Arch. Immunol. Ther. Exp. (2010) 58:435–448
DOI 10.1007/s00005-010-0102-1

REVIEW

How do Tumors Actively Escape from Host Immunosurveillance?

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Received: 1 March 2010 / Accepted: 28 May 2010 / Published online: 5 October 2010

Abstract The immunological background for the process of tumor growth is still obscure. However, our understanding of what happens could have important consequences, namely in the context of cancer immunotherapy. A tumor is able to grow in the host environment either because it is recognizable as normal tissue and tolerated by host immune cells, or because it can "escape" from host immunosurveillance. According to the second option the mechanisms of tumor recognition and consequent destruction are actively disturbed by such processes as: change of tumor immunogenicity, production of tumor-derived regulatory molecules, and interaction of cancer cells with tumor-infiltrating immune cells. The results of studies devoted to the problem of immunoregulation in the tumor environment seem to support the "escape" hypothesis.

Keywords Tumor · Immunosurveillance · Immunoediting

Abbreviations

TAA	Tumor-associated antigens
ROI	Reactive oxygen intermediates
NK	Natural killer cells
NKT	Natural killer T cells
CTL	Cytotoxic T lymphocytes
IFN	Interferon
STAT-1	Signal transducer and activator of transcription-1
TGF	Transforming growth factor
bFGF	Basic fibroblast growth factor
FGF	Fibroblast growth factor
PDGF	Platelet-derived growth factor
EGF	Epidermal growth factor
VEGF	Vascular-endothelial growth factor
HIF-1α	Hypoxia-inducible factor-1α
PGE_2	Prostaglandin E_2
IL	Interleukin
MMPs	Matrix metalloproteinases
PI3K	Phosphoinositide 3-kinase
Akt	Protein kinases B
MAPK	Mitogen-activated protein kinase
CAFs	Cancer-associated fibroblasts
TAMs	Tumor-associated macrophages
NRP	Neuropilin
MDSC	Myeloid-derived suppressor cells
CCL	Chemokine (C–C motif) ligand
CXCL	Chemokine (C–X–C motif) ligand
HLA	Human leukocyte antigen
MHC	Major histocompatibility complex
NF-κB	Nuclear factor-κB
KIR	Killing inhibitory receptor
ILT	Immunoglobulin-like transcript
DCs	Dendritic cells
NKG2	Activating receptor of NK cells
NKp44	NK cell p44-related protein
CCR	Chemokine (C–C motif) receptor
CXCR	Chemokine (C–X–C motif) receptor

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LMP	Low-molecular mass polypeptide
MART-1/MelanA	Melanoma-associated antigen recognized by T cells
IDO	Indoleamine 2,3-dioxygenase
RCAS1	Cancer antigen expressed on SiSo cells
TNF	Tumor necrosis factor
TRAIL	TNF-related apoptosis-inducing ligand
c-FLIP	Fas-associated death domain-like interleukin-1 converting enzyme inhibitory protein
COX-2	Cyclooxygenase-2
15-PGDH	15-hydroxyprostaglandin dehydrogenase
NO	Nitric oxide
TCR	T cell receptor
MC	Mast cells
RANTES	Regulated on activation, normal T cell expressed and secreted
Tregs	T regulatory cells
TILs	Tumor-infiltrating lymphocytes

Introduction

There are two models proposed to describe why established tumors, once initiated, can grow and usually do not undergo spontaneous rejection mediated by host immune cells. According to the first model immune rejection does not occur because the tumor is recognized as immunologically normal tissue. Tumor cells do not provoke immune attack because they do not indicate expression of signaling molecules for activation of host innate immune cells. To be sure, tumor cells express tumor-associated antigens (TAA), but this group of non-mutated tissue antigens can be normally present on host cells, and therefore are less likely to induce an effective anti-tumor immune response (Cloosen et al. 2007; Yu et al. 2004). The proof that TAA are not effectively immunogenic originates from observations of immunotherapy techniques using cancer vaccines or T cells having high affinity receptors for TAA antigens. Such immune manipulation could enhance TAA immunogenicity and thus break the state of immune tolerance towards the tumor; however, this produces considerable risk of serious autoimmune reactions (Gilboa 2001; Monach et al. 1995). In the later phase of growth, once vascularized, tumors could become more immunogenic due to necrotic changes in the tumor itself as well as in the surrounding tissue, production of reactive oxygen intermediates (ROI), and expression of neoantigens (tumor-specific antigens) (Ludewig et al. 2000). However, despite the presence of tumor-infiltrating immune cells tumors are extremely rarely subjected to inhibition of growth or elimination mediated by the host immune system. The first model provides a possible explanation that immune changes which accompany progressive tumor growth are negligible in the context of breaking immune tolerance.

The second model is based on the assumption that a mechanism of immunosurveillance exists in the host which plays an active role in suppressing the initiation and further growth of tumors. The main effectors of immunosurveillance are natural killer (NK) cells, natural killer T cells (NKT) and CD8 cytotoxic T lymphocyte (CTL) cells patrolling the host tissues, as well as interferon (IFN)-γ and perforins secreted by them. The confirmation of this model was initially found in mice studies. Knocked-out IFN-$\gamma R^{-/-}$ or signal transducer and activator of transcription (STAT)-$1^{-/-}$ mice insensitive to IFN-γ showed dramatically increased sarcoma induction upon 3-methylcholanthrene treatment (Shankaran et al. 2001). Similarly, both B and T deficient recombination activating gene-$2^{-/-}$ and perforin knocked-out mice were also highly susceptible to 3-methylcholanthrene-induced sarcoma growth and spontaneous lymphoma development (Smyth et al. 2000; Van den Broek et al. 1996). Also the role of NK, NKT and $\gamma\delta$ T cells for immunosurveillance in mice was demonstrated in immunologically manipulated animals (Gao et al. 2003; Smyth et al. 2001). Human clinical studies seem to support the conclusions arising from animal experiments. High numbers of tumor-infiltrating lymphocytes (TILs) and NK cells were found in tumors of different organs and in many of them were connected with improved patient outcome (reviewed in Kim et al. 2007; Reiman et al. 2007). The group of cancer patients with better prognosis also showed the presence of both tumor-specific T cellular and humoral antibody responses (reviewed in Whiteside 2010). Moreover, it is a commonly known fact that transplant recipients subjected to immunosuppressive drugs have 3–8 times multiplied risk of cancer compared with a control population, and that risk of cancer occurrence and progression in advanced age is greater mostly due to immunosenescence (Vial and Descotes 2003). According to the immunosurveillance paradigm, the growing tumor is considered to have "escaped" from host control, which has not been effective enough.

The model of immunosurveillance has been incorporated into the "immunoediting" hypothesis, which proposes that by elimination of tumor cells sensitive to host immune attack, the immune system edits for survival of immuno-resistant cancer cells. Therefore, we can say that the host immune system "shapes" tumor phenotype, which is especially true for solid tumors (Dunn et al. 2004; Khong and Restifo 2002). The observation that immunotherapy, despite its initial efficacy, "produces" later resistant tumor

recurrences and metastases supports the idea of "shaping" the tumor phenotype. Moreover, many observations suggest that a tumor is probably an active member of immunological interplay with the host, and is capable of "shaping" the pattern and intensity of the host immune response. According to the immunoediting hypothesis the interactions between the immune system and tumor are characterized by three stages: elimination, equilibrium and escape. Mechanisms engaged in the elimination phase are practically analogical to mechanisms of immunosurveillance. However, the end results of this phase may vary depending on the occurrence of pro-inflammatory signals which accompany the process of tumor immune killing. "Danger signals" produced by dying tumor cells, such as uric acid, heat-shock proteins or extracellular matrix derivatives (Powell and Horton 2005; Shi et al. 2003), may activate immune cells. A local inflammatory reaction of limited intensity usually helps to eradicate the tumor, while excessive inflammation could promote tumor progression by stimulation of feedback loops dependent on transforming growth factor (TGF)-β and interleukin (IL)-10 secretion (Kim et al. 2005). Another possible explanation for tumor growth is genetic instability which creates cells resistant to immune eradication (Whiteside 2010). During the next stage in the immunoediting process, called the equilibrium phase, tumor cells are subjected to immune selection which results in elimination of sensitive tumor cells and production of resistant tumor variants. Similarly as in the elimination phase, the equilibrium phase is occult, and could last for many years (Kim et al. 2007). The third stage is escape and clinical manifestation of the tumor. This review presents contemporary data on tumor immunology, which all together seem to support the "immunoediting/escape" hypothesis.

Vascularization of the Tumor

Initial tumor growth occurs in avascular conditions. However, constant enlargement of the tumor is dependent on the so-called "vascular switch", which is followed by creation of new vessels, as well as increased growth and metastatic potential (McMahon 2000). Tumor vessels have different structure compared to vessels found inside normal tissues. They are usually tortuous, with irregular shape and chaotic structure which result in grossly disturbed flow of poorly oxygenated blood. Many intra-tumor vessels have mosaic composition as they are built from both endothelial and tumor cells, and some are composed from only tumor cells ("vascular mimicry") (Cao 2005; Ferrara 2010). A large number of tumor-derived pro-angiogenic factors have been identified, including: fibroblast growth factor (FGF), basic FGF (bFGF), platelet-derived growth factor (PDGF), platelet-derived endothelial cell growth factor, angiopoietin-1, TGF-β, and, probably most important, vascular-endothelial growth factor (VEGF) (reviewed in McMahon 2000; Yoshiji et al. 2002). Moreover, many malignant tumors also secrete inhibitors of angiogenesis such as angiostatin or thrombospondin (O'Reilly et al. 1997). Several inhibitors of angiogenesis are present in the tumor environment and neighborhood, including platelet factor-4, IFN-inducible protein-10, IFN-α and IFN-γ, IL-12, IL-10, angiostatin and finally endostatin (reviewed in Nishida et al. 2006; O'Reilly et al. 1997). Vessel abnormalities inside the tumor represent the result of an imbalanced interplay between these pro- and anti-angiogenic factors acting in its environment.

The proteins belonging to the VEGF family show a potent influence on angiogenesis. Induction of VEGF expression depends on many different signals, including mutant *p53*, *PTEN, Ras* and *Raf* genes, hypoxia-inducible factor (HIF)-1α, and also a variety of growth factors (PDGF, EGF) and cytokines (TNF-α, TGF-β, PGE_2 and IL-1β). Secretion of VEGF and growth factors initiates endothelial cell growth and increases expression of matrix metalloproteinases (MMPs), which through the breakdown of extracellular matrix components augment endothelial cell division and spread (reviewed in Cao et al. 2009; Greenhough et al. 2009; Fang et al. 2007; McMahon 2000; Moeller et al. 2004). Moreover, over-activity of MMPs, especially MMP-2 and MMP-9, is associated with tumor invasiveness and the potential to metastasize (Chlenski et al. 2003). VEGF is also responsible for the survival of newly formed vessels inside the tumor (Benjamin and Keshet 1997). Endothelial cells recruited to the tumor not only form new vessels but also secrete growth and anti-apoptotic factors which stimulate tumor spread (reviewed in Folkman 2003). The VEGF family consists of several molecules (VEGF-A, VEGF-B, VEGF-C, VEGF-D) indicating slightly different activity, which, excluding VEGF-B, stimulate specifically angio- and/or lymphangiogenesis during embryonal development, physiological conditions and cancer. The dominant role for VEGF-A in tumor vascularization is mediated through binding to the VEGFR-2 (KDR/Flk-1) receptor, expressed on both endothelial and tumor cells (Meyer et al. 1999). Receptor VEGFR-1 (Flt-1) however, has stronger affinity to VEGF-A than VEGFR-2, and can function as a decoy receptor (reviewed in Sullivan and Brekken 2010). Binding of VEGF-A to VEGFR-2 receptor on tumor cells activates an intracellular cascade of phosphoinositide 3-kinase (PI3K), protein kinases B (Akt) and mitogen-activated protein kinase (MAPK), which not only regulates tumor angiogenesis, but also activates cell survival and proliferation (Fang et al. 2007; Sullivan and Brekken 2010). Many types of tumors have also the ability to induce lymphangiogenesis, which

is regulated by multiple angiogenic factors, including VEGF-A, VEGF-C, VEGF-D, FGF and angiopoietin-2 (Stacker et al. 2002). It was shown that IL-12 and IFN-γ are potent inhibitors of VEGF-dependent angiogenesis (Majewski et al. 1996). There is also a possibility that tumor necrosis factor (TNF)-α, IL-4 and IL-10 inhibit pro-angiogenic signals originating from endothelial cells, cancer-associated fibroblasts (CAFs) and tumor-associated macrophages (TAMs), respectively (reviewed in Blankenstein 2005).

Some additional pathways could interfere with the interaction between VEGF and its receptors or alternatively activate neoangiogenesis. Neuropilins (NRP-1, NRP-2), originally described for their role in axon migration, were found to modulate angio- and lymphangiogenesis, as indicated studies showing that blocking of NRP-1 and NRP-2 inhibited tumor growth and lymphatic metastases, respectively (reviewed in McMahon 2000). FGF is capable of promotion of angiogenesis independently from VEGF. It was also found that delta-like ligand-4, binding to Notch receptors and important for cell–cell communication, may mediate tumor angiogenesis (reviewed in Ferrara 2010). Tumor stroma is also engaged in vascular development. One of the previously underestimated populations of cells resident in tumor stroma is that of CAFs (reviewed in Östman and Augsten 2009). This population of cells produces growth factors exerting tumor-promoting activity, such as VEGF, EGF, FGF, TGF-β, PDGF or insulin-like growth factor (Kalluri and Zeisberg 2006; Östman and Heldin 2007). Previous studies showed that CAFs are an alternative source of VEGF-A capable of compensating the lack of tumor-derived VEGF-A (reviewed in Ferrara 2010; Kammertoens et al. 2005). The population of CAFs also showed expression of chemokines CCL5, CXCL12 and CXCL14, which are responsible for tumor metastatic potential (Karnoub et al. 2007), increased angiogenesis (Orimo et al. 2005), and influx of macrophages into the tumor (Augsten et al. 2009). Other cell populations which function as regulators of neovascularization and belong to TAMs and $CD11^{+}Gr1^{+}$ myeloid-derived suppressor cells (MDSC) are described below.

The role of VEGF family members and VEGF receptors has been confirmed in many clinical studies. The presence of these molecules has been found on numerous human tumors, including uterine, endometrial, ovarian, gastric, colon, and prostate cancers. Moreover, a significant correlation between VEGF expression and patient outcome was observed in colorectal, lung, breast and many other cancers (reviewed in McMahon 2000; Nishida et al. 2006). It was also found that treatment with VEGF inhibitors in many cases suppressed tumor growth (reviewed in Ferrara 2010).

Mechanisms of Immunologic Escape of the Tumor

Change of Immunogenicity

Changes in antigen processing and presentation, expression of natural cytotoxicity receptors or co-stimulatory pathways could account for tumor escape from both innate and adaptive immune recognition. It was shown that cancer cells could selectively lose human leukocyte antigen (HLA) class I molecules, as well as being able to shed major histocompatibility complex (MHC) class I-related molecules (Garcia-Lora et al. 2003; Wu et al. 2004). The reason for that originates from genetic mutations of the tumor, downregulation of some genes or microsatellite instability (Reiman et al. 2007). These mechanisms secure the tumor against CTL-dependent cytotoxicity. However, activated NK cells should be able to recognize and kill such cells. To avoid both CTL and NK cell-dependent attack, tumor cells show an aberrant expression of immunomodulatory non-classical HLA class I antigen HLA-G on the surface which could limit the anti-tumor effector immunity (Chang et al. 2003). The presence of HLA-G molecules has been confirmed in many cancers (Lin et al. 2007; Urosevic and Dummer 2008). During early stages of tumor growth host immunosurveillance is connected with IFN-γ production, which unfortunately upregulates HLA-G expression on cancer cells. Other trigger factors for HLA-G expression are hypoxia via HIF-1α, and chronic inflammation in the tumor environment via nuclear factor (NF)-κB factor (Mouillot et al. 2007). Immunosuppressive IL-10 was also shown to upregulate HLA-G in the "escape" stage of tumor growth (Urosevic and Dummer 2003). Several receptors for HLA-G which function as killing inhibitory receptors (KIR) have been identified: KIR2DL4/p49, immunoglobulin-like transcript (ILT)-2, and ILT-4. Their expression was confirmed on NK cells, and also on many other immune cells, such as T and B lymphocytes, macrophages and dendritic cells (DCs). Therefore, HLA-G is able not only to inhibit NK cytotoxicity, but also to modulate DCs activity, followed by inhibition of proliferative T cell responses (reviewed in Gomes et al. 2007; Pistoia et al. 2007; Sheu and Shih 2007; Urosevic and Dummer 2008). Additionally to constant expression of HLA-G membrane form, tumors are able to secrete its soluble form, having strong systemic immunoregulatory properties. Soluble HLA-G induces Fas-dependent apoptosis of activated T $CD8^{+}$ CTLs and decreases T $CD4^{+}$ activity. Concentration of HLA-G soluble form correlates with tumor size (Ugurel et al. 2001). HLA-G could also be present in exosomes disseminated into the circulation from the tumor site (Urosevic and Dummer 2008). Antigen HLA-G also has a stabilizing effect on HLA-E, which exerts additional suppressive

signals to lymphocytes through CD94/NKG2A KIR (Gomes et al. 2007). Apart from the tumor itself, tumor-infiltrating immune cells also acquire the HLA-G positive phenotype. This fact has profound consequences, because it induces a strongly immunosuppressive environment inside which effector cells via contact with HLA-G antigens on regulatory cells, and via trogocytosis of membrane fragments containing HLA-G from DCs, turn into tolerogenic cells (reviewed in Urosevic and Dummer 2008).

Moreover, soluble HLA class I chain-related molecule released from cancer cells could further disturb CTLs and NK cell cytotoxicity by downregulation of activating NKG2D receptor, natural cytotoxicity receptor NKp44 and chemokine receptors CCR7 and CXCR1 (Doubrovina et al. 2003). Absence of co-stimulatory molecules CD80 and CD86 on the surface of tumor cells produces anergy in $CD4^+$ T lymphocytes recognizing HLA class II antigens (Byrne and Halliday 2003). Tumors also evade immune recognition by hypo-inducibility of MHC antigens upon IFN-γ stimulation or changes in intracellular ways of antigen processing, including acquired deficits in antigen peptide transporter-1 and low-molecular mass polypeptide (LMP)2 and LMP7 immunoproteasome subunits (Seliger et al. 2000). Surprisingly, tumors are able to lose antigens spontaneously or in the response to adoptive T $CD8^+$ therapy, as was shown in the case of melanoma-associated antigen recognized by T cells (MART-1/MelanA). The MART-1-targeted therapy was initially effective only in HLA-A2 positive patients and in primary tumors, but both melanoma metastases and tumors in recurrently treated patients showed loss of expression of MART-1 and HLA-A2 molecules (Abdel-Wahab et al. 2003; Dunn et al. 2004; Kageshita et al. 2001).

In models of adoptive transfer of tumor-specific $CD8^+$ cytotoxic T cells effective tumor rejection required cross-presentation of cancer antigens by TAMs and other stromal cells, such as endothelial cells and CAFs. Killing these components proved that tumor antigens could be effectively presented to CTLs by stromal cells, which were a target for CTL attack, which prevented the outgrowth of cancer antigen variants (reviewed in Kammertoens et al. 2005). The higher the ratio of cross-presentation to direct presentation by tumor cells, the greater the probability of an anti-tumor response occurring instead of a state of tolerance. The observed ratio depends on tumor growth potential, its dimensions and apoptosis rate (Wodarz and Jansen 2003).

Tumor-derived Immunoregulatory Molecules

Tumor-derived indoleamine 2,3-dioxygenase (IDO)-dependent tryptophan depletion in the tumor environment, and upregulation of Fas-ligand on cancer cells contribute to enhanced apoptosis of cytotoxic cells, and thus work for tumor resistance (Byrne and Halliday 2003; Uyttenhove et al. 2003; Van den Eynde et al. 2007). The presence of receptor-binding cancer antigen expressed on SiSo cells (RCAS1) on the tumor surface has similar consequences (Wicherek et al. 2003). Conversely, cancer cells are also resistant to apoptosis activation. One of the pathways studied recently is the mitochondrial pathway of apoptosis selectively induced in transformed cancer cells by interaction of TNF-related apoptosis-inducing ligand (TRAIL) with tumor TRAIL-R1 and TRAIL-R2 receptors. TRAIL is expressed constitutively on NK cells, and upon stimulation on NK cells and DCs (Dunn et al. 2004; Smyth et al. 2003). Some tumors are capable of expression of cellular Fas-associated death domain-like IL-1 converting enzyme inhibitory protein (c-FLIP), which being an analog of caspase-8 possessing anti-apoptotic activity secures tumor cells from TRAIL-dependent apoptosis. Elevated expression of c-FLIP was found in melanoma, colorectal, gastric, gallbladder and pancreatic cancers and was shown to be independent bad prognostic factor in some of them (Zong et al. 2009). Some tumors worked out other mechanisms of TRAIL-dependent resistance such as lack of caspase-8 and -10 expression (neuroblastoma), inactivation of pro-apoptotic Bax protein (mismatch repair-deficient human tumors), oversecretion of IL-8 (ovarian carcinoma), overexpression of mutant *PTEN* gene (prostate and breast cancer), and finally upregulation of the Akt/NF-κB intracellular pathway (reviewed in Wang and El-Deiry 2003; Xu et al. 2010). Activation of TRAIL-dependent tumor killing could be an attractive therapeutic option and is currently being extensively studied. An example of this approach is the use of recombinant TRAIL together with quinacrine blocking NF-κB signaling (Jani et al. 2010) or with sensitization of tumor cells to TRAIL with oxidative stress (White-Gilbertson et al. 2009). Moreover, the tumor is resistant to some alternative ways of apoptosis such as Fas-mediated lysis by activated lymphocytes, due to increased expression of the Bcl-2 molecule (Hishii et al. 1999).

Expression on the surface of the tumor of membrane-bound regulatory proteins such as CD46, CD55 or CD59 inactivates components of the complement system, making the tumor resistant to complement attack (Gorter and Meri 1999). Some other tumor-derived molecules could account for its resistance to immune effectors. Soluble form of intercellular adhesion molecule-1 shed from the tumor surface could protect the tumor from binding to effector cells (Sánchez-Rovira et al. 1998). A similar function is played by exosomes, vesicles loaded with TAA and immunosuppressive molecules, which spread all over the body and induce tolerant host reactions to the tumor (Valenti et al. 2007). Local hypoxic conditions together

with chronic inflammation in the tumor environment provoke cancer cells to generate free adenosine, which protects the tumor from cytotoxic T cells by decreasing IL-12 and TNF-α secretion, and by increasing IL-10 secretion from tumor macrophages (Link et al. 2000; Zhang et al. 2005a).

There are also cytokines which adversely affect host immunosurveillance. Patients with cancer are characterized by a defect of Th1 cytokine production and a shift towards Th2 cytokine activity, which favors tumor growth and its potential to metastasize. The Th2 biased responses are represented by increased serum concentrations of Th2-type cytokines (IL-4, IL-6, IL-10) and simultaneous decreased concentration of Th1 cytokine IFN-γ (Lathers et al. 2003; Lauerova et al. 2002). Defect of Th1 activity was also shown in peripheral blood $CD4^+$ and $CD3^+$ T cells and was correlated with tumor progression (Agarwal et al. 2003; Mainou-Fowler et al. 2003; Smyth et al. 2003).

Immunosuppressive factors, such as TGF-β, IL-6 and IL-10, were shown to be secreted directly by tumor cells (Spaner 2004). Among them, TGF-β seems to play one of the most important functions promoting tumor progression. It was shown that TGF-β negatively influences anti-tumor capabilities of host cytotoxic $CD8^+$ lymphocytes. This activity is multi-directional and is based on impairment of Fas-mediated apoptosis of cancer cells, downregulation of IFN-γ secretion and disturbed expression of perforin and granzymes by cytotoxic $CD8^+$ lymphocytes (Jarnicki et al. 2006). The tumor, through the secretion of TGF-β, also facilitates the recruitment of regulatory $CD4^+$ and $CD8^+$ T cells secreting IL-10 and TGF-β, which further suppress host immunity (Jarnicki et al. 2006). IL-6 in both auto- and paracrine mechanisms contributes to tumor cell proliferation, formation of metastases and resistance to chemotherapy (Ogata et al. 1997), as well as to silencing of tumor suppressor genes (Hodge et al. 2005). Another immunosuppressive cytokine, IL-10, has been detected in specimens biopsied from many solid tumors (Gotlieb et al. 1992; Kruger-Krasagakes et al. 1994; Pisa et al. 1992), and its expression was found to be even more increased in metastatic tumors, suggesting a role for IL-10 to promote cancer metastatic potential (Dummer et al. 1996).

It is now a broadly accepted opinion that an association between inflammation and cancer development really exists (Balkwill and Mantovani 2001; Coussens and Werb 2002). Prostaglandin E_2 (PGE_2) is a cytokine which mediates both tumor growth and inflammation. It was found that chronic inflammation may account for about 15% of cancers. The observation that prophylactic use of non-steroid anti-inflammatory drugs reduces the risk of colorectal cancer by 40%, as well as anti-tumor effects exerted by use of selective cyclooxygenase (COX)-2 inhibitors (so-called COXIBs), has led to recognition of the relevance of the COX-2-PGE_2 pathway in tumor development. COX-2 is upregulated by pro-inflammatory cytokines, HIF-1α and tumor promoters, and it was confirmed that COX-2-derived PGE_2 is highly expressed in colorectal, gastric and breast cancers (reviewed in Greenhough et al. 2009; Wang and DuBois 2006). The concentration of PGE_2 depends on the functional balance between production dependent on COX-2/PGE_2 synthase activity and degradation which occurs upon 15-hydroxyprostaglandin dehydrogenase (15-PGDH) function. Loss of 15-PGDH activity accompanies tumor progression. Biological effects exerted by PGE_2 are mediated by specific receptors (EP1–EP4) which were shown to be differently regulated in several tumors. The importance of PGE_2 for tumor growth is based on both paracrine and autocrine PGE_2 multidirectional function which mediates many different intracellular pathways. Prostaglandin PGE_2 can activate EGF receptor and thus stimulate metastatic potential of tumor cells, as was shown in colorectal cancer. PGE_2-dependent activation of the Ras/MAPK signaling pathway stimulates tumor proliferation. Through stimulation of the peroxisome proliferator activated receptor δ transcription factor and downstream PI3K/Akt pathway and independently by increasing NF-κB activity PGE_2 inhibits tumor cell apoptosis (reviewed in Wang and DuBois 2006; Wang et al. 2009). Overexpression of COX-2 also stimulates secretion of VEGF and bFGF, which through a positive feedback loop enhance autocrine PGE_2 secretion (Fujiwaki et al. 2002; Wang and DuBois 2006). The pro-angiogenic potential of PGE_2 also depends on nitric oxide (NO) activity, through modulation of the NO/cGMP intracellular pathway (Namkoong et al. 2006). Thus COX-2 influences tumor angiogenic potential and its overexpression predicts shorter survival in some cancer patients (Gallo et al. 2002; Zhang and Sun 2002). Prostaglandin PGE_2 is also engaged in changing of tumor chemokine (RANTES, CXCR4) expression, thus decreasing the influx of immune cells into the tumor, and increasing tumor migration and invasive abilities (Wang and DuBois 2006). PGE_2 was additionally shown to provoke deactivation of complement compounds and upregulation of pro-cancerous Th2 cytokines (IL-4, IL-10) in the tumor environment (reviewed in Greenhough et al. 2009; Wang and DuBois 2006). Moreover, the above-mentioned cytokines together with PGE_2 cause inhibition of DCs differentiation and maturation, with impairment of DC migration towards local lymph nodes (reviewed in Bennaceur et al. 2009). PGE_2 may also induce IDO expression on peri-tumoral DCs (von Bergwelt-Baildon et al. 2006).

The relationship between the cancer and inflammation is also documented by the results of studies on another pro-inflammatory cytokine, IL-23, which belongs to the

same family as IL-12 (reviewed in Langowski et al. 2007). However, IL-23 presents quite different activity compared to IL-12, and does not augment IFN-γ secretion. In physiological circumstances IL-23 is secreted from activated DCs and macrophages upon bacterial stimulation, and receptor sites for IL-23 are present on T lymphocytes, NK and NKT cells, DCs and macrophages (Parham et al. 2002). IL-23 promotes the inflammatory function of memory T cells belonging to a subpopulation of IL-17-secreting Th17 cells. In the tumor environment Th17 cells originate from naïve T cells subjected to stimulation by IL-6 and TGF-β produced by the tumor itself. Additionally to IL-17, Th17 cells release other inflammatory mediators such as IL-1, IL-8, TNF-α, PGE_2 and chemokines which augment the inflammatory reaction. The increased expression of both IL-23 and IL-17 was observed in many malignant tumors, and correlated with intensity of neutrophil and macrophage infiltrate. Moreover, IL-17 promotes tumor growth by enhancing angiogenesis and stimulating expression of MMPs partially through activation of the IL-6/STAT3 pathway (reviewed in Langowski et al. 2007; Whiteside 2010). It was shown that overexpression of IL-23 resulted in a decrease of $CD8^+$ CTLs in tumor immune cell infiltrate and led to downregulation of MHC molecules on cancer cells (Langowski et al. 2007). Although there are some papers indicating a positive role for IL-23 in controlling early virus-derived tumors (Liu et al. 2009), excessive continuous presence of IL-23 during further tumor growth suggests its role for shaping the pro-tumor inflammatory environment. Interestingly, preparation of DCs for vaccination purposes could unintentionally trigger IL-23 secretion, thus adversely influencing vaccine anti-tumor responses (Sender et al. 2010). The most important immunoregulatory molecules present on the tumor surface and secreted to its environment are presented in Fig. 1.

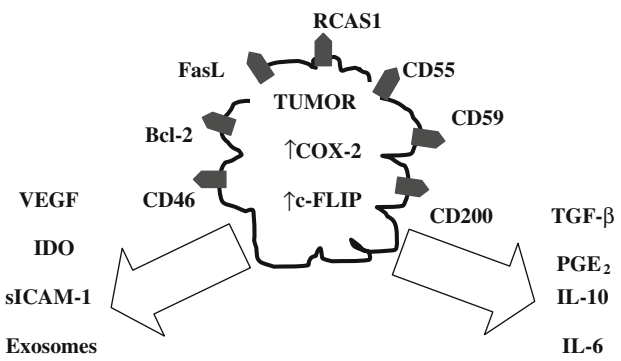

Fig. 1 Some of the most important tumor-derived immunoregulatory molecules, both expressed on the surface or inside of cancer cells and secreted to tumor environment

Role of Immune Regulatory and Inflammatory Cells in Tumor Environment

Cytokines in the cancer environment are also a product of many different populations of immune cells infiltrating tumor stroma (tumor infiltrating lymphocytes TILs). Many studies have found that development of tumor and an unfavorable prognosis for cancer patients were accompanied by accumulation of natural $CD4^+CD25^+Foxp3^+$ T regulatory cells (Tregs) in peripheral blood, as well as of peripherally induced Tregs in the tumor itself and in tumor-draining lymph nodes (reviewed in Wilczynski et al. 2008). Immunoregulatory function exerted by Tregs could effectively inhibit host defense against cancer based on cytotoxic effectors such as $CD8^+$ lymphocytes, NK, NKT cells and antigen-specific T $CD4^+CD25^-$ lymphocytes (Hiura et al. 2005; Nishikawa et al. 2005). However, recent studies (Erdman et al. 2010) suggest, concurrently with the "hygiene hypothesis", that Tregs triggered and stimulated by recognition of gut bacteria could reduce tumor risk through downregulation of inflammation. This was found to be true even for tumors of other than gastrointestinal origin. Individuals with proper function of this mechanism are able to control the tumor initiation by IL-10-stimulated Tregs with anti-inflammatory phenotype. In "hygienic" individuals this protective reaction is limited and instead pro-carcinogenic Th17-dependent activity occurs (Erdman et al. 2010). Additionally, a population of $CD8^+$ immunosuppressor T cells induced by plasmacytoid DCs has been identified in ovarian cancer patients (Wei et al. 2005).

Another group of regulatory cells, called Tr1, represents a population of IL-10-producing T cells generated upon immature DCs stimulation (Fiore et al. 2005). The detailed profile of secreted cytokines specific for Tr1 cells includes IL-10, TGF-β and trace amounts of IFN-γ (Groux et al. 1997). Murine studies showed that expansion of Tr1 cells enhanced tumor progression, while their depletion helped to restore anti-tumor immunity (Zhang et al. 2005b). The possible role of Tr1 cells for human pathology and unfavorable outcome was confirmed in studies of different types of tumors (Loskog et al. 2007; Moore et al. 2001). It was shown that Tr1 cells primed by COX-2 were associated with inhibition of DC maturation and contributed to increased growth of head and neck squamous cancer (Bergmann et al. 2007). The next population of immunoregulatory T cells with a profile of secreted cytokines similar to Tr1 cells is that of Th3 cells. In addition to TGF-β they are able to produce IL-4 and IL-10 (MacDonald 1998). The importance of Tr1/Th3 infiltrate for progression of B16 melanoma has been documented (Seo et al. 2002). The ability to produce TGF-β upon activation makes Tr1/Th3 cells one of the potential targets for anti-cancer immunotherapy. Cytokine TGF-β is engaged in a plethora

of immune functions inside the tumor environment. Some of the most important ones are as follows (reviewed in Moutsopoulos et al. 2008; Yu et al. 2006): control of Th17 cell differentiation, inhibition of DC maturation, stimulation of VEGF production, generation of $CD4^+CD25^+Foxp3^+$ Tregs, decrease of activity of NKT cells and, through the TGF-βRII receptor, of T $CD8^+$ and NK cytotoxic cells.

The next population of lymphocytes probably engaged in immunoregulatory mechanisms existing inside the tumor is a population of $CD4^+$ Th17 T cells, which upon stimulation by IL-23 produce IL-17 (Bi et al. 2007; Castellino and Germain 2006; Steinman 2007). However, the results of studies concerning the role of Th17 cells and IL-17 have been inconclusive, as they have indicated its functional ambiguity for both promotion and rejection of tumors (Benchetrit et al. 2002; Bettelli et al. 2006; Langowski et al. 2006; Numasaki et al. 2003).

A distinct population of lymphocytes is that of natural killer T lymphocytes (NKT cells) expressing both T cell receptor and receptors characteristic for NK cells. Two subpopulations of NKT cells dependent on the presence (NKT I) or absence (NKT II) of the invariant Vα14Jα18 T cell receptor (TCR) Vβ chain have been recognized, and it was found that while NKT I cells mediate tumor rejection, the NKT II cells allow for its growth (Terabe et al. 2005). NK cells are usually thought to be important anti-cancer effectors. However, a subset of regulatory NK cells possessing anti-T $CD8^+$ and anti-DC cytotoxic activity could adversely influence host defense (Ferlazzo et al. 2003; Hayakawa et al. 2004; Rabinovich et al. 2003).

Recent years have brought some interesting data concerning the role of mast cells (MC), which have traditionally been connected with allergy and parasitic infections. However, it was found that MC infiltrating the tumor are able to release molecules such as VEGF and heparanase, which both have pro-angiogenic effects and stimulate cancer growth, and could cooperate with Treg cells in diminishing anti-tumor responses (reviewed in Galinsky and Nechushtan 2008). Many studies have indicated that increased MC numbers in solid tumors were correlated with poor patient outcome (Fisher et al. 1989; Iamaroon et al. 2003; Ribatti et al. 2003, 2005). In contrast, a positive role of MC for patient survival was suggested in some other studies performed on breast cancer and non-small cell lung carcinoma (Dabiri et al. 2004; Welsh et al. 2005). The protective role of MC obtained in these investigations could be attributed to heparin, IL-2, IL-21 or TNF-α secretion (Galinsky and Nechushtan 2008). Taking into consideration these opposite results, one could conclude that the function of tumor-infiltrating MC might depend on other variables (e.g. microvessel density) present in the tumor environment. The study performed on 44 ovarian cancer patients seems to support this statement (Chan et al. 2005).

Macrophages constitute one of the major immune cell populations responsible for both tumor rejection and promotion (Ostrand-Rosenberg 2008; Sica et al. 2008; Siveen and Kuttan 2009), but their function is determined by the way they are activated. The presence of IFN-γ, granulocyte–macrophage colony stimulating factor, TNF-α or lipopolysaccharide shifts their activity into the so-called M1 profile, while stimulation by IL-4, IL-10, IL-13 or TGF-β results in the M2 profile (Mills et al. 2000). Macrophages of M1 type could effectively destroy tumor cells through production of Th1 cytokines and stimulation of T $CD8^+$ CTLs (Ostrand-Rosenberg and Sinha 2008). Conversely, macrophages of M2 type produce mainly IL-6, IL-10, TGF-β, and VEGF. This cell subset constitutes the vast majority of TAMs, which play a pivotal role in tumor progression (Biswas et al. 2006; Ostrand-Rosenberg 2008; Sica et al. 2008). It was shown that most aggressively growing tumors are infiltrated by large numbers of TAMs (Lin et al. 2006). Recruitment of macrophages into tumors is regulated by Th2 cytokines, chemokines (Ben-Baruch 2006; Mantovani et al. 2006; Sica et al. 2008), and hypoxia (Talks et al. 2000). Colony-stimulating factor-1 and TGF-β are major cytokines that are believed to play an important role in recruitment of macrophages into the tumors. Both of them are expressed constitutively on the surface of solid tumors (Lin et al. 2001; Wojtowicz-Praga 2003), and correlate with intensity of TAM infiltrate (Lin et al. 2001; Walker et al. 1994) and poor prognosis for the patients (Lin et al. 2001; Sapi 2004). The chemokines CCL2 (monocyte chemotactic protein-1) and CCL5 (RANTES) were found to be expressed predominantly by solid tumors (Luboshits et al. 1999; Negus et al. 1995, 1997; Saji et al. 2001; Ueno et al. 2000; Valkovic et al. 1998; Zhou et al. 2004). Their overexpression correlated with intra-tumor TAM content as well as with a bad survival ratio (Negus et al. 1997; Saji et al. 2001; Ueno et al. 2000; Valkovic et al. 1998). A hypoxic environment inside solid tumors is another attractant for macrophages. Anaerobic conditions increase expression of endothelin-2 and VEGF, which become a stimulus for macrophage recruitment into hypoxic areas of the tumor (Grimshaw et al. 2002; Raghunand et al. 2003). Adaptation of TAMs to a hypoxic environment depends on function of HIF-1α, which not only helps TAMs to function in an anaerobic environment, but also contributes to pro-angiogenic and pro-metastatic TAM activity (Cramer et al. 2003). Clinical studies seem to confirm that there is enhancement of invasiveness and peritoneal metastatic activity in ovarian cancer under hypoxic conditions (Kim et al. 2006). TAMs secrete Th2 cytokines, enhance intratumor angiogenesis (by VEGF, TGF-β and FGF) and augment extracellular matrix remodeling (by MMPs), thus

promoting tumor growth and intravasation of cancer cells into blood vessels, resulting in increased tumor metastatic potential (Ostrand-Rosenberg 2008; Sica et al. 2008). Despite the fact that in general TAMs are functionally biased to M2 type, there are subsets of TAMs additionally secreting some amounts of Th1 cytokines, for instance TNF-α. Although TNF-α is considered to be an anti-tumor cytokine, it also has some pro-tumor activities. It might contribute to DNA damage, induce angiogenic factors and act as a growth factor for cancer cells (Balkwill 2002). Investigations performed on ovarian cancer indicated that TAMs were also able to inhibit host T effectors by expression of the B7-H4 co-stimulatory molecule, which was identified as a negative regulator of T cell activation (Kryczek et al. 2006). TAMs could also exert immunoregulatory effects by secretion of NO and ROI. Investigations have confirmed that tumors compared to normal tissues are characterized by both higher expression of NO synthase and production of ROI, and that their activity is related to TAMs (Bogdan 2001; MacMicking et al. 1997; Malmberg 2004; Thomsen and Miles 1998). Defective M1-type functions showed by TAMs are probably caused by disturbed activation of NF-κB in response to pro-inflammatory stimuli present in advanced tumors, including TNF-α (Huang et al. 1999; Sica et al. 2000). Factor NF-κB is responsible for regulation of transcription of many genes, including those for cytokines, chemokines and anti-apoptotic molecules (Ostrand-Rosenberg 2008). The role of NF-κB in tumor promotion and anti-cancer therapy has been extensively studied (reviewed in Ben-Baruch 2006).

DCs are professional antigen-presenting cells of myeloid or plasmacytoid origin (Colonna et al. 2004; O'Neill et al. 2004). Progressive tumors usually contain DCs having immature $CD4^{-}CD8^{-}$ phenotype (iDCs). Opposite to mature DCs, these cells indicate pro-tolerogenic functions and are unable to effectively stimulate cytotoxic responses (Bell et al. 1999; Liu et al. 2005; Zou et al. 2001). Immature DCs exert activating effects, mediated through TGF-β and IL-10, on T $CD4^{+}CD25^{+}Foxp3^{+}$ Tregs, thus promoting tumor growth (Dercamp et al. 2005; Ghiringhelli et al. 2005). Interactions between DCs and Tregs mediated through cytotoxic T lymphocyte antigen-4 could compromise anti-tumor immunity in an IDO-dependent way (Chen et al. 2005). The presence of IDO-positive DCs was confirmed in tumor-draining lymph nodes in cases of melanoma, breast, colon, lung and pancreatic cancers, and the intensity of such infiltrate was correlated with poor prognosis (Munn et al. 2002). Expression of IDO on DCs is probably upregulated by PGE_2 present in the tumor environment (von Bergwelt-Baildon et al. 2006). Another mechanism by which DCs could regulate Treg activity depends on the CD200/CD200-receptor pathway. Molecule CD200 is a type Ia membrane protein belonging to co-stimulatory molecules, which exerts suppressive effects through binding to the CD200 receptor (CD200R). Both CD200 and CD200R are present on the surface of myeloid DCs. It was shown that stimulation of CD200R on DCs created tumor supporting reactions mediated by Th2 cytokines and increased Treg activity, while blocking CD200/CD200R interactions with monoclonal anti-CD200 antibodies resulted in a shift towards Th1 activity. Moreover, tumors themselves (including ovarian cancer) are capable of expressing CD200 molecules, thus influencing DC function (Gorczynski et al. 2001; McWhirter et al. 2006). The tumor environment also contains many cytokines and other immunoregulatory factors that modulate DC function in order to compromise host immunity. Among them are cytokines such as IL-10, IL-6, TGF-β, PGE_2, VEGF, factors such as IDO and ROI, and finally tumor antigens and metabolites, which all inhibit maturation of DCs and promote their suppressive activities (reviewed in Bennaceur et al. 2009). Use of DC-based vaccines in cancer immunotherapy has been extensively studied (Fujii et al. 2009).

MDSC characterized by $CD11b^{+}/Gr\text{-}1^{+}$ phenotype are a multifunctional and heterogeneous population of cells whose function links the mechanisms of chronic inflammation and tumor progression (Bennaceur et al. 2009). This unique cell population possesses the common feature of suppressing host anti-tumor responses mediated by T $CD8^{+}$ CTLs, NK cells and NKT cells, as well as of blocking DC maturation (Bunt et al. 2007a; Serafini et al. 2006; Sinha et al. 2005; Yanagisawa et al. 2006). MDSC are also capable of inducing tumor mutations, and they augment formation of new blood vessels and tumor metastatic potential (Bennaceur et al. 2009). Cytokines IL-1β, IL-6 and PGE_2 increase accumulation and suppressive activity of MDSCs (Bunt et al. 2006, 2007b; Song et al. 2005; Sinha et al. 2007b). The pleiotropic effects of MDSCs are mediated through production of arginase and ROI (Kusmartsev and Gabrilovich 2006; Rodriguez and Ochoa 2006; Serafini et al. 2006), modification of the TCR molecule on T $CD8^{+}$ CTLs (Nagaraj et al. 2007), induction of T $CD4^{+}CD25^{+}Foxp3^{+}$ Tregs and promotion of a Th2-biased environment by secretion of IL-10 and blocking macrophage-derived IL-12 production (Huang et al. 2006; Sinha et al. 2007a). The main cell populations taking part in immunoregulation of tumor growth are presented in Fig. 2.

Conclusion

Tumors seem to be involved in active immunological interplay with the host. This fact has deep consequences for treatment options. It means that efficient anti-cancer

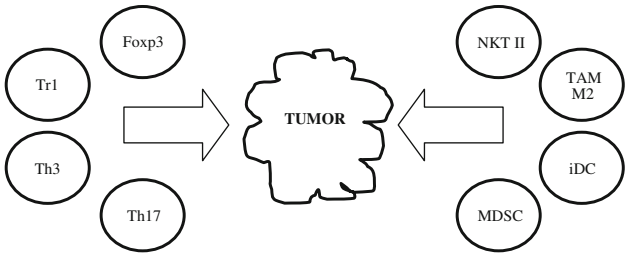

Fig. 2 The main immune cell populations both being regulated by the tumor and augmenting its growth

management should be based not only on the ability to overcome tolerance towards the tumor, but also on active fight against tumor "escape" capabilities. However, this goal is difficult to achieve at present. Chemotherapy, which is broadly used in many treatment protocols, usually seriously compromises the host immune response by causing bone marrow suppression. Through its effectiveness in killing only some tumor cell populations, chemotherapy "shapes" the tumor phenotype and produces resistant recurrences. The same adverse effects are frequently observed during immunotherapy. Moreover, due to the complexity of mechanisms engaged in tumor "escape" the single treatment approaches are highly ineffective. It is highly feasible that in the future standard therapies and immune therapies could be integrated to cure cancer. Identification of new tumor-specific antigens could also help in improving immunotherapy efficacy. New techniques of immunotherapy should also focus on destruction of intra-tumor stromal cells.

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