Chapter 5
Development of Antitumor Cellular Immunity

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Abstract A dazzling picture of many different types of innate and adaptive immune cells that have infiltrated a patient's tumor emerges when a tumor section is studied under the microscope. There is good evidence that patient survival depends on the numbers, type, character and localization of particular tumor-infiltrating immune cells, in particular T cells and macrophages. Here we discuss the events governing the arousal of a spontaneous tumor-specific T cell response and how the tumor-rejecting efficacy of this T cell response is regulated by the intratumoral cytokine milieu, the expression of inhibitory molecules and co-infiltrating immune cells. Finally, we describe approaches to change the local micromilieu so that the net outcome is a strong induction of an anti-tumor immune response coupled to a better infiltration of tumors under conditions that allows these immune cells to exert their function and to control tumor outgrowth.

Keywords Tumor microenvironment · Immune infiltration · Tumor escape mechanism · Combination therapy · Tumorigenesis · Antitumor immunity · T cells

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5.1 Immune Infiltration of Tumors is Associated with Clinical Outcome

The transformation of cells and the outgrowth of carcinomas take place in the face of the immune system. Nevertheless, the immune system is able to eradicate tumors, to stop them in their growth and/or to prevent its progression to metastasis, a concept which is called immunosurveillance (Swann and Smyth 2007; Vesely et al. 2011; Zitvogel et al. 2006; Smyth et al. 2006). The effector arm of the immune system is an effective suppressor mechanism of tumor outgrowth but it is opposed by other parts of the immune system displaying tumor promoting functions. The combination of these two acting sides of the immune system may determine the way a tumor develops and is called cancer immunoediting (Dunn et al. 2002; Schreiber et al. 2011). The role of the immune system in cancer is demonstrated by a multitude of immunohistochemical studies on different types of tumors showing that the magnitude and type of immune cell infiltrating a patient's tumor is correlated with the final clinical outcome of the cancer patients. To be more precise, patients with tumors evidently infiltrated with CD8+ T lymphocytes [in cervical cancer: (Piersma et al. 2007), in breast cancer: (Marrogi et al. 1997; Menegaz et al. 2008; Mahmoud et al. 2011), in ovarian cancer: (Zhang et al. 2003), in non small cell lung cancer (NSCLC): (Al-Shibli et al. 2008; Dieu-Nosjean et al. 2008; Hiraoka et al. 2006; Nelson 2008), in melanoma: (Clemente et al. 1996; Haanen et al. 2006) and memory T cells (i.e. CD45RO+) as described for colorectal cancer (Pages et al. 2005; Galon et al. 2006; Nosho et al. 2010)], but also other immune cells such as dendritic cells (DC) (Eisenthal et al. 2001; Zeid and Muller 1993), type 1 macrophages (M1) (Algars et al. 2012; Kinouchi et al. 2011; Erreni et al. 2011; Ohri et al. 2009; Forssell et al. 2007; Ohno et al. 2003) and B cells (Nielsen et al. 2012; Martinet et al. 2011; Ladanyi et al. 2011; Schmidt et al. 2008; Erdag et al. 2012) form groups of patients that have a favorable prognosis in terms of disease free period and survival (Zhang et al. 2003; Pages et al. 2005; Galon et al. 2006; Erdag et al. 2012; Oble et al. 2009; Sato et al. 2005; Denkert et al. 2010; Wang et al. 2012; Kashimura et al. 2012; Nelson 2010).

In contrast, a dense infiltration of tumors CD4+ forkhead box P3 (FoxP3)-positive regulatory T cells (Tregs) is related to a worse prognosis of the cancer patient (Curiel et al. 2004; Shen et al. 2010; Jacobs et al. 2010; Yamagami et al. 2011; Elkord et al. 2010; Raghavan and Quiding-Jarbrink 2011; Mathai et al. 2012; Kim et al. 2012). The exception to the rule might be the infiltration of Tregs in colorectal cancer, where these cells are believed to suppress tumor promoting interleukin 17 (IL-17)-producing T cells (Correale et al. 2010; Ladoire et al. 2011; Whiteside 2012). IL-17-producing T cells have been discovered only 6 years ago and their function was heavily debated as investigators showed tumor promoting and tumor suppressive functions of T cells producing IL-17. However, it is imperative to understand that the production of IL17 is not synonymous to a T helper 17 (Th17) cell, and that other cells of the immune system can produce IL-17 as well. The few reports on Th17 cells in the human microenvironment suggest

that Th17 are correlated with improved patient survival (Wilke et al. 2011a, b; Zamarron and Chen 2011). Most recently, Th17 were reported to have stem cell-like features that allow them to promote long-term anti tumor immunity (Wei et al. 2012). These Th17 are polyclonal functional [produce not only IL-17 but also interferon alpha (IFN-γ), tumor necrosis factor alpha (TNF-α) and granulocyte macrophage colony-stimulating factor (GM-CSF)], are highly resistant to apoptosis, have a highly proliferative renewal capacity and are able to persist in time (Kryczek et al. 2011). Importantly, in many tumor types (among which cervical cancer, breast cancer, colon carcinoma, tonsillar carcinoma and gastric cancer) the ratio between the effector T cells (i.e. CD8+ T cells) and the inhibitory T cells, such as Tregs, has been found to form an (independent) prognostic factor for the patients' outcome (Shen et al. 2010; Jordanova et al. 2008; Liu et al. 2011; Shah et al. 2011; Yoon et al. 2012; Suzuki et al. 2010; Nasman et al. 2012). Notably, the capacity of T cell to infiltrate the tumor can also be hampered as a result of an elevated lymph drainage from tumors to the lymph node (Harrell et al. 2007; Thomas et al. 2012) through mechanical stress acting on stromal cell functions and on the extracellular matrix (Swartz and Lund 2012) and may lead to an overall poor immune infiltration of tumors. In addition to Tregs, the infiltration of tumors with type 2 macrophages (M2) (van Dongen et al. 2010; Bronkhorst et al. 2011; Kurahara et al. 2011; Heusinkveld and van der Burg 2011; Allavena and Mantovani 2012), immature myeloid cells and myeloid-derived suppressor cells (MDCSs) (Montero et al. 2012; Poschke and Kiessling 2012; Gabrilovich et al. 2012) also has a negative impact on the clinical outcome of the patient.

5.2 The Influence of the Intratumoral Cytokine Milieu

An important aspect of the tumor is the cytokine profile within the tumor microenvironment. Some of these cytokines may help to reject tumor cells whereas others promote tumor growth. The critical role of the inflammatory cytokine IFN-γ and the cytotoxic components such as granzymes and granulysin in controlling the tumor growth has been demonstrated in mice studies (Koebel et al. 2007) as well as in patient cohorts (Galon et al. 2006; Tosolini et al. 2011). IFN-γ is produced by tumor infiltrating natural killer (NK), T and NKT cells and the levels are even further increased through IL-12, produced by well activated antigen presenting cells (APCs) (Yoshimoto et al. 1998; Okamura et al. 1995). It upregulates major histocompatibility complex (MHC) on tumor cells, induces the immunoproteasome in APCs, recruits lymphocytes and skews naïve T cells into Th1 cells via IL-12 producing APCs. Furthermore, IFN-γ produced by Th1 cells at the tumor site is found to be very important for the recruitment of CD8+ cytotoxic T cells (CTLs) into the tumor as well as for the sustainment of CD8+ T cell effector function (Bos and Sherman 2010; Wong et al. 2008). In addition, the cytokines IL-2 and type 1 interferons (i.e. IFN-α) are proinflammatory cytokines that via activated T cells (producing IL-2) and/or proper APC activation (by IFN-α

and IL-2) endow CTLs with the ability to kill tumor cells (Mocellin et al. 2002; Gajewski 2012). The chemokines CXCL9/10/11 and/or CCL5 (RANTES) are held responsible for the attraction of effector lymphocytes (expressing CXCR3 and/or CCR5, respectively) from the circulation into the tumor (Rahir and Moser 2012; Abastado 2012; Koizumi et al. 2007; Verbeke et al. 2011).

Good examples of tumor promoting cytokines, that work either by inducing an immune suppressive environment for the infiltrated effector cells and/or by alteration of the tumor vasculature, are transforming growth factor β (TGF-β), IL-10, vascular endothelial growth factor (VEGF), IL-6, prostaglandin E2 (PGE2) and the enzyme indoleamine 2,3-dioxygenase (IDO). TGF-β, released upon tissue damage in order to remodel/repair the tumor tissue, has multiple roles inside the tumor. It regulates the suppression of infiltrated effector T and B cells (Flavell et al. 2010), activates Tregs via tolerogenic DC (Yang et al. 2010; Bierie and Moses 2010) and recruits NK cells, neutrophils and/or macrophages to the tumor but inhibits their function (Bierie and Moses 2010). TGF-β enhances tumor cell migration via chemotaxis of fibroblasts that facilitate the invasion of tumor cells into the normal tissue (Shieh et al. 2011; Padua and Massague 2009), and it also alters the extracellular matrix in the tumor (Swartz and Lund 2012). Another tumor promoting cytokine, IL-10, is produced by intratumoral DCs, macrophages, Tregs and/or Th2 cells and is able to inhibit the cytokine production and function of tumor-specific effector T cells (Moore et al. 2001; Joss et al. 2000). IL-10 downregulates cell surface MHC expression on APCs and on tumor cells resulting in non-optimal stimulation of CTLs and a less effective attack of tumor cells (Kim et al. 1995; Steinbrink et al. 1999). In addition, IL-10 also decreases the expression of B7 costimulatory molecules on APCs and inhibits the production of proinflammatory cytokines and chemokines by these APCs (de Waal Malefyt et al. 1991; Ding et al. 1993). Furthermore, IL-10 is involved in the development of Tregs and their suppressive action (Wei et al. 2005; Zou 2006).

PGE2 is produced by several inflamed tumors and promotes tumor angiogenesis, metastasis and converts the differentiation of immune stimulatory APCs (monocytes, M1 macrophages, DCs) towards tumor promoting APCs (Herfs et al. 2009; Obermajer et al. 2011; Heusinkveld et al. 2011). VEGF, produced by both tumor cells and APCs, stimulates angiogenesis within the tumor tissue but also stimulates myeloid cell differentiation and function towards so called type 2 DCs (DC2; CD11c-CD123+), which are involved in skewing the T cell response towards Th2 (Osada et al. 2008; Sheng et al. 2011; Schmid and Varner 2010). The cytokine IL-6 can be produced by tumor cells, tumor resident macrophages as well as by T cells upon trauma. Similar to PGE2, IL-6 skews monocyte differentiation towards M2 macrophages (Sheng et al. 2011; Dijkgraaf et al. 2012a; Waetzig and Rose-John 2012). IDO produced by tumor infiltrating APCs and certain tumor cells can inhibit the effector function of T cells by starving them from tryptophan (Muller and Prendergast 2007; Singer et al. 2011; Soliman et al. 2010). IDO expression in APCs is induced as a result of Forkhead box O3 (FOXO3) activation (Watkins et al. 2011). Of note, Tregs can be induced by the kynurenine system activated by IDO expressing APCs (Watkins et al. 2011; Mandi and Vecsei 2012).

The macrophages, MDSCs and Tregs are attracted to the tumor by the chemokines CCL1, CCL2 and CXCL8, which also promote angiogenesis, and by CCL21, CCL22 and/or hypoxia-induced CCL28 (Facciabene et al. 2011; Shields et al. 2010; Hoelzinger et al. 2010). In cervical cancer patients it has been observed that the expression of CCL2 within the tumor correlates with decreased survival (Zijlmans et al. 2006; Kleine-Lowinski et al. 1999), however, in primary ovarian tumors the overexpression of CCL2 is related to a higher susceptibility of tumor cells to chemotherapy regimens and associated with increased survival (Fader et al. 2010), indicating that not simply the expression of CCL2 but also co-conditioning factors are likely to determine the outcome of CCL2 expression. Furthermore, the chemokines CXCR4 (Mishra et al. 2011) and CXCR16/CXCL16 (Deng et al. 2010a) can promote tumor growth and metastasis by cross talk with the cancer-associated fibroblasts (Lazennec and Richmond 2010). These fibroblasts are also involved in regulating tumor growth by the secretion of soluble factors that are either pro-tumorigenic (e.g.IL-10 and TGF-β), enhancing tumor growth, vascularization and invasion, or by the secretion of factors that indirectly can suppress tumor growth by activating immune cells (Rasanen and Vaheri 2010; Joyce and Pollard 2009).

So in summary, the balance between the tumor promoting and anti-tumor facets of the immune system is dictating whether the tumor is progressively growing or controlled and perhaps eradicated. The mechanism behind the infiltration of the tumor by immune cells is believed to be an orchestration of several factors, each of which may influence the attraction and entrance of immune cells to the tumor. Several factors have been described to be responsible for this infiltration [excellently reviewed by Rahir and Moser (2012)]: (1) the vasculature of the tumor tissue, (2) the guidance of blood cells in their extravasation (leaving the blood stream into the tissue) by adhesion molecules, (3) the attraction of the cells by chemokines produced within the tumor microenvironment, (4) tumor antigens expressed on tumor cells or APCs within the tumor or (5) at the lymphoid site and (6) the presence of CD4+ Th1 and/or Th17 cells not only helping the optimal priming of CD8+ T lymphocytes but also having an important role within the tumor, namely as helper cells favoring the entry into and the accumulation of CD8+ T cells in the tumor tissue by inducing a strong inflammatory environment. Overall, there is clear evidence that tumor infiltrating immune cells can dictate the final outcome of a developing tumor. The mechanisms underlying tumor-induced initiation of immune cell infiltration and the spontaneous priming of tumor-specific T cells, however, are still not very well understood.

5.3 Development of Tumor-Specific T Cell Immunity

The primary site for the induction of an adaptive immune response against pathogens is the lymph node (LN) (Martin-Fontecha et al. 2009; Breart and Bousso 2006). Consequently, it has always been assumed that priming of T cells either

following vaccination or by exposure to tumor-derived antigens also occurs in the LN. Indeed, tumor-derived antigens were taken up within the tumor by APCs, carried to the tumor-draining lymph node (TDLN), processed and presented in MHC class II to CD4+ T cells and in MHC class I—via a process called cross-presentation—to CD8+ T cells (van Mierlo et al. 2002; Melief 2003; Melief 2008). However, as most tumor types first metastasize to the TDLN one can envisage alternative routes such as the cross-presentation of tumor antigens by APCs that have ingested antigens from dying/dead tumor cells directly within this TDLN. Alternatively, these LN resident tumor cells might also directly present tumor antigens to activate T cells as was shown in mouse models (Zinkernagel 2002; Ochsenbein et al. 2001) and in vitro for melanoma (Verdegaal et al. 2011). In agreement with the common believe that T cells are primed in the LN is the fact that especially TDLN harbor tumor-specific T cells. In early stage melanoma, tumor-reactive T cells are detectable at higher frequencies in the TDLN than in blood (Molenkamp et al. 2006; Vuylsteke et al. 2006). Similarly, in cervical cancer we readily detected polyclonal populations of human papillomavirus type 16 (HPV16) oncoproteins E6- and E7-specific CD4+ and CD8+ T cells in almost all TDLN (de Vos van Steenwijk et al. 2010; van Poelgeest et al. 2012).

Interestingly, accumulating evidence suggests that immune responses may also be directly induced within the tumor environment. Immunohistochemistry studies have revealed the presence of LN-like structures, called ectopic LNs or tertiary lymphoid structures, present within tumors of the lung, colon and oropharynx (i.e. those originating from the tonsils in the head and neck region) (Dieu-Nosjean et al. 2008; Coppola et al. 2011; Randall 2010). In human NSCLC these ectopic LNs were found to harbor high density of Lamp-positive DCs (i.e. matured DCs), which have the capacity to appropriately prime a tumor-specific T cell response. Indeed, the presence of such tertiary lymphoid structures was associated with better clinical outcome (Dieu-Nosjean et al. 2008). Studies of these LN-like structures in colorectal cancer showed that they comprised follicles with CD3+ T cells in the cortex like zone and CD20+ B cells within the follicular structure as well as CD21+ DCs in the follicular germinal centers. Moreover, the T and B cell areas displayed proliferative cells as determined by Ki-67 suggesting that these structures indeed resemble secondary and/or tertiary lymph nodes (Coppola et al. 2011). These phenomena were recapitulated in a tumor mouse model where the injection of DCs—genetically modified to produce the chemokine (C–C motif) ligand 21 (CCL-21) that induces the homing and localization of lymphocytes to the lymphoid organs by binding to CCR7—resulted in lymphoid structure formation within the tumor mass, priming of naïve T cells and subsequent tumor regression (Kirk et al. 2001). These findings suggest that the site of T cell priming is not exclusive to the normal LNs and confirm that ectopic LNs may play an important role in the development of a clinically effective antitumor response. Indeed just recently, a 12-chemokine gene signature in metastatic melanoma was correlated to the presence of these ectopic LN as well as a better clinical outcome for these patients (Messina et al. 2012). Interestingly, the development of tertiary LN-like structures is not exclusively found in solid tumors (Dieu-Nosjean et al. 2008; Coppola et al. 2011; Randall 2010;

Coppola and Mule 2008), but can also be found in autoimmune diseases (such as rheumatoid arthritis) (Timmer et al. 2007; Takemura et al. 2001), chronic inflammation (Olszewski 2002; Winter et al. 2010), transplantation (Sato et al. 2011) and even develops at the site of vaccination (Harris et al. 2012).

Irrespective of the site of activation, an important aspect of T cell priming is the context in which this occurs. One can envisage that the activation and functional polarization of T cells directly by tumors cells in LNs is determined by the immunogenicity of the antigen, co-stimulatory and inhibitory molecules on tumor cells and by tumor-produced immunosuppressants (IL-10, IDO, Galectins) (Joss et al. 2000; de Waal Malefyt et al. 1991; Singer et al. 2011; Soliman et al. 2010; Wilke et al. 2011; Yang et al. 2008; Rabinovich and Croci 2012). In the cross-presentation route the outcome is dependent on the activation status of the DCs that carry, process and present the tumor antigens to the T cells (Melief 2003; Steinman et al. 2003). In addition, the local micromilieu may have an impact. The presence of metastatic tumor cells has been reported to favor a tolerogenic milieu for example in early cervical cancer (Battaglia et al. 2009). However, one should bear in mind that also the lymph drainage from tumors to the LN is elevated when compared to drainage from normal tissues (Harrell et al. 2007; Thomas et al. 2012). This suggests that the TDLN microenvironment can be shaped by tumor-derived cytokines, chemokines and other compounds that may support or suppress an antitumor response.

For instance, suppression may occur through the specific accumulation of Tregs in TDLN as was found in patients with an unfavorable course of colorectal cancer (Deng et al. 2010b) but it may also directly influence the capacity to elicit tumor immunity in TDLN as was demonstrated in a mouse model where tumor cells directly injected in the LN of naïve mice were readily eradicated whereas tumor cells injected in the TDLN of tumor-bearing mice continued to grow in the face of the immune system (Preynat-Seauve et al. 2007). In line with this notion are reports showing that TDLN can harbor functionally impaired T cells (Baitsch et al. 2011; Contassot et al. 2009; Mantovani et al. 2008) and even antigen-specific Tregs (van der Burg et al. 2007).

Clearly, if tumors can affect T cell priming at a distance they for sure can accomplish this at the short range. Therefore, it is highly likely that the quality of the T cell response elicited in the ectopic LNs may also be determined by the local milieu. The previously mentioned positive correlation between the cellular content of these ectopic LNs and the clinical outcome of patients was associated with the presence of CD4+ Th1-specific T box transcription factor (Tbet) positive (IFN-γ-associated) T cells in the tumor (Dieu-Nosjean et al. 2008; Coppola et al. 2011; Randall 2010). In contrast, these lymphoid tissues have also been detected in breast cancers but here these structures comprised DCs that induced IL-13 producing CD4+ Th2 cells and this was associated with a non-beneficial clinical response. These Th2 cells promoted tumor growth potentially via the enhanced differentiation of macrophages to a M2 phenotype (Aspord et al. 2007; DeNardo and Coussens 2007). Thus, whereas ectopical LNs can elicit tumor-immunity they

are likely under the same control of the tumor with respect to the micromilieu that determines final outcome. The questions on why, how and at what site LN-like structures are generated, still have to be answered but it seems that they develop at pathological sites where an adaptive immune response is needed (e.g. the tumor, the inflammation site, the transplanted organ, the vaccine injection site). B cells have also been detected in ectopic LN structures found in tumor of colorectal carcinoma patients (Coppola et al. 2011) and the presence of tumor resident B cells is related to better prognosis for patients with breast, ovarian, colorectal, cervical and non-small cell lung cancer (Nelson 2010). Activated B cells can facilitate T cell responses but resting B cells are likely to inhibit the development of effective T cell responses (Nelson 2010; Qin et al. 1998; DiLillo et al. 2010), however their exact role is still unclear.

Thus, tumor-specific T cell responses are not necessarily induced in the TDLN but may also happen directly within LN structures in the tumor. In both cases it is likely to occur under conditions that are controlled by all kinds of tumor-derived and immune cell produced factors together determining the type and efficacy of these activated T cells.

5.4 Initiation of the Immune Response

The next question is what factors are responsible for the priming of a tumor-specific immune response during tumor development? Several mechanisms have been described.

Upon exposure to carcinogens or genotoxic events cellular DNA may get damaged resulting in a cell cycle arrest (senescence). This DNA damage response (DDR) pathway dependents on the activation of the DNA double-strand break checkpoint kinase ataxia telangiectasia (ATM) mutated kinase and checkpoint kinase 2 (CHK2) (Di Leonardo et al. 1994; Lombard et al. 2005; Zhan et al. 2010; Gordon and Nelson 2012) as well as the accumulation of the tumor suppressor gene p53 and the upregulation of the tumor suppressors $p16^{ink4a}$ and $P19^{Arf}$ (Braig and Schmitt 2006; Hornsby 2007; Mallette et al. 2007). The DDR pathway is activated to allow the cell to repair the damage or to force it into programmed cellular death (i.e. apoptosis) when the damage is beyond repair [reviewed in (Gordon and Nelson 2012; Zhou and Elledge 2000)]. Importantly, activation of the DDR pathway can result in NF-κB activation leading to the production of inflammatory cytokines (e.g. IL-1β, IL-6, IL-15), chemokines (e.g. MCP-1, CXCL-1), and adhesion molecules (e.g. ICAM-1) which may attract immune cells such as monocytes (by MCP-1) and neutrophils (by CXCL-1) and help T cells (by ICAM-1 and IL-15) (Stagg et al. 2007; Biton and Ashkenazi 2011; Fumagalli and d'Adda di Fagagna 2009; Kloster et al. 2011; Rodier et al. 2009).

Whether the transition to senescence upon acute oncogenic stress is mediated through the autophagy pathway remains under debate (Young et al. 2009) but this pathway is a cellular survival mechanism that limits cellular damage upon the

cellular stress and is generally known to be the first defense mechanism of cells to internal stress. Autophagy may also result in cell death either via apoptosis or necrosis. The necrotic cell death is mediated by cell death ligands such as TNF-α and Fas ligand (FasL, CD95L) (Shen and Codogno 2012). Nowadays, it is believed that the tumor cells need to undergo apoptosis and not senescence as in the latter case they remain in an unresponsive state but are still able to secrete all kind of tumor promoting factors (Kahlem et al. 2004). One of the endpoints of apoptosis is an efficient engulfment of the intact cell corpse by professional phagocytes. DCs and macrophages attracted by the release of lysophosphatidylcholine from apoptotic cells (Lauber et al. 2003) are able to do this and to present the ingested tumor antigens to B and/or T cells (Albert et al. 1998).

In addition, exposure to carcinogens or genotoxic events may result in the expression of NK cell- and CD8+ T cell-expressed NKG2D ligands, such as MHC class I chain-related chain A (MICA) and MICB, ringing the alarm bells of the immune system and facilitating the killing of tumor cells by these effector cells (Gasser et al. 2005; Hayakawa and Smyth 2006).

During necrotic cell death a number of damage (or danger)-associated molecular pattern molecules (DAMPs) can be released. DAMPs can initiate and perpetuate immune responses in the absence of infections with pathogens. The most common known DAMPs are RNA, DNA, adenosine-5′-triphosphate (ATP), uric acid, high mobility group box 1 (HMBG1), heat shock proteins (hsp) and hyaluronic acid (Tang et al. 2012). For instance, HMGB-1 is released by damaged cells and necrotic cells but not by apoptotic cells (Scaffidi et al. 2002) and can bind to TLR2, TLR4 and the receptor for advanced glycation endproducts (RAGE), which are all implicated in inflammatory reactions (Sims et al. 2010). Notably, HMGB-1 mediated inflammation is repressed by the co-expression of CD24 (Chen et al. 2009). The soluble HMBG1 was shown to activate DCs via its binding to TLR4. This interaction results in the inhibition of lysosomal degradation of tumor antigens leaving the antigen intact for the cross-presentation route and subsequent presentation in MHC at the cell surface as well as upregulates the production of pro-IL-1β. Furthermore, dying tumor cells release ATP which can act on a series of purinergic receptors, among which P2X7 has the highest affinity for ATP. When present on APCs, the receptor ligation causes the K+ efflux-dependent assembly of the inflammasome, which in turn activates caspase-1 required for the proteolytic processing of pro-IL-1β and the secretion of mature IL-1β and subsequently to induce adaptive immunity (Franchi et al. 2009; Kepp et al. 2011; Martins et al. 2009; Schroder and Tschopp 2010). Importantly, the production of IL-1β was found to be essential for the efficient priming of T cells (Ghiringhelli et al. 2009). Similarly, uric acid can also activate the NALP3 inflammasome. It activates the inflammasome pathway in DCs resulting in the production of active IL-1β and IL-18 (Martinon et al. 2006). Furthermore, tumor-derived DNA can be ingested by professional APCs where it binds to the intracellular DNA sensor (i.e. IFI/p204 or DDX41) starting a signaling cascade via the endoplasmic reticulum situated stimulator of interferon genes (STING), the activation of IRF3 and the type I IFN transcription pathway to induce IFN-β production (Fuertes et al. 2011;

Gajewski et al. 2012; Romano et al. 2012; Zhang et al. 2011). Consequently, cross presentation of tumor antigens to CD8+ T cells by CD8α+ DC occurs after the initial production of IFN-β by plasmacytoid DC (Gajewski et al. 2012; Di Domizio et al. 2012).

More recently it has been demonstrated that not only dying/dead tumor cells can elicit an anti-tumor response. Tumor-derived exosomes, which are micro-vessels of the tumor cells armed with tumor antigens presented by MHC, integrins and cytokines, can activate T cells once taken up by APCs, processed and optimally presented to T cells (Wieckowski et al. 2009). However, it should be noted that when these exosomes (also) harbor FasL and cytokines like IL-10 and TGF-β, they can stimulate cancer associated fibroblasts and Tregs (Webber et al. 2010; Szajnik et al. 2010).

A more indirect way of tumors to attract the immune system is by its growth. An expanding tumor requires increasing amounts of nutrients and oxygen and thus starts to support the formation of blood vessels. This vascularization as well as the invasion of the tumor cells into the surrounding tissue provokes pro-inflammatory signals which may lead to the activation of DCs and the induction of an immune response (Fuchs and Matzinger 1996). Tumor growth and associated tissue remodeling utilizes proteases to cleave components of the extracellular matrix. One of these is biglycan. This protease is able to trigger TLR-2 and TLR-4 on macrophages and DCs thereby inducing pro-inflammatory cytokine production (Schaefer et al. 2005; Edwards 2012). In line with this is the observation that the group of patients of whom their HPV-induced cervical tumor deeply invaded the surrounding tissue not only displayed an HPV-specific T cell response but also was the group of patients who benefitted most from concurrent radiotherapy (Heusinkveld et al. 2012).

In conclusion, during the development of the tumor, its growth and the invasion of the surrounding tissue the immune system is alarmed via several mechanisms. The result can be a response of the adaptive immune system which not necessarily may be effective as tumors raise several hurdles to suppress immunity. These hurdles need to be overcome before an effective control of the tumor ensues.

5.5 Improving the Effect of Spontaneous Tumor-Specific Immune Responses

The chronic inflammatory nature of the tumor microenvironment, with high numbers of tumor associated M2 macrophages, tolerogenic DCs, MDSCs, and Tregs, is not likely to sustain the capacity of effector cells to exert their anti-tumor function (Wang et al. 2008). In addition, the beneficial clinical effect of T cells can be impaired via downregulation of cell surface MHC class I on tumor cells (Jordanova et al. 2008; Garrido et al. 2010; Maleno et al. 2011; del Campo et al. 2012), the upregulation of the non-classical MHC class I molecule HLA-E

(Gooden et al. 2011) as well as by T cell expressed inhibitory molecules of which programmed cell death protein 1 (PD-1) (Weber 2010; Topalian et al. 2012; Karim et al. 2009), cytotoxic T lymphocyte antigen 4 (CTLA-4) (Weber 2010; Hodi et al. 2010), T cell immunoglobulin and mucin domain 3 (TIM-3) (Ngiow et al. 2011), lymphocyte activation gene 3 (LAG3), CD94/NKG2A (Gooden et al. 2011), V-domain Ig suppressor of T cell activation (VISTA) (Wang et al. 2011), CD200 and BTLA (Pardoll 2012; Haymaker et al. 2012; Fourcade et al. 2012) are known to impair T cell stimulation and effector function (Pardoll 2012; Pentcheva-Hoang et al. 2009; Gajewski et al. 2006; Sakuishi et al. 2010; Wherry 2011; Woo et al. 2012), thereby allowing the tumor cells to escape from the immune attack. The impairment of T cell expansion and their function via these inhibitory molecules can readily be relieved by blocking the inhibitory molecules expressed by T cells or their ligands on APC or tumor cells with monoclonal antibodies. The anti-CTLA-4 antibody ipilimumab has been approved for the treatment of melanoma (Hodi et al. 2010) and there is also strong evidence that antibodies blocking the inhibitory molecule PD-1 or its ligand PD-L1 enhance the anti-tumor immune response (Topalian et al. 2012; Brahmer et al. 2012).

Initial and ongoing efforts in the development of active immunotherapeutic approaches concern the enhancement of effector cell function and frequencies, for instance by vaccination (Melief and van der Burg 2008). Strategies to boost the spontaneous anti-tumor response are the use of chemotherapeutic agents. The group of Zitvogel et al. incisively studied the response of tumors beyond the stereotypical apoptotic pathway and found that a number of chemotherapeutic agents rendered tumor-cell death immunogenic resulting in the uptake of tumor antigen by local APC, activation of these APC via concomitant release of danger signals and subsequently the activation of an anti-tumor response (Kepp et al. 2011; Green et al. 2009; Hannani et al. 2011; Locher et al. 2010). Also radiation has been found to induce this immunogenic cell death and to elicit a vigorous response of the immune system (Kepp et al. 2011; Hannani et al. 2011; Golden et al. 2012). Radiation is likely to facilitate the tumor-specific immune response as cervical cancer patients with pre-existing tumor-immunity displayed clinical better responses upon radiotherapy (Heusinkveld et al. 2012). Recent studies show that indeed high numbers of IFN-γ-producing effector cells are required (Kenter et al. 2008; Welters et al. 2010; Porter et al. 2011; Powell et al. 2006; Restifo et al. 2012) but generally are not sufficient as these effector cells need to travel to the tumor and, within this microenvironment, should not encounter too much suppression. New efforts, therefore, aim at simultaneously changing the tumor microenvironment by shifting the balance towards the tumor-rejecting immune cells. Several common approaches are being explored by many research groups. Interestingly, some types of chemotherapy may have side effects that stimulate the immune system, for instance by the depletion of Tregs (Ghiringhelli et al. 2007; Vermeij et al. 2012) and MDSCs (Suzuki et al. 2005), thereby alleviating a number of immunosuppressive mechanisms and/or through direct and indirect stimulatory effects of immune effectors (Zitvogel et al. 2008). In addition, tumor-promoting M2 macrophages were found to be more susceptible to chemotherapy than

tumor-rejecting M1 macrophages or DC (Dijkgraaf et al. 2012b). Notably, the effects of chemotherapy may differ per patient as we recently found that chemotherapy applied to tumor cells with an activated NF-κB signaling pathway in fact enhanced their capacity to drive monocyte to M2 macrophage differentiation in an IL-6 and/or PGE2 dependent manner (Dijkgraaf et al. 2012b). There are numerous other pharmacological approaches to overcome the immunosuppressive mechanisms of myeloid cells which aim at the inhibition of immunosuppressive function, blocking their recruitment, and forcing their maturation (Gabrilovich et al. 2012). Preferably one would like to re-polarize the suppressive myeloid cells towards activated M1 macrophages as can be achieved by certain chemotherapeutic compounds (Kodumudi et al. 2010), the combined treatments with immune potentiating compounds (IL-12, CpG, IL10-blocking antibodies), agonistic CD40 antibodies or by inhibition of NF-κB signaling (Gabrilovich et al. 2012). Activation of M1 macrophages by anti-CD40 has resulted in tumor control both in mice and humans (Beatty et al. 2011; Lum et al. 2006). Alternatively, one may re-polarize these suppressive myeloid cells via the cognate interaction with Th1 cells (Heusinkveld et al. 2011), but this requires enough tumor-specific Th1 cells to be aroused and homed to the tumor. Such a clinically active Th1 response can be achieved through vaccination (Kenter et al. 2009; Gao et al. 2012). The inhibitory effect of Tregs may be counteracted by low doses of cyclophosphamide, denileukin diftitox (Ontak), dacluzimab (anti-CD25 antibody) or other drugs (Vermeij et al. 2012; Jacobs et al. 2012; Powell et al. 2008; Rasku et al. 2008; Rech and Vonderheide 2009). Improved T cell responses have been seen when these treatments were combined with vaccination (Vermeij et al. 2012; Rech and Vonderheide 2009; Dannull et al. 2005; Morse et al. 2008; Walter et al. 2012).

Apart from removing or inhibiting suppressive mechanisms the polarization of the spontaneously induced immune responses and their capacity to exert their cancer-rejecting function will benefit from a change of the local micromilieu towards what is seen during acute inflammation or tissue rejection (Wang et al. 2008). Currently, topical application of the TLR-7 ligand imiquimod can result in the elimination of pre-malignant and malignant lesions, including high grade vulvar intraepithelial neoplasia (van Seters et al. 2008; Winters et al. 2008) and basal cell carcinoma (Ghafouri-Fard 2012; Roozeboom et al. 2012). Imiquimod has also been applied to melanoma in situ when presented in the head and neck region (Ellis et al. 2012). Topical treatment with imiquimod results in the increased infiltration of lesions by CD4+ and CD8+ T cells as well as DCs (Daayana et al. 2010; Hermanns-Le et al. 2003; Ooi et al. 2006). More experimental approaches are the intratumoral injections with pro-inflammatory agents such as CpG, Poly I:C, CD40L plasmid DNA, which alone or in combinations were shown to improve T cell homing, activation of local APCs and the induction of a local cytokine milieu that favors the induction and antitumor effects of a tumor-specific Th1/CTL response (Amos et al. 2011; Fan et al. 2012; Grauer et al. 2008; Stone et al. 2009), known to be important for tumor control (Fridman et al. 2011). Similar effects can be observed when cytokines cocktails are injected near TDLNs (Berinstein et al. 2012).

A powerful option to create such a tumor rejecting milieu that is already applied in clinical trials is the use of the immune modulator IFN-α. This cytokine is used to treat chronic viral hepatitis infection and malignancies (Pasquali and Mocellin 2010). It enhances the differentiation of antigen-specific Th1 cells, promotes the generation of CTL and sustains the survival of T cells (Belardelli et al. 2002; Huber and Farrar 2011). Moreover, type I IFNs promote the differentiation of monocytes into DCs and enhance DC activity (Mohty et al. 2003; Parlato et al. 2001; Santini et al. 2002; Santini et al. 2000; Santodonato et al. 2003; Tosi et al. 2004). In addition, IFN-α enhances the expression of HLA class I and II on tumor cells (Beniers et al. 1991; Cangemi et al. 2003), and high doses of IFN-α intravenously given to melanoma patients results in decreased levels of Tregs (Mozzillo and Ascierto 2012) and reduces the numbers of neutrophils (Verdegaal et al. 2011), which are known independent prognostic factors for short survival (Schmidt et al. 2007). Moreover, daily injections of IFN-α complemented with the adoptive transfer of tumor-reactive T cells in metastatic melanoma patients can lead to clinical success (Verdegaal et al. 2011). In addition, the co-injection of IFN-α with vaccines resulted in a consistent enhancement of vaccine-specific CD4+ and CD8+ T cells and increased the percentage of blood circulating DC precursors in mice and men (Sikora et al. 2009; Di Pucchio et al. 2006; Zeestraten et al. 2012). Another cytokine which is considered to be used as an immunomodulatory therapy is the use of IFN-γ. This cytokine is known to induce M1 macrophages and the expression of cytotoxic ligands on tumor cells, to enhance tumor antigen processing and presentation as well as to steer and sustain the adoptive immune responses against tumors (Ikeda et al. 2002). In addition, it can directly affect tumor growth and tumor angiogenesis (Ikeda et al. 2002). Recombinant IFN-γ has been used in the past to treat cutaneous T cell lymphoma (Kaplan et al. 1990) and more recently for both cutaneous T- and B-cell lymphomas by the intratumoral injection of adenovirus-IFN-γ. This resulted in systemic immune activation that polarized the immune response to Th1 responses and increased the antibody response to tumor antigens (Dummer et al. 2010). However, IFN-γ may also have some unwanted immunological effects (Wilke et al. 2011) warranting careful immunomonitoring of local events.

In summary, there are a couple of non-exclusive treatment options that potentially can boost the expansion and efficacy of spontaneously aroused, vaccine-induced, and ex vivo expanded infused tumor-specific T cell by modulation of the systemic and local immune environment. It is highly likely that the best control of tumors is only achieved when a number of modalities are used together.

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