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Review

Interactions between cancer stem cells, immune system and some environmental components: Friends or foes?

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ABSTRACT

Cancer stem cells (CSCs) are a subgroup of tumor cells that are characterized by their tumor initiating capacity, low proliferation rate, self-renewal capacity, pluripotency and chemoresistance. The immune system, including innate and adaptive immune cells, plays pro-tumorigenic and anti-tumorigenic roles in cancer biology. Immunosurveillance often initially successfully eradicates tumor cells. However, following a phenomenon referred to as immunoediting, cancer cells may ultimately evade immune destruction, thus enabling tumor progression. Here, we review how CSCs both escape immune destruction and foster establishment of an immunosuppressive tumor microenvironment through intricate interactions with and recruitment of a broad range of immune cells, including natural killer (NK) cells, myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), tumor-associated macrophages (TAMs), cytotoxic T-lymphocytes (CTLs) and T helper (Th) cells. Further elucidation of CSC-immune cell interactions and the underlying signaling mechanisms will open up novel opportunities to improve cancer immunotherapy.

1. Introduction

The term cancer initiating cells, or more commonly, cancer stem cells (CSCs), refers to a subgroup of tumor cells that exist within the tumor mass and are characterized by tumorigenic and self-renewal properties and resistance to chemotherapy. The idea of CSCs was first put forward fifty years ago [1,2]. Since then, these cells have been regarded as a driving force behind tumor initiation and dissemination [3]. In fact, CSCs display greater resistance to radiation and chemotherapeutic agents compared to other cancer cells and, therefore, they are able to survive conventional therapies, resulting in local and distant relapse of the disease [4]. The concept that the immune system recognizes and destroys nascent transformed cells, including tumor cells, arose from the cancer immunosurveillance hypothesis described by Burnet and Thomas [5]. The relationship between the immune system and cancer has been widely investigated for over a century and was first emphasized by Rudolph Virchow more than 150 years ago [6].

The CSCs' microenvironment includes a broad range of components, including immune cells that interact with CSCs, such interactions that promote changes in CSCs, which, over time, lead to their acquiring the ability to evade destruction by the immune system, a phenomenon known as cancer immunoediting. Sometimes, these changes are so powerful that the immune system promotes the development of CSCs [7]. It has also been shown that the tumor microenvironment directly promotes tumor development by inducing both local immunosuppression and the CSC phenotype [8].

Here, we comprehensively review the complex interactions between CSCs and a wide range of immune cells in the tumor microenvironment, covering immunosurveillance, immunoediting and immune escape during tumor development.

2. Definition of cancer stem cell (CSC)

There is increasing evidence that the tumor mass is highly heterogeneous, containing relatively small subgroups of cells with characteristics of stem cells. These are commonly known as "tumor-

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initiating cells" or CSCs [9,10]. Indeed, some of the key stem cell transcription factors are over-expressed in CSCs, such as SRY (sex-determining region Y) box-2 (SOX2), Octamer-binding transcription factor 4 (OCT4), kruppel-like factor 4 (KLF4), NANOG and cMYC, which maintain pluripotency [11]. CSCs are traditionally characterized by their chemoresistance [12], their capacity to self-renew, their multidrug resistance (MDR), their capacity to divide into different lineages, and to sustain homeostasis inside the tumor [13]. As such, CSCs behave similarly to embryonic stem cells or multipotent adult stem cells. For normal stem cells, cell fate determination and self-renewal are controlled by both cell-intrinsic and cell-extrinsic pathways. Impairment in these pathways leads to the expansion of stem cells and can be regarded as a key event in carcinogenesis [14–20]. For instance, many of the signaling pathways that regulate self-renewal of normal stem cells are impaired in CSCs, consequently leading to uncontrolled self-renewal and neoplastic CSC growth [21]. Multiple studies have shown that MDR in the CSC population is due to the over-expression of P-glycoproteins and/or ABC transporters (or drug efflux pumps), such as ABCC1/MRP1, ABCB1 and ABCG2 [19–22]. In the 20th century, Bonnet and Dick first proposed the concept of CSCs and studied it in human acute myeloid leukemia (AML) [23]. In contrast to most tumor cells, which are called non-CSCs or 'bulk' tumor cells, CSCs have the ability to initiate and sustain neoplastic progression, dissemination and relapse [24–26]. CSCs can be in a quiescent phase of the cell cycle but are not necessarily. In addition, they are characterized by high expression levels of transporters and anti-apoptosis proteins and by resistance to DNA damage [27].

In specifying and describing the subpopulation of cells with activities identical to those of stem cell in solid tumors, several markers, namely CD133, CD44, CD24, and aldehyde dehydrogenases (ALDH) are commonly used [14,28–30]. There are two strategies for CSC division, including symmetric cell division, which yields two CSCs, and asymmetric CSC division, which gives rise to one CSC and one non-CSC. Symmetric cell division produces CSCs instantaneously, while asymmetric division may sustain long-term survival of the progeny [13,31] (Fig. 1).

3. Tumor immunosurveillance

Malignancy can be countered completely by the immune system in a process known as immunosurveillance [32]. During 1950s, the cancer immunosurveillance hypothesis was formally put forward to describe a possible function of adaptive cellular immunity in eliminating tumor cells [33]. CSCs have been reported to have lower immunogenicity when compared to non-CSCs [34,35]. As such, tumor cell growth is monitored and thereby, a first line of defense is constituted by innate immunity. Stress results in upregulation of ligands that help activate natural killer (NK) cell receptors, a response that activates an adaptive immune response [36] and other immune stimulatory surface molecules help identify and eliminate tumor cells. The main molecules responsible for tumor immunosurveillance include interferon-gamma [37], interleukin-12 (IL-12) [38], death receptor (DR4) and DR5 [39], perforin [40] and the recombination activating genes RAG1 [41] and RAG2 [37]. Loss of any of these culminates in more frequent or faster spontaneous or carcinogen-induced tumorigenesis [42]. In addition, both bulk tumor cells and CSCs may modify the biological properties of stromal cells, endothelial cells and immune cells in their unique microenvironments, consequently facilitating tumor progression and the emergence of drug-refractory tumor phenotypes [43–45]. Therefore, the interactions between tumor cells and nearby normal cellular components probably play a critical role in tumor initiation, progression, and responsiveness to anticancer therapeutics [46].

4. The CSC niche in the microenvironment

In healthy tissues, stem cells are concentrated in areas filled with blood vessels and stromal cells, otherwise known as the 'stem cell niche'(SCN). This niche is believed to protect stem cells against apoptotic stimuli and to strike a proper balance between stem-cell self-renewal and differentiation. In fact, it has been suggested that, in the tumor microenvironment, CSCs reside in a niche that is vital for their maintenance [47], similar to normal stem cells. Developmental cell-intrinsic pathways, such as Hedgehog, Wnt and Notch, control the function of normal stem cells and are frequently impaired in cancers [17,18,48,49]. Extrinsic signals that control stem cell behavior originate in the stem cell microenvironment or niche. This niche consists of extracellular components, as well as various cell types [50]. Like normal stem cells, CSCs need input from the surrounding microenvironment to establish an optimal balance between self-renewal and differentiation. Such input might influence tumor initiation,

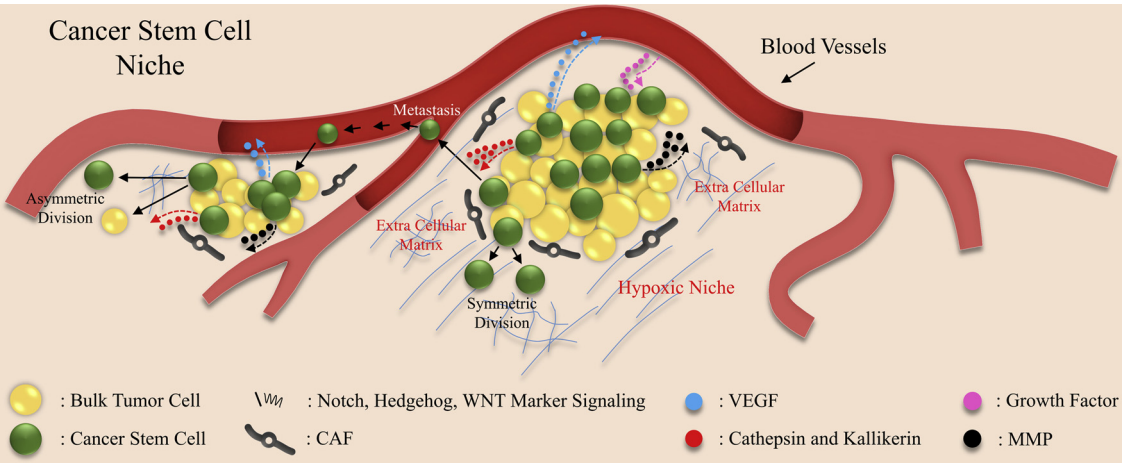

Fig. 1. Cancer stem cells (CSCs) niche and the function of this tumor cells in this site.
Cancer cells that create a special place in the vicinity of the vein that is known cancer stem cell niche (CSCN). This niche is believed to protect CSCs which protects them from the destructive of these cells. CSCs have symmetric division and asymmetric division. CSCs in this milieu with the hypoxic situation in extra cellular matrix (ECM) produce some factors that help to growth and progression this cells. Signaling of WNT, Notch, Hedgehog are developmental intrinsic pathways for CSCs. Endothelial cells produce and secret growth factors for CSCs. CSCs with producing and secreting metalloproteinase matrix (MMPs), cathepsins and kallikreins could promote cancer cell migration. Vascular endothelial growth factor (VEGF) that was produced by CSCs, elevate angiogenesis. Cancer associated fibroblasts (CAFs) that are in ECM have been identified as two potential tumor promoters. These CSCs with going into the vessel and then exhale from the bloodstream and enter to another place cause metastatic of tumor.

progression and outcome [51–54]. The cancer stem cell niche (CSCN) is rich in soluble factors, growth factors, adipose cells, cytokines, prostaglandins and extracellular matrix (ECM) components, while cancer-associated fibroblasts (CAFs), mesenchymal stem cells (MSCs), immune cells and endothelial cells are the key cellular players [55–57], and they all influence tumor growth and metastasis [50]. In the CSCN, metabolites, such as lactate, glutamine and ketone bodies reprogram again the metabolism of stromal stem cells and cancer cells advocating adaption of tumor cells to dynamic fluctuation of CSCN. Tumor cells in the CSCN stimulate CAFs to reprogram their metabolism, adopting a glycolytic phenotype. In other words, increases in glucose uptake and lactate secretion serve as nutrients for adjacent cancer cells [58,59]. On the one hand, lactate secretion increases acidity in the CSCN, which results in higher ECM protease activity and this promotes migration and metastasis. However, lactate is absorbed by cancer cells and this reprograms their metabolism from a glycolytic to a respiratory mode (OXPHOS), thus fostering ongoing tumor growth [60]. CSCs also express a great number of cellular proteases, including matrix metalloproteinases (MMPs), cathepsins and kallikreins [61]. This leads to degradation and remodeling of ECM and enables tumor cell migration.

Hypoxia-inducible factors (HIFs), which are produced by mesenchymal stem cells (MSCs) and a subset of cancer cells [62,63], facilitate metabolic shifts in cells in hypoxic environments, including the CSC's microenvironment. In addition, hypoxia stimulates epithelial-to-mesenchymal transition (EMT) in CSCs, a process necessary for metastasis, by activating EMT transcription factors, a process that results in loss of E-cadherin expression, among others [64,65]. In the tumor microenvironment, HIFs play a central role in the maintenance and proliferation of CSC and bulk cancer cells. Further, HIFs promote the differentiation and/or proliferation of host cells including, dendritic cells (DCs), endothelial cells (ECs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs). In addition to regulating cells that modify T cell function, HIF also directly promotes the activation and differentiation of different functional subsets of T cells, including cytolytic T lymphocytes (CTLs), regulatory T cells (Tregs), and interleukin (IL)-17-producing T cells (Th17) [66] (Table 1). Recently, researchers are increasingly interested in the significance of the CSCN in controlling the biological properties of CSCs with the goal to enhance the response of tumors to drugs and therapeutic agents [3] (Fig. 1).

5. CSCs and harnessing the immune system

The field of cancer immunology is rapidly evolving [67] and the principles of cancer immunoediting have set the scene for better understanding the dual host-protective and tumor sculpting actions of immunity from cancer and establishing a basis for new individualized cancer immunotherapies [68].

Changes in tumor immunogenicity, which lead to immune-resistant types of cancer, are initiated by the anti-tumor response in the immune system and it is used to identify immunoediting [69].

Experts believe that three major categories of cells participate in the immunoediting process: the cancer cells, which are heterogeneous, the immune cells, and the specialized stromal cells, including CAFs, endothelial cells, etc. As the CSC model is increasingly accepted, some argue that CSCs may be the key players in all three phases of the immunoediting process [70] (Table 1). The immunoediting concept, primarily put forward to explain the dynamics of the immune system in malignancies, is characterized by three Es (the Elimination, Equilibrium, and Escape phases). This model is now widely accepted in the field of cancer immunity [37,38,71].

The elimination phase in the immunoediting process represents a component of the cancer immunosurveillance theory and is used to define the ability of the innate and adaptive immune system to recognize and destroy cancer cells [71–73]. Cancer cell lysis occurs via secretion of perforin from cytolytic immune cells (i.e., NK cells, NKT cells, γδT cells, and CD8 + T cells), ADCC, or CDC [74]. The properties of low immunogenicity and quiescent behavior, which are exclusive to stem cells, may help CSCs remain detached in their niches, safe from the highly active and functional immune system during this elimination phase [75].

In the next stage, the equilibrium phase, the malignancy is contained but not eliminated. As this is a temporary and transitional stage, it is difficult to model in an in vivo setting. Hence, many aspects still remain to be elucidated. However, it is plausible that, thanks to their low proliferation rate and high resistance to immune-mediated killing, CSCs may already escape immune destruction, which is the key feature of tumor cells in the third phase of immunoediting, while bulk tumor cells are eradicated by the immune system [76]. The ongoing increase in heterogeneity and genetic variation of cancer cells may then ultimately enable them to definitively evade immune destruction [71–73].

At the molecular level, complex interactions have been identified between CSCs and the immune system. Studies have shown that CSCs,

Table 1
The soluble factors that affected on CSC and CSCN.

Soluble factors in CSC's niche/microenvironment		Produced by	Function	Reference
Growth factors		Fibroblasts, CSCs	Growth of CSCs	[48,213,214]
Cytokines	) TGFβ, IL-4, IL-6, IL-10, PGE2 (	CSCs	Protect CSCs from being destroyed	[70]
	CXCL12, IL-6, IL-8	MSCs	Generation of CSCs and their maintenance	[96,101]
	TGF-B	Tregs	Promote EMT of CSCs	[132]
	IL-17	Tregs	Development of CSCs	[131]
	IL-22	NK/T cells	Promote the CSC phenotype	[149,150]
	IL-12, IL-23, CXCL19 and CXCL10	M1 macrophages	Development of immune cells against CSCs	[156,157]
	Type II cytokines	M2 macrophages (TAM)	Promote CSCs growth	[156]
	MFG-E8 and IL-6	MDSCs	Promote tumorigenesis and drug resistance in CSCs	[170]
	PDGF, TGF-β, IL-8 and CXCL12		Promote proliferation and invasion of CSCs	[75]
	(iNOS), (ROS), (COX-2), and TGF-β		Suppress immune function to promote CSCs	[175,189]
Lactate		CSCN/CAFs	Increases acidity of CSCN and promote CSC metastasis	[58,59,60]
MMP		CSCs	Degradation and remodeling of ECM to promote CSC metastasis	[61]
Cathepsins		CSCs	Degradation and remodeling of ECM to promote CSC metastasis	[61]
Kallikreins		CSCs	Degradation and remodeling of ECM to promote CSC metastasis	[61]
HIF		MSC/some cancer cells	Mediate metabolic switches/ CSC maintenance and proliferation	[62,63,66]
VEGF		CSCs/Tregs	Promotion of angiogenesis in the CSCN and influence the stemness, progress of CSCs	[120,130]

Abbreviations: CSC, cancer stem cells; CSCN, cancer stem cell niche; EMT, epithelial-to-mesenchymal transition; ECM, extracellular matrix; HIF, hypoxia-induced factors, MDSC, myeloid derived suppressor cells; MSC, mesenchymal stem cells; MMP, matrix metalloproteinase; TAM, tumor-associated macrophages; Treg, regulatory T cells.

associated with different tumor types, express CD47, CD200, FasL, RCAS1, Bcl-2, BclxL, survivin, increased inhibitory NK cell receptor ligands, non-classical HLA Class I molecules, such as E, F and G, decreased histocompatibility complex I (MHC I) or absent MHC II and costimulatory molecules. In addition, CSCs show inadequate antigen presentation and secrete a repertoire of molecules, such as TGF-β, IL-4, IL-6, IL-10 and PGE2, that protect them against destruction by both innate and adaptive immune cells [70,71,77].

The stochastic model of tumor hierarchy suggests that cancer cells constitute a dynamic population that switches between differentiated and undifferentiated states [78]. Possibly, the more differentiated cancer cells with no apparent functions may act as a reservoir for dedifferentiation into CSCs at a later stage. Investigating the features of these so-called 'free rider cells' will be critical for our understanding of CSC biology [79].

6. Interactions between cytotoxic T-lymphocytes and cancer stem cells

T cells mediate an immune response after recognizing pathogen-derived antigens presented by antigen-presenting cells (APCs) and non-immune cells [80]. T cell receptors (TCR) of CD8 + T cells identify antigens presented by MHC I molecules [81]. In order to activate CD8 + naive T cells to become cytotoxic T-lymphocytes (CTLs), these cells must recognize an antigenic peptide presented by APCs. Subsequently, they are activated and expand clonally. Full activation requires not only signaling through the TCR, but also secondary signaling through co-stimulatory molecules [82]. Although CSCs express low levels of ligands for secondary signals (B7.1 [CD80] and B7.2 [CD86]), they do represent elevated degrees of the inhibitory co-stimulatory molecular ligand PD-L1 (CD274 or B7-H1). As such, CSCs may prevent the differentiation of CD8+ naive T cells into CTL, but they are unable to inhibit the cytotoxicity of differentiated and activated CTL [83] (Fig. 2). CSCs suppress their MHC I molecules [84], indicating that low MHC I expression may enable them to escape from the T cell response and survive [34]. Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) is a vital negative regulator of T cell responses [85], and may cause T cell exhaustion and hence T cell dysfunction in various types of cancer [86]. CSCs are able to up-regulate CTLA-4 and thus, the binding of the CTLA-4 receptor to CD80/86 expressed on APCs acquires a co-inhibitory effect on T cells [87,88].

Activated CTLs can eradicate target cells in different ways: by releasing perforins and granzymes, which leads to the activation of the caspase cascade resulting in apoptosis, and also by secreting cytokines, especially interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) [81,89]. CTLs play a very important role in the immune responses to tumor cells, as they can recognize CSCs in an antigen-specific manner [82]. It has been found that CSCs express several tumor-associated antigens (TAAs) and that CTLs recognize CSCs in both laboratory and natural conditions [90,91]. It has been shown that CSCs are less immunogenic when compared to non-CSCs, and they may suppress many tumor-associated antigens, thus limiting the ability of the adaptive immune system to recognize them and mount an antigen-specific response to CSCs [92].

CTLs can multiply only when sufficient supply of glucose is available and die from nutrient deprivation. In contrast to tumor cells, CTLs are mobile and move relatively freely across the microenvironment. However, this CTL motility is energy-consuming, in particular when the movement is random [47]. On the other hand, CSCs are able to shun the anti-tumor immune response by creating a 'protective shield' of non-stem cancer cells around themselves. This shield both creates a physical barrier between CSCs and CTLs, and promotes competition for common resources, such as glucose, between non-stem cancer cells and CTLs. It has been suggested that competition for resources can provide an additional mechanism by which CTLs are incapacitated and hence another contribution to immune evasion [47].

At present, treatments using chimeric antigen receptor-modified T (CAR-T) cells containing an extracellular binding domain of a single-chain fragment of the antibody variable region (scFv) and the intracellular signaling domains of CD3zeta have been developed. CAR-T cells are able to specifically recognize antigens expressed on the surface of CSCs – or other cancer cells. Several potential antigens, such as epithelial cell adhesion molecule (EpCAM), CD44, CD90, CD133, and also ALDH have been recognized [93]. CAR-T cell therapy has proved successful in patients with hematologic malignancies, and their safety and feasibility for the treatment of patients with solid tumors have been confirmed [94].

7. Interactions between mesenchymal stem cells and CSCs

MSCs allude to a heterogeneous subset of stromal stem cells, which can be extracted from most adult tissues. They proliferate as adhesive cells and are morphologically similar to fibroblasts [95]. MSCs enter the bloodstream from the bone marrow and are essential components of the

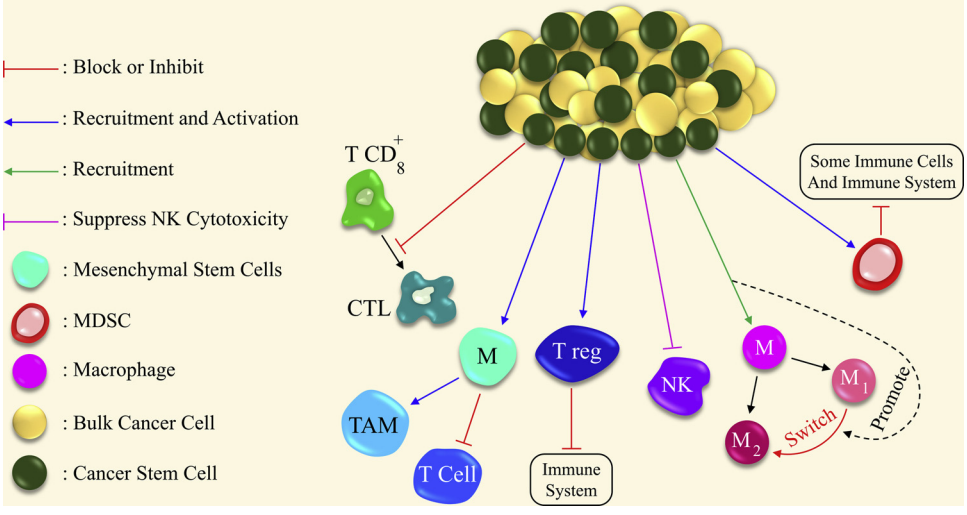

Fig. 2. Interaction of cancer stem cells (CSCs) with various immune cells and the affected to each other.
This schematic picture describes the direct effect of cancer stem cells (CSCs) on immune cells. The CSCs prevents the differentiation of the naive T cells to CTLs, that this action is favorable for CSCs. Mesenchymal stem cells (MSCs), by changing the function of the T cells, inhibit the antitumor activity of these T cells. Also, MSCs help to promoting the tumor by recruiting and activating tumor associated macrophage (TAM) cells. One of the tricks of CSCs is the recruiting and activating of immunosuppressive cells like regulatory T (Tregs) and myeloid-derived suppressor cells (MDSC) cells for repressing the immune responses. Suppressing cytotoxicity function of natural killer (NK) cells is another trick of CSCs. It is interesting to say that CSCs by recruiting macrophages and promote the switch of type 1 Macrophage (M1) to type 2 macrophage (M2) action favor of great state for promoting themselves and weakening responses of immune system.

tumor microenvironment [96] (Table 1). They serve many functions, including tissue repair, immunomodulation and stem cell homeostasis [97–99]. In addition, MSCs have a significant impact on the clinical course of human malignancies through their modulating CSC functions [96,100].

Hypoxia inducible factor-1α (HIF-1α) regulates cellular oxygen homeostasis. Cancer cells often express higher than normal HIF-1α levels [63]. This enables tumor cells to cope with hypoxic conditions. It promotes tumor angiogenesis and metabolic reprogramming. Additionally, HIF-1α induces expression of chemokine (C-X-C motif) ligand 16 (CXCL16) in order to recruit MSCs. This stimulates MSCs to produce chemokine (C-C motif) ligand 5 (CCL5), which in turn recruits TAMs [66]. Interestingly, the CSC population is maintained by activating the NK-kB pathway via secretion of CXCL12, IL-6, and IL-8 [101] (Table 1). It has been shown that cytokines mediate crosstalk between MSCs and cancer cells affecting the tumor niche by promoting the generation and maintenance of CSCs [96]. With regard to immunosuppressive effectors, one particularly striking recent observation is the identification of CAFs and MSCs as two potential tumor promoters [102].

In the tumor microenvironment, MSCs are able to differentiate into stromal fibroblasts [103]. Fibroblasts from tumor tissues display an activated phenotype and are able to secrete many immunosuppressive factors, such as tumor growth factor β (TGF-β) and vascular endothelial growth factor (VEGF), among other factor [102]. Increased VEGF secretion in the microenvironment may promote maturation and dendritic cell (DC) differentiation and improve anti-tumor immune responses in cancer patients [104]. TGF-β [105] is caused to the debilitation of MHC II expression and subsequent antigen processing [106] as well the gross expansion of population of the immune-suppressive Treg cells [83]. MSCs show reduced levels of MHC I [84], another indication suggesting reduced class I expression by CSC populations [107]. MHC I antigens are essential for immune recognition of transformed cells [108]. Therefore, selective or complete down-regulation of class I molecules may make class I MHC-restricted CTLs unable to lyse some target tumor cells [109,110]. Also, it is believed that class I MHC molecules are regulated not only on immune cells and normal stem cells, but also on cancer cells [111].

In the microenvironment of CSCs, MSCs interact with a number of immune cells and display immune-modulatory functions. MSCs suppress the cytotoxicity potential of NK cells and prevent activation of T cells through shifting immune cell functions towards immune suppression [112]. In addition, CSCs can facilitate immune suppression by recruiting MSCs, so that recruited cells regulate immune competence by releasing IL-10 or by producing the enzyme indoleamine-2,3- dioxygenase (IDO). IDO induces tolerance and a shift from Th1 to Th2 immune response [113]. As a result, attracted MSCs help create an immunosuppressive microenvironment with reduced immune surveillance, which in turn fosters CSC maintenance and promotes tumor growth [114])Fig. 2).

8. Interactions between regulatory T cells (Tregs) and CSCs

The intricate crosstalk between CSCs and immune cells also includes Treg cells. In the past, Tregs were classified into two groups, those formed in the thymus (natural) and those differentiated in the periphery (induced) [115]. The latter cells (iTregs) are characterized as the $CD4^+CD25^+FOXP3^+$ T cell subpopulation, with FOXP3 being an important transcriptional regulator of the development and function of Treg cells [116,117]. The Treg cells put certain limitations on pathogenic immune responses to self-antigens and foreign antigens [118]. This Treg cell-mediated immunosuppression is primarily achieved through the production of various cytokines, such as IL-10, IL-35, and TGF-B [119]. In tumors, Treg cells are recruited in various ways, which primarily involves chemokine attractants. For example, tumor cells produce CCL22 and CCL28, which attract Treg cells to the environment of CSCs [120–123]. The effector Treg cells, marked by expression of CCR4 (C-C motif chemokine receptor 4), are the predominant Tregs in the tumor niche [124]. These $FOXP3^+$ cells were recently found to be associated tumor progression. The Treg cells help in immune evasion of CSCs and an increasing body of literature has highlighted the role of tumor-associated macrophages (TAMs) and tumor-associated fibroblasts (TAFs) in recruiting the Treg cells to the tumor microenvironment [118].

CSCs produce TGF-β [70,125], which induces Treg to iTreg differentiation by stimulating the synthesis of the transcription factor FOXP3 and thereby decreases antitumor immunity [126,127]. Treg infiltration has been shown to occur early during tumor formation and the Treg cell population also expands while the tumor develops. As the Treg infiltrate increases, it inhibits further accumulation of CD8 + T cells and the simultaneous secretion of inflammatory cytokines, such as interferon γ (IFN-γ), tumor necrosis factor (TNF), interleukin 6, and chemokine (C-C motif) ligand 2 (CCL2), which is required to elicit an adaptive immune response. Overall, these events promote CSC maintenance [128].

Treg cells also influence angiogenesis and VEGF levels in the CSC microenvironment [120]. Treg cells produce VEGFA in response to hypoxia in the microenvironment and this promotes angiogenesis. Several cell types have been identified as producers of VEGFA and induction of angiogenesis. However, Tregs seem to be an important source of VEGFA [129] and their ability to promote angiogenesis positively affects the stemness, progress and control of CSCs [130]. Intriguingly, recent studies show that, under certain circumstances, FOXP3+ Tregs express IL-17, which, together with hypoxia, plays an important role in CSCs development [131].

Tregs also produce TGF-β and this cytokine is a major inducer in this the epithelial-to-mesenchymal transition (EMT), a process in which tumor cells obtain the capacity to migrate, invade, metastasize and acquire stem cell characteristics [132]. Many studies have demonstrated that CSCs actively recruit immune-suppressive cells to the tumor microenvironment. In addition to immune cell modulatory functions, these tumor-associated immune-suppressive cells, which mainly consist of Treg cells, are known to support CSCs through multiple pathways [133] (Table 1) (Fig. 2).

9. CSCs display resistance to NK cell cytotoxicity

NK cells are traditionally defined as innate lymphoid cells capable of killing virally-infected or malignantly transformed cells in a MHC I unrestricted manner [134]. About 95% of peripheral blood NK cells are characterized as $CD56^{dim}$ $CD16^+$ and exert intense cytotoxic activity. The remaining 5% is $CD56^{bright}$ $CD16^-$ and shows cytotoxicity through production of strong cytokines [135].

The death receptor and granule-dependent pathways are two typical cytotoxic mechanisms of NK cells. Fas-Ligand (FasL or CD95 L) and the TNF-related apoptosis-inducing ligand (TRAIL) are both expressed on NK cell membranes and trigger the death receptor pathway. Acting as a receptor for their ligands in target cells, this results in direct lysis of target tumor cells [136].

The granule-dependent pathway is activated after NK cells attach to the target cell, with subsequent delivery of cytotoxic granules, containing Perforin and proteases called Granzymes, to the coupled target cell [137]. NKG2D, NKp30, NKp44, and NKp46 are the activation receptors on the surface of NK cells [138], whereas the inhibitory receptors of these cells are KIR, CD94/NKG2A and CD300a [139]. The ligands for key NK activation receptors, such as NKG2D, include MHC-Ib molecules (e.g., MICA and MICB), which are upregulated following cellular stress, such as rapid proliferation, viral infection, and CSCs [138]. Unlike TAMs and tumor associated neutrophils (TANs), which can exert either pro- or anti-tumor activities during cancer development, NK cells are exclusively anti-tumor contenders [104,140].

The vulnerability of CSCs to NK cell-mediated cytotoxicity is higher

than their parental cells or their differentiated counterparts. The susceptibility of CSCs to NK invasion is associated with the up-regulation of the natural activating cytotoxicity receptors, especially NKp30 and NKp44, on the exterior of NK cells, as well as the increased presentation of their respective ligands on the exterior of CSCs in these receptors [135]. In addition, Tallerico and colleagues reported lower levels of MHC I expression on CSCs than non-CSCs, indicating that the differences seen in MHC I expression were related to NK cells' effective targeting of CSCs [135]. Moreover, CSCs are vulnerable to NK cell-mediated cytotoxicity due to preferential upregulation of the NK cell activation ligands MICA/B, Fas, and death receptor 5 (DR5) on CSCs [141].

Although CSCs are more susceptible to NK cell-mediated cytotoxicity, CSCs adopt traits that enable them to block NK cell function and increase inhibitory NK cell receptor ligands [70,104,140]. In addition, Wang et al. reported evasion of immunosurveillance and reduced NK killing of CSCs in some forms of cancer when CSCs shed MICA and MICB and apparently recruit Tregs to promote an immune evasive state [142,143]. NK cell cytotoxicity is also suppressed after interacting with CSCs [144–146]. On the other hand, interaction of NK cells with the refractory tumors does not lead to suppression of NK cell cytotoxicity [147].

One reason for decreased lysis of stem cells by NK cells was found to be linked to competitive lysis of monocytes by the NK cells in microenvironment of some of CSCs. Hence, although monocyte lysis by NK cells may help inhibit NK cell lysis of stem cells to some extent, interplay between monocytes and stem cells can also lead to the stem cells becoming resistant to NK cell cytotoxicity. Thus, although the presence of monocytes decreases the killing of stem cells by the NK cells, synergistic secretion of IFN-γ by NK cells in the presence of monocytes and some of CSCs can show a reverse association between IFN-γ secretion and cytotoxicity, a phenomenon called 'split anergy'. The reduced cytotoxicity of NK cells was observed in parallel with improved split anergy. Thus, this is one mechanism by which tumor cells may escape immune destruction and this expedites metastasis [148].

Another important strategy that contributes to CSC immune evasion is the production of IL-22 by NK and T cells, which was found to promote a CSC phenotype, indicating that CSCs have multiple mechanisms for immune evasion [149,150]. Similar to CAR-T cells, preclinical evidence from new advances in NK cell engineering, such as the generation of CAR-NK cells, suggest that NK cells may also be effective in recognizing and killing target tumor cells after genetic modification. CAR-NK cells are a particularly promising tool as a novel cellular immunotherapy against resistant malignancies. We expect that the ability to direct more potent NK cell-mediated cytotoxicity against refractory tumors via CAR expression will further fuel the recent revolution in cancer treatment using immunotherapeutic approaches [151] (Fig. 2).

10. Tumor-associated macrophages

Monocytes and macrophages refer to subsets of leukocytes with special roles in tissue homeostasis and immunity. Generally, monocytes differentiate while an inflammation or pathogen challenge is in progress, whereas tissue-resident macrophages are important for expansion, homeostasis, and resolution of inflammation [152]. Macrophages are also found in tumor tissues and hence are referred to as tumor-associated macrophages (TAMs). With the proposition that macrophages differentiate into classically or alternatively activated phenotypes, the significance of TAMs is now coming into light [153]. Monocytes or macrophages are typically placed into two poles, so-called M1 or M2 macrophages [154].

10.1. The influence of M1 macrophages on CSCs

Classically activated macrophages, otherwise known as M1-polarized macrophages, are activated by cytokines such as IFN-γ, create high levels of reactive nitrogen and oxygen intermediates [155] and secrete proinflammatory and immuno-stimulatory cytokines, such as IL-12, IL-23, CXCL19 and CXCL10 in the niche of CSCs. In turn, this stimulates the development of Th1, Th17 and NK cells. Amongst them are the infiltrating M1 tumor-associated macrophages, which are noted (or realized) in the primary steps of tumorigenesis and are capable of releasing proinflammatory cytokines and in turn restrain tumor growth, [156,157]. In several murine models of carcinogenesis, tumor progression is largely linked to a phenotypic shift from M1 to M2 in TAM [158] (Table 1).

10.2. The influence of M2 macrophages on CSCs

Researchers believe that TAMs are similar to M2-polarized macrophages, also known as alternatively activated macrophages, which are activated by Th2 cytokines (e.g., IL-4, IL-10, and IL-13), as well as MSCs [52,159]. Regarded as a major component of the tumor microenvironment, TAMs regulate CSC functions in several ways [46,160]. It has been shown that TAMs and TANs are both necessary for protecting CSCs from the continuous immune surveillance in the tumor niche [161–163]. M2 tumor-associated macrophages are particularly powerful during late stages of tumor formation. Some of their products, specifically Type II cytokines, are capable of inducing an anti-inflammatory reaction and thereby promote tumor growth [156]. In preliminary tumors and at metastatic locations, TAMs act in complex bidirectional interactions with tumor cells, fibroblasts, CSCs, mesenchymal stem cells, endothelial cells, T, B, as well as NK cells. Macrophages are able to destroy tumor cells and raise tumor-destructive responses, but several lines of evidence suggest that TAMs promote progression of established tumors by stimulating proliferation and survival of CSCs, as well as angiogenesis and lymphangiogenesis, and skewing and relaxing effective T cell responses [3,162,164].

Wu et al found that CSF-1 and CCL2, which are factors enriched in some of CSC microenvironments, mediated recruitment of macrophages and they tip the balance of the polarization of the monocyte pool toward the immune-suppressive M2 phenotype [165,166]. VEGF-A [167] is a major proangiogenic cytokine produced by TAMs. Under hypoxic conditions, HIF-1α and HIF-2α contribute to the production of VEGF-A by TAMs and thus promote CSCs angiogenesis and metastasis induced by TAMs [168,169].

In the niche of CSCs, TAMs promote tumorigenesis and drug resistance in several ways. They generate and secrete MFG-E8 and IL-6. This activates the transcription factor STAT3, which carries various signals of cytokines and growth factors from the cell membrane to nucleus, as it translocates from the cytoplasm to the nucleus [170]. In addition, TAMs activate the Hedgehog pathway in CSCs [46] and promote proliferation and invasion of CSCs by releasing PDGF, TGF-β and the stemness-favoring cytokines IL-8 and CXCL12 [75]. A good strategy for targeting TAM is reprogramming the TAMs to anti-tumor M1 phenotypes through inhibiting anti-inflammatory cytokine IL-10, or co-activating the pro-inflammatory CD40, IL-12, IL-8 and TNF-α by antagonizing TLR-7. This was shown to effectively reverse tumor development [171]. Finally, dynamic shifts between M1 and M2 phenotypes were found to vary within different tumor microenvironments [172,173] (Table 1) (Fig. 2).

11. The role of MDSCs in the promotion and growth of CSCs

Myeloid-derived suppressor cells (MDSCs) are a subset of immature myeloid cells. These granulocytes infiltrate into the tumor microenvironment and exert immunosuppressive effects, in part by affecting CSC function [133,174]. Researchers generally believe that MDSCs are hematopoietic progenitor cells produced in the bone marrow that do not undergo terminal differentiation to mature monocytes or neutrophils prior to being released into the circulation [175]. In certain pathological conditions, such as the CSC microenvironment, this cell

population greatly expands and this results in highly immuno-suppressive activity, as their name suggests [133,176]. One important feature of human tumor-resident MDSCs is that they are very similar to human peripheral blood neutrophils. In fact, MDSC subpopulations are characterized by $CD33^+$ $CD11b^+$ HLA-DR^- and arginase-1^+ (Arg-1). As such, MDSCs that infiltrate the CSC microenvironment seem to be a modified version of a neutrophils that have adapted to their environment and adopted an immunosuppressive function [174,176,177].

Studies in both mice and humans have identified two different types of MDSCs: polymorphonuclear MDSCs (PMN-MDSCs), which are morphologically and phenotypically similar to neutrophils, and monocytic MDSCs (M-MDSCs), which are similar to monocytes [178–180]. In the tumor microenvironment and peripheral lymphoid organs, the prominent functions of MDSCs can be observed. The peripheral lymphoid organs mainly contain PMN-MDSCs with limited immunosuppressive activity and a significant role in the arrangement and regulation of tumor-specific immune responses that occur during the expansion of tumor-specific T cell tolerance. Differentiation of M-MDSCs into dendritic cells (DC) and macrophages is inhibited in these tissues. However, in the tumor microenvironment, MDSCs become more suppressive. Here, M-MDSCs are more abundant compared to PMN-MDSCs, and they rapidly differentiate to TAMs [181].

Recent studies have shown that the two MDSC subsets can polarize from a classically activated phenotype (M1) to an alternatively activated state (M2). M2-polarized MDSCs are known for their suppressive capability, anti-inflammatory activity and immune tolerance. On the other hand, M1 cells display pro-inflammatory and immunostimulatory activities [182].

MDSCs can suppress immune system function and support CSCs in a number of ways [183]. CSCs can produce VEGF and SDF-1 in order to recruit perivascular cells or produce granulocyte colony-stimulating factor (G-CSF) in order to recruit MDSCs into the tumor and the CSC microenvironment [133]. In addition, various cancer cells that produce chemokines, such as CCL2, CCL15, CXCL5, and CXCL12, can recruit MDSCs to these sites [184–187]. MDSC recruitment promotes CSC maintenance, because these myeloid cells suppress immune function through multiple mechanisms [188]. These include production of arginase, inducible nitric oxide synthase (iNOS), reactive oxygen species (ROS), cyclooxygenase-2 (COX-2), and TGF-β, which together prevent T cells proliferation and function [175,189]. For example, it has been shown that T cell dysfunction is induced by MDSC-secreted IL10, TGF-β, reactive oxygen species (ROS), arginase and nitric oxide synthase (NOS) [190]. Yamashina et al. demonstrated that CSCs secrete immunosuppressive cytokines (GM-CSF among others). Interestingly, chemo-resistant CSCs secrete cytokines that induce MDSCs and M2 macrophages to a greater extent than non-chemo-resistant CSCs [191]. Another study showed that MDSCs promote TANs under the influence of TGF-β [192]. These cells have many pro-tumorigenic effects and also impair T cell and NK cell responses. In particular, they inhibit CD8 + T cell activation and effector function, which supports CSCs [178].

Lastly, it is important to note that there are close interactions between MDSCs and other immunosuppressive cell populations [178]. It is widely accepted that Treg induction is one of the most important mechanisms by which MDSCs inhibit T cells [193–195]. In addition, the aforementioned cells promote CSC maintenance and function (Table 1) (Fig. 2).

12. The indirect influence of T helper 2 and T helper 17 cells on CSCs

12.1. T helper 2 cells

A subset of T cells is called T helper 2 (Th2) cells. These lymphocytes organize protective type 2 immune responses, such as those that target helminths, and facilitate tissue repair. In addition, they contribute to chronic inflammatory diseases, including asthma and allergies [196]. Th2 cells can indirectly promote CSCs via several routes.

The progression of many cancer types displays a shift from Th1 cells, a subset of T cells responsible for activating M1 macrophages, to Th2 cytokine production. This shift is largely found in the tumor microenvironment, especially in carcinomas with poor prognosis [197]. The interleukins produced and secreted by Th2 cells include IL-4, IL-5, IL-9, IL-10, IL-13 and IL-25 [198]. The Th2 cytokines IL-4 and IL-13 have been shown to stimulate TAMs in the tumor microenvironment to develop into polarized or alternatively activated M2 macrophages [199]. This indirectly promote CSCs.

In addition, the interactions between Th2 cells and the tumor microenvironment, particularly with MSCs, inhibits immune-mediated tumor suppression [200–202]. Since the relationship between MSCs and the microenvironment of CSCs is essential for maintaining cancer stemness [203], Th2s indirectly promote CSC stemness.

12.2. T helper 17 cells

Th17 lymphocytes, another subset of T cells, are vital modulators of adaptive immunity [204,205]. IL-17 and IL-22 are known as the major secretory products of these cells [206]. Thereby, Th17 cells are able to cooperate with Th1 cells to increase IFN-?? and IL-17 levels, which in turn recruits antitumor CTLs and causes inflammation [207]. Several reports have shown that inflammatory signals induced in the tumor milieu regulate the functional fate and antitumor activity of Th17 cells [208]. Increased expression of IL-22 leads to activation of STAT3 signaling and promotes tumor growth [209]. Since STAT3 signaling promotes CSC maintenance [210], Th17 also indirectly support CSCs.

It has also been shown that Th17 cells promote the immunosuppressive effect of MDSCs [211], thus providing another way in which Th17 support CSCs.

Despite these observations, Th17 cells have been associated with both good and poor patient prognoses. The high plasticity of these cells toward the cells exhibiting either pathogenic or anti-inflammatory activities suggests that Th17 cells have diverse functions during tumorigenesis, which remain to be fully elucidated. However, it has become clear that this depends on the type of malignancy [212].

13. Conclusions

The relationship between the immune system and a tumor is intricate. The immune system can play pro-tumorigenic and anti-tumorigenic roles. Innate and adaptive immune cells can kill tumor cells, but they often do not succeed in destroying CSCs, because CSCs can shift their phenotypes, as well as modulate the function of immune cells. CSCs can produce, express or secrete factors and surface proteins that suppress the immune cells' ability to eradicate CSCs. In addition, CSCs recruit immune cells to the tumor microenvironment that have immunosuppressive activity, thus promoting their own survival. Hence, immune cells contribute to maintenance, growth, development and migration of CSCs and, ultimately, development of the tumor as a whole. Therefore, targeting CSCs by immunotherapy-based approaches, such as equipping cells with CAR, will aid in eliminating these tumor-initiating cells.

Conflict of interest

The authors disclose no conflict of interest.

References

[1] E. Batlle, H. Clevers, Cancer stem cells revisited, Nat. Med. 23 (10) (2017) 1124.
[2] F. Vahidian, H. Mohammadi, M. Ali-Hasanzadeh, A. Derakhshani, M. Mostaan, M. Hemmatzadeh, B. Baradaran, MicroRNAs and breast cancer stem cells: potential role in breast cancer therapy, J. Cell. Physiol. 234 (4) (2019) 3294–3306.

[3] C. Raggi, H. Mousa, M. Correnti, A. Sica, P. Invernizzi, Cancer stem cells and tumor-associated macrophages: a roadmap for multitargeting strategies, Oncogene 35 (6) (2016) 671.
[4] A. Chopra, X. Liu, H. Liu, Cancer Stem Cells: Metastasis and Evasion From the Host Immune Responses, Cancer Stem Cells: Targeting the Roots of Cancer, Seeds of Metastasis, and Sources of Therapy Resistance, Elsevier Inc., 2016.
[5] G.P. Dunn, A.T. Bruce, H. Ikeda, L.J. Old, R.D. Schreiber, Cancer immunoediting: from immunosurveillance to tumor escape, Nat. Immunol. 3 (11) (2002) 991.
[6] J.L. Adams, J. Smothers, R. Srinivasan, A. Hoos, Big opportunities for small molecules in immuno-oncology, Nat. Rev. Drug Discov. 14 (9) (2015) 603.
[7] J. Codony-Servat, R. Rosell, Cancer stem cells and immunoresistance: clinical implications and solutions, Transl. Lung Cancer Res. 4 (6) (2015) 689.
[8] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, cell 144 (5) (2011) 646–674.
[9] M. Al-Hajj, M.W. Becker, M. Wicha, I. Weissman, M.F. Clarke, Therapeutic implications of cancer stem cells, Curr. Opin. Genet. Dev. 14 (1) (2004) 43–47.
[10] M.S. Wicha, Cancer stem cells and metastasis: lethal seeds, AACR (2006).
[11] K. Hattermann, C. Flüh, D. Engel, H.M. Mehdorn, M. Synowitz, R. Mentlein, J. Held-Feindt, Stem cell markers in glioma progression and recurrence, Int. J. Oncol. 49 (5) (2016) 1899–1910.
[12] T. Wang, J.F. Fahrmann, H. Lee, Y.-J. Li, S.C. Tripathi, C. Yue, C. Zhang, V. Lifshitz, J. Song, Y. Yuan, JAK/STAT3-regulated fatty acid β-oxidation is critical for breast cancer stem cell self-renewal and chemoresistance, Cell Metab. 27 (1) (2018) 136–150 e5.
[13] T. Hillen, H. Enderling, P. Hahnfeldt, The tumor growth paradox and immune system-mediated selection for cancer stem cells, Bull. Math. Biol. 75 (1) (2013) 161–184.
[14] J.E. Visvader, G.J. Lindeman, Cancer stem cells: current status and evolving complexities, Cell Stem Cell 10 (6) (2012) 717–728.
[15] T.C. Somervaille, C.J. Matheny, G.J. Spencer, M. Iwasaki, J.L. Rinn, D.M. Witten, H.Y. Chang, S.A. Shurtleff, J.R. Downing, M.L. Cleary, Hierarchical maintenance of MLL myeloid leukemia stem cells employs a transcriptional program shared with embryonic rather than adult stem cells, Cell Stem Cell 4 (2) (2009) 129–140.
[16] J.E. Visvader, Cells of origin in cancer, Nature 469 (7330) (2011) 314.
[17] G. Dontu, K.W. Jackson, E. McNicholas, M.J. Kawamura, W.M. Abdallah, M.S. Wicha, Role of Notch signaling in cell-fate determination of human mammary stem/progenitor cells, Breast Cancer Res. 6 (6) (2004) R605.
[18] S. Liu, G. Dontu, M.S. Wicha, Mammary stem cells, self-renewal pathways, and carcinogenesis, Breast Cancer Res. 7 (3) (2005) 86.
[19] M. Dean, ABC transporters, drug resistance, and cancer stem cells, J. Mammary Gland Biol. Neoplasia 14 (1) (2009) 3–9.
[20] N. Montazami, M. Aghapour, S. Farajnia, B. Baradaran, New insights into the mechanisms of multidrug resistance in cancers, Cell. Mol. Biol. 61 (7) (2015) 70–80.
[21] G. Dontu, M. Al-Hajj, W.M. Abdallah, M.F. Clarke, M.S. Wicha, Stem cells in normal breast development and breast cancer, Cell Prolif. 36 (2003) 59–72.
[22] S. Saha, S. Mukherjee, P. Khan, K. Kajal, M. Mazumdar, A. Manna, S. Mukherjee, S. De, D. Jana, D.K. Sarkar, Aspirin suppresses the acquisition of chemoresistance in breast cancer by disrupting an NFκB–IL6 signaling axis responsible for the generation of cancer stem cells, Cancer Res. (2016).
[23] D. Bonnet, J.E. Dick, Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell, Nat. Med. 3 (7) (1997) 730.
[24] S.J. Morrison, J. Kimble, Asymmetric and symmetric stem-cell divisions in development and cancer, nature 441 (7097) (2006) 1068.
[25] M.F. Clarke, A.T. Hass, Cancer stem cells, Rev. Cell Biol. Mol. Med. (2006).
[26] P.A. Beachy, S.S. Karhadkar, D.M. Berman, Tissue repair and stem cell renewal in carcinogenesis, Nature 432 (7015) (2004) 324.
[27] C.Y. Park, D. Tseng, I.L. Weissman, Cancer stem cell–directed therapies: recent data from the laboratory and clinic, Mol. Ther. 17 (2) (2009) 219–230.
[28] E. Charafe-Jauffret, C. Ginestier, F. Bertucci, O. Cabaud, J. Wicinski, P. Finetti, E. Josselin, J. Adelaide, T.-T. Nguyen, F. Monville, ALDH1-positive cancer stem cells predict engraftment of primary breast tumors and are governed by a common stem cell program, Cancer Res. (2013) canres. 4704.2013.
[29] W.W. Hwang-Verslues, W.-H. Kuo, P.-H. Chang, C.-C. Pan, H.-H. Wang, S.-T. Tsai, Y.-M. Jeng, J.-Y. Shew, J.T. Kung, C.-H. Chen, Multiple lineages of human breast cancer stem/progenitor cells identified by profiling with stem cell markers, PLoS One 4 (12) (2009) e8377.
[30] S.B. Keysar, A. Jimeno, More than markers: biological significance of cancer stem cell-defining molecules, Mol. Cancer Ther. (2010) 1535–7163 MCT-10-0530.
[31] H. Enderling, L. Hlatky, P. Hahnfeldt, Immunoediting: evidence of the multifaceted role of the immune system in self-metastatic tumor growth, Theor. Biol. Med. Model. 9 (1) (2012) 31.
[32] S. Dadi, S. Chhangawala, B.M. Whitlock, R.A. Franklin, C.T. Luo, S.A. Oh, A. Toure, Y. Pritykin, M. Huse, C.S. Leslie, Cancer immunosurveillance by tissue-resident innate lymphoid cells and innate-like T cells, Cell 164 (3) (2016) 365–377.
[33] M. Burnet, Cancer—a biological approach: I. The processes of control. II. The significance of somatic mutation, Br. Med. J. 1 (5022) (1957) 779.
[34] T. Di Tomaso, S. Mazzoleni, E. Wang, G. Sovena, D. Clavenna, A. Franzin, P. Mortini, S. Ferrone, C. Doglioni, F.M. Marincola, Immunobiological characterization of cancer stem cells isolated from glioblastoma patients, Clin. Cancer Res. (2010) 1078 CCR-09-2730.
[35] K. Chikamatsu, G. Takahashi, K. Sakakura, S. Ferrone, K. Masuyama, Immunoregulatory properties of CD44+ cancer stem-like cells in squamous cell carcinoma of the head and neck, Head Neck 33 (2) (2011) 208–215.
[36] D.H. Raulet, N. Guerra, Oncogenic stress sensed by the immune system: role of natural killer cell receptors, Nat. Rev. Immunol. 9 (8) (2009) 568.
[37] V. Shankaran, H. Ikeda, A.T. Bruce, J.M. White, P.E. Swanson, L.J. Old, R.D. Schreiber, IFNγ and lymphocytes prevent primary tumour development and shape tumour immunogenicity, Nature 410 (6832) (2001) 1107.
[38] C.M. Koebel, W. Vermi, J.B. Swann, N. Zerafa, S.J. Rodig, L.J. Old, M.J. Smyth, R.D. Schreiber, Adaptive immunity maintains occult cancer in an equilibrium state, Nature 450 (7171) (2007) 903.
[39] N. Finnberg, A.J. Klein-Szanto, W.S. El-Deiry, TRAIL-R deficiency in mice promotes susceptibility to chronic inflammation and tumorigenesis, J. Clin. Invest. 118 (1) (2007).
[40] M.E. van den Broek, D. Kägi, F. Ossendorp, R. Toes, S. Vamvakas, W.K. Lutz, C.J. Melief, R.M. Zinkernagel, H. Hengartner, Decreased tumor surveillance in perforin-deficient mice, J. Exp. Med. 184 (5) (1996) 1781–1790.
[41] R. Nepal, A. Zaheen, W. Basit, L. Li, S. Berger, A. Martin, AID and RAG1 do not contribute to lymphomagenesis in Eμ c-myc transgenic mice, Oncogene 27 (34) (2008) 4752.
[42] D. Hanahan, R.A. Weinberg, The hallmarks of cancer, cell 100 (1) (2000) 57–70.
[43] M. Sultan, K.M. Coyle, D. Vidovic, M.L. Thomas, S. Gujar, P. Marcato, Hide-and-seek: the interplay between cancer stem cells and the immune system, Carcinogenesis 38 (2) (2016) 107–118.
[44] L.A. Gilbert, M.T. Hemann, DNA damage-mediated induction of a chemoresistant niche, Cell 143 (3) (2010) 355–366.
[45] C.J. Lord, A. Ashworth, The DNA damage response and cancer therapy, Nature 481 (7381) (2012) 287.
[46] M. Jinushi, M. Baghdadi, S. Chiba, H. Yoshiyama, Regulation of cancer stem cell activities by tumor-associated macrophages, Am. J. Cancer Res. 2 (5) (2012) 529.
[47] I. Kareva, Immune evasion through competitive inhibition: the shielding effect of non-stem cancer cells, arXiv preprint arXiv 1408 (2014) 0755.
[48] S. Liu, G. Dontu, S. Patel, J. Dutcher, H. Smithkort, M.S. Wicha, Bmi-1 regulates self-renewal of normal and malignant human mammary stem cells, AACR (2006).
[49] T. Reya, H. Clevers, Wnt signalling in stem cells and cancer, Nature 434 (7035) (2005) 843.
[50] A. Albini, M.B. Sporn, The tumour microenvironment as a target for chemoprevention, Nat. Rev. Cancer 7 (2) (2007) 139.
[51] M.R. Junttila, F.J. de Sauvage, Influence of tumour micro-environment heterogeneity on therapeutic response, Nature 501 (7467) (2013) 346.
[52] S.I. Grivennikov, F.R. Greten, M. Karin, Immunity, inflammation, and cancer, Cell 140 (6) (2010) 883–899.
[53] H. Korkaya, S. Liu, M.S. Wicha, Breast cancer stem cells, cytokine networks, and the tumor microenvironment, J. Clin. Invest. 121 (10) (2011) 3804–3809.
[54] C. Raggi, P. Invernizzi, J.B. Andersen, Impact of microenvironment and stem-like plasticity in cholangiocarcinoma: molecular networks and biological concepts, J. Hepatol. 62 (1) (2015) 198–207.
[55] T. Borovski, E.M. Felipe De Sousa, L. Vermeulen, J.P. Medema, Cancer stem cell niche: the place to be, Cancer Res. (2011).
[56] K.A. Moore, I.R. Lemischka, Stem cells and their niches, Science 311 (5769) (2006) 1880–1885.
[57] M.R. Alison, S.M. Lim, L.J. Nicholson, Cancer stem cells: problems for therapy? J. Pathol. 223 (2) (2011) 148–162.
[58] T. Fiaschi, A. Marini, E. Giannoni, M.L. Taddei, P. Gandellini, A. De Donatis, M. Lanciotti, S. Serni, P. Cirri, P. Chiarugi, Reciprocal metabolic reprogramming through lactate shuttle coordinately influences tumor-stroma interplay, Cancer Res. (2012) canres. 1949.2012.
[59] S. Pavlides, I. Vera, R. Gandara, S. Sneddon, R.G. Pestell, I. Mercier, U.E. Martinez-Outschoorn, D. Whitaker-Menezes, A. Howell, F. Sotgia, Warburg meets autophagy: cancer-associated fibroblasts accelerate tumor growth and metastasis via oxidative stress, mitophagy, and aerobic glycolysis, Antioxid. Redox Signal. 16 (11) (2012) 1264–1284.
[60] P. Chiarugi, P. Cirri, Metabolic exchanges within tumor microenvironment, Cancer Lett. 380 (1) (2016) 272–280.
[61] P. Friedl, K. Wolf, Tumour-cell invasion and migration: diversity and escape mechanisms, Nat. Rev. Cancer 3 (5) (2003) 362.
[62] A.A. Kiani, J. Abdi, R. Halabian, M.H. Roudkenar, N. Amirizadeh, M. Soleiman Soltanpour, A. Kazemi, Over expression of HIF-1α in human mesenchymal stem cells increases their supportive functions for hematopoietic stem cells in an experimental co-culture model, Hematology 19 (2) (2014) 85–98.
[63] F. Agani, B.-H. Jiang, Oxygen-independent regulation of HIF-1: novel involvement of PI3K/AKT/mTOR pathway in cancer, Curr. Cancer Drug Targets 13 (3) (2013) 245–251.
[64] B. Bao, A.S. Azmi, S. Ali, A. Ahmad, Y. Li, S. Banerjee, D. Kong, F.H. Sarkar, The biological kinship of hypoxia with CSC and EMT and their relationship with deregulated expression of miRNAs and tumor aggressiveness, Biochim. et Biophys. Acta (BBA)-Rev. Cancer 1826 (2) (2012) 272–296.
[65] B. Krishnamachary, D. Zagzag, H. Nagasawa, K. Rainey, H. Okuyama, J.H. Baek, G.L. Semenza, Hypoxia-inducible factor-1-dependent repression of E-cadherin in von Hippel-Lindau tumor suppressor–null renal cell carcinoma mediated by TCF3, ZFHX1A, and ZFHX1B, Cancer Res. 66 (5) (2006) 2725–2731.
[66] G. Peng, Y. Liu, Hypoxia-inducible factors in cancer stem cells and inflammation, Trends Pharmacol. Sci. 36 (6) (2015) 374–383.
[67] V.R. Zellmer, S. Zhang, Evolving concepts of tumor heterogeneity, Cell Biosci. 4 (1) (2014) 69.
[68] D. Mittal, M.M. Gubin, R.D. Schreiber, M.J. Smyth, New insights into cancer immunoediting and its three component phases—elimination, equilibrium and escape, Curr. Opin. Immunol. 27 (2014) 16–25.
[69] R. Kim, M. Emi, K. Tanabe, Cancer immunoediting from immune surveillance to immune escape, Immunology 121 (1) (2007) 1–14.

[70] V.S. Bruttel, J. Wischhusen, Cancer stem cell immunology: key to understanding tumorigenesis and tumor immune escape? Front. Immunol. 5 (2014) 360.
[71] G.P. Dunn, L.J. Old, R.D. Schreiber, The three Es of cancer immunoediting, Annu. Rev. Immunol. 22 (2004) 329–360.
[72] R.D. Schreiber, L.J. Old, M.J. Smyth, Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion, Science 331 (6024) (2011) 1565–1570.
[73] G.P. Dunn, C.M. Koebel, R.D. Schreiber, Interferons, immunity and cancer immunoediting, Nat. Rev. Immunol. 6 (11) (2006) 836.
[74] M.D. Vesely, M.H. Kershaw, R.D. Schreiber, M.J. Smyth, Natural innate and adaptive immunity to cancer, Annu. Rev. Immunol. 29 (2011) 235–271.
[75] V. Plaks, N. Kong, Z. Werb, The cancer stem cell niche: how essential is the niche in regulating stemness of tumor cells? Cell Stem Cell 16 (3) (2015) 225–238.
[76] S. Fulda, Regulation of apoptosis pathways in cancer stem cells, Cancer Lett. 338 (1) (2013) 168–173.
[77] C. Maccalli, A. Volontè, C. Cimminiello, G. Parmiani, Immunology of cancer stem cells in solid tumours. A review, Eur. J. Cancer 50 (3) (2014) 649–655.
[78] L.N. Abdullah, E.K.-H. Chow, Mechanisms of chemoresistance in cancer stem cells, Clin. Transl. Med. 2 (1) (2013) 3.
[79] F. Francescangeli, P. Contavalli, M.L. De Angelis, M. Baiocchi, G. Gambara, A. Pagliuca, A. Fiorenzano, C. Prezioso, A. Boe, M. Todaro, Dynamic regulation of the cancer stem cell compartment by Cripto-1 in colorectal cancer, Cell Death Differ. 22 (10) (2015) 1700.
[80] J.S. Blum, P.A. Wearsch, P. Cresswell, Pathways of antigen processing, Annu. Rev. Immunol. 31 (2013) 443–473.
[81] J. Neefjes, M.L. Jongsma, P. Paul, O. Bakke, Towards a systems understanding of MHC class I and MHC class II antigen presentation, Nat. Rev. Immunol. 11 (12) (2011) 823.
[82] Y. Hirohashi, T. Torigoe, T. Tsukahara, T. Kanaseki, V. Kochin, N. Sato, Immune responses to human cancer stem-like cells/cancer-initiating cells, Cancer Sci. 107 (1) (2016) 12–17.
[83] J. Wei, J. Barr, L.-Y. Kong, Y. Wang, A. Wu, A.K. Sharma, J. Gumin, V. Henry, H. Colman, R. Sawaya, Glioma-associated cancer-initiating cells induce immunosuppression, Clin. Cancer Res. (2010) 1078 CCR-09-1983.
[84] K. Le Blanc, C. Tammik, K. Rosendahl, E. Zetterberg, O. Ringdén, HLA expression and immunologic propertiesof differentiated and undifferentiated mesenchymal stem cells, Exp. Hematol. 31 (10) (2003) 890–896.
[85] C.J. Wang, F. Heuts, V. Ovcinnikovs, L. Wardzinski, C. Bowers, E.M. Schmidt, A. Kogimtzis, R. Kenefeck, D.M. Sansom, L.S. Walker, CTLA-4 controls follicular helper T-cell differentiation by regulating the strength of CD28 engagement, Proc. Natl. Acad. Sci. 112 (2) (2015) 524–529.
[86] S.N. Waggoner, M. Cornberg, L.K. Selin, R.M. Welsh, Natural killer cells act as rheostats modulating antiviral T cells, Nature 481 (7381) (2012) 394.
[87] J.D. Comber, R. Philip, MHC class I antigen presentation and implications for developing a new generation of therapeutic vaccines, Ther. Adv. Vaccines 2 (3) (2014) 77–89.
[88] S.H. Yoon, Immunotherapy for non-small cell lung cancer, Tuberc. Respir. Dis. 77 (3) (2014) 111–115.
[89] K.M. Edwards, J.E. Davis, K.A. Browne, V.R. Sutton, J.A. Trapani, Anti-viral strategies of cytotoxic T lymphocytes are manifested through a variety of granule-bound pathways of apoptosis induction, Immunol. Cell Biol. 77 (1) (1999) 76–89.
[90] Y. Hirohashi, T. Torigoe, S. Inoda, R. Morita, V. Kochin, N. Sato, Cytotoxic T lymphocytes: sniping cancer stem cells, Oncoimmunology 1 (1) (2012) 123–125.
[91] H. Saijo, Y. Hirohashi, T. Torigoe, V. Kochin, H. Takahashi, N. Sato, Cytotoxic T lymphocytes: the future of cancer stem cell eradication? Immunotherapy 5 (6) (2013) 549–551.
[92] A. Volonté, T. Di Tomaso, M. Spinelli, M. Todaro, F. Sanvito, L. Albarello, M. Bissolati, L. Ghirardelli, E. Orsenigo, S. Ferrone, Cancer-initiating cells from colorectal cancer patients escape from t cell–mediated immunosurveillance in vitro through membrane-bound IL-4, J. Immunol. (2013) 1301342.
[93] I.-S. Hong, G.-B. Jang, H.-Y. Lee, J.-S. Nam, Targeting cancer stem cells by using the nanoparticles, Int. J. Nanomedicine 10 (Spec Iss) (2015) 251.
[94] Y. Guo, K. Feng, Y. Wang, W. Han, Targeting cancer stem cells by using chimeric antigen receptor-modified T cells: a potential and curable approach for cancer treatment, Protein Cell (2017) 1–11.
[95] A. Uccelli, L. Moretta, V. Pistoia, Mesenchymal stem cells in health and disease, Nat. Rev. Immunol. 8 (9) (2008) 726.
[96] S. Liu, C. Ginestier, S.J. Ou, S.G. Clouthier, S.H. Patel, F. Monville, H. Korkaya, A. Heath, J. Dutcher, C.G. Kleer, Breast cancer stem cells are regulated by mesenchymal stem cells through cytokine networks, Cancer Res. (2011).
[97] P. Bianco, "Mesenchymal" stem cells, Annu. Rev. Cell Dev. Biol. 30 (2014) 677–704.
[98] R. Hass, C. Kasper, S. Böhm, R. Jacobs, Different populations and sources of human mesenchymal stem cells (MSC): a comparison of adult and neonatal tissue-derived MSC, Cell Commun. Signal. 9 (1) (2011) 12.
[99] Y. Yang, C. Melzer, V. Bucan, J. von der Ohe, A. Otte, R. Hass, Conditioned umbilical cord tissue provides a natural three-dimensional storage compartment as in vitro stem cell niche for human mesenchymal stroma/stem cells, Stem Cell Res. Ther. 7 (1) (2016) 28.
[100] J. Corre, E. Labat, N. Espagnolle, B. Hébraud, H. Avet-Loiseau, M. Roussel, A. Huynh, M. Gadelorge, P. Cordelier, B. Klein, Bioactivity and prognostic significance of growth differentiation factor GDF15 secreted by bone marrow mesenchymal stem cells in multiple myeloma, Cancer Res. (2012) canres. 0188.2011..
[101] S.M. Cabarcas, L.A. Mathews, W.L. Farrar, The cancer stem cell niche—there goes the neighborhood? Int. J. Cancer 129 (10) (2011) 2315–2327.
[102] T. Yaguchi, H. Sumimoto, C. Kudo-Saito, N. Tsukamoto, R. Ueda, T. Iwata-Kajihara, H. Nishio, N. Kawamura, Y. Kawakami, The mechanisms of cancer immunoescape and development of overcoming strategies, Int. J. Hematol. 93 (3) (2011) 294–300.
[103] N. Erez, M. Truitt, P. Olson, D. Hanahan, Cancer-associated fibroblasts are activated in incipient neoplasia to orchestrate tumor-promoting inflammation in an NF-κB-dependent manner, Cancer Cell 17 (2) (2010) 135–147.
[104] A. Jewett, H.-C. Tseng, A. Arasteh, S. Saadat, R.E. Christensen, N.A. Cacalano, Natural killer cells preferentially target cancer stem cells; role of monocytes in protection against NK cell mediated lysis of cancer stem cells, Curr. Drug Deliv. 9 (1) (2012) 5–16.
[105] R. Luwor, B. Baradaran, L. Taylor, J. Iaria, T. Nheu, N. Amiry, C. Hovens, B. Wang, A. Kaye, H. Zhu, Targeting Stat3 and Smad7 to restore TGF-β cytostatic regulation of tumor cells in vitro and in vivo, Oncogene 32 (19) (2013) 2433.
[106] A. Facoetti, R. Nano, P. Zelini, P. Morbini, E. Benericetti, M. Ceroni, M. Campoli, S. Ferrone, Human leukocyte antigen and antigen processing machinery component defects in astrocytic tumors, Clin. Cancer Res. 11 (23) (2005) 8304–8311.
[107] T. Cabrera, E. Lara, J.M. Romero, I. Maleno, L.M. Real, F. Ruiz-Cabello, P. Valero, F.M. Camacho, F. Garrido, HLA class I expression in metastatic melanoma correlates with tumor development during autologous vaccination, Cancer Immunol. Immunother. 56 (5) (2007) 709–717.
[108] D. Guerry, M. Alexander, M. Herlyn, L. Zehngebot, K. Mitchell, C. Zmijewski, E. Lusk, HLA-DR histocompatibility leukocyte antigens permit cultured human melanoma cells from early but not advanced disease to stimulate autologous lymphocytes, J. Clin. Invest. 73 (1) (1984) 267–271.
[109] H.T. Khong, Q.J. Wang, S.A. Rosenberg, Identification of multiple antigens recognized by tumor-infiltrating lymphocytes from a single patient: tumor escape by antigen loss and loss of MHC expression, J. Immunother. (Hagerstown, Md.: 1997) 27 (3) (2004) 184.
[110] N. Aptsiauri, T. Cabrera, R. Mendez, A. Garcia-Lor, F. Ruiz-Cabello, F. Garrido, Role of altered expression of HLA class I molecules in cancer progression, Immune-Mediated Diseases, Springer, 2007, pp. 123–131.
[111] M.Y. Mapara, M. Sykes, Tolerance and cancer: mechanisms of tumor evasion and strategies for breaking tolerance, J. Clin. Oncol. 22 (6) (2004) 1136–1151.
[112] R. Hass, A. Otte, Mesenchymal stem cells as all-round supporters in a normal and neoplastic microenvironment, Cell Commun. Signal. 10 (1) (2012) 26.
[113] R. Lotfi, C. Kaltenmeier, M.T. Lotze, C. Bergmann, Until death do us part: necrosis and oxidation promote the tumor microenvironment, Transfus. Med. Hemotherapy 43 (2) (2016) 120–132.
[114] C. Melzer, J. von der Ohe, H. Lehnert, H. Ungefroren, R. Hass, Cancer stem cell niche models and contribution by mesenchymal stroma/stem cells, Mol. Cancer 16 (1) (2017) 28.
[115] M.E. Himmel, K.G. MacDonald, R.V. Garcia, T.S. Steiner, M.K. Levings, Helios+ and Helios− cells coexist within the natural FOXP3+ T regulatory cell subset in humans, J. Immunol. (2013) 1201379.
[116] G.L. Cvetanovich, D.A. Hafler, Human regulatory T cells in autoimmune diseases, Curr. Opin. Immunol. 22 (6) (2010) 753–760.
[117] D. Haribhai, J.B. Williams, S. Jia, D. Nickerson, E.G. Schmitt, B. Edwards, J. Ziegelbauer, M. Yassai, S.-H. Li, L.M. Relland, A requisite role for induced regulatory T cells in tolerance based on expanding antigen receptor diversity, Immunity 35 (1) (2011) 109–122.
[118] H. Toge, T. Inagaki, Y. Kojimoto, T. Shinka, I. Hara, Angiogenesis in renal cell carcinoma: the role of tumor-associated macrophages, Int. J. Urol. 16 (10) (2009) 801–807.
[119] D.A. Vignali, L.W. Collison, C.J. Workman, How regulatory T cells work, Nat. Rev. Immunol. 8 (7) (2008) 523.
[120] A. Facciabene, X. Peng, I.S. Hagemann, K. Balint, A. Barchetti, L.-P. Wang, P.A. Gimotty, C.B. Gilks, P. Lal, L. Zhang, Tumour hypoxia promotes tolerance and angiogenesis via CCL28 and T reg cells, Nature 475 (7355) (2011) 226.
[121] T. Maruyama, K. Kono, S. Izawa, Y. Mizukami, Y. Kawaguchi, K. Mimura, M. Watanabe, H. Fujii, CCL17 and CCL22 chemokines within tumor microenvironment are related to infiltration of regulatory T cells in esophageal squamous cell carcinoma, Dis. Esophagus 23 (5) (2010) 422–429.
[122] Y. Mizukami, K. Kono, Y. Kawaguchi, H. Akaike, K. Kamimura, H. Sugai, H. Fujii, CCL17 and CCL22 chemokines within tumor microenvironment are related to accumulation of Foxp3+ regulatory T cells in gastric cancer, Int. J. Cancer 122 (10) (2008) 2286–2293.
[123] J. Wei, J. Barr, L.-Y. Kong, Y. Wang, A. Wu, A.K. Sharma, J. Gumin, V. Henry, H. Colman, W. Priebe, Glioblastoma cancer-initiating cells inhibit T-cell proliferation and effector responses by the signal transducers and activators of transcription 3 pathway, Mol. Cancer Ther. (2010) 1535–7163 MCT-09-0734.
[124] A. Tanaka, S. Sakaguchi, Regulatory T cells in cancer immunotherapy, Cell Res. 27 (1) (2017) 109.
[125] R. Derynck, Y.E. Zhang, Smad-dependent and Smad-independent pathways in TGF-β family signalling, Nature 425 (6958) (2003) 577.
[126] V.C. Liu, L.Y. Wong, T. Jang, A.H. Shah, I. Park, X. Yang, Q. Zhang, S. Lonning, B.A. Teicher, C. Lee, Tumor evasion of the immune system by converting CD4+ CD25− T cells into CD4+ CD25+ T regulatory cells: role of tumor-derived TGF-β, J. Immunol. 178 (5) (2007) 2883–2892.
[127] F. Ghiringhelli, P.E. Puig, S. Roux, A. Parcellier, E. Schmitt, E. Solary, G. Kroemer, F. Martin, B. Chauffert, L. Zitvogel, Tumor cells convert immature myeloid dendritic cells into TGF-β–secreting cells inducing CD4+ CD25+ regulatory T cell proliferation, J. Exp. Med. 202 (7) (2005) 919–929.
[128] P. Yu, Y. Lee, W. Liu, T. Krausz, A. Chong, H. Schreiber, Y.-X. Fu, Intratumor depletion of CD4+ cells unmasks tumor immunogenicity leading to the rejection

of late-stage tumors, J. Exp. Med. 201 (5) (2005) 779–791.
[129] S. Gupta, K. Joshi, J. Wig, S.K. Arora, Intratumoral FOXP3 expression in infiltrating breast carcinoma: Its association with clinicopathologic parameters and angiogenesis, Acta Oncol. 46 (6) (2007) 792–797.
[130] X. Yu, H. Li, X. Ren, Interaction between regulatory T cells and cancer stem cells, Int. J. Cancer 131 (7) (2012) 1491–1498.
[131] S. Yang, B. Wang, C. Guan, B. Wu, C. Cai, M. Wang, B. Zhang, T. Liu, P. Yang, Foxp3+ IL-17+ T cells promote development of cancer-initiating cells in colorectal cancer, J. Leukoc. Biol. 89 (1) (2011) 85–91.
[132] M. Shipitsin, L.L. Campbell, P. Argani, S. Weremowicz, N. Bloushtain-Qimron, J. Yao, T. Nikolskaya, T. Serebryiskaya, R. Beroukhim, M. Hu, Molecular definition of breast tumor heterogeneity, Cancer Cell 11 (3) (2007) 259–273.
[133] E.Y.-T. Lau, N.P.-Y. Ho, T.K.-W. Lee, Cancer stem cells and their microenvironment: biology and therapeutic implications, Stem Cells Int. (2017).
[134] A.E. Zamora, S.K. Grossenbacher, E.G. Aguilar, W.J. Murphy, Models to study NK cell biology and possible clinical application, Curr. Protoc. Immunol. 110 (1) (2015) 14.37. 1-14.37. 14.
[135] R. Castriconi, A. Daga, A. Dondero, G. Zona, P.L. Poliani, A. Melotti, F. Griffero, D. Marubbi, R. Spaziante, F. Bellora, NK cells recognize and kill human glioblastoma cells with stem cell-like properties, J. Immunol. 182 (6) (2009) 3530–3539.
[136] K. Takeda, Y. Hayakawa, M.J. Smyth, N. Kayagaki, N. Yamaguchi, S. Kakuta, Y. Iwakura, H. Yagita, K. Okumura, Involvement of tumor necrosis factor-related apoptosis-inducing ligand in surveillance of tumor metastasis by liver natural killer cells, Nat. Med. 7 (1) (2001) 94.
[137] E.M. Mace, J. Zhang, K.A. Siminovitch, F. Takei, Elucidation of the integrin LFA-1-mediated signaling pathway of actin polarization in natural killer cells, Blood (2010) blood-2009-12-261487.
[138] Z. Dambrauskas, H. Svensson, M. Joshi, A. Hyltander, P. Naredi, B.-M. Iresjö, Expression of major histocompatibility complex class I-related chain A/B (MICA/B) in pancreatic carcinoma, Int. J. Oncol. 44 (1) (2014) 99–104.
[139] E. Vivier, D.H. Raulet, A. Moretta, M.A. Caligiuri, L. Zitvogel, L.L. Lanier, W.M. Yokoyama, S. Ugolini, Innate or adaptive immunity? The example of natural killer cells, Science 331 (6013) (2011) 44–49.
[140] R. Castriconi, A. Dondero, F. Bellora, L. Moretta, A. Castellano, F. Locatelli, M.V. Corrias, A. Moretta, C. Bottino, Neuroblastoma-derived TGF-β1 modulates the chemokine receptor repertoire of human resting NK cells, J. Immunol. (2013) 1202693.
[141] E. Ames, R.J. Canter, S.K. Grossenbacher, S. Mac, M. Chen, R.C. Smith, T. Hagino, J. Perez-Cunningham, G.D. Sckisel, S. Urayama, NK cells preferentially target tumor cells with a cancer stem cell phenotype, J. Immunol. (2015) 1500447.
[142] S.A. Patel, J.R. Meyer, S.J. Greco, K.E. Corcoran, M. Bryan, P. Rameshwar, Mesenchymal stem cells protect breast cancer cells through regulatory T cells: role of mesenchymal stem cell-derived TGF-β, J. Immunol. (2010) ji_0903143.
[143] B. Wang, Q. Wang, Z. Wang, J. Jiang, S.-C. Yu, Y.-F. Ping, J. Yang, S.-L. Xu, X.-Z. Ye, C. Xu, Metastatic consequences of immune escape from NK cell cytotoxicity by human breast cancer stem cells, Cancer Res. (2014).
[144] S. Aggarwal, M.F. Pittenger, Human mesenchymal stem cells modulate allogeneic immune cell responses, Blood 105 (4) (2005) 1815–1822.
[145] Z. Selmani, A. Naji, I. Zidi, B. Favier, E. Gaiffe, L. Obert, C. Borg, P. Saas, P. Tiberghien, N. Rouas-Freiss, Human leukocyte antigen-G5 secretion by human mesenchymal stem cells is required to suppress T lymphocyte and natural killer function and to induce CD4+ CD25highFOXP3+ regulatory T cells, Stem Cells 26 (1) (2008) 212–222.
[146] G.M. Spaggiari, A. Capobianco, H. Abdelrazik, F. Becchetti, M.C. Mingari, L. Moretta, Mesenchymal stem cells inhibit natural killer–cell proliferation, cytotoxicity, and cytokine production: role of indoleamine 2, 3-dioxygenase and prostaglandin E2, Blood 111 (3) (2008) 1327–1333.
[147] A. Jewett, B. Bonavida, Target-induced inactivation and cell death by apoptosis in a subset of human NK cells, J. Immunol. 156 (3) (1996) 907–915.
[148] A. Jewett, M. Cavalcanti, B. Bonavida, Pivotal role of endogenous TNF-alpha in the induction of functional inactivation and apoptosis in NK cells, J. Immunol. 159 (10) (1997) 4815–4822.
[149] I. Kryczek, Y. Lin, N. Nagarsheth, D. Peng, L. Zhao, E. Zhao, Y. Dou, S. Owens, W. Zgodzinski, M. Majewski, IL-22+ CD4+ T cells promote colorectal cancer stemness via STAT3 transcription factor activation and induction of the methyltransferase DOT1L (TUM10P. 1022), Am. Assoc. Immnol. (2015).
[150] J.I. Luna, S.K. Grossenbacher, W.J. Murphy, R.J. Canter, Targeting cancer stem cells with natural killer cell immunotherapy, Expert Opin. Biol. Ther. 17 (3) (2017) 313–324.
[151] K. Rezvani, R. Rouce, E. Liu, E. Shpall, Engineering natural killer cells for cancer immunotherapy, Mol. Ther. 25 (8) (2017) 1769–1781.
[152] F. Ginhoux, S. Jung, Monocytes and macrophages: developmental pathways and tissue homeostasis, Nat. Rev. Immunol. 14 (6) (2014) 392–404.
[153] L. Yang, Y. Zhang, Tumor-associated macrophages: from basic research to clinical application, J. Hematol. Oncol. 10 (1) (2017) 58.
[154] L. Parisi, E. Gini, D. Baci, M. Tremolati, M. Fanuli, B. Bassani, G. Farronato, A. Bruno, L. Mortara, Macrophage polarization in chronic inflammatory diseases: Killers or Builders? J. Immunol. Res. 2018 (2018).
[155] J.M. Brown, L. Recht, S. Strober, The promise of targeting macrophages in cancer therapy, Clin. Cancer Res. (2017).
[156] D.F. Quail, J.A. Joyce, Microenvironmental regulation of tumor progression and metastasis, Nat. Med. 19 (11) (2013) 1423.
[157] G. Solinas, S. Schiarea, M. Liguori, M. Fabbri, S. Pesce, L. Zammataro, F. Pasqualini, M. Nebuloni, C. Chiabrando, A. Mantovani, Tumor-conditioned macrophages secrete migration-stimulating factor: a new marker for M2-polarization, influencing tumor cell motility, J. Immunol. (2010) ji_1000413.
[158] R. Zaynagetdinov, T.P. Sherrill, V.V. Polosukhin, W. Han, J.A. Ausborn, A.G. McLoed, F.B. McMahon, L.A. Gleaves, A.L. Degryse, G.T. Stathopoulos, A critical role for macrophages in promotion of urethane-induced lung carcinogenesis, J. Immunol. (2011) 1100558.
[159] S. Ostrand-Rosenberg, Immune surveillance: a balance between protumor and antitumor immunity, Curr. Opin. Genet. Dev. 18 (1) (2008) 11–18.
[160] J. Yang, D. Liao, C. Chen, Y. Liu, T.H. Chuang, R. Xiang, D. Markowitz, R.A. Reisfeld, Y. Luo, Tumor-associated macrophages regulate murine breast cancer stem cells through a novel paracrine EGFR/Stat3/Sox-2 signaling pathway, Stem Cells 31 (2) (2013) 248–258.
[161] T.A. Wynn, A. Chawla, J.W. Pollard, Macrophage biology in development, homeostasis and disease, Nature 496 (7446) (2013) 445.
[162] R. Noy, J.W. Pollard, Tumor-associated macrophages: from mechanisms to therapy, Immunity 41 (1) (2014) 49–61.
[163] S. Sarkar, A. Döring, F.J. Zemp, C. Silva, X. Lun, X. Wang, J. Kelly, W. Hader, M. Hamilton, P. Mercier, Therapeutic activation of macrophages and microglia to suppress brain tumor-initiating cells, Nat. Neurosci. 17 (1) (2014) 46.
[164] A. Mantovani, P. Allavena, A. Sica, F. Balkwill, Cancer-related inflammation, Nature 454 (7203) (2008) 436.
[165] A. Wu, J. Wei, L.-y. Kong, Y. Wang, W. Priebe, W. Qiao, R. Sawaya, A.B. Heimberger, Glioma cancer stem cells induce immunosuppressive macrophages/microglia, Neuro Oncol. (2019).
[166] W. Zhou, S.Q. Ke, Z. Huang, W. Flavahan, X. Fang, J. Paul, L. Wu, A.E. Sloan, R.E. McLendon, X. Li, Periostin secreted by glioblastoma stem cells recruits M2 tumour-associated macrophages and promotes malignant growth, Nat. Cell Biol. 17 (2) (2015) 170.
[167] F.Z. Shahneh, B. Baradaran, F. Zamani, L. Aghebati-Maleki, Tumor angiogenesis and anti-angiogenic therapies, Hum. Antibodies 22 (1, 2) (2013) 15–19.
[168] S. Joshi, A.R. Singh, M. Zulcic, D.L. Durden, A macrophage dominant PI-3K isoform controls hypoxia induced HIF1alpha & HIF2alpha stability and tumor growth, angiogenesis and metastasis, Mol. Cancer Res. (2014) molcanres.0682.2014..
[169] J.-W. Gu, P. Rizzo, A. Pannuti, T. Golde, B. Osborne, L. Miele, Notch signals in the endothelium and cancer" stem-like" cells: opportunities for cancer therapy, . 4 (1) (2012) 7.
[170] C.P. Lim, X. Cao, Structure, function, and regulation of STAT proteins, Mol. Biosyst. 2 (11) (2006) 536–550.
[171] X. Tang, C. Mo, Y. Wang, D. Wei, H. Xiao, Anti-tumour strategies aiming to target tumour-associated macrophages, Immunology 138 (2) (2013) 93–104.
[172] C. Guiducci, A.P. Vicari, S. Sangaletti, G. Trinchieri, M.P. Colombo, Redirecting in vivo elicited tumor infiltrating macrophages and dendritic cells towards tumor rejection, Cancer Res. 65 (8) (2005) 3437–3446.
[173] L.S. Ojalvo, W. King, D. Cox, J.W. Pollard, High-density gene expression analysis of tumor-associated macrophages from mouse mammary tumors, Am. J. Pathol. 174 (3) (2009) 1048–1064.
[174] E. Safarzadeh, M. Orangi, H. Mohammadi, F. Babaie, B. Baradaran, Myeloid-derived suppressor cells: important contributors to tumor progression and metastasis, J. Cell. Physiol. 233 (4) (2018) 3024–3036.
[175] D.I. Gabrilovich, S. Nagaraj, Myeloid-derived suppressor cells as regulators of the immune system, Nat. Rev. Immunol. 9 (3) (2009) 162.
[176] L.A. Elliott, G.A. Doherty, K. Sheahan, E.J. Ryan, Human tumor-infiltrating myeloid cells: phenotypic and functional diversity, Front. Immunol. 8 (2017) 86.
[177] D. Peng, T. Tanikawa, W. Li, L. Zhao, L. Vatan, W. Szeliga, S. Wan, S. Wei, Y. Wang, Y. Liu, Myeloid-derived suppressor cells endow stem-like qualities to breast cancer cells through IL6/STAT3 and NO/NOTCH cross-talk signaling, Cancer Res. (2016).
[178] J.E. Talmadge, D.I. Gabrilovich, History of myeloid-derived suppressor cells, Nat. Rev. Cancer 13 (10) (2013) 739.
[179] D. Marvel, D.I. Gabrilovich, Myeloid-derived suppressor cells in the tumor microenvironment: expect the unexpected, J. Clin. Invest. 125 (9) (2015) 3356–3364.
[180] S. Ugel, F. De Sanctis, S. Mandruzzato, V. Bronte, Tumor-induced myeloid deviation: when myeloid-derived suppressor cells meet tumor-associated macrophages, J. Clin. Invest. 125 (9) (2015) 3365–3376.
[181] V. Kumar, P. Cheng, T. Condamine, S. Mony, L.R. Languino, J.C. McCaffrey, N. Hockstein, M. Guarino, G. Masters, E. Penman, CD45 phosphatase inhibits STAT3 transcription factor activity in myeloid cells and promotes tumor-associated macrophage differentiation, Immunity 44 (2) (2016) 303–315.
[182] W.-C. Yang, G. Ma, S.-H. Chen, P.-Y. Pan, Polarization and Reprogramming of Myeloid-derived Suppressor Cells, Oxford University Press, 2013.
[183] B. Otvos, D.J. Silver, E.E. Mulkearns-Hubert, A.G. Alvarado, S.M. Turaga, M.D. Sorensen, P. Rayman, W.A. Flavahan, J.S. Hale, K. Stoltz, Cancer stem cell-secreted macrophage migration inhibitory factor stimulates myeloid derived suppressor cell function and facilitates glioblastoma immune evasion, Stem Cells 34 (8) (2016) 2026–2039.
[184] B. Huang, Z. Lei, J. Zhao, W. Gong, J. Liu, Z. Chen, Y. Liu, D. Li, Y. Yuan, G.-M. Zhang, CCL2/CCR2 pathway mediates recruitment of myeloid suppressor cells to cancers, Cancer Lett. 252 (1) (2007) 86–92.
[185] S. Inamoto, Y. Itatani, T. Yamamoto, S. Minamiguchi, H. Hirai, M. Iwamoto, S. Hasegawa, M.M. Taketo, Y. Sakai, K. Kawada, Loss of SMAD4 promotes colorectal cancer progression by accumulation of myeloid-derived suppressor cells through CCL15-CCR1 chemokine axis, Clin. Cancer Res. (2015) clincanres.0726.2015.
[186] L.-Y. OuYang, X.-J. Wu, S.-B. Ye, R.-x. Zhang, Z.-L. Li, W. Liao, Z.-Z. Pan, L.-M. Zheng, X.-S. Zhang, Z. Wang, Tumor-induced myeloid-derived suppressor cells

promote tumor progression through oxidative metabolism in human colorectal cancer, J. Transl. Med. 13 (1) (2015) 47.
[187] L. Yang, J. Huang, X. Ren, A. Gorska, A. Chytil, M. Aakre, D. Carbone, L. Matrisian, A. Richmond, P.C. Lin, Abrogation of TGFß Signaling In Mammary Carcinomas Recruits Gr-1+ CD11b+ Myeloid Cells That Promote Metastasis, AACR, 2008.
[188] B. Otvos, J. Finke, M. Vogelbaum, J.D. Lathia, Interrogating the interactions between myeloid derived suppressor cells and cancer stem cells in glioblastoma, J. Immunother. Cancer 1 (S1) (2013) P268.
[189] S. Ostrand-Rosenberg, Myeloid-derived suppressor cells: more mechanisms for inhibiting antitumor immunity, Cancer Immunol. Immunother. 59 (10) (2010) 1593–1600.
[190] T.F. Greten, M.P. Manns, F. Korangy, Myeloid derived suppressor cells in human diseases, Int. Immunopharmacol. 11 (7) (2011) 802–807.
[191] T. Yamashina, M. Baghdadi, A. Yoneda, I. Kinoshita, S. Suzu, H. Dosaka-Akita, M. Jinushi, Cancer stem-like cells derived from chemoresistant tumors have a unique capacity to prime tumorigenic myeloid cells, Cancer Res. (2014) canres. 2169.2013..
[192] R.J. Moore, D.M. Owens, G. Stamp, C. Arnott, F. Burke, N. East, H. Holdsworth, L. Turner, B. Rollins, M. Pasparakis, Mice deficient in tumor necrosis factor-α are resistant to skin carcinogenesis, Nat. Med. 5 (7) (1999) 828.
[193] S. Nagaraj, K. Gupta, V. Pisarev, L. Kinarsky, S. Sherman, L. Kang, D.L. Herber, J. Schneck, D.I. Gabrilovich, Altered recognition of antigen is a mechanism of CD8+ T cell tolerance in cancer, Nat. Med. 13 (7) (2007) 828.
[194] B. Huang, P.-Y. Pan, Q. Li, A.I. Sato, D.E. Levy, J. Bromberg, C.M. Divino, S.-H. Chen, Gr-1+ CD115+ immature myeloid suppressor cells mediate the development of tumor-induced T regulatory cells and T-cell anergy in tumor-bearing host, Cancer Res. 66 (2) (2006) 1123–1131.
[195] M.R. Garcia, L. Ledgerwood, Y. Yang, J. Xu, G. Lal, B. Burrell, G. Ma, D. Hashimoto, Y. Li, P. Boros, Monocytic suppressive cells mediate cardiovascular transplantation tolerance in mice, J. Clin. Invest. 120 (7) (2010) 2486–2496.
[196] J.A. Walker, A.N. McKenzie, T H 2 cell development and function, Nat. Rev. Immunol. (2017).
[197] J.R. McWhirter, A. Kretz-Rommel, A. Saven, T. Maruyama, K.N. Potter, C.I. Mockridge, E.P. Ravey, F. Qin, K.S. Bowdish, Antibodies selected from combinatorial libraries block a tumor antigen that plays a key role in immunomodulation, Proc. Natl. Acad. Sci. 103 (4) (2006) 1041–1046.
[198] Y.Y. Wan, GATA3: a master of many trades in immune regulation, Trends Immunol. 35 (6) (2014) 233–242.
[199] B.-Z. Qian, J.W. Pollard, Macrophage diversity enhances tumor progression and metastasis, Cell 141 (1) (2010) 39–51.
[200] M.E. Castro-Manrreza, J.J. Montesinos, Immunoregulation by mesenchymal stem cells: biological aspects and clinical applications, J. Immunol. Res. 2015 (2015).
[201] A. Fierabracci, A. Del Fattore, R. Luciano, M. Muraca, A. Teti, M. Muraca, Recent advances in mesenchymal stem cell immunomodulation: the role of microvesicles, Cell Transplant. 24 (2) (2015) 133–149.
[202] V. Kaewkangsadan, C. Verma, J.M. Eremin, G. Cowley, M. Ilyas, O. Eremin, Crucial contributions by T lymphocytes (effector, regulatory, and checkpoint inhibitor) and cytokines (TH1, TH2, and TH17) to a pathological complete response induced by neoadjuvant chemotherapy in women with breast cancer, J. Immunol. Res. (2016).
[203] P. Barcellos-de-Souza, G. Comito, C. Pons-Segura, M.L. Taddei, V. Gori, V. Becherucci, F. Bambi, F. Margheri, A. Laurenzana, M. Del Rosso, Mesenchymal stem cells are recruited and activated into carcinoma-associated fibroblasts by prostate cancer microenvironment-derived TGF-β1, Stem Cells 34 (10) (2016) 2536–2547.
[204] Sd.C. Gonçalves-de-Albuquerque, R. Pessoa-e-Silva, L.A. Trajano-Silva, T.C. de Goes, R. de Morais, C.íntiaNda C. Oliveira, V. de Lorena, M. de Paiva-Cavalcanti, The equivocal role of Th17 cells and neutrophils on immunopathogenesis of Leishmaniasis, Front. Immunol. 8 (2017) 1437.
[205] 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. (2017).
[206] K. Eyerich, V. Dimartino, A. Cavani, IL-17 and IL-22 in immunity: driving protection and pathology, Eur. J. Immunol. 47 (4) (2017) 607–614.
[207] K. Pietras, A. Östman, Hallmarks of cancer: interactions with the tumor stroma, Exp. Cell Res. 316 (8) (2010) 1324–1331.
[208] S.R. Bailey, M.H. Nelson, R.A. Himes, Z. Li, S. Mehrotra, C.M. Paulos, Th17 cells in cancer: the ultimate identity crisis, Front. Immunol. 5 (2014) 276.
[209] R. Jiang, Z. Tan, L. Deng, Y. Chen, Y. Xia, Y. Gao, X. Wang, B. Sun, Interleukin-22 promotes human hepatocellular carcinoma by activation of STAT3, Hepatology 54 (3) (2011) 900–909.
[210] M.-W. Chen, S.-T. Yang, M.-H. Chien, K.-T. Hua, C.-J. Wu, S. Hsiao, H. Lin, M. Hsiao, J.-L. Su, L.-H. Wei, The STAT3-miRNA-92-Wnt signaling pathway regulates spheroid formation and malignant progression in ovarian cancer, Cancer Res. (2017).
[211] B. Singh, Crosstalk Between MDSCs and Th17, AACR, 2017.
[212] L. Guéry, S. Hugues, Th17 cell plasticity and functions in cancer immunity, Biomed Res. Int. (2015).
[213] P. Dvorak, D. Dvorakova, A. Hampl, Fibroblast growth factor signaling in embryonic and cancer stem cells, FEBS Lett. 580 (12) (2006) 2869–2874.
[214] N. Gotoh, Control of stemness by fibroblast growth factor signaling in stem cells and cancer stem cells, Curr. Stem Cell Res. Ther. 4 (1) (2009) 9–15.