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Review

The connection between the Th17 cell related cytokines and cancer stem cells in cancer: Novel therapeutic targets

Ayaz Shahid, Mausumi Bharadwaj*

Molecular Biology Group, National Institute of Cancer Prevention and Research, Indian Council of Medical Research (ICMR), Department of Health Research, Noida, 201301, India

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ABSTRACT

Cancer Stem Cells (CSCs) are the subpopulation of cells present in the different types of cancers with capabilities of self-renewal, differentiation, and tumorigenicity when transplanted into an animal host. The research work on the CSC has been providing a promising approach for the improvement of cancer therapies in the future. The CSCs have a close connection with the cytokines related with the T helper 17 (Th17) cell and other factors present in the tumor microenvironment, and these play a pivotal role in tumor progression and metastasis. The properties of CSCs are well defined in various type of tumor which is mainly developed by chemically and spontaneously in murine cancer model but in human defined primarily on acute myeloid leukemia, glioma, and breast cancer. The role of Th1, Th2, Natural Killer cells are well described in the cancer biology, but the Th17 cells are the subset which is recently exploited, and lots of research are going on. In this Review, we summarize current findings of the characteristics and functions of the Th17 cell and its signature cytokines in different cancers and their interconnections with cancer stem cells and with their markers. We have also discussed the functional properties of CSCs and how the CSCs markers can be distinguished from normal stem cells markers. We have also talked about the strategies that are efficiently targeting of CSCs and Th17 cells in different cancers.

1. Introduction

The cancer is broadly acknowledged to be a heterogeneous disease, in which cells interconnect with several other cell types. This complex system within the cancer can influence its behavior. Although it is clear that cancer heterogeneity is related to metastasis, recurrence, and therapy resistance, the exact mechanisms behind these are still to be uncovered [1]. According to the World Health Organization, cancer is still one of the significant reasons for mortality in the world [2]. The remarkable ability of different cancers to relapse despite different chemotherapies suggested that minimal residual disease contains a subpopulation of cells with a vast capacity for self-renewal and regeneration [3]. This subpopulation of cells present in the heterogeneous tumor cell population is called cancer stem cells (CSCs). In the cancer progression, CSCs by nature are more resilient to radiation and chemotherapy than the non-CSCs cells, and therefore play an essential role in the persistence of cancer residual disease and recurrence [4,5]. So if we want to eradicate cancer, we have to eliminate this drug-resistant subpopulation of cells first.

The cytokine dis-balance is the leading cause of immune function disorder that might lead to cancer occurrence and development [6]. An essential characteristic of effective anticancer therapy is its ability to target cancerous cells without damaging healthy cells selectively. Recognizing cancer cells, specific characteristics that distinguish them from healthy cells is of great importance in cancer therapies. One such unique feature is the markers which are present in cancer cells. The cytokines have important roles in cell differentiation, mobility, proliferation, and protection against pathogens [7].

Consequently, the dysregulation in cytokine secretion leads to various chronic inflammatory diseases, including cancers, and so modulating the cytokine network using either biological or small chemical agents offers therapeutic potential. Th17 cells are mainly involved in maintaining mucosal immunity homeostasis, and it also plays an important role in the context of autoimmunity, cancer, and HIV infection [8]. Recent pieces of evidence show that Th17 cell related cytokines have an oncogenic role in cancer metastasis by enhancing the angiogenesis and tumor immune evasion [9]. The role of Th17 cell related cytokines are the cancer and microenvironment specific, and this dual functions of Th17 cells mainly depend on the recruitment of neutrophils, NK and CD4+ and CD8 + T cells [10]. The first author of this

* Corresponding author. Present address: Molecular Biology Group, National Institute of Cancer Prevention and Research, Indian Council of Medical Research (ICMR), Department of Health Research, Noida, 201301, India.
E-mail address: mausumi.bharadwaj@gmail.com (M. Bharadwaj).

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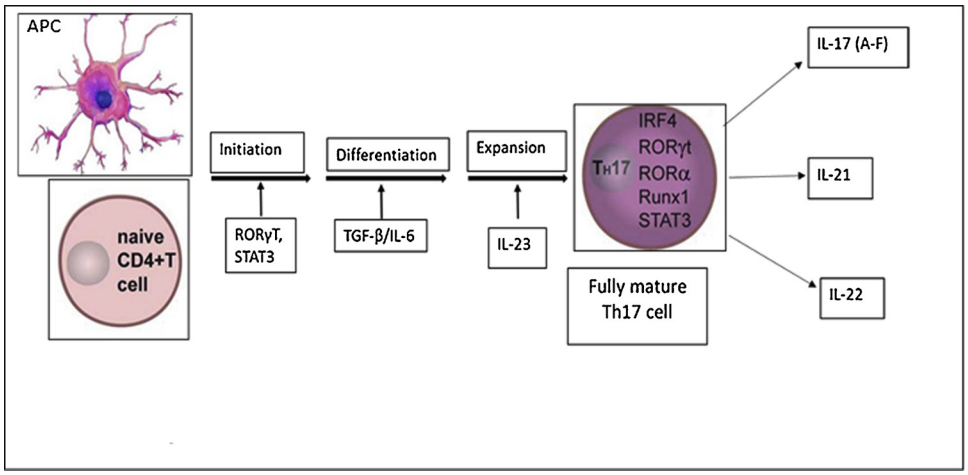

Fig. 1. The Initiation, Differentiation, and Expansion of Th17 cells: Following activation by antigen-presenting cells (APC) such as dendritic cells (DCs), naive CD4 + T cells can be polarized into mature Th17 cells. The Th17 cells are characterized by expression of the transcription factors retinoic acid receptor-related orphan receptor-γt (RORγt), RORα, signal transducer and activator of transcription 3 (STAT3), Interferon regulatory factor 4 (IRF 4) and Runt-related transcription factor 1 (RUNX1). The IL-6, TGF-β, and IL-23 can promote and/or stabilize initiation, Th17 cell differentiation, and expansion. Furthermore, IL-17 (A-F), IL-21, and IL-22 are secreted by mature Th17 cells. (Ref. K. Agnieszka, K. Marta, G. Krzysztof, The role of Th17 cells in tumor immunity, Acta Haematologica Polonica, 45 (2014) 155-160).

review article is currently working on one of the projects which is based on T helper 17 cells in lung cancer and their role in regulation of CSCs markers which is funded by Indian council of medical research (ICMR), New Delhi, India and previously we have also worked on the role of T-cell immunotherapy in cervical cancer [11].

Here, we summarize the current knowledge of Th17 cell cytokines and CSCs and their role in cancer pathogenesis and their interconnections. We also discuss CSCs markers and provide insights into new therapeutic approaches for more specific targeting and eradication of CSCs in cancer.

2. The Th17 cells: Origin, differentiation, and functions

The Th17 cells are the central interest in the field of autoimmunity diseases and cancer. Those Th cells subset which can produce interleukin-17 (IL-17) primarily IL-17A and IL-17 F are called Th17 cells, but these cells also produce other cytokines such as IL-21 and IL-22 in some specific conditions [12] (Fig. 1). Since 1989 when Mosmann and Coffman showed that murine CD4 + T cells differentiate into two subsets of reciprocal patterns of cytokine secretion and function, defined as CD4 + T helper type 1 (Th1) and Th2 [13]. This classic classification was changed by the discovery of a new CD4+ helper T cells population, named CD4 + Th-17 [13]. More recently, the new Th subsets such as Th9 and Th22 cells were also discovered which play roles in the modulation of host immune responses [14,15]. The Th17 cells express retinoic acid-related orphan receptor-γt (RORγt) as the first transcription factor and gene profiling analysis demonstrates that two transcription factors which are ROR-γt and RORα are necessary for Th17 differentiation and these two receptors correlate with increasing Th17 differentiation and upregulation of IL-17 mainly in mice [16,17]. The Th17 cell differentiation is regulated through a reciprocal relationship with Tregs, whose primary function is to suppress T-cell responses against self and foreign antigens [18]. The Transforming Growth Factor-β (TGF-β) induces forkhead box protein P3 (Foxp3)+ Treg cells from naive CD4 + T cells in the absence of IL-6. This causes suppression of RORγt and leads naïve CD4 + T cells in developing into Tregs [19]. The modulation of the differentiation pathway between Th17 and Treg cells may allow a shift in the balance between proinflammatory and regulatory mechanisms and result in new treatment targets in chronic inflammatory disorders [20]. In human, TGF-β is essential for the induction of RORC in naïve T cells, although the expression and functions of RORC are inhibited at high concentrations of TGF-β [21]. However, inflammatory cytokines, such as IL-21, IL-1β, IL-6, and IL-23, relieve the inhibition of RORC in CD4 + T cells and trigger the expression of IL-17 [22,23].

The number of Th17 cells in humans and mice is small (relative to Th1 cells) under non-pathological conditions [24,25]. Murine Th17 cells under steady-state reside in the intestine where they are generated due to the presence of specific members of the commensal microbiota, including the segmented filamentous bacteria (SFB) [26–28]. The Tumor infiltrating IL-17 producing cells in Esophageal Squamous Cell Carcinoma may have played the critical roles and treated as a prognostic marker [29]. The relationship of IL-17 expression and the clinicopathological features, as well as the clinical result, implies an important function of IL-17 in colorectal cancer, and it is a marker of a favorable prognosis. Th17 cells might also contribute to tumor progression and poor prognosis in cervical adenocarcinoma [30]. Huang et al. revealed that IL-17 promotes IL-6, IL-8, and VEGF production in lung adenocarcinoma via STAT1 signaling. IL-6, IL-8, and VEGF are multifunctional cytokines that are regarded as biomarkers and are strongly associated with multiple aspects of lung cancer [31]. The NF-κB is a crucial transcription factor in the regulation of MMP9 expression, and Th-17 has been reported to be able to activate NF-κB signaling [32–34], IL-17A could activate NF-κB and subsequently upregulate MMP2 and MMP9 expression. This effect could be effectively inhibited by NF-κB inhibitor, suggesting that the upregulating role of IL-17A in MMP2 and MMP9 expression might be through the activation of NF-κB. Moreover, characterization of the impact of IL-17A on HCC invasion and metastasis may drive to the association of novel diagnostic markers and therapeutic targets [35].

The Th17 cells are mainly significant contributors to host defense against bacterial and fungal pathogens, primarily through neutrophil recruitment and production of anti-microbial peptides, chemokines, and acute phase reactants [36]. The Th17 cell relayed cytokines are particularly important at mucosal surfaces and other environmental interfaces. It activates several receptors of chemokine and also helps in its secretion of chemokine the site of inflammation, for example, the expression of CCL20 and CCR6. The Th17 cells also increase the expression of intracellular adhesion molecule 1 (ICAM1) on epithelial cells and induce the secretion of matrix metalloproteinases (MMPs) that are involved in tissue remodeling and damage [37]. The naïve T cells may convert into pathogenic or non-pathogenic Th17 cells, and it depends upon the various cytokines present during the differentiation process. The pathogenic Th17 cells show higher effector molecules, including chemokines/pro-inflammatory cytokines such as IL-22, IL-3, Cxcl3, Ccl4, Ccl5, and transcription factors such as Stat4 and Tbx2. The non-pathogenic Th17 cells display upregulation of molecules associated with immune suppression cytokines such as IL-10, and transcription factors such as Ikzf3 [38,39]. Th17 cells secreted both IL-17A and IFN-γ have been described as pathogenic cells intensifying disease pathogenesis. Recently, various investigations conducted on mice reported the presence of non-pathogenic Th17 cells able to produce IL-10 and promoting immune-suppressive properties limiting tissue inflammation [40–44]. There is laboratory evidence establishing the idea that

pathogenic Th17 cells can change into non-pathogenic cells [40]. The pathogenic versus non-pathogenic characteristics of Th17 cells in cancer remains questionable and is possible depending on the type of cancer. Cytokines such as granulocyte macrophage-colony-stimulating factor (GM-CSF), prostaglandin E2, and Notch signaling molecule RBPJ are associated with Th17 pathogenicity [45–47].

An important characteristic of IL-17 is its powerful co-operative impact with other cytokines in controlling down-stream gene/protein expression. This synergy is shown in the fact that IL-17 solely is not a strong inducer of inflammatory pathways such as NF-κB, despite the vigorous in vivo effects of an IL-17 deficiency [48]. Chemokines perform a pivotal role in recruiting immune cells to the place of inflammation, and the function of IL-17 in controlling chemokine production is complex, with positive effects exerted on the production of some chemokines and negative exerted impacts on others. IL-17 synergizes with TNF in up-regulating the expression of a subset of chemokines and cytokines including CXCL1, CXCL8, CCL20, and IL-6 [49–52]. Whereas TNF causes transcription of the genes for CXCL1 and CXCL8 by stimulating the NF-B signaling pathway, IL-17 seems to act chiefly by stabilizing their mRNAs [49,50]. Intriguingly, still, IL-17 negatively regulates TNF elicited production of other chemokines, including CCL5, CX3CL1, and CCL27 [53–56]. Furthermore, in a mouse model of allergic asthma, IL-17 performs as a negative controller by repressing expression of the eosinophil chemokine CCL11 and Th2 chemokine CCL17 [57]. Very little is known at present regarding the mechanism(s) for the repressive effects of IL-17 on these chemokines

2.1. Different types of Th17 cell related cytokines and their role in inflammation

Adequate immune responses against invading pathogens are achieved through a network of cytokines, whose functions are to induce the development and maturation of cells from the lymphoid and myeloid lineages, and the activation of their effector functions. The CD4 + helper T cells play an essential role in the initiation and regulation of immune responses. Naïve CD4 + T cells proliferate and differentiate into different effector subsets when they are activated mainly by IL-6, TGF-beta, and IL-23, and the local cytokine milieu mostly influences at the time of activation. The Th17 cells mainly secreted the following cytokines.

2.1.1. IL-17

The IL-17 is a well-known proinflammatory cytokine ubiquitously performs several biologic functions such as inducing the production of other cytokines, chemokines, and prostaglandins [58]. Other cell types can also secrete IL-17 when triggered with suitable stimuli *in vitro* or *in vivo* during inflammation or infection, such as δγT cells, Natural killer (NK) cells, Group 3 innate lymphoid cells (ILC3), lymphoid-tissue inducer (LTi)-like cells and invariant natural killer T (iNKT) cells [59–61]. The IL-17 family has six members, including IL-17A (previously named IL-17), IL-17B, IL-17C, IL-17D, IL-17E (IL-25) and IL-17 F, but not all the cytokines of the IL-17 family are produced by Th17 cells at all the time. This is the case only for IL-17A and IL-17 F [62]. All the IL-17 family cytokines are expressed at various location in the body, and it transmitted the signals by interacting with its transmembrane receptor. Till now, there are only five members of the human IL-17 receptor family have been identified, designated as IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE [25]. The gene encoding IL-17RA is located on chromosome 22, and the others are encoding IL-17RB, -17RC, -17RD and -17RE cluster on chromosome 3 [63]. The precise nature of their respective receptor complexes has not been defined, as IL-17RA and IL-17RC have very different affinities for IL-17A and IL-17 F. The IL-17 cytokines family are used as a direct linkage between inflammatory responses and T-cell activation. Although it is critical in keeping the host from the attack of various types of pathogens and dysregulation in the production of Th17 cell cytokine can also lead in excessive proinflammatory cytokine expression and chronic inflammation, which results in autoimmunity and tissue damage. The IL-17 family cytokines have been linked to various types of diseases, including rheumatoid arthritis (RA), inflammatory bowel disease, multiple sclerosis (MS) and psoriasis [63]. The IL-17A and IL-17 F, which have similar receptors, might readily be expected to function redundantly in stimulating the inflammation. The IL-17A, IL-17 F, and IL-17A–IL-17 F all signal through the same receptor subunits, IL-17RA and IL-17RC, which together form a heteromeric complex. Although these two related genes also performed different roles in some instances [64,65]. Recent studies on IL-17 significantly enhance our understanding of protective inflammation during pathogen infection and chronic inflammation associated with autoimmune diseases [66].

2.1.2. IL-21

The Interleukin-21 (IL-21) identified in 2000 as a CD4 + T cell-derived cytokine and mainly binds with the IL-2R-related orphan receptor [67,68]. It is a pleiotropic cytokine that is composed of four α-helical bundles and produced primarily by natural killer T (NKT) cells, T follicular helper (TFH) cells and Th17 cells with lower levels of production by numerous other populations of lymphohematopoietic cells. The biological functions of IL-21 are performed by a receptor which is heterodimeric and formed by the common γ-chain subunit that is shared with IL-15, -13, -9, -7, and IL-2 receptors [67–69]. The primary function in the mouse is to suppress the stimulation of Treg cells in the periphery, Th17 cell development and expansion [70,71]. Human IL-21 deregulated IL-17 F and IL-17A production and T-cell proliferation and to counteract suppression by Tregs. Other pro-inflammatory cytokines secreted from human Th17 cells include TNF-α, IL-22, and IL-26 [64].

The IL-21 is strongly related to inflammation and autoimmunity. There are previous studies which showed that the IL-21 levels are increased, which leads to autoimmunity in the mouse model [72]. The elevated amounts of IL-21 have subsequently been reported in many autoimmune diseases, including inflammatory bowel diseases (IBDs), type 1 diabetes (T1D), and systemic lupus erythematosus (SLE) [73–75]. The IL-21 induced Jak/STAT signaling which is linked to the differentiation of human B-cells into an Ig-secreting plasma cell, while STAT3 is required for IL-21 induced IL-17 expression by Th17-polarized cells [76,77].

2.1.3. IL-22

Firstly, two groups of scientist cloned the Interleukin-22 (IL-22) from activated T-cells, where its ability to stimulate epithelial cells but not immune cells [78,79]. It is an α-helical class II cytokine of the IL-10 family [80,81]. The gene of IL-22 is located on chromosome 12 in humans, close to the loci encoding interferon-gamma and IL-26 [82]. The STAT3 is the primary activator of IL-22 production in many cells downstream of IL-6, IL-21, and IL-23 [83]. IL-22 is mainly induced by the IL-23, and it's down streaming signaling causes the differentiation of Th17 cells by activating STAT3 [84,85]. IL-23 and IL-1β also activate IL-22 production in invasive lobular carcinoma and γδT cells, while invariant NKT cells in the lymph node require CD1d stimulation in addition to both cytokines [86,87]. These signaling pathways produce anti-microbial peptides and pro-inflammatory molecules, and it also promotes tissue repair by inducing epithelial cell proliferation and survival. Anti-microbial peptides and pro-inflammatory molecules are produced by IL-22 are supposed to be essential for the role of regulation of bacterial infections of the host defense system, and also in limiting tissue destruction during graft versus host disease, thymus involution hepatitis and colitis. [88–91].

2.2. The role of Th17 cell related cytokines in cancer pathogenesis

The Th17 cell subpopulation has been described in many types of cancers, including colorectal, melanoma, breast cancer, ovary, and liver

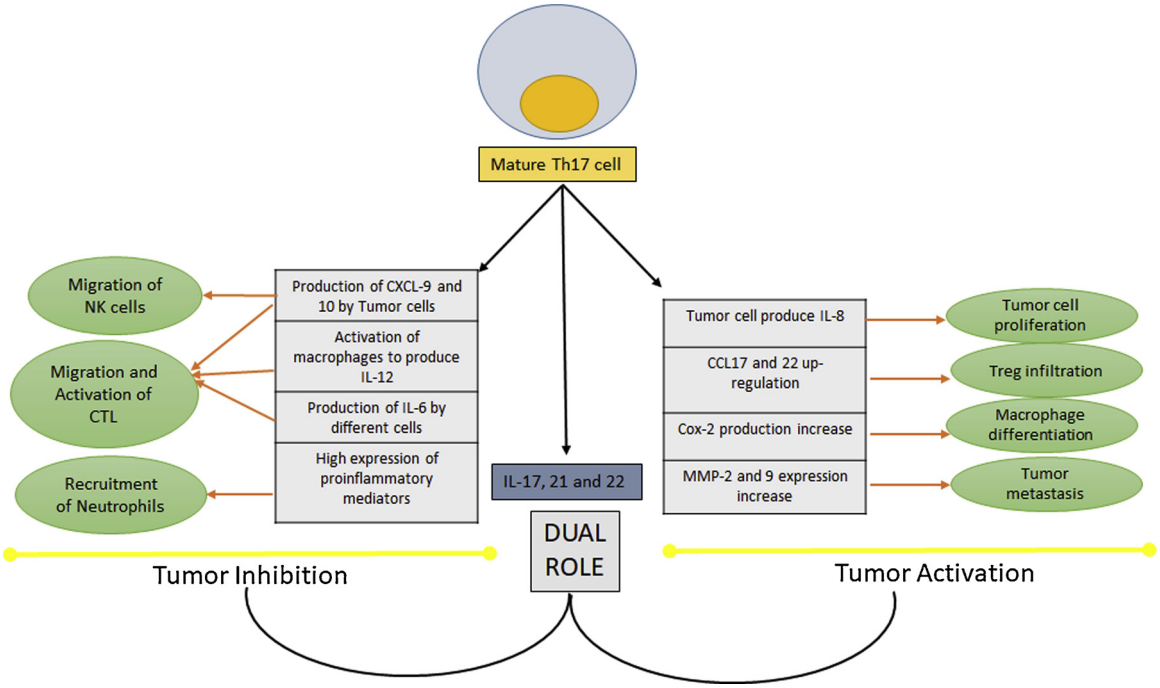

Fig. 2. Dual function of Th17 cells: The Th17 cell related cytokines show their antitumor property by recruiting various types of immune cells, including CTLs, NK cells, and neutrophils. On the contrary Th17 cell related cytokines also increasing Treg infiltration in the tumor tissue and stimulating M2 macrophages differentiation. They also show their pro-tumor functions by increasing tumor cell proliferation and metastasis. (Ref. Z. Asadzadeh, H. Mohammadi, E. Safarzadeh, M. Hemmatzadeh, A. Mahdian-Shakib, F. Jadidi-Niaragh, G. Azizi, B. Baradaran, The paradox of Th17 cell functions in tumor immunity, Cell Immunol, 322 (2017) 15-25. doi: 10.1016/j.cellimm.2017.10.015).

cancer [92–96], but it is performed dual functions by either promote or inhibit tumor progression and the exact mechanism of their involvement in tumor immunity is unknown (Fig. 2). The development of cancer is affected by many factors, and it depends on the production of the pro-inflammatory factors, angiogenic cytokines, antitumor immunity, and the immunogenicity of the tumor [97–99]. The critical role of IL-17A and IL-17 F in intestinal tumorigenesis and colorectal cancer (CRC) are well-known, and enough information is not available about the function of other IL-17 family members. In CRC, IL-17B is augmented, IL-17C revealed different expression by the grade of differentiation, and IL-17E remained unchanged. In the opposite direction, IL-17 F is reduced in CRC compared to healthy control. The IL-17RA, IL-17RB, and IL-17RC are all expressed in both healthy control and CRC [100]. There are several independent studies have demonstrated that IL-17 inhibits tumor apoptosis and promotes tumor proliferation. Knockdown of the IL-17 receptor (IL-17R-/-) in 4T1 mouse mammary cancer cells enhances apoptosis and decreases tumor growth in vivo [100], whereas in another study, the number of apoptotic cells observed significantly increases in IL-17R-/- lymphoma tumor mice, with proliferating cells reduced considerably in IL-17R-/- mice when compared with wild-type mice [101]. By using IL-22 deficient mice, different groups have demonstrated that endogenous IL-22 promoted tumorigenesis in several mouse models of inflammation/carcinogen-induced cancer [102–104]. It also enhances expression of inducible nitric oxide synthase (iNOS) and Interferon- γ (IFN-γ) in colon carcinoma cells; thus contributes to the conversion of nitrites associated with tumorigenic inflammation in the colon [104].

The potential mechanisms responsible for the promotion of tumor growth activity by Th17 cells involve angiogenesis in which IL-17 influences the proliferation of tumor cells by stimulation of new vessels formation due to its pro-inflammatory as well as angiogenic activity. This induces VEGF, which markedly promotes inflammatory and tumor angiogenesis [105]. Although the details remain unclear, accumulating evidence has demonstrated that IL-17 might play an oncogenic role by inhibiting tumor cell apoptosis, impairing antitumor responses, promoting tumor angiogenesis, and promoting tumor metastasis and invasion. The PGE2, inducing, and working with IL-23, favors the expansion of human Th17 cells and enhances IL-23-induced IL-17 production by memory T cells [106]. Circulating human Foxp3 + IL-17 + T cells have *in vitro* suppressive activity. Although the origin and function of these coexpressions are currently unknown, it is possible that these cells are in transition during early Treg or Th17 differentiation. [107]. Pancreatic carcinoma cells themselves secrete VEGF in response to IL-22 stimulation and IL-22 from tumor-infiltrating lymphocytes of colorectal cancer patients also increased VEGF expression in mice with colorectal carcinoma xenografts [108,109]. The treatment of CD8 + T cells with IL-21 *in vitro* resulted in their enhanced longevity in vivo, even after regression of the primary melanoma. TILs from primary human tumors are expanded in the presence of APCs that artificially expressed IL-2, IL-15, or IL-21.

3. Cancer stem cells: origin and properties

Various important questions are emerging in the cancer stem cell field; (a). Does cancer all the time initiate from stem cells (normal) that lose control over the mechanism of regulation and growth in the cell? (b). Can differentiate or progenitor cells attain stem cell properties by mutations and start cancer pathogenesis? Even though the above two questions are mainly attached with the CSC models, they are challenging to show experimentally, because the quantity of early progenitor cells or cancer stem cells and normal stem in a tumor is usually very few. Stem cells are mainly found at the highest point of the developmental hierarchy, which has properties such as the self-renew and which maintained to all the cell lineages in corresponding tissues. Two daughter cells have been produced in each cell division of stem cells. The first daughter leftovers a stem cell (self-renewal), and the second daughter cell develops into the progenitor cell that through the expansion and further differentiation into mature cells and this property of stem cells is present from rodent to human [110]. The capacity of adult stem cells to be self-renewal and long-lived and multi-lineage

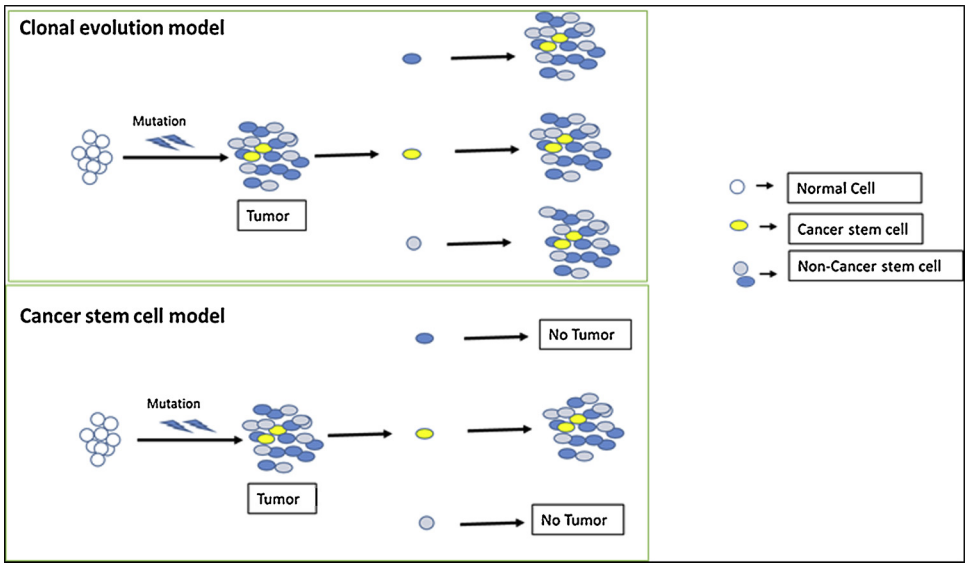

Fig. 3. The Models of tumor growth: According to the (1). Clonal evolution model, tumor growth posits that all cancer cells are equipotent and can either self-renew or give rise to non-proliferative cells in a stochastic manner and all cell can generate tumor (shown in a figure, all cells are equally responsible to the tumor). (2). In the cancer stem cell (CSC) model, only a subset of cancer cells known as CSCs present extensive self-renewal properties and have the potential to generate the tumor. All other cells, except CSCs, are not able to generate the tumor.

differentiation makes these cells exceptionally unique and vital in normal physiology and pathological conditions [111]. Although many tumors in human as well as in rodent contain cells that display stem cell-like features, the identity of the normal cells that acquire the first genetic 'hits' that lead to tumor initiation has remained elusive.

There is mainly two concepts of stem cell theory of cancer (Fig. 3): The first assumes that every cancerous cell can proliferate and regenerate a tumor extensively. Due to this assumption, all the cancer cells have an equal probability of restoring cancer. In contrast, the second concept suggests that only a small amount of cells within the tumor population can start and maintain tumor growth. By inference, a functional heterogeneity exists within the pool of cells that make up a tumor and suggests that isolating and purifying this small population can generate a highly potent population of tumor-initiating cells [112,113]. It is possible that the development of CSCs might involve at least two or more of the following events: (i) a change in the microenvironment of the stem cell niche within a tissue; (ii) alterations in cellular metabolism, cell cycle control and/or progression and signaling pathways as a result of mutations and epigenetic changes; and (iii) amplification of cell populations with an altered molecular phenotype that give rise to heterogeneous primary tumors and metastases.

Cancers are observed as abnormal and heterogeneous tissues comprising a variety of cells that originate from a rare and unique subset of cancer cells having a self-renewal potential and capacity to differentiate into multiple cell lineages [114]. Within the tumors, the large amount of the cancer cells does not have any tumorigenic and metastatic property, but only a few cells within the tumor have both. With the help of autoradiography and radiolabeling, various studies were carried out on mouse model to explain the hierarchy of cells. By the radiolabeling of DNA, only in the undifferentiated areas, new labeling occurred. Later on, DNA label moves in well-differentiated regions as well. The part closer to the center contains progenitor cells capable of undergoing a limited number of cell divisions to form several daughter cells [115]. The CSCs lies at the center, which is different from other cancer cells and have the potential of self-renewal. This division of CSCs in the tissue may be present in the human also, but it is not verified yet. One or both of the daughter cells hold the characteristic of the stem cell in self-renewing mitosis. The other cell transforms in the progenitor cell, which has the ability of the limited number of cell divisions and gives rise to the pool of differentiated cancer cells.

The stem cells are defined by a remarkably indefinite potential for self- renewal and multi-lineage differentiation while maintaining an undifferentiated status [116]. The intratumoral phenotypic heterogeneity not only from the results of genetic variation but also from the plasticity of tumor cells that are observed in response to micro-environmental stimuli. In recent years, CSCs have been recognized as essential components in carcinogenesis in human as well as in mouse, and they could form the basis of many tumor types. The CSCs have been isolated from various cancers, including breast, brain, blood, melanoma, head and cervix, lung, organs of the gastrointestinal and reproductive tract [117]. The current anticancer therapies mostly fail to eradicate CSC clones and instead favor the expansion of the CSC pool and select for resistant CSC clones, thus leading to a fatal outcome of the disease but CSC is not fully proven in human and is under fierce debate.

3.1. Cancer stem cell markers in various types of cancer

The first probable identification of CSCs was carried out with leukemic peripheral blood specimen from a patients of acute myeloid leukemia (AML), in which the surface markers of leukemic stem cells were defined as CD34 + CD38-phenotype [118]. When the small immature subset of CD34 + CD38 − cells transplanted into non-obese diabetic/severe combined immunodeficiency (NOD/SCID) mice, these cells were able to reinitiate same leukemia, whereas the significant abundant subset of CD34 + CD38 + cells was ineffective [118]. This experiment provided the first convincing evidence that progenitor cells can give rise to leukemic stem cells. There are various types of cell surfaces markers such as CD44, CD133, and ALDH1 present on the cancer stem cells [119,120] (Table 1).

The CD44 + is one of the cancer stem cell markers which is reported as at least one characteristic of CSCs in many cancerous tissues of human as well as in rodent, including in breast, pancreas, gastric, prostate, ovarian, and colon. The CSC phenotype commonly includes CD44 +, which likely points to important roles for CD44 in tumors, such as in facilitating adhesion, migration, and invasion. Another CSCs marker has recently been discussed in depth is CD133 [121]. The CD133 (Prominin-1) was discovered as the target of the AC133 monoclonal antibody, specific for the CD34 + population of hematopoietic SCs (HSC). Freshly isolated CD133 + cancer cells from human cancer tissues such as colorectal, gallbladder cancer, and ovarian cancer of any other tumors gave rise to long-term tumor spheroids and xenograft tumors in immunodeficient mice [122–125]. More recently, elevated ALDH activity has been employed as a CSC marker in multiple tumor types [125]. It is present almost in every tissue. The main functions are catalyzing the oxidation of aldehydes and function in cellular detoxification, retinoic acid (RA) metabolism and signaling, development, protection from reactive oxygen species (ROS), and

Table 1
Cell surface markers associated with cancer stem cells.

Cancer Stem Cell Marker	Biological Role	Tumor type
CD44	Hyaluronic acid receptor	*Breast, Colon, Liver, Ovarian, Pancreas, Gastric*
CD90	Tissue specific differential glycosylation	*Brain, Liver*
CD117	Growth factor receptor	*Ovary*
CD133	Marker for hematopoietic stem cells.	*Breast, Prostate, Colon, Glioma, Liver, Lung, Ovary*
CD166	Activated leukocyte cell adhesion molecule (ALCAM)	*Colorectal, Lung*
ALDH	Alcohol metabolism	*Lung, Breast*
EpCAM	Cell-cell contact adhesion strength	*Colon, Pancreas, Liver*
ABCG2	ATP-binding cassette transporter	*Lung, Breast, Brain*

maintenance of the eye and vision [125]. The recent study on human tissues sample showed that the regulation of ALDH in prostate cancer stem cells (PCSCs) and its role in prostate tumor radio-resistance [126]. The ALDH proteins and general activity have been implicated in radiation resistance and tumor recurrence in several cancers, including esophageal cancer of human origins [127]. All the above CSCs markers are an important contributor to CSC function in cancers, and currently, these are using in anticancer target strategies.

To understand the biology of cancer stem cells, we must define the distinctive properties of the normal stem cells. In recent decades significant research work has been carried out in the discovery and characterization of CSC markers in various cancers. Most of the markers of CSCs are found on normal stem cells. This causes a problem to their possible use as therapeutic targets in cancer treatment. Currently, the most reliable selection for a therapeutic target would be oncofetal stem cell markers because these are not expressed in normal adult stem cells. Else, there is no definite difference available between cancer stem cell and normal markers.

Interestingly, most of the current CSC surface markers are derived from known normal embryonic or adult stem cell surface markers, and most of the stem cell markers described so far are proteins [128–130]. Only a few stem cell markers have been displayed to be glycans bound to lipids or proteins (Table 2). The question is whether these glycans can perform a significant role as CSC markers in a more comprehensive sense. The answer is yes because CSC markers are different from their normal CSC markers by the expression of tumor-specific glycans. It is the fact that the glycosylation of cellular glycoproteins is changed in cancer has been well known for many years. [131]. However, it does not merely extend this idea to stem cell markers but claims that this is not a random process. It appears to be selective to the proteins as well as to the glycans involved.

3.2. Interconnection between Th17 cell cytokines and cancer stem cells

The CSCs interact with and in turn, are regulated by cells in the tumor microenvironment. These interactions involve various inflammatory cytokines, which in turn activate several pathways in cancer cells, including Th17 cell cytokines network. The location of stem cells has been identified in normal organs, and it has been proposed that the communication of microenvironment with stem cells is essential for the maintenance of stemness [132]. The CSCs may localize at a specific niche like stem cells in normal organs [133]. Due to the significance of the tumor microenvironment, it is a reasonable strategy to regulate the stem cell niche to inhibit CSC survival.

Soluble mediators and cell to cell communications are two main factors from CSCs can affect CSCs produce th17 differentiation [134], such as IL-6 in multiple myeloma, breast cancer, and Squamous cell carcinoma with a comparatively significant concentration rather than other cancer cells [134,135]. Furthermore, IL-23 produced by ovarian CSCs has been commonly reported that plays a fundamental role in the maturation and maintenance of Th17 cells phenotype [136]. Also, CCL5, a chemokine that actively attracts Th17 cells, has been identified in breast cancer at primary and metastatic tumor sites, ovarian, gastric, and prostate cancers [137]. In addition to soluble factors secreted by CSCs that affect Th17, the existence of stemness genes in Th17 cells can potentiate that they can convey between CSCs and CD4 + T cells through the cell to cell communication. This, in turn, can cause Th17 cells differentiation. Several mechanisms of intercellular communication have been already well documented, including chemical synapses, gap junctions, and plasmodesmata. High sensitive nanotubular structures can be set presumably between immune cells, tumor cells, and also between infiltrating T cells and distant tumor cells, facilitate simplify selective transfer and communication [138]. Immediately, stemness genes might shift from CSCs to T cells through tunneling nanotubes and differentiate CD4 + T cells to long-lived Th17 stem-like cells. STAT3, a pleiotropic transcription factor stimulated downstream of cytokines, is overexpressed in gastric cancer stem cells and metastatic tumor samples [139]. Activated STAT3 can be either pro-oncogenic or tumor-suppressive according to the tumor etiology and mutational landscape, and it considers as a critical transcription factor for Th17 differentiation [140,141]. Therefore, we can conclude that STAT3 might be able to pass through membrane structures between cancer stem cells and CD4+ uncommitted T cells to change the shift them to Th17 cells.

Some stem cell subsets possess a strong invasive capability, whereas other stem cell subsets are in a quiescent state and do not differentiate. The cells displayed extremely weak tumorigenicity and a poor invasive ability and only played a role in the maintenance of primary tumor growth. Therefore, these stem cells were defined as quiescent stem cells. The dormant state of stem cells is not permanent. Under appropriate external environmental stimuli, quiescent stem cells may undergo an invasive transformation and become invasive stem cells [142].

Table 2
Gycan related stem cell markers.

Stem cell markers (Glycans)	Nature (Carbohydrate part)	Tumor Type/Source
CD15	Galβ1-4[Fucα1-3]GlcNAcβ1-3Galβ1-	Globlastomas
CD77	Galα1-4Galβ1-4Glcβ1-	Burkitt lymphoma, breast cancer, germ cell carcinomas
CD173	Fucα1-2Galβ1-4GlcNAcβ1-	ESC cell lines
CD174	Fucα1-2Galβ1-4[Fucα1-3]GlcNAcβ1-	Breast cancer
CD175	GalNAcα1-	ESC cell lines
CD176	Galβ1-3GalNAcα1-	Leukemias

Reference for this table. [U. Karsten, S. Goletz, What makes cancer stem cell markers different?, Springerplus. 4;2(1) (2013) 301.].

Various cytokines or stimuli are involved in the activation of quiescent CSCs such as IL-17 which transform the quiescent gastric CSCs into invasive gastric CSCs [142]. In the cancer progression, the interaction between Th-17 cells and CSCs has aroused pronounced interests of the scientists in recent years. Yang et al. showed that when the sphere cells co-cultured with Foxp3 + IL-17 + cells, they could express more CSCs markers (CD133, CD44s, CD166, Ep-CAM, and ALDH1) than the control sphere cells, and when neutralizing with the anti-IL-17 antibody, all the cell markers was abolished [143]. The Lotti et al. reported that IL-17A could contribute to CSCs maintenance through the IL-17A receptor in CRC, and then promote pro-tumorigenic CSCs behavior, as well as contribute to CSC therapeutic resistance [144]. It is also established that one of the functions of IL-17 in CSLCs (ovarian CD133 + cancer stem-like cells) is to stimulate the self-renewal [145]. Therefore, to study the Th17 cell related cytokines that transformed the dormant stem cell into the active is of immense clinical significance. It has been recognized that the inflammatory niche is an essential part of CSCs microenvironment to continue the inflammation, via enhancing signaling of proliferation and induction of metastasis and invasion. The Th17 cell cytokines may influence tumor growth by regulating cancer stem cells populations

4. Cancer stem cells and Th17 cytokines: implications for therapeutic applications

4.1. Cancer therapy by targeting Th17 cells and its related cytokines

To understand the properties of Th17 cells in tumor immunity would generate opportunities for the progression of new therapeutic approaches for cancer treatment [146]. Two primarily different strategies should be used based on cancer type and the clinical influence of Th17 cell cytokines. The first strategies are to nullify the detrimental inflammation caused by Th17 cell cytokines that are linked with poor prognosis and the second one is to stimulate antitumor responses of Th17 cell cytokines in conditions that are related with enhanced prognosis. For human T-cells, the IL-23 and IL-1b can promote the differentiation of human Th17 cells, and IL-6 may further augment Th17 cells differentiation if added on top of IL-23 and IL-1b [146–149]. Although early studies indicated that TGF-β was dispensable for human Th17 cells development [146,147], more recent studies also suggest that TGF-β, at least at the low dose, is still required [149–151]. The inhibition of SOCS3 and enhancement of STAT3 activation is at least one of the mechanisms of TGF-β promotion of Th17 cell development [152]. The Therapeutics that block IL-23, IL-1β or IL-6 already have demonstrated efficacy in the clinic even before the discovery of Th17 cells. An IL-1 receptor antagonist (IL-1Ra, Kineret) that blocks the function of IL-1β has been used to treat Rheumatoid arthritis (RA) [153,154].

Effective antitumor Th17 cells are less prone to apoptosis than their Th1 cell counterparts, although the reasons for this are not clearly understood. The antitumor activities of CD8 + T cells have gained the attention in the field of tumor immunology because these cells produce IFN-γ, GM-CSF, and TNF and can specifically lyse antigen-presenting MHC class I tumors [155]. The IL-17 producing CD8 + T cells have greatly enhanced expression of RORγt, decreased expression of eomesodermin, and their canonical cytotoxic activity is diminished [16]. Like their CD4 + counterparts, these CD8 + T cells can acquire the ability to produce IFN-γ and mediate regression of large, established tumors. This enhanced antitumor activity is associated with increased in vivo expansion and persistence of the transferred cells.

The antitumor effects of IL-21 have been observed in many preclinical models of tumor immunotherapy including bladder, pancreatic, colon, and mammary cancer, and are mainly related to an increased NK and CD8 + T cell activity [156–162]. Activation of the cytotoxic signaling to activate the NK cells and CD8 + T cells is important for cancer immunotherapy. The early research provided convincing evidence that IL-21 is a promising anticancer agent [163] and IL-21 also stimulates cytotoxicity and induces production of IFN-γ and perforin by NK cells [164]. Injection of IL-21, alone or in combination with other cytokines led to tumor regression and subsequent in a significant delay in the tumor growth [165–167]. Some studies show that IL-21 strongly induces apoptosis of diffuse mantle cell lymphoma chronic lymphocytic leukemia cells and large B-cell lymphoma, via activation of STAT1 or STAT3. This leading to the modified expression of BCL2 family proteins and the activation of caspases [168–171].

Accumulative results strongly suggest that the inhibition of IL-22 and IL-22R1 activity may be beneficial in several diseases, including various cancer, whereas strengthened IL-22R1-mediated signaling might alleviate several other conditions [172]. This comes as no surprise since IL-22 promotes proliferation, cell motility, angiogenesis, and dysplasia in so many organs. Therefore, blockade of IL-22 signaling may represent a viable method for anticancer therapies [173]. A direct IL-22-neutralizing antibody, ILV-094, has completed Phase I and II trials for psoriasis and rheumatoid arthritis respectively, and is recruiting for a Phase I trial for patients with atopic dermatitis [174]. The neutralization of IL-22 may improve disease control and quality of life for late-stage disease patients by reducing metastasis, chemoresistance, and inflammation associated with cancer. Although IL-22BP is a natural antagonist of IL-22, therefore, seem like an attractive candidate for targeting IL-22. Some studies have shown that IL-22BP may even stabilize IL-22 to some extent and thus increase its levels. Development of neutralizing antibodies that would block IL-22RA1 could also be beneficial in anti-cancer therapy, as this treatment would selectively and specifically affect receptor-bearing cells (including tumor cells), potentially also inhibiting the protumoral effects of IL-22 sibling cytokines IL-20 and IL-24 [175].

The discovery of Th17 cells and their biology has significantly advanced our understanding of the pathogenesis of many human diseases, including cancer. Besides, Th17 responses are also crucial for host defense in various infectious diseases. The development of therapeutics that target Th17 cells, combined with strategies to identify patients with dominant Th17 disease signatures, may provide successful efficacy against cancer while alleviating safety concerns.

4.2. Cancer therapy by targeting cancer stem cells

A fundamental property of CSCs is its capacity to maintain tumor propagation. CSCs may also be inherently resistant to chemotherapy and contribute to tumor relapse, although the CSCs that propagate the tumor and the cancer cells that are resistant to medical therapy can be different. The successful elimination of cancer requires anticancer treatment that affects the differentiated cancer cells and the potential CSC population [176]. At present, conventional anticancer therapies kill rapidly growing differentiated tumor cells, thus reducing tumor mass but potentially leaving behind CSCs. Conventional treatments become less effective when tumors progress from an organ-confined disease into locally invasive and metastatic cancers. This is because of genetic aberrations producing overexpression signaling pathways of oncogene as well as down-regulation of tumor suppressor gene products such as Rb, p53, PTEN or in cancer cells. Therefore, identification and targeting of cancer stem cells represent a significant challenge in modern cancer therapy, and researchers are trying to find new molecular therapies explicitly directed against these cells. Thus, molecular therapies against CSCs were reported to be more effective, as they induce tumor regression by reducing the occurrence of new cancer cells [177,178].

Along with the latest reports aiming at characterizing the molecular mechanisms that govern stemness in cancer, several therapeutic approaches have been developed and tested for the elimination of CSCs. However, no anti-CSC therapy has shown sufficient effectiveness to be approved for clinical use. Thus, therapies targeting the metabolic networks that mediate cancer cell stemness could be an innovative and

efficient strategy to target this cell population.

An ideal drug regime would kill differentiated cancer cells and, at the same time, selectively and quickly target and kill the CSCs to avoid toxic side effects for other cell types and to counteract the evasive mutagenic potential of CSCs. The identification of CSC markers and their exploitation in targeted chemotherapy is the ultimate goal of present-day cancer research. Specific therapeutic targeting of CSCs requires intricate knowledge of the biology of these cells. The presence of active transmembrane ABC transporter family members, such as multidrug resistance transporter 1 (MDR1) and ABCG2, can facilitate the efflux of DNA binding dyes such as Hoechst 33342 in cells with cancer stem cell activity known as the 'side population' (SP) [179]. The SP fraction has been identified in numerous cancers, including neuroblastoma, breast cancer, prostate cancer, and gastrointestinal carcinoma, and their chemoresistance is due to the ability of multidrug-resistant stem/progenitor cells to efflux anticancer drugs such as mitoxanthrone, gemcitabine, doxorubicin or 5-fluorouracil [180–183]. Several studies using mouse models of cancer have shown that targeting oxidative metabolism, the primary source of energy for CSCs in these models, sensitizes this population to chemotherapies, thus leading to their depletion. One example is the population of slow cycling JARID1B + cells in melanoma that has an upregulation of OXPHOS enzymes. Treatment of melanoma cells with several drugs, including cisplatin and vemurafenib, an inhibitor of mutant BRAF, causes enrichment of the JARID1B + population, and subsequent therapy resistance. When inhibiting OXPHOS using either ATP-synthase inhibitors (oligomycin and Bz-423) or complex I inhibitors (rotenone and phenformin), JARID1B + cells were sensitized to the anticancer agents that initially failed to eliminate them. The new therapeutic strategies target signaling pathways that are involved in the self-renewal processes of cancer stem/progenitor populations and block the growth of differentiated tumor cells. Thus, novel small molecules and specific antibodies have the potential not only to reduce tumor mass but also to eradicate the self-renewable source of CSCs [184].

5. Conclusion

The discovery may contribute to cancer cure research, which provided to the understanding of cancer pathogenesis and metastasis. In the last several years, an extensive study of Th17 cells enhanced our knowledge about their functions. They are a unique lineage of Th lymphocytes and are described by a particular cytokine production profile, transcription regulation, and immune activities. Therefore, the relationship between Th17 cells and tumor immunopathology are highly dependent on context, but a better understanding of these contexts could be used to develop and refine new cancer therapies. The link between CSCs and tumor niche related cytokines releasing cell is still poorly understood, but some studies connected the Th17 cell cytokines with CSCs. In this review, we have also discussed the CSC markers, but we need to discover more specific markers and understand their physiological roles to apply this knowledge to novel therapeutic targeting strategies better. Stem cell-mediated antibody therapy targeting CSC foci in a tumor is one of the emerging hopes in cancer therapeutics.

Contributors

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