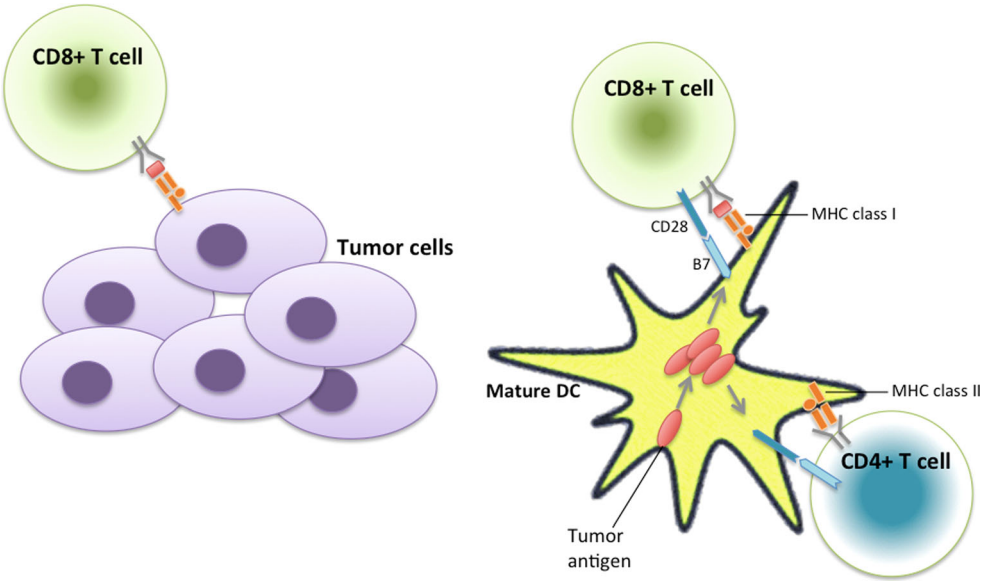

Fig. 2 After tumor antigen is presented to dendritic cells, DC can activate CD4+ T cells and CD8+ T cells at the same time with the absence of different MHC class molecules. CD8+ cytotoxic T cells are activated by MHC class I and co-stimulatory signal while MHC class II with also a co-stimulatory signal can activate CD4+ T helper cells. Activated T helper cells eventually either activate CD8+ T cells or initiate a negative signal against immune system based on the absence of different environmental cytokines

activation of CTLs. There are four main classes of helper T cells that have been separated from each other according to their effects within host immune system as T_H1, T_H2, T_H17, and T_{reg}, and the transition is driven by the amount and the type of the cytokines in the environment [6, 36]. CD4+ cells can cause anti-cancer immune response by producing related cytokines to stimulate CD8+ with the activity of T_H1 and T_H2 helper T cells. They also have the capability to facilitate the activation of CD8+ and improve the destroying capacity of those cells and macrophages. T_H1 can achieve this activation of macrophages and CD8+ by producing IFN-γ, TGF-β, and IL-2 cytokines while T_H2 helper T cells have different kinds of cytokines and target immune cells. Specific cytokines can be listed as IL-4, IL-5, and IL-6 to facilitate B cell proliferation and antigen production [6]. For the bacterial and viral infection and allergic or atopic inflammations, those T_H1 and T_H2 helper T cells are dominant in the host. The responsibility of these T_H1 and T_H2 helper T cells is not restricted with only CD8+ stimulation, as it is shown that in a study from 1998, those cells are very important for anti-tumor immunity [37]. For example, macrophages that are stimulated by the activity of T_H1 cytokines produce nitric oxide that can perform as an anti-cancer agent. Besides, activation of DCs can also be achieved by the secretion of IFN-γ from the T_H1 cells. These cytokine molecules increase the level of IL-12, which is related with activation of DCs, and as a result, those activated DCs can stimulate the CTLs [38–40]. As said before, T_H2 cells are common helper T cells for the response to allergic inflammations and extracellular pathogens; however, those cells are also important for the tumor immunity which are related with the special molecule as eosinophils. These molecules are recruited by the T_H2 helper T cell and show the capability to destroy cancer cells by their specific cytotoxic protein products [37, 41].

T_H17 cells in tumor microenvironment

T_H17 is another subtype of CD4+ cells, which are basically responsible for the autoimmunity, controversial tumor immunity, disrupting immune tolerance, and response against extracellular bacteria. T_H17 cells are referred as the most special helper T cell subset since they either can promote or can prevent cancer cell growth and metastasis with different subsets and various cytokines that are produced by those subsets [42–44]. Their differentiation depends on the coming signals and existing cytokines in the environment. These T_H17 cells can be differentiated into T_H1 if there are necessary cytokines for the differentiation as IL-12 and newly forming T_H1 cells loss their ability to secrete IL-17 and get the ability to produce and secrete IFN-γ. The increasing amount of T_H1 T helper cells can facilitate the stimulation of CD8+ cells and can assist in destroying cancer cells [42].

In addition to this, immune response can be improved by the specific factors as granulocyte-macrophage colony-stimulating factors (GM-CSF) that are produced by those T_H17 cells in cancer patients. Also, there are other produced cytokines as tumor necrosis factor alpha (TNF-α), IL-2, and IFN-γ, but no IL-10. T_H17 specifically those cytokines can behave like the cytokines that are produced during the viral infections, and those cytokines have the capability to influence and mediate local cancer immune response that is showed against cancer. As said before, there are specific cytokines that are produced in different cancer patients as melanoma, breast, and colon cancers which produce T_H17 cells in microenvironment that secrete IL-8 and TNF-α, but not IL-2 [42, 45].

The behavior of those T_H17 cells can be specified in tumor microenvironment according to the cancer type or the coming signal from environment or cancer tissue. T_H17 cells can behave controversial, as they can act for improvement of anti-

cancer immune response by differentiating to T_H1 cells, or they can act for the regulation of this immune response. In regulation process, T_H17 cells have the capability to stimulate and recruit T_{reg} toward the tumor area. T_{reg} cells can block or inhibit the anti-cancer immune response by their specific antigens that affect the CD8+ and its cytotoxic activity. As a general behavior of T_H17 cells, it has two different forms, as effector and regulator, which are converted to those forms by the composition of different types of cytokines affecting natural T_H17 cells. T_H17 cells gain a $T_H1/17$ type of characteristics in the presence of IL-1b, IL-6, and IL-12 that resulted in the initiation of CTLs and in the regression of tumors, while in the presence of TGF-β, T_H17 cells transit into TH17/ Treg cells and start to express Foxp3 in addition to RORγ-t that causes the blockage of CD8+ T cells which feed the tumor cells and keep their progression [42].

There have been many studies carried out on the role and the functions of T_H17 in different types of cancer including lymphomas. The level of T_H17 cells was found very low in follicular lymphoma (FL) compared to that in other non-Hodgkin lymphomas. It was also suggested that malignant B cells compress the activation of T_H17 cells and their differentiation that cause the presence of a reduced number of T_H17 in FL. The inhibitory effects of B cells are also associated with the escalated T_{reg} cells in number and differentiation. As already mentioned before, the increased level of T_{reg} cells with a lack of T_H17 differentiation will result in the inhibition of immune response against the tumor and its microenvironment in FL [6, 46].

T_{reg} cells in tumor microenvironment

T_{regs} are regulatory T cells that can be also named as suppressive T cells. They have the both CD4 and CD25 receptors on the surface, and those receptors can be used for identification of those T_{reg} cells in many research. In addition to those receptor set, there is a specific transcription factor for the T_{reg} cells as FOXP3 which is an effective factor for the appropriate function and proper development of those cells. Naive T cells can be converted to regulatory T_{reg} cells in the existence of TGF-β and IL-6 cytokines by increasing the expression of some specific transcriptional factors as Stat3, Gfi1, and ROR and produce IL-17 and IL-10 without production of IFN-γ. Besides, there is another molecule that is secreted by those regulatory T_{reg} molecules as adenosine, which can act as an immunosuppressive molecule to prevent the anti-cancer immune response. Human immune system involves T_{reg} cells in thymus, peripheral blood, lymph nodes, and spleen, and in many cancer types, higher produced levels of T_{reg} were detected in breast, colon, lymphomas, lung, and melanoma. In addition to vital roles of T_{reg}, their presence and densities have been shown as a prognostic indicator in cancer patients. For instance, there are an increased number of T_{reg} cells around the ovarian cancer microenvironment and those highly existed numbers of T_{reg} cells affect the progression of cancer and patient survival rate with poor prognosis. As ovarian cancer does, malign melanoma or breast cancer patients with relapses also have the increased amount of T_{reg} compared to non-relapsed patients. This situation was also confirmed by the studies in liver cancer patients with the same outcome [6, 42, 45].

Conclusion

Solid tumors in humans have their own specific microenvironment including inflammatory, stromal, and cancerous cells within cancer stem cells. The poor progression of the disease or the aggressiveness of the tumor is mostly related with its niche. The factors involved the formation of that environment or the initiator molecules mostly cytokines or chemokines that are secreted from the different cell components which are resident in this specific microenvironment. The different compounds of tumor microenvironment include CAFs, epithelial cells, cancerous cells, cancer stem cells, or mesenchymal stem cells and immune cells such as lymphocytes (T cells, B cells), DCs, macrophages, or NK cells. Although immune cells cooperate with the immune response against foreign antigens, tumor cells have the capacity to escape from the immune attacks through different mechanisms. Also, immune cells could play roles on this escape mechanism, or they can promote the growth of the tumor because each of them could act differently according to environmental conditions. As a major part of the immune system, cell-mediated immunity within T cells generates the immune response against the tumor antigens. The tumor cells can mediate the T cell response by secreting cytokines that promote the immunosuppressive environment. Specifically, T cell subsets (T_H1, T_H2, T_H17, and T_{reg}) form the majority of T cell-mediated immune response by the following: (i) T_H1 cells are believed to be more effective compared to T_H2 and favor the immune response and CTL activity in order to make the tumor regress and shrink; (ii) T_H2 cells also support the CTL activity, but distinctly, they also initiate B cell activity to enhance B cell-mediated immune response; (iii) T_H17 cells, the most studied T cell subtype in tumor immunity, which are also known as having stem cell-like plastic features, resulted in having contravariant effects that are based on the type of cytokine presence and the transcription factors; and (iv) T_{regs} are the regulatory T cells which prevent the CTL activity, and conversely to other T cell subsets, they promote the tumor growth.

The failure against the immune cells/attack is basically known as the biggest challenge in cancer treatment. Although there are many studies that investigate the role of T cells in tumors and its environmental pattern, it is still needed to illustrate other possible mechanism of tumor cells' escape from the immune system on the specific type of cancer since each type

of disease can act differently against the immune cells. Also, the T cell subsets that are found in the microenvironment can be used as a target against cancer by using their contrast features, and they can be activated properly against specific tumor antigens. Still, there is much to be investigated and elucidated in immune system and tumor relationship, in which each new information makes us a step ahead in cancer treatment, since the best way to cure cancer is passing through the very own fighting mechanisms of the body itself.

Research perspectives

Although there have been many studies conducting on understanding the roles of T cells in tumor microenvironment and their effects on cancer progression, there are many mechanisms still unknown. How T cells act in response to different cytokines in tumor microenvironment and how those actions affect the fate of the disease could be focused on to clear and detail them. Also, it is thought that there are different T_H cell subsets that are not identified yet. Additionally, plasticity of T_H17 cells and their dual role in cancer have been understood in a basic level, but there might be new signals or environmental effectors that define the action of T_H17 cells. The termination fate of T_H cells could also be more studied on since after the activation, it is still not known if T_H cells would die or how they survive in the circulation system. T cells and their action on cancer represent a wide study area with its unknown or needed-to-be-detailed mechanisms. Additionally, new studies lead to understand the roles of immune system on cancer and help us to overcome tumor progression with the help of the body's own defense mechanism.

Compliance with ethical standards

Conflict of interest The authors do not have any kind of conflict of interest affecting the compilation of the current knowledge in this area for writing this review. They apologize to the ones whose elegant studies are not included here because of space limitations.

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