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Failure of immunological cells to eradicate tumor and cancer cells: an overview

Rohit SHARMA[1], Daizee TALUKDAR[1], Parth MALIK[2], Tapan Kumar MUKHERJEE[1,*]
[1]Department of Biotechnology, Maharishi Markandeshwar University, Mullana, Ambala, India
[2]Centre for Nano Sciences, Central University of Gujarat, Gandhinagar, India

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Abstract: Inflammation can be broadly understood as a successive immune response of an organism's immune system towards nonnative or foreign antigens. This is a protective mechanism of the immune system, mediated by diverse immunological cells, to ensure homeostasis of an individual. Once activated, these immunological cells release a number of cytokines, chemokines, reactive oxygen species, reactive nitrogen species, histamines, prostaglandins, and other materials leading to inflammation. Tumor cells express altered proteins due to mutations of their genes, DNA modifications such as histone modification, DNA methylation, or other mechanisms of altered protein expression. The body's immunological cells actively recognize these altered proteins, now acting as tumor antigens, and eliminate the tumor cell; this is popularly known as tumor immunosurveillance. However, in unmanaged or inexorable circumstances, tumor cells escape from immunosurveillance mechanisms. This ultimately leads to the cascading events of cancer development and progression. T regulatory cells, tumor-associated macrophages, and myeloid-derived suppressor cells are pronounced cells involved in immunosuppression. These cells not only dodge the immune system's surveillance but also significantly increase the survival, proliferation, and metastasis rates of tumor cells. They hinder T cytotoxic activation by secreting inhibitory cytokines (which inhibit the antitumor activity of natural killer cells) along with dendritic cells and disrupt presentation of antigens, ultimately leading to cancer development. On their own, these cells have emerged as promising therapeutic targets in cancer immunotherapy. This review highlights some of the mechanisms by which these cells escape immunosurveillance and mediate immune suppression.

Key words: Tumor, cancer, inflammation, immunosurveillance, escape, immunosuppression

1. Introduction

Cancer is a broad term that refers to about 200 diseases that share 7 common characteristics that govern the transformation of normal cells to cancer cells. First, cancer cells stimulate their own growth; second, they resist inhibitory signals that might otherwise stop their growth; third, they resist their own programmed cell death (apoptosis); fourth, they stimulate the growth of blood vessels to supply nutrients to tumors (angiogenesis); fifth, they can multiply forever; sixth, they invade local tissue and spread to distant sites (metastasis); and finally, they have the capacity to invade the immune system (Hanahan and Weinberg, 2011). Cancer results from a series of molecular events that lead to the alteration of genetic sequence. The genetic alteration may be due to intrinsic agents (e.g., hormones, estrogen), extrinsic agents (e.g., UV radiation, chemical carcinogen), some pathogenic viruses (e.g., human papillomavirus), or bacteria (e.g., *Helicobacter pylori*). Besides genetic changes, epigenetic modifications (e.g., DNA methylation/acetylation) progressively alter the normal properties of the cells. As these cells grow, they develop new characteristics, including changes in the cell structure, decreased cell adhesion, and the production of new enzymes (Challis and Stam, 1987). These heritable characteristics allow the cell and its progeny to divide and grow uncontrollably, even in the presence of normal cells in the surroundings that typically inhibit the overgrowth of nearby cells. Such changes allow these cells to spread and invade other tissues. Thus, cells bearing greater amounts of accumulated epigenetic changes (changes in the activity of genes without changes in the genetic sequence) or genetic mutations may escape from the regulated proliferation and acquire the ability to continuously proliferate without further differentiation and apoptosis. The continuous proliferation forms a mass of cells called a "neoplasia". Neoplasias can be classified as either "benign" or "malignant", depending on their nature. In benign neoplasia, the rate of cell proliferation is slow and is confined to the site of origin; these types of cells are called tumor cells. With time and further exposure to intrinsic and extrinsic agents, tumor cells may convert to malignant cells (also called cancer cells), which have a

* Correspondence: tapanmu@yahoo.com

higher rate of proliferation and invasion to the surrounding tissues. Invasion then depends upon the novel adhesive interaction of the malignant cell with the extracellular matrix component of the basement membrane and mesenchymal tissue. Furthermore, cancer cells also make specific heterotypic contacts with endothelial cells to gain access to blood and lymph vessels (Okegawa et al., 2004). In 1863, Virchow hypothesized that the origin of cancer is at sites of chronic inflammation (Balkwill and Mantovani, 2001). Indeed, chronic inflammation is a risk factor for tumor development (Chow et al., 2012). The afflicted tissues are healed by a multifunctional network of chemical signals, which further involves the activation and directed migration of neutrophils, monocytes, and eosinophils to the sites of damage (Chettibi and Ferguson, 1999). An environment rich in inflammatory cells, growth factors, activated stroma, and DNA-damage–promoting agents leads to sustained cell proliferation, thus initiating neoplastic risk (Bernestein et al., 2008). Thus, the immune system can not only suppress tumor growth and cell proliferation; it can also exert selection pressure on tumor cells and facilitate tumor growth by providing a favorable tumor microenvironment (Chow et al., 2012). Many cells of the immune system are involved in enhancing the growth of tumor cells. T regulatory (Treg) cells play a vital role. Additionally, myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) are also known to help the survival and proliferation of tumor cells by immunosuppression. The immunosurveillance hypothesis was formulated in 1950 and suggested that the immune system of the host recognizes antigens of newly arising tumors and eliminates these tumors before they become clinically evident (Burnet, 1957). Recent work has shown that the immune system may also promote the emergence of primary tumors with reduced immunogenicity that are capable of escaping immune recognition and destruction (Shankaran et al., 2001). The following paragraphs describe, step by step, the mechanisms of tumor and cancer cell recognition by the immune system, the mechanisms of immunosurveillance, and the escape mechanisms of these cells from immunosurveillance.

2. Recognition of cancer cells by the immune system

The immune system comprises a network of cells, tissues, and organs working simultaneously to defend the body against attacks by "foreign" invaders. These are primarily microbes (germs): tiny, infection-causing agents such as viruses, mycoplasma, bacteria, parasites, and fungi. The key to a healthy immune system is its remarkable ability to distinguish between the body's own cells as "self" and foreign cells as "nonself" (Houghton, 1994). The body's immune defenses normally coexist peacefully with cells that carry distinctive "self" marker molecules. However, when immune system cells encounter antigens carrying markers that say "foreign", they quickly launch an attack. Anything that can trigger this immune response is called an immunogen. This may be microbe, such as a virus, or even a mere part of a microbe, such as protein molecule of a microbe (Hougton et al., 2001). The conversion of a normal cell to a cancerous cell is accompanied by altered surface antigens. The immune system recognizes these altered proteins (antigens) on tumor/cancer cells as foreign antigens and it launches an attack on these cells; this is famously known as tumor immunosurveillance. However, the immune system cannot patrol everywhere to provide body-wide surveillance, flushing out and eliminating all cells that become cancerous. Moreover, tumor cells are devoid of mechanisms to escape from immunosurveillance. In 1909, Ehrlich first proposed that cancer may occur spontaneously in vivo and that the immune system is able to both recognize and protect the organism against cancer cells. About 50 years later, Thomas and Burnet took Ehrlich's idea and proposed that a special type of immune cell, namely the T cell, is the pivotal sentinel in the immune system response against cancer. This contribution led to the coinage of the term "immune surveillance" or "immunosurveillance" to describe the concept where the immune system is on alert against tumor cells (Petrausch et al., 2009). In the 1970s, T cells were identified as effector cells and T-cell–mediated cellular immunity (which is famously known as T cytotoxic action) was postulated as the "principal process" of tumor immunosurveillance (Naor, 1979). However, later discoveries proved that cells involved in innate immunity (e.g., natural killer [NK] cells, macrophages, dendritic cells [DCs]) and even B-cell–mediated humoral responses play a significant role in tumor immunosurveillance. However, there has been growing recognition that the primary tumors are able to escape the immune recognition and destruction by adopting a wide array of escape mechanisms, as described below (Dunn et al., 2002, 2004).

3. Escape mechanisms in tumor immunosurveillance

Tumor escape from host immunosurveillance is a concept that was formulated alongside the theory of immunosurveillance (Burnet, 1970). Mechanisms that may exist for the escape of tumors from immunosurveillance are of course not mutually exclusive but rather a combination of several different characteristics (Figure) (Real et al., 2001): failure to express the major histocompatibility complex (MHC) antigen; decreased and heterogeneous expression of tumor antigen (TA); and abnormal expression of accessory molecules by tumor cells. In addition to these, many other factors allow tumor cells to escape immunosurveillance. Some may escape due to the secretion of soluble factors with immune downregulatory effects by tumor cells or the induction of suppressor cells. Sometimes changes in the

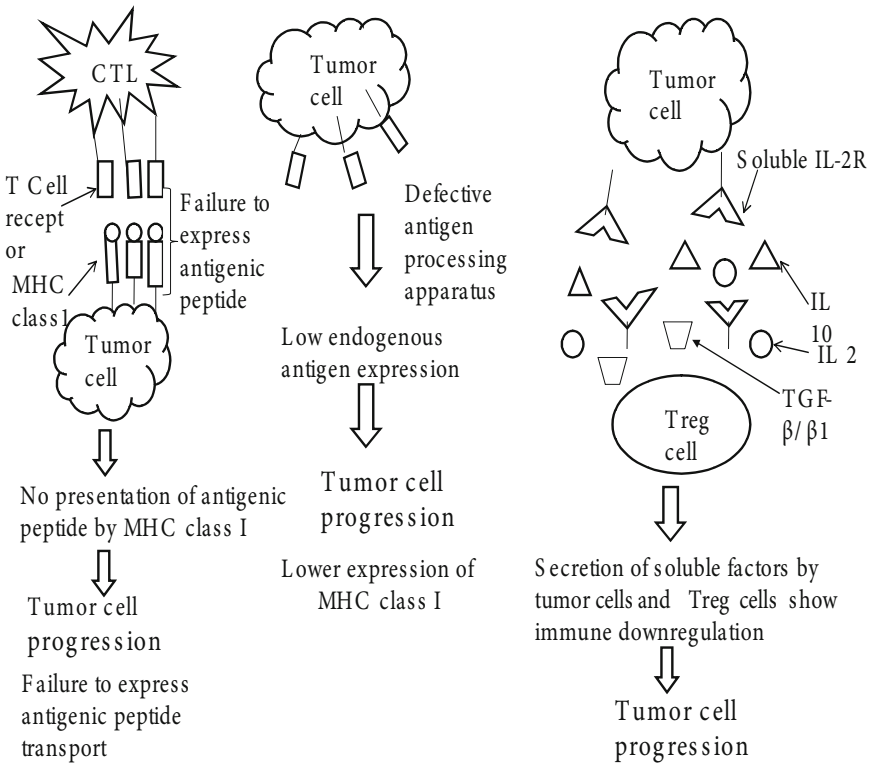

Figure. Various strategies employed by tumor cells to escape immune surveillance. These strategies employed include inefficient antigen presentation by MHC class I and secretion of inhibitory cytokines such as IL-2R, IL-10, IL-35, and TGF-β/β1. Inefficient antigen presentation leads to a weak immune response, whereas inhibitory cytokines suppress immune response by inhibiting T-cell proliferation and suppressing the cytolytic activities of T cells and NK cells against tumor cells. The cumulative effect is a weak immune reaction against tumor cells, leading to tumor survival, growth, proliferation, and metastasis.

T-cell signal transduction molecules lead to escape of the tumor from immunosurveillance (Kim et al., 2007).

3.1. Failure to express MHC molecule and of antigenic peptide transport

Antigenic peptides are present at the surface of antigen-presenting cells by MHC molecules. The class I MHC-peptide complex interacts with $CD8^+$-containing cytotoxic lymphocytes and the class II MHC-peptide complex interacts with $CD4^+$-containing T cells. The class I MHC molecule consists of a membrane α chain attached to a soluble β chain. The loss of MHC antigen can be caused by immunoselection, as demonstrated in vivo (Wölfel et al., 1989) and in vitro (Garcia-Lora et al., 2001) in mice. Even when tumor cells do not downregulate all human leukocyte antigen (HLA) alleles, they may completely delete genes encoding some of them (Lehmann et al., 1995). This theory of escape from immunosurveillance was further studied in a murine model, in which the loss of a single class I allele converted a normally rejected murine tumor to a progressor, despite the fact that MHC alleles were being expressed by the tumor to present tumor antigens. The reason for such loss of recognition was because the tumor antigen, which was originally being presented by the allele that the tumor had lost, was still being recognized by the immune system and this diverted the response from other tumor antigens. Therefore, downregulation of MHC antigens provides a powerful strategy for avoiding T-cell detection (Amiot et al., 1998).

3.2. Decreased and heterogeneous expression of tumor antigens

Antigen-processing defects that also result in HLA expression may affect antigen downregulation. Restifo et al. (1993) directly showed that human tumor cell lines have a defective antigen-processing apparatus, which results in low levels of surface class I MHC and a lack of endogenous antigen expression. The cells had little mRNA for LMP-2, LMP-7, TAP-1, and TAP-2, but these defects were reversible with interferon (IFN)-γ.

3.3. Abnormal expression of accessory molecules by tumor cells

Antitumor responses are commonly triggered by the presentation of the tumor antigen to T cells by host DCs. If an abnormality happens in their function, tumor immunity will be severely affected. In 1996, it was reported that mature DCs from tumor-bearing mice were compromised in their antigen-presenting capacity (Gabrilovich et al., 1996). Moreover, the development of DCs from a bone marrow precursor was inhibited by tumor-derived soluble products, which suggests that the maturation of antigen-presenting cells can be altered by the tumor.

3.4. Secretion of immunosuppressive agents

The serum samples of cancer patients contain immunosuppressive agents, many of which may be acute phase reactants with nonspecific inhibitory properties. Acute phase reactant proteins (APPs) are a large and varied group of glycoproteins in serum released into the bloodstream in response to a variety of stressors. Synthesis of APPs and changes to their composition are fast processes that intervene in the acute phase reaction stage and are present in the initial period and during the evolution of pathological phenomena (e.g., inflammations, trauma, immunopathies, and bacterial or neoplastic disease). The most significant proteins in this group are C-reactive proteins, fibrinogen, ferritin, serum amyloid protein A, α1-antichymotrypsin, α1-antitrypsin, α1-acid glucoprotein, haptoglobulin, and ceruloplasmin. An increase or decrease in APP serum concentration occurs after 2–4–6 days of disease. The majority of APP quantitative changes are the result of hepatocyte dysfunctions correlated with plasma protein synthesis. There are mostly changes of APP gene transcription induced by cytokines, interleukins, interferons, or tumor necrosis factors (Wigmore et al., 1997). Reactivity to nontumor antigens may be depressed in cancer patients and contribute to their increased susceptibility to infection (Scheibenbogen et al., 1997). In 1993, it was reported that melanoma cells express large amounts of CD58, and this inhibits melanoma cell lysis (Altomonte et al., 1993). CD58 is a novel surface marker that promotes self-renewal of tumor-initiating cells in colorectal cancer. It also exhibits epithelial–mesenchymal transition ability and tumorigenicity, both in vitro and in vivo. Furthermore, activated CD58 upregulates the β-catenin pathway (it is a dual function protein that regulates the coordination of cell-to-cell adhesion as well as gene transcription) and thus promotes self-renewal of colorectal tumor-initiating cells (Yu et al., 2014). Increased levels of intercellular adhesion molecule 1 (ICAM-1) in the plasma of cancer patients has also been reported in disease progression. ICAM-1, also known as CD54, is a protein in humans that is encoded by the *ICAM1* gene. This gene encodes a cell surface glycoprotein that is typically expressed on endothelial cells and cells of the immune system. It binds to integrins of type CD11a, CD11b, and CD8. It is continuously present in low concentrations in the membranes of leukocytes and endothelial cells. Upon cytokine stimulation, the concentrations greatly increase. ICAM-1 can be induced by interleukin-1 (IL-1) and tumor necrosis factor (TNF) and is expressed by the vascular endothelium, macrophages, and lymphocytes. ICAM-1 is a ligand for leukocyte function-associated antigen-1 (LFA-1, integrin), a receptor found on leukocytes. When activated, leukocytes bind to endothelial cells via ICAM-1, then transmigrate into tissues (Rothlein, 1986). Serum level of soluble Fas measured in patients with hepatocellular carcinoma were found to be significantly higher (median: 4.07 ng/mL) than levels in age-matched healthy donors (0.29 ng/mL). Tumors can also exert some nonspecific suppressive activity by secreting adenosine as a result of their hypoxic metabolism. Adenosine directly suppresses tumoricidal lymphocyte functions (Hoskin et al., 1994). Adenosine can produce IL-10 by inhibiting IL-12, further contributing to immunosuppressive activity (Link et al., 2000). IL-10 also downregulates the expression of NK target structures. Tumors also secrete various other cytokines; for example, breast carcinoma predominantly secretes IL-4, IL-6, IL-8, IL-10, TGF-β, and CCL5, while uveal carcinoma secretes IL-6, IL-8, IL-10, IL-17, TNF-α, and vascular endothelial growth factor (VEGF), which influence immune response. Cytokines directly affect tumor growth by acting as growth promoters or growth inhibitors and indirectly affect tumor growth by attracting inflammatory cell types and affecting angiogenesis. With the advent of cloning techniques, recombinant forms of different cytokines have been developed that have emerged as pivotal candidates with significant antitumor potential for cancer therapy. This important goal has been difficult to achieve due to the toxicity of most cytokines, which could not be dissociated from their antitumoral functions (Onfray et al., 2007). Melanoma cells may secrete IL-15, which enhances expression of the downregulatory NK inhibitory receptor on T cells, as well as possibly depressing the expression of MHC class I molecules on tumor cells (Mingari et al., 1998). On the other hand, it is also a T-cell growth factor and an antiapoptotic factor. Once again, cytokines have contradictory effects.

3.5. Role of T regulatory cells in tumor immunosuppression

Treg cells are a subset of the T-cell population, expressing the high-affinity IL-2 receptor (CD25) (Piccirillo et al., 2002), cytotoxic T lymphocyte antigen-4 (CTLA-4) (Tai et al., 2012), glucocorticoid-induced tumor necrosis factor receptor (GITR) (Buechele et al., 2012), and the lineage-specific transcription factor forkhead box p3 (FOXP3) (Hori et al., 2003) as surface proteins. Treg cells suppressing immune responses via cell–cell interactions

and/or the production of suppressor cytokines is currently well established. They are developmentally classified into natural FOXP3$^+$-expressing Tregs (Tn) generated in the thymus and antigen-induced or adaptive Tregs (Ti) generated in the periphery. Most natural Tregs constitutively express the IL-2 receptor α chain (CD25) and their development and function depend on the expression of the transcription factor FOXP3 (Sakaguchi et al., 2004). Adaptive Tregs are induced from naïve T cells by specific modes of antigenic stimulation, especially in a particular cytokine milieu (Roncarolo et al., 2006). They include IL-10–secreting T regulatory 1 (Tr1) cells, transforming growth factor (TGF)-β–secreting T helper (Th3) cells, certain γ/δ T-cell receptor (TCR)-expressing CD4$^-$CD8$^-$ T cells, and CD8$^+$CD28$^-$ T cells. Tregs are commonly overexpressed in head and neck cancer (Wild et al., 2010), lung cancer (Shimizu et al., 2010), pancreatic cancer (Tan et al., 2009), breast cancer (Ma et al., 2012), liver cancer (Pedroza-Gonzalez et al., 2013), ovarian cancer (Wei et al., 2005), and gastrointestinal cancer (Yuan et al., 2011), either in the circulation or in the tumor itself. Tregs' presence at tumor sites has often been correlated with tolerance induced by the host immune system towards the tumor, leading to a poor prognosis in the cancer patients. Tregs have been implicated in dampening antitumor immunity against malignant cells by suppressing immunological responses to tumor antigens. Tregs that are considerably upregulated in the tumor microenvironment affect both the innate and adaptive immune responses, and hence they induce and maintain immune cell tolerance in the tumor microenvironment. Tregs also exhibit considerable prognostic value; elevated levels of Treg cells are valuable and independent prognostic biomarkers. However, high numbers of Tregs are actually associated with a poor prognosis, as the presence of Tregs in the tumor microenvironment diminishes antitumor immune responses (Badoual et al., 2006; Tao et al., 2012).

3.5.1. Mechanism of Treg-mediated immune suppression

Treg cells exhibit immune-suppressive activities possibly by 2 mechanisms: 1) cell–cell contact-dependent and 2) cytokine stimulation-dependent.

3.5.1.1. Cell–cell contact

These mechanisms involve physical interaction between a Treg cell and the target cell. Treg cells express a number of cell surface-bound factors, such as TGF-β/β1, that interact with ligands such as MHC-II on target cells. The target cells are thus inhibited via direct cell–cell interaction rather than via secreted cytokines (Nakamura et al., 2001). Various types of immunosuppressive cells and their surface markers and perspective functions are summarized in the Table.

3.5.1.1.1. CD4$^+$ CD25$^+$-expressed T regulatory cells in tumor immunosuppression

CD4$^+$ CD25$^+$ cells mediate immune suppression by inhibiting NK cells' ability to remove damaged cells. NK cells are the mainstay of immune systems participating in tumor-immune surveillance in various cancers (Borg et al., 2004; Castriconi et al., 2004; Waldhauer and Steinle, 2008). NK cells are cytolytic cells that recognize and kill malignant cells without prior sensitization, thus serving as the earliest effectors. There is an inverse correlation between NK cell activity and Treg cell expansion in cancer patients (Ghiringhelli et al., 2005). NK group 2 member D (NKG2D), a NK cell receptor, recognizes various ligands on stressed or damaged cells as in tumors and lyses these cells. CD4$^+$ CD25$^+$ T cells express TGF-β on their surface and inhibit NK cells in a cell-to-cell contact-dependent manner. The inhibition of NK cells is mainly due to the downregulation of NKG2D by TGF-β–expressing Treg cells (Ghiringhelli et al., 2005). In a similar study in 2010, Zhou et al. found that forced FOXP3 expression in polyclonal CD4$^+$ T cells induced Treg cells and suppressed NK cell functions in a TGF-β–dependent manner. Another cytokine, TGF-β1, has been frequently expressed in tumors (Kong et al., 1996; Hasegawa et al., 2001; Narai et al., 2002). TGF-β1 expressed on the surface of Treg cells significantly inhibited the surface expression of NKG2D, whereas blocking anti-TGF-β1 mAbs completely restored surface NKG2D to normal levels. These studies concluded that the role of TGF-β and TGF-β1 in inhibiting NK cells was via a cell-to-cell contact mechanism (Lee et al., 2004). CD4$^+$ CD25$^+$ cells were also found to inhibit DCs. DCs are a pivotal player involved in the initiation of immune reactions by preferably activating naïve T cells (Banchereau and Steinman, 1998). Treg cells continuously express increased LFA-1 and CTLA-4 at higher levels than naïve T cells (Tn) (Itoh et al., 1999; Read et al., 2000; Salmon et al., 2000; Takahashi et al., 2000). CTLA-4 upregulates LFA-1–mediated cell adhesion and clustering (Schneider et al., 2000). CD4$^+$ CD25$^+$ regulatory T cells inhibit DCs via cell-to-cell contact in a 2-step process. The initial step involves aggregation of Tregs around DCs dependent on LFA-1 and the second step involves LFA-1– and CTLA-4–dependent active downmodulation of CD80/86 expression on DCs. CD80/86 are important surface coreceptors that greatly enhance DCs' ability to activate T cells. Downregulation of these receptors greatly suppresses immune system (Onishi et al., 2008). In 2008, Liang et al. reported another putative mechanism of cell-contact inhibition of DCs involving lymphocyte activation gene-3 (LAG-3) engagement of MHC class II. LAG-3 is a CD4-related transmembrane protein expressed by Treg cells. Interaction between LAG-3 and MHC II inhibits DCs. This interaction induces an ITAM-mediated inhibitory signaling pathway, involving

Table. Various immunosuppressive cells expressing a wide array of surface markers that significantly suppress immune surveillance. These surface markers adopt various pathways such as inhibition of NK cells, inhibition of DC cells, and inhibition of T cell activation and proliferation, eventually leading to immunosuppression.

S. no.	Cell type	Surface marker expressed	Function/characteristic	Reference
1	Treg cell			
a	CD4+ CD25+	CD25+ LFA-1, CTLA-1	Inhibiting NK cells by downregulating NKG2D Inhibiting DCs by downregulating CD80/86+	Narai et al., 2002 Onishi et al., 2008
b	γδ	CD27, CD28	T cell inhibition, inhibiting DC maturation	Peng et al., 2005, 2007
c	CD4+ CD25– FOXP3+FOXP3+		Inhibiting T-cell proliferation	Yang et al., 2007
d	CD4+, CD69+ CD25–	CD69+, CD25–FOXP3+, D122+	Suppressing T cell proliferation	Esplugues et al., 2003
e	CD8+ FOXP3+FOXP3+ CD122+		Inhibiting T cell proliferation Inhibiting CD8+, CD4+	Kiniwa et al., 2007 Endharti et al., 2005
f	Tim3+	Tim3+, FOXP3+ PD-1+	Dysfunctional CD8+ Inhibiting NK cell cytotoxic function	Gao et al., 2012 Wen et al., 1994
g	CD8+ CD28–	CD28–, CD57+	Inhibiting T cell proliferation	Mueller and Fusenig, 1999
h	CD8+Tc17	CCR6, CTLA-4, GITR	Suppressing proliferation of $CD4^+$ naïve T cells and $CD8^+$ effector T	Li et al., 2011
2	MDSCs	NF-kB, STAT1/3/6, arginase 1	Inhibiting CD8+ T cells Inhibiting T cell activation	Wiers et al., 2000 Kusmartsev et al., 2004
3	TAMs	CD206, CD80+ 15-Lox2, FOXP3+, legumain	Poor antigen presentation Tumor angiogenesis and metastasis	Daurkin et al., 2011 Luo et al., 2006

FcγRγ and ERK-mediated recruitment of SHP-1 that suppresses DC maturation and its immunostimulatory capacity.

3.5.1.1.2. γδ T regulatory cells in tumor immunosuppression

γδ Treg cells are a new subset of Treg cells identified in human diseases, including cancer. Human γδ Tregs were shown to have considerable immune-suppressive potential. These cells induced responder T cells and DCs into senescent immune cells. γδ Treg-induced senescent T cells resulted in a significantly decreased expression of CD27 and CD28 costimulatory molecules, indicating their dysfunction. Similarly, senescent DCs also exhibited impaired costimulation, suppressed secretion of effector cytokines, and upregulated immune-suppressive molecule PD-L1 (Ye et al., 2013). These cumulative effects of both senescent T cells and DCs converted into suppressive immune cells have negative regulatory effects on immune responses. Mouse γδ T cells suppressed the immune system via the Fas/Fas ligand pathway and TGF-β/IL-10 secretion (Kapp et al., 2004; Pennington et al., 2005). A human breast tumor study showed that γδ Treg-mediated immune suppression was due to some unknown soluble factor, independent of TGF-β and IL-10 secretion. γδ Treg cells suppress naïve and effector T-cell function by inhibiting $CD4^+$, $CD8^+$, Vg9Vd2 T cells and DCs' maturation and activity (Ye et al., 2013). The suppressive mechanism implies that TLR8-mediated signaling is involved, as treatment with TLR8 ligands reversed γδ1 Treg cells' suppressive function both in vivo and in vitro (Peng et al., 2005, 2007).

3.5.1.1.3. $CD4^+$ $CD25^-$ $FOXP3^+$-expressed T regulatory cells in tumor immunosuppression

Yang et al. (2007) showed that $CD4^+$ $CD25^-$ $FOXP3^+$ naïve T cells in the tumor microenvironment of B lymphoma cells were induced to $CD4^+$ $CD25^-FOXP3^+$ cells. FOXP3+ expression is essential for the development and regulatory activity of T cells (Fontenot et al., 2003; Hori et al., 2003). These cells represent novel mechanisms by which B lymphoma dodges immunosurveillance mechanisms of the body. Lymphoma B cells express CD70 and CD27 in addition to CD86/80. Interaction between CD70 and CD27 drives the activation-induced FOXP3 expression in $CD4^+CD25^-$ cells. However, the exact mechanism behind this immune suppression by $CD4^+$ $CD25^-$ $FOXP3^+$ cells in lymphoma B cells is still not clear and requires further elucidation.

3.5.1.1.4. $CD69^+$ $CD4^+$ $CD25^-$-expressed T regulatory cells in tumor immunosuppression

$CD69^+CD4^+CD25$ Treg cells are a $CD4^+$ Treg subset characterized by a lack of CD25 and FOXP3 expression that is considerably underexplored. These cells do not secrete IL-10, TGF-β, IL-2, or IFN-γ, but do express membrane-bound TGF-β1 and an increased percentage of CD122. These cells suppress T-cell proliferation, with CD69-deficient mice having enhanced antitumor immunity (Esplugues et al., 2003). CD69 has been implicated in apoptosis in monocytes and eosinophils and triggers the inhibitory signal for IL-1 receptor- or CD3-mediated T-cell proliferation (Cosulich et al., 1987; Ramirez et al., 1996; Walsh et al., 1996). In addition, these cells were recently found to be associated with leukemia relapse after allogeneic hematopoietic stem cell transplantation, suggesting their immune-suppressive potential (Zhao et al., 2013). The $CD69^+$ $CD4^+$ $CD25^-$ cells mediate immune suppression via membrane-bound TGF-β1 in a cell contact-dependent manner. These cells further activate the MAPK/ERK pathway, which maintains sustainable expression of TGF-B1 and further strengthens the immune suppressive potential of these cells (Han et al., 2009).

3.5.1.1.5. $CD8^+$ $FOXP3^+$-expressed T regulatory cells in tumor immunosuppression

$CD8^+$ $FOXP3^+$ Treg cells present in prostate tumor-derived tumor infiltrating lymphocytes (TILs) suppress immune responses. Their suppressive function can be regulated by TLR8 ligands. The suppressive function of $CD8^+$ Treg cells mediated by TLR8 is made evident by the fact that human TLR8 signaling results in the reversal of their suppressive function. Thus, modulation of Treg cell function by targeting TLR8 may improve the efficacy of immunotherapy for cancer (Kiniwa et al., 2007).

3.5.1.2. Cytokine secretion

3.5.1.2.1. IL-10–mediated tumor immunosuppression

IL-10 is an immunoregulatory cytokine with potent antiinflammatory and immunosuppressive activities. It inhibits T-cell proliferation in both Th1 and Th2 cells. Studies have demonstrated a negative correlation between NK cell cytotoxicity and serum IL-10 levels (Szkaradkiewicz et al., 2010). Treg cells produce high levels of IL-10, which restricts NK cells' cytotoxicity by inhibiting production of IFN-γ, IL-2, IL-12, and IL-18 (Wen et al., 1994; Szkaradkiewicz et al., 2010). In gastric tumors, *H. pylori* stimulates high production of proinflammatory cytokines, mainly of IL-1, IL-6, IL-8, and TNF-α (Konturek et al., 2003; Zambon et al., 2005). T-cell immunoglobulin mucin 3 (TIM-3), an inhibitory molecule expressed by $FOXP3^+$ Tregs, has been speculated to mediate immune suppression through IL-10 secretion. TIM-3 is a key regulator of dysfunctional or exhausted $CD8^+$ cells. TIM-3 expression in TILs in nonsmall cell lung cancer showed that TIM-3 marks functionally exhausted $CD8^+$ T cells and is likely responsible for immunosurveillance failure (Gao et al., 2012). $TIM\text{-}3^+$ cells frequently coexpress the inhibitory receptor PD-1 and both $TIM3^+$ and $PD\text{-}1^+$ result in the generation of dysfunctional/exhausted CD8+ T cells in cancer. $TIM3^+$ Treg cells probably exert immunosuppressive functions by expressing higher levels of effector molecules, such as IL-10, than their $TIM3^-$ counterparts (Sakuishi et al., 2013). Therefore, decreased NK cell cytotoxicity and elevation of IL-10 serum levels synergistically result in neoplastic transformation and enhanced tumor growth. $CD8^+$ $FOXP3^+$ Treg cells, which are present in elevated levels in prostate, nasopharyngeal, and colorectal cancers (Kiniwa et al., 2007; Chaput et al., 2009; Li et al., 2011), also actively suppress T-cell proliferation via secretion of IL-10. Two major categories of $CD8^+$ Treg cells have been described: 1) nonspecific immune suppression (mediated by $CD8^+CD25^+$, $CD8^+CD122^+$, $CD8^+CD45$ RC low) and 2) antigen-specific immune suppression (mediated by $CD8^+CD282$, $CD8^+CD75s^+$, $CD8^+CD45RChi$ TC1, and TCR peptide-specific CD8aa Treg cells) (Tang et al., 2005). $CD8^+CD122^+$ Treg cells directly control $CD8^+$ and $CD4^+$ cells without intervention of APCs via release of IL-10 (Endharti et al., 2005).

$CD8^+$ $CD28^-$ ($CD8^+$ $CD57^+$)-expressed Treg cells, characterized by loss of $CD28^-$ and gain of $CD57^+$ (Merino et al., 1998; Bandrés et al., 2000), also mediate immunosuppression via IL-10 release. $CD28^+$ generates a costimulatory signal for the full-fledged activation and survival of CD8+ T cells. $CD8^+$ cells then proliferate into CTL, perform their effector function, and die by apoptosis, while some are retained as memory cells for future antigenic challenge. Due to persistent antigenic challenge and repetitive cycles of stimulation/proliferation, CD28 expression is progressively and irreversibly downregulated on the surface of $CD8^+$ T cells (Kaech et al., 2002; Brenchley et al., 2003). This leads to the accumulation of highly antigen-experienced $CD8^+CD28^-$ T cells with shortened telomeres. $CD8^+CD28^-$ Treg cells mediate their immunosuppressive effects by the production of inhibitory cytokines IL-10 (Filaci et al., 2007) or GM-CSF (Tsuchiya et al., 1988; Tsuruta et al., 1998; Mueller and Fusenig, 1999; Mueller et al., 1999), hence inhibiting both T-cell proliferation and tumor-specific cytotoxicity.

3.5.1.2.2. IL-35–mediated tumor immunosuppression

IL-35 is a heterodimeric cytokine belonging to the IL-12 family, consisting of the Epstein–Barr virus-induced gene-3 and IL-12p35 subunits. IL-35 is highly expressed by mouse $FOXP3^+$ Treg cells (Collison et al., 2007) and stimulated human Treg cells (Chaturvedi et al., 2011; Seyerl

et al., 2011). There are contradictory reports regarding the role of IL-35. While some authors suggest that IL-35 has immunosuppressive potential, others report its antitumorigenic and apoptotic potential. A study by Wang et al. showed IL-35 to be an immunosuppressive cytokine that inhibits T cell proliferation and converts naïve T cells into IL-35–producing induced Treg cells. Further IL-35 induced tumor growth by increasing myeloid cell accumulation, enhancing tumor angiogenesis, and blocking antitumor CTL response (Wang et al., 2013). In another study, Long et al. showed that IL-35 has antitumor potential, as its overexpression in various human cancer cell lines resulted in cell growth inhibition in vitro. IL-35 overexpression induces G1 cell cycle arrest and increases apoptosis via TNF-α and IFN-γ stimulation and downregulation of cyclin D1, survivin, and Bcl_2 expression (Long et al., 2013).

3.5.1.2.3. IL-17–mediated tumor immunosuppression

IL-17–producing $CD8^+$ T cells (Tc17 cells) were first derived from the $CD8^+$ T-cell lineage in nasopharyngeal carcinoma (NPC). Tc17 cells from TILs of NPC patients can suppress the proliferation of $CD4^+$ naïve T cells and $CD8^+$ effector T cells in vitro. Tc17 cells expressed high levels of TNFα and CCR6 and low levels of CTLA4 and GITR (Li et al., 2011). $CD4^+$ Th17 cells secreting 1L-17 have also been implicated to have a role in solid tumors. There are contradictory reports regarding the role of IL-17 in tumorigenesis, with some reports asserting that Th17 cells promote tumor growth via the IL-6/STAT3 pathway, upregulation of IL-8, and induction of tumor angiogenesis (Charles et al., 2009; Inozume et al., 2009; Kuang et al., 2010). However, others suggest that Th17 cells have an antitumor function, as healthy Th17 cells number signify a better outcome.

3.6. Role of myeloid-derived suppressor cells in tumor immunosuppression

MDSCs are a heterogeneous population of immature myeloid cells that increase in various cancers. MDSCs have been differentiated into 2 distinct subtypes: granulocytic and monocytic (Schmielau et al., 2001; Zea et al., 2005; Mirza et al., 2006; Filipazzi et al., 2007; Mandruzzato et al., 2009; Poschke et al., 2010; Gowda et al., 2011). MDSC generation in the bone marrow is induced by various cancer-derived factors, such as G-CSF, IL-6, GM-CSF, IL-1β, prostaglandin E2, TNF-α, and VEGF. These immunosuppressive MDSCs are then recruited to the tumor site by cytokines like CCL2, CXCL12, and CXCL5 (Sawanobori et al., 2008). The immunosuppressive potential of MDSCs is also dependent on signal transducers, transcription activators (STAT1, STAT3, STAT6), and the nuclear factor kappa light-chain-enhancer of activated B-cell transcription factors (Gabrilovich and Nagaraj, 2009). MDSCs have a considerable role in immune suppression in the tumor microenvironment, mainly by producing arginase 1, releasing reactive oxygen species (ROS) and nitric oxide (NO), and secreting immune-suppressive cytokines. Arginase is an essential amino acid for T-cell activation. MDSCs sequester arginine and also degrade it by producing arginase 1, hence suppressing $CD4^+$ and $CD8^+$ T cells (Bronte et al., 2003; Kusmartsev et al., 2004; Bronte and Zanovello, 2005). Another mechanism of MDSC-mediated immune suppression is ROS and peroxynitrite production. ROS and peroxynitrite inhibit $CD8^+$ T cells by catalyzing the nitration of the TCR and preventing T cell–peptide–MHC interactions essential for $CD8^+$ activation (Wiers et al., 2000). MDSCs have thus emerged as a potential target in cancer immunotherapeutics with triterpenoids (Thimmulappa et al., 2007), arginase (Serafini et al., 2008), cyclooxygenase 2 (Sinha et al., 2007), phosphodiesterase-5 inhibitors (Serafini et al., 2006), and nitroaspirin (Nagaraj et al., 2010; Molon et al., 2011; Mundy-Bosse et al., 2011) as promising inhibitors of MDSC metabolism and expression.

3.7. Role of tumor-associated macrophages in tumor immunosuppression

Tumor-associated macrophages (TAMs) are derived from circulating monocytes or resident tissue macrophages, primarily the M2 ($F4/80^+/CD206^+$) macrophage population, having little cytotoxicity for tumor cells because of their limited production of NO and proinflammatory cytokines (Mills et al., 2000). The poor antigen-presenting capability of TAMs accounts for their immune-suppressive functions. TAMs are found in elevated levels in the tumor microenvironment and are responsible for tumor growth, survival, progression, and metastasis. TAMs stimulate tumor angiogenesis by secreting various proangiogenic and immunosuppressive cytokines such as IL-10 and CCL2 (Biswas and Mantovani, 2010; Corzo et al., 2010; Qian and Polard, 2010). In 2011, Daurkin et al. showed that TAMs isolated from renal cell carcinoma (RCC) tumors had a high 15-lipoxygenase-2 (15-LOX2) expression and secreted substantial amounts of 15(S)-hydroxyeicosatetraenoic acid, its major bioactive lipid product. TAMs isolated from RCC were capable of inducing T lymphocytes, $FOXP3^+$, and CTLA-4 coreceptor. This TAM-induced FOXP3 and CTLA-4 expression in T cells was independent of lipoxygenase and could not be reversed by inhibiting lipoxygenase activity (Daurkin et al., 2011). Thus, 15-LOX2 expression enhances the immunosuppressive potential of TAMs as well as Treg cells. In another study in 2006, Luo et al. reported that legumain, a novel acidic cysteine endopeptidase of the C13 family of cysteine proteases, was responsible for the immunosuppressive attributes of TAMs in breast cancer (Lin et al., 2013). Legumain encoded by the asparaginyl endopeptidase gene was found to be highly upregulated

in many murine and human tumor tissues (Liu et al., 2003; Murthy et al., 2005), leading to increased tumor progression, angiogenesis, and metastasis.

4. Conclusion

The human immune system uses a complex array of putative mechanisms to combat exogenous as well endogenous antigens. Tumor cells in the body express specialized antigens, specifically in the tumor microenvironment. Such cells expressing these antigens are recognized as alien molecules by the immune system and it employs complex biomechanisms ensuring rectification. This process is known as immunosurveillance. However, certain cells, such as Treg cells, MDSCs, and TAMs, dodge this immunosurveillance and contribute to tumor growth, survival, proliferation, and metastasis. These cells express surface markers including FOXP3, CTLA, GITR, $CD28^+$, $CD69^+$, and $CD57^+$, enabling them to suppress the immune system via secretion of cytokines. These cells inhibit $CD4^+$ $CD8^+$ effector T-cell proliferation by hindering antigen presentation by NK cells or DCs, or secreting inhibitory cytokines such as IL-10, IL-35, IL-17, or TGF-β/β1. These various subsets of $CD4^+$ $CD8^+$ T cells, TAMs, and MDSCs represent novel targets in deciphering the biology of the tumor microenvironment, under which they modulate and suppress the host's immune response against tumor cells. Targeting these surface markers is a potential strategy in cancer immunotherapy. Understanding these concepts of immunology may lead to potential strategies to modulate immunosuppressive effects in the field of cancer research.

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References

Altomonte M, Gloghini A, Bertola G, Gasparollo A, Carbone A, Ferrone S, Maio M (1993). Differential expression of cell adhesion molecules CD54/CD11 and CD58/CD2 by human melanoma cells and functional role in their interaction with cytotoxic cells. Cancer Res 53: 3343–3348.

Amiot L, Onno M, Lamy T, Dauriac C, Le Prise PY, Fauchet R, Drenou B (1998). Loss of MHC molecules in B lymphomas is associated with an aggressive clinical course. Br J Haematol 100: 655–663.

Badoual C, Hans S, Rodriguez J, Peyrard S, Klein C, Agueznay NH, Mosseri V, Laccourreye O, Bruneval P, Fridman WH et al. (2006). Prognostic value of tumor-infiltrating CD4+ T-cell subpopulations in head and neck cancers. Clin Cancer Res 12: 465–472.

Balkwill F, Mantovani A (2001). Inflammation and cancer: back to Virchow. Lancet 357: 539–545.

Banchereau J, Steinman RM (1998). Dendritic cells and the control of immunity. Nature 392: 245–252.

Bandrés E, Merino J, Vázquez B, Inogés S, Moreno C, Subirá ML, Sánchez-Ibarrola A (2000). The increase of IFN-gamma production through aging correlates with the expanded CD8(+high) CD28(-) CD57(+) subpopulation. Clin Immunol 96: 230–235.

Bernstein H, Payne CM, Bernstein C, Garewal H, Dvorak K (2008). Cancer and aging as consequences of un-repaired DNA damage. In: Kimura H, Suzuki A, editors. New Research on DNA Damages. New York, NY, USA: Nova Science Publishers, pp. 1–47.

Biswas S, Mantovani A (2010). Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. Nat Immunol 11: 889–896.

Blair GE, Cook GP (2008).Cancer and the immune system: an overview. Oncogene 27: 5868.

Borg C, Terme M, Taieb J, Menard C, Flament C, Robert C, Maruyama K, Wakasugi H, Angevin E, Thielemans K et al. (2004). Novel mode of action of c-kit tyrosine kinase inhibitors leading to NK cell-dependent antitumor effects. J Clin Invest 114: 379–388.

Brenchley JM, Karandikar NJ, Betts MR, Ambrozak DR, Hill BJ, Crotty LE, Casazza JP, Kuruppu J, Migueles SA, Connors M et al. (2003). Expression of CD57 defines replicative senescence and antigen-induced apoptotic death of CD8+ T cells. Blood 101: 2711–2720.

Bronte V, Serafini P, Mazzoni A, Segal DM, Zanovello P (2003). L-arginine metabolism in myeloid cells controls T-lymphocyte functions. Trends Immunol 24: 302–306.

Bronte V, Zanovello P (2005). Regulation of immune responses by L-arginine metabolism. Nat Rev Immunol 5: 641–654.

Buechele C, Baessler T, Wirths S, Schmohl JU, Schmiedel BJ, Salih HR (2012). Glucocorticoid-induced TNFR-related protein (GITR) ligand modulates cytokine release and NK cell reactivity in chronic lymphocytic leukemia (CLL). Leukemia 5: 991–1000.

Burnet FM (1957). Cancer: a biological approach. Br Med J 1: 779–786.

Burnet FM (1970). Immunological Surveillance. Oxford, UK: Pergamon Press.

Castriconi R, Dondero A, Augugliaro R, Cantoni C, Carnemolla B, Sementa AR, Negri F, Conte R, Corrias MV, Moretta L et al. (2004). Identification of 4Ig-B7-H3 as a neuroblastoma-associated molecule that exerts a protective role from an NK cell-mediated lysis. P Natl Acad Sci USA 101: 12640–12645.

Challis GB, Stam HJ (1990). The spontaneous regression of cancer. A review of cases from 1900 to 1987. Acta Oncologica 29: 545–550.

Chaput N, Louafi S, Bardier A, Charlotte F, Vaillant JC, Ménégaux F, Rosenzwajg M, Lemoine F, Klatzmann D, Taieb J et al. (2009). Identification of CD8+CD25+FOXP3+ suppressive T cells in colorectal cancer tissue. Gut 58: 520–529.

Charles KA, Kulbe H, Soper R, Escorcio-Correia M, Lawrence T, Schultheis A, Chakravarty P, Thompson RG, Kollias G, Smyth JF et al. (2009). The tumor-promoting actions of TNF-alpha involve TNFR1 and IL-17 in ovarian cancer in mice and humans. J Clin Invest 119: 3011–3023.

Chaturvedi V, Collison LW, Guy CS, Workman CJ, Vignali DA (2011). Cutting edge: human regulatory T cells require IL-35 to mediate suppression and infectious tolerance. J Immunol 186: 6661–6666.

Chettibi S, Ferguson MWJ (1999). Wound repair: an overview. In: Gallin JI, Snyderman R, editors. Inflammation: Basic Principles and Clinical Correlates. 3rd ed. Philadelphia, PA, USA: Lippincott Williams & Wilkins, pp. 865–881.

Chow MT, Moller A, Smyth MJ (2012). Inflammation and immune surveillance in cancer. Semin Cancer Biol 22: 23–32.

Chretien AS, Le Roy A, Vey N, Prebet T, Blaise D, Fauriat C, Olive D (2014). Cancer-induced alterations of NK-mediated target recognition: current and investigational pharmacological strategies aiming at restoring NK-mediated anti-tumor activity. Front Immunol 5: 122.

Collison LW, Workman CJ, Kuo TT, Boyd K, Wang Y, Vignali KM, Cross R, Sehy D, Blumberg RS, Vignali DA (2007). The inhibitory cytokine IL-35 contributes to regulatory T-cell function. Nature 450: 566–569.

Corzo CA, Condamine T, Lu L, Cotter MJ, Youn JI, Cheng P, Cho HI, Celis E, Quiceno DG, Padhya T et al. (2010). HIF-1α regulates function and differentiation of myeloid-derived suppressor cells in the tumor microenvironment. J Exp Med 207: 2439–2453.

Cosulich ME, Rubartelli A, Risso A, Cozzolino F, Bargellesi R (1987). Functional characterization of an antigen involved in an early step of T-cell activation. P Natl Acad Sci USA 84: 4205–4209.

Daurkin I, Eruslanov E, Stoffs T, Perrin GQ, Algood C, Gilbert SM, Rosser CJ, Su LM, Vieweg J, Kusmartsev S (2011). Tumor-associated macrophages mediate immunosuppression in the renal cancer microenvironment by activating the 15-lipoxygenase-2 pathway. Cancer Res 71: 6400–6409.

Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD (2002). Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol 3: 991–998.

Dunn GP, Old LJ, Schreiber RD (2004). The immunobiology of cancer immunosurveillance and immunoediting. Immunity 21: 137–148.

Endharti AT, Rifa IM, Shi Z, Fukuoka Y, Nakahara Y, Kawamoto Y, Takeda K, Isobe K, Suzuki H (2005). Cutting edge: CD8+CD122+ regulatory T cells produce IL-10 to suppress IFN-gamma production and proliferation of CD8+ T cells. J Immunol 175: 7093–7097.

Esplugues E, Sancho D, Vega-Ramos J, Martínez C, Syrbe U, Hamann A, Engel P, Sanchez-Madrid F, Lauzurica P (2003). Enhanced antitumor immunity in mice deficient in CD69. J Exp Med 197: 1093–1106.

Filaci G, Fenoglio D, Fravega M, Ansaldo G, Borgonovo G, Traverso P, Villaggio B, Ferrera A, Kunkl A, Rizzi M et al. (2007). CD8+ CD28- T regulatory lymphocytes inhibiting T cell proliferative and cytotoxic functions infiltrate human cancers. J Immunol 179: 4323–334.

Filipazzi P, Valenti R, Huber V, Pilla L, Canese P, Iero M, Castelli C, Mariani L, Parmiani G, Rivoltini L (2007). Identification of a new subset of myeloid suppressor cells in peripheral blood of melanoma patients with modulation by a granulocyte-macrophage colony-stimulation factor-based antitumor vaccine. J Clin Oncol 25: 2546–2553.

Finn OJ (2008). Molecular origins of cancer. Cancer immunology. N Engl J Med 358: 2704–2715.

Fontenot JD, Gavin MA, Rudensky AY (2003). Foxp3 programs the development and function of CD4+CD25+ regulatory T cells. Nat Immunol 4: 330–336.

Gabrilovich DI, Chen HL, Girgis KR, Cunningham HT, Meny GM, Nadaf S, Kavanaugh D, Carbone DP (1996). Production of vascular endothelial growth factor by human tumor inhibits the functional maturation of dendritic cells. Nature Med 2: 1096–1103.

Gabrilovich DI, Nagaraj S (2009). Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol 9: 162–174.

Gao X, Zhu Y, Li G, Huang H, Zhang G, Wang F, Sun J, Yang Q, Zhang X, Lu B (2012). TIM-3 expression characterizes regulatory T cells in tumor tissues and is associated with lung cancer progression. PLoS One 7: e30676.

Garcia-Lora A, Algarra I, Gaforio JJ, Ruiz-Cabello F, Garrido F (2001). Immunoselection by T lymphocytes generates repeated MHC class 1 deficient metastatic tumor variants. Int J Cancer 91: 109–119.

Ghiringhelli F, Ménard C, Terme M, Flament C, Taieb J, Chaput N, Puig PE, Novault S, Escudier B, Vivier E et al. (2005). CD4+CD25+ regulatory T cells inhibit natural killer cell functions in a transforming growth factor–dependent manner. J Exp Med 202: 1075–1085.

Gowda M, Godder K, Kmieciak M, Worschech A, Ascierto ML, Wang E, Marincola FM, Manjili MH (2011). Distinct signatures of the immune responses in low risk versus high risk neuroblastoma. J Transl Med 9: 170.

Han Y, Guo Q, Zhang M, Chen Z, Cao X (2009). CD69+ CD4+ CD25- T cells, a new subset of regulatory T cells, suppress T cell proliferation through membrane-bound TGF-B1. J Immunol 182: 111–120.

Hanahan D, Weinberg RA (2011). Hallmarks of cancer: the next generation. Cell 144: 646–674.

Hasegawa Y, Takanashi S, Kanehira Y, Tsushima T, Imai T, Okumura K (2001). Transforming growth factor-β1 level correlates with angiogenesis, tumor progression, and prognosis in patients with nonsmall cell lung carcinoma. Cancer 91: 964–971.

Hori S, Nomura T, Sakaguchi S (2003). Control of regulatory T cell development by the transcription factor Foxp3. Science 299: 1057–1061.

Hoskin DW, Butler JJ, Drapeau D, Haeryfar SM, Blay J (2002). Adenosine acts through an A3 receptor to prevent the induction of murine anti-CD3-activated killer T cells. Int J Cancer 99: 386–395.

Houghton AN (1994). Cancer antigens: immune recognition of self and altered self. J Exp Med 180: 1–4.

Houghton AN, Gold JS, Blachere NE (2001). Immunity against cancer: lessons learned from melanoma. Curr Opin Immunol 13: 134–140.

Inozume T, Hanada K, Wang QJ, Yang JC (2009). IL-17 secreted by tumor reactive T cells induces IL-8 release by human renal cancer cells. J Immunother 32: 109–117.

Itoh M, Takeshi T, Noriko S, Yuhshi K, Jun S, Fujio O, Shimon S (1999). Thymus and autoimmunity: production of CD25+CD4+ naturally anergic and suppressive T cells as a key function of the thymus in maintaining immunologic self-tolerance. J Immunol 162: 5317–5326.

Kaech SM, Wherry EJ, Ahmed R (2002). Effector and memory T-cell differentiation: implications for vaccine development. Nat Rev Immunol 2: 251–262.

Kapp LA, Kapp LM, McKenna KC (2004). γδ T cells play an essential role in several forms of tolerance. Immunol Res 29: 93–102.

Kim R, Emi M, Tanabe K (2007). Cancer immunoediting from immunosurveillance to immunoescape. Immunity 121: 1–14.

Kiniwa Y, Miyahara Y, Wang HY, Peng W, Peng G, Wheeler TM, Thompson TC, Old LJ, Wang RF (2007). CD8+ FOXP3+ regulatory T cells mediate immunosuppression in prostate cancer. Clin Cancer Res 13: 6947–6458.

Kong FM, Washington MK, Jirtle RL, Anscher MS (1996). Plasma transforming growth factor reflects disease status in patients with lung cancer after radiotherapy: a possible tumor marker. Lung Cancer 16: 47–59.

Konturek PC, Kania J, Konturek JW, Nikiforuk A, Konturek SJ, Hahn EG (2003). *H. pylori* infection, atrophic gastritis, cytokines, gastrin, COX-2, PPAR*γ* and impaired apoptosis in gastric carcinogenesis. Med Sci Monit 9: SR53–66.

Kuang DM, Peng C, Zhao Q, Wu Y, Chen MS, Zheng L (2010). Activated monocytes in peritumoral stroma of hepatocellular carcinoma promote expansion of memory T helper 17 cells. Hepatology 51: 154–164.

Kusmartsev S, Nefedova Y, Yoder D, Gabrilovich DI (2004). Antigen-specific inhibition of CD8+ T cell response by immature myeloid cells in cancer is mediated by reactive oxygen species. J Immunol 172: 989–999.

Lee JC, Lee KM, Kim DW, Heo DS (2004). Elevated TGF-β1 secretion and down-modulation of NKG2D underlies impaired NK cytotoxicity in cancer patients. J Immunol 172: 7335–7340.

Lehmann F, Marchand M, Hainaut P, Pouillart P, Sastre X, Ikeda H, Boon T, Coulie PG (1995). Differences in the antigens recognized by cytolytic T cells on two successive metastasis of a melanoma patient are consistent with immune selection. Eur J Immunol 25: 340–347.

Li J, Huang ZF, Xiong G, Mo HY, Qiu F, Mai HQ, Chen QY, He J, Chen S, Zheng LM et al. (2011). Distribution, characterization, and induction of CD8 + regulatory T cells and IL-17-producing CD8 + T cells in nasopharyngeal carcinoma. J Transl Med 9: 189.

Liang B, Workman C, Lee J, Chew C, Dale BM, Colonna L, Flore M, Li N, Schweighoffer E, Greenberg S et al. (2008). Regulatory T cells inhibit dendritic cells by lymphocyte activation gene-3 engagement of MHC class II. J Immunol 180: 5916–5926.

Lin Y, Wei C, Liu Y, Qiu Y, Liu C, Guo F (2013). Selective ablation of tumor-associated macrophages suppresses metastasis and angiogenesis. Cancer Sci 104: 1217–1225.

Link AA, Kino T, Worth JA, McGuire JL, Crane ML, Chrousos GP, Wilder RL, Elenkov IJ (2000). Ligand activation of the adenosine A2a receptors inhibits IL-12 production by human monocytes. J Immunol 164: 436–442.

Liu C, Sun C, Huang H, Janda K, Edgington T (2003). Overexpression of legumain in tumors is significant for invasion/metastasis and a candidate enzymatic target for prodrug therapy. Cancer Res 63: 2957–2964.

Long J, Zhang X, Wen M, Kong Q, Lv Z, An Y, Wei XQ (2013). IL-35 over-expression increases apoptosis sensitivity and suppresses cell growth in human cancer cells. Biochem Biophys Res Commun 430: 364–369.

Luo Y, Zhou H, Krueger J, Kaplan C, Lee SH, Dolman C, Markowitz D, Wu W, Liu C, Reisfeld RA et al. (2006). Targeting tumor-associated macrophages as a novel strategy against breast cancer. J Clin Invest 116: 2132–2141.

Ma C, Zhang Q, Ye J, Wang F, Zhang Y, Wevers E, Schwartz T, Hunborg P, Varvares MA, Hoft DF et al. (2012). Tumor-infiltrating γδ T lymphocytes predict clinical outcome in human breast cancer. J Immunol 189: 5029–5036.

Mandruzzato S, Solito S, Falisi E, Francescato S, Chiarion-Sileni V, Mocellin S, Zanon A, Rossi CR, Nitti D, Bronte V et al. (2009). IL4Ra+ myeloid-derived suppressor cell expansion in cancer patients. J Immunol 182: 6562–6568.

Merino J, Martınez-Gonzalez MA, Rubio M, Inoges S, Sanchez-Ibarrola A, Subira ML (1998). Progressive decrease of CD8high+ CD28+ CD57- cells with ageing. Clin Exp Immunol 112: 48–51.

Mills CD, Kincaid K, Alt JM, Heilman MJ, Hill AM (2000). M-1/M-2 macrophages and the Th1/Th2 paradigm. J Immunol 164: 6166–6173.

Mingari MC, Ponte M, Bertone S, Schiavetti F, Vitale C, Bellomo R, Moretta A, Moretta L (1998). HLA class I-specific inhibitory receptors in human T lymphocytes: interleukin 15-induced expression of CD94/NKG2A in superantigen- or alloantigen-activated CD8+ T cells. P Natl Acad Sci USA 95: 1172–1177.

Mirza N, Fishman M, Fricke I, Dunn M, Neuger AM, Frost TJ, Lush RM, Antonia S, Gabrilovich DI (2006). All-trans-retinoic acid improves differentiation of myeloid cells and immune response in cancer patients. Cancer Res 66: 9299–9307.

Molon B, Ugel S, Del Pozzo F, Soldani C, Zilio S, Avella D, De Palma A, Mauri P, Monegal A, Rescigno M et al. (2011). Chemokine nitration prevents intratumoral infiltration of antigen-specific T cells. J Exp Med 208: 1949–1962.

Mueller MM, Fusenig NE (1999). Constitutive expression of G-CSF and GM-CSF in human skin carcinoma cells with functional consequence for tumor progression. Int J Cancer 83: 780–789.

Mueller MM, Herold-Mende CC, Riede D, Lange M, Steiner HH, Fusenig NE (1999). Autocrine growth regulation by granulocyte colony-stimulating factor and granulocyte macrophage colony-stimulating factor in human gliomas with tumor progression. Am J Pathol 155: 1557–1567.

Mundy-Bosse BL, Lesinski GB, Jaime-Ramirez AC, Benninger K, Khan M, Kuppusamy P, Guenterberg K, Kondadasula SV, Chaudhury AR, La Perle KM et al. (2011). Myeloid-derived suppressor cell inhibition of the IFN response in tumor-bearing mice. Cancer Res 71: 5101–5110.

Murthy RV, Arbman G, Gao J, Roodman GD, Sun XF (2005). Legumain expression in relation to clinicopathologic and biological variables in colorectal cancer. Clin Cancer Res 11: 2293–2299.

Nagaraj S, Schrum AG, Cho HI, Celis E, Gabrilovich DI (2010). Mechanism of T cell tolerance induced by myeloid-derived suppressor cells. J Immunol 184: 3106–3116.

Nakamura K, Kitani A, Strober W (2001). Cell contact-dependent immunosuppression by CD4+ CD25+ regulatory T cell is mediated by cell surface-bound transforming growth factor β. J Exp Med 194: 629–643.

Naor D (1979). Suppressor cells: permitters and promoters of malignancy? Adv Cancer Res 29: 45–125.

Narai S, Watanabe M, Hasegawa H, Nishibori H, Endo T, Kubota T, Kitajima M (2002). Significance of transforming growth factor as a new tumor marker for colorectal cancer. Int J Cancer 97: 508–511.

Okegawa T, Pong RC, Li Y, Hsieh JT (2004). The role of cell adhesion molecule in cancer progression and its application in cancer therapy. Acta Biochim Pol 51: 445–457.

Onishi Y, Fehervari Z, Yamaguchi T, Sakaguchi S (2008). Foxp3+ natural regulatory T cells preferentially form aggregates on dendritic cells in vitro and actively inhibit their maturation. P Natl Acad Sci USA 29: 10113–10118.

Pedroza-Gonzalez A, Verhoef C, Ijzermans JN, Peppelenbosch MP, Kwekkeboom J, Verheij J, Janssen HL, Sprengers D (2013). Activated tumor-infiltrating CD4+ regulatory T cells restrain antitumor immunity in patients with primary or metastatic liver cancer. Hepatology 57: 183–194.

Peng G, Guo Z, Kiniwa Y, Voo KS, Peng W, Fu T, Wang DY, Li Y, Wang HY, Wang RF (2005). Toll-like receptor 8 mediated-reversal of CD4+ regulatory T cell function. Science 309: 1380–1384.

Peng G, Wang HY, Peng W, Kiniwa Y, Kook HS, Wang RF (2007). Tumor-infiltrating γδ T cells suppress T and dendritic cell function via mechanisms controlled by a unique toll-like receptor signaling pathway. Immunity 27: 334–348.

Pennington DJ, Vermijlen D, Wise EL, Clarke SL, Tigelaar RE, Hayday AC (2005). The integration of conventional and unconventional T cells that characterizes cell-mediated responses. Adv Immunol 87: 27–59.

Petrausch U, Poehlein CH, Jensen SM, Twitty C, Thompson JA, Assmann I, Puri S, LaCelle MG, Moudgil T, Maston L et al. (2009). Cancer immunotherapy: the role regulatory T cells play and what can be done to overcome their inhibitory effects. Curr Mol Med 9: 673–682.

Piccirillo CA, Letterio JJ, Thornton AM, McHugh RS, Mamura M, Mizuhara H, Shevach EM (2002). CD4 (+) CD25 (+) regulatory T cells can mediate suppressor function in the absence of transforming growth factor β1 production and responsiveness. J Exp Med 196: 237–246.

Poschke I, Mougiakakos D, Hansson J, Masucci GV, Kiessling R (2010). Immature immunosuppressive CD14+HLA-DR–/low cells in melanoma patients are Stat3hi and overexpress CD80, CD83, and DC-sign. Cancer Res 70: 4335–4345.

Qian B, Pollard J (2010). Macrophage diversity enhances tumor progression and metastasis. Cell 141: 39–51.

Ramirez R, Carracedo J, Castedo M, Zamzami N, Kroemer G (1996). CD69-induced monocyte apoptosis involves multiple nonredundant signaling pathways. Cell Immunol 172: 192–199.

Read S, Malmstrom V, Powrie F (2000). Cytotoxic T lymphocyte-associated antigen 4 plays an essential role in the function of CD25 (+) CD4 (+) regulatory cells that control intestinal inflammation. J Exp Med 192: 295–302.

Real LM, Jimenez P, Kirkin A, Serrano A, Garcia A, Canton J, Zeuthen J, Garrido F, Ruiz-Cabello F (2001). Mechanism of immune evasion can coexist in melanoma tumor cell lines derived from the same patient. Cancer Immunol Immunother 49: 621–628.

Restifo NP, Esquivel F, Kawakami Y, Yewde JW, Mulé JJ, Rosenberg SA, Bennink JR (1993). Identification of human cancer deficient in antigen processing. J Exp Med 177: 265–272.

Roncarolo MG, Gregori S, Battaglia M, Bacchetta R, Fleischhauer K, Levings MK (2006). Interleukin-10-secreting type 1 regulatory T cells in rodents and humans. Immunol 212: 28–50.

Rothlein RD (1986). A human intercellular adhesion molecule (ICAM-1) distinct from LFA-1. J Immunol 137: 1270–1274.

Sakaguchi S (2004). Naturally arising CD4+ regulatory T cells for immunologic self-tolerance and negative control of immune responses. Annu Rev Immunol 22: 531–562.

Sakuishi K, Ngiow SF, Sullivan JM, Teng MWL, Kuchroo VK, Smyth MJ, Anderson AC (2013). TIM3+FOXP3+ regulatory T cells are tissue-specific promoters of T-cell dysfunction in cancer. Oncoimmunology 2: e23849.

Salazar-Onfray F, López MN, Mendoza-Naranjo A (2007). Paradoxical effects of cytokines in tumor immune surveillance and tumor immune escape. Cytokine Growth Factor Rev 18: 171–182.

Salomon B, Lenschow DJ, Rhee L, Ashourian N, Singh B, Sharpe A, Bluestone JA (2000). B7/CD28 costimulation is essential for the homeostasis of the CD4+CD25+ immunoregulatory T cells that control autoimmune diabetes. Immunity 12: 431–440.

Sawanobori Y, Ueha S, Kurachi M, Shimaoka T, Talmadge JE, Abe J, Shono Y, Kitabatake M, Kakimi K, Mukaida N et al. (2008). Chemokine-mediated rapid turnover of myeloid-derived suppressor cells in tumor-bearing mice. Blood 111: 5457–5466.

Scheibenbogen C, Lee KH, Stevanovic S, Witzens M, Willhauck M, Waldmann V, Naeher H, Rammensee HG, Keilholz U (1997). Analysis of the T-cell response to tumor and viral peptide antigen by an IFN gamma-ELISPOT assay. Int J Cancer 71: 932–936.

Schmielau J, Finn OJ (2001). Activated granulocytes and granulocyte-derived hydrogen peroxide are the underlying mechanism of suppression of T-cell function in advanced cancer patients. Cancer Res 61: 4756–4760.

Schneider H, Valk E, da Rocha Dias S, Wei B, Rudd CE (2005). CTLA-4 up-regulation of lymphocyte function-associated antigen 1 adhesion and clustering as an alternate basis for coreceptor function. P Natl Acad Sci USA 102: 12861–12866.

Serafini P, Meckel K, Kelso M, Noonan K, Califano J, Koch W, Dolcetti L, Bronte V, Borrello I (2006). Phosphodiesterase-5 inhibition augments endogenous antitumor immunity by reducing myeloid-derived suppressor cell function. J Exp Med 203: 2691–2702.

Serafini P, Mgebroff S, Noonan K, Borrello I (2008). Myeloid-derived suppressor cells promote cross-tolerance in B-cell lymphoma by expanding regulatory T cells. Cancer Res 68: 5439–5449.

Seyerl M, Kirchberger S, Majdic O, Seipelt J, Jindra C, Schrauf C, Stockl J (2011). Human rhinoviruses induce IL-35-producing Treg via induction of B7–H1 (CD274) and sialoadhesin (CD169) on DC. Eur J Immunol 40: 321–329.

Shankaran V, Ikeda H, Bruce AT, White JM, Swanson PE, Old LJ, Schreiber RD (2001). IFNγ and lymphocytes prevent primary tumor development and shape tumor immunogenicity. Nature 410: 1107–1111.

Shimizu K, Nakata M, Hirami Y, Yukawa T, Maeda A, Tanemoto K (2010). Tumor infiltrating Foxp3+ regulatory T cells are correlated with cyclooxygenase-2 expression and are associated with recurrence in resected non-small cell lung cancer. J Thorac Oncol 5: 585–590.

Sinha P, Clements VK, Fulton AM, Ostrand-Rosenberg S (2007). Prostaglandin E2 promotes tumor progression by inducing myeloid-derived suppressor cells. Cancer Res 67: 4507–4513.

Smyth MJ, Dunn GP, Schreiber RD (2006). Cancer immunosurveillance and immunoediting: the roles of immunity in suppressing tumor development and shaping tumor immunogenicity. Adv Immunol 90: 1–50.

Szkaradkiewicz A, Karpiński TM, Drews M, Borejsza-Wysocki M, Majewski P, Andrzejewska E (2010). Natural killer cell cytotoxicity and immunosuppressive cytokines (IL-10, TGF-β1) in patients with gastric cancer. J Biomed Biotechnol 2010: 901564.

Tai X, Van Laethem F, Pobezinsky L, Guinter T, Sharrow SO, Adams A, Granger L, Kruhlak M, Lindsten T, Thompson CB et al. (2012). Basis of CTLA-4 function in regulatory and conventional CD4 (+) T cells. Blood 119: 5155–5163.

Takahashi T, Tagami T, Yamazaki S, Uede T, Shimizu J, Sakaguchi N, Mak TW, Sakaguchi S (2000). Immunologic self-tolerance maintained by CD25(+)CD4(+) regulatory T cells constitutively expressing cytotoxic T lymphocyte-associated antigen. J Exp Med 192: 303–310.

Tan MC, Goedegebuure PS, Belt BA, Flaherty B, Sankpal N, Gillanders WE, Eberlein TJ, Hsieh CS, Linehan DC (2009). Disruption of CCR5-dependent homing of regulatory T cells inhibits tumor growth in a murine model of pancreatic cancer. J Immunol 182: 1746–1755.

Tang XL, Smith TR, Kumar V (2005). Specific control of immunity by regulatory CD8 T cells. Cell Mol Immunol 2: 11–19.

Tao H, Mimura Y, Aoe K, Kobayashi S, Yamamoto H, Matsuda E, Okabe K, Matsumoto T, Sugi K, Ueoka H (2012). Prognostic potential of FOXP3 expression in non-small cell lung cancer cells combined with tumor-infiltrating regulatory T cells. Lung cancer 75: 95–101.

Thimmulappa RK, Fuchs RJ, Malhotra D, Scollick C, Traore K, Bream JH, Trush MA, Liby KT, Sporn MB, Kensler TW et al. (2007). Preclinical evaluation of targeting the Nrf2 pathway by triterpenoids (CDDO-Im and CDDO-Me) for protection from LPS-induced inflammatory response and reactive oxygen species in human peripheral blood mononuclear cells and neutrophils. Antioxid Redox Signal 9: 1963–1970.

Tsuchiya Y, Igarashi M, Suzuki R, Kumagai K (1988). Production of colony-stimulating factor by tumor cells and the factor-mediated induction of suppressor cells. J Immunol 141: 699–708.

Tsuruta N, Yatsunami J, Takayama K, Nakanishi Y, Ichinose Y, Hara N (1998). Granulocyte-macrophage-colony stimulating factor stimulates tumor invasiveness in squamous lung carcinoma. Cancer 82: 2173–2183.

Waldhauer I, Steinle A (2008). NK cells and cancer immunosurveillance. Oncogene 27: 5932–5943.

Walsh GM, Williamson ML, Symon FA, Willars GB, Wardlaw AJ (1996). Ligation of CD69 induces apoptosis and cell death in human eosinophils cultured with granulocyte-macrophage colony-stimulating factor. Blood 87: 2815–2821.

Wang Z, Liu JQ, Liu Z, Shen R, Zhang G, Xu J, Basu S, Feng Y, Bai XF (2013). Tumor derived IL-35 promotes tumor growth by enhancing myeloid cell accumulation and angiogenesis. J Immunol 190: 2415–2423.

Wei S, Kryczek I, Zou L, Daniel B, Cheng P, Mottram P, Curiel T, Lange A, Zou W (2005). Plasmacytoid dendritic cells induce $CD8^+$ regulatory T cells in human ovarian carcinoma. Cancer Res 65: 5020–5026.

Wen QS, Zhang GZ, Kong XT (1994). Modulation effect of cimetidine on the production of IL-2 and interferon-γ in patients with gastric cancer. Zhonghua Zhong Liu Za Zhi 16: 299–301 (in Chinese with English abstract).

Wiers KM, Lathers DM, Wright MA, Young MR (2000). Vitamin D3 treatment to diminish the levels of immune suppressive CD34 cells increases the effectiveness of adoptive immunotherapy. J Immunother 23: 115–124.

Wigmore SJ, Fearon KCH, Maingay JP, Lai P, Ross JA (1997). Interleukin-8 can mediate acute-phase protein production by isolated human hepatocytes. Am J Physiol 273: 720–726.

Wild CA, Brandau S, Lindemann M, Lotfi R, Hoffmann TK, Lang S, Bergmann C (2010). Toll-like receptors in regulatory T cells of patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 136: 1253–1259.

Wölfel T, Klehmann E, Müller C, Schütt KH, Meyer zum Büschenfelde KH, Knuth A (1989). Lysis of human melanoma cells by autologous cytolytic T cells clones. Identification of human histocompatibility leukocyte antigen A2 as a restriction element for three different antigens. J Exp Med 170: 797–810.

Xu S, Wen Z, Jiang Q, Zhu L, Feng S, Zhao Y, Wu J, Dong Q, Mao J, Zhu Y (2014). CD58, a novel surface marker, promotes self-renewal of tumor-initiating cells in colorectal cancer. Oncogene (in press).

Yang ZZ, Novak AJ, Ziesmer SC, Witzig TE, Ansell SM (2007). CD70+ non-Hodgkin lymphoma B cells induce Foxp3 expression and regulatory function in intratumoral CD4+CD25 T cells. Blood 110: 2537–2544.

Yasushi O, Zoltan F, Tomoyuki Y, Shimon S (2008). Foxp3+ natural regulatory T cells preferentially form aggregates on dendritic cells in vitro and actively inhibit their maturation. P Natl Acad Sci USA 105: 10113–10118.

Ye J, Ma C, Hsueh EC, Eickhoff CS, Zhang Y, Varvares MA, Hoft DF, Peng G (2013). Tumor-derived γδ regulatory T cells suppress innate and adaptive immunity through the induction of immunosenescence. J Immunol 190: 2403–2414.

Yuan XL, Chen L, Zhang TT, Ma YH, Zhou YL, Zhao Y, Wang WW, Dong P, Yu L, Zhang YY et al. (2011). Gastric cancer cells induce human CD4+Foxp3+ regulatory T cells through the production of TGF-β1. World J Gastroenterol 17: 2019–2027.

Zambon CF, Basso D, Navaglia F, Belluco C, Falda A, Fogar P, Greco E, Gallo N, Rugge M, Di Mario F et al. (2005). Pro- and antiinflammatory cytokines gene polymorphisms and *Helicobacter pylori* infection: interactions influence outcome. Cytokine 29: 141–152.

Zea AH, Rodriguez PC, Atkins MB, Hernandez C, Signoretti S, Zabaleta J, McDermott D, Quiceno D, Youmans A, O'Neill A et al. (2005). Arginase-producing myeloid suppressor cells in renal cell carcinoma patients: a mechanism of tumor evasion. Cancer Res 65: 3044–3048.

Zhao X, Wang X, Chang Y, Zhao X, Zhang X, Liu D, Xu L, Liu K , Huan X (2013). Non-traditional CD4+ CD25–CD69+ regulatory T cells is correlated to leukemia relapse after allogeneic hematopoietic stem cell transplantation. Blood 122: 3259.

Zhou H, Chen L, You Y, Zou L, Zou P (2010). Foxp3-transduced polyclonal regulatory T cells suppress NK cell functions in a TGF-beta dependent manner. Autoimmunity 43: 299–307.