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Review

Tumor blood vessels, a difficult hurdle for infiltrating leukocytes

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Abstract

In spite of a gradual improvement of its therapy, cancer is still a deadly disease for millions of patients. Immunotherapy is one of promising treatment strategies, but several mechanisms counteract the development of a proper anti-tumor immune response and the formation of an effective inflammatory infiltrate. One of the difficult hurdles is the hampered recruitment of leukocytes from the blood into the tumor site. It has been demonstrated that tumor cells evolved mechanisms to escape immunity, based on down regulation of endothelial adhesion molecules. This paper reviews the endothelial cell adhesion molecules that mediate leukocyte recruitment and the regulation of them during tumor development. In addition, an overview will be given of the translational development and clinical application of the specific composition of adhesion molecules on tumor endothelium, in diagnosis and therapy.

Keywords: Leukocyte; Endothelial cell; Inflammation; Cancer; Infiltration; Interaction

Contents

1. Introduction

Cancer is a diverse, complex and deadly disease that afflicts millions of people each year. In search of a remedy for this terrible disease, different strategies have been explored. About 50% of cancer patients are curable with surgery, radiation

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therapy, and chemotherapy, which leaves 50% of the patients without a future. Therefore, other strategies for cancer treatment have to be investigated. One promising approach is immunotherapy, especially the design of methods that generate tumor-specific immune effector cells through the use of tumor vaccines or cytokine therapies [1–4]. All such approaches are dependent on the ability of tumor-specific effector cells to cross the vessel wall into the tumor. The recruitment of immune cells into a tissue is under the control of tissue-specific microenvironmental factors that regulate leukocyte and endothelial adhesion molecule expression and leukocyte-vessel wall interactions necessary for extravasation. This transendothelial migration of leukocytes is a multistep adhesion cascade that is mediated by a variety of tissue-specific endothelial adhesion molecules. This review summarizes the adhesion molecules involved in leukocyte recruitment in general, giving special attention to the role of less investigated and more recently discovered adhesion molecules. As will become clear from this review, tumors have evolved mechanisms to escape immune surveillance, one of which is the suppression of adhesion molecules on its blood vessels, making extravasation out of their vessels a difficult hurdle for anti-tumor immunity. In addition, imaging and therapy modalities that exploit the specific balance of endothelial cell adhesion molecules in order to improve cancer treatment will be discussed.

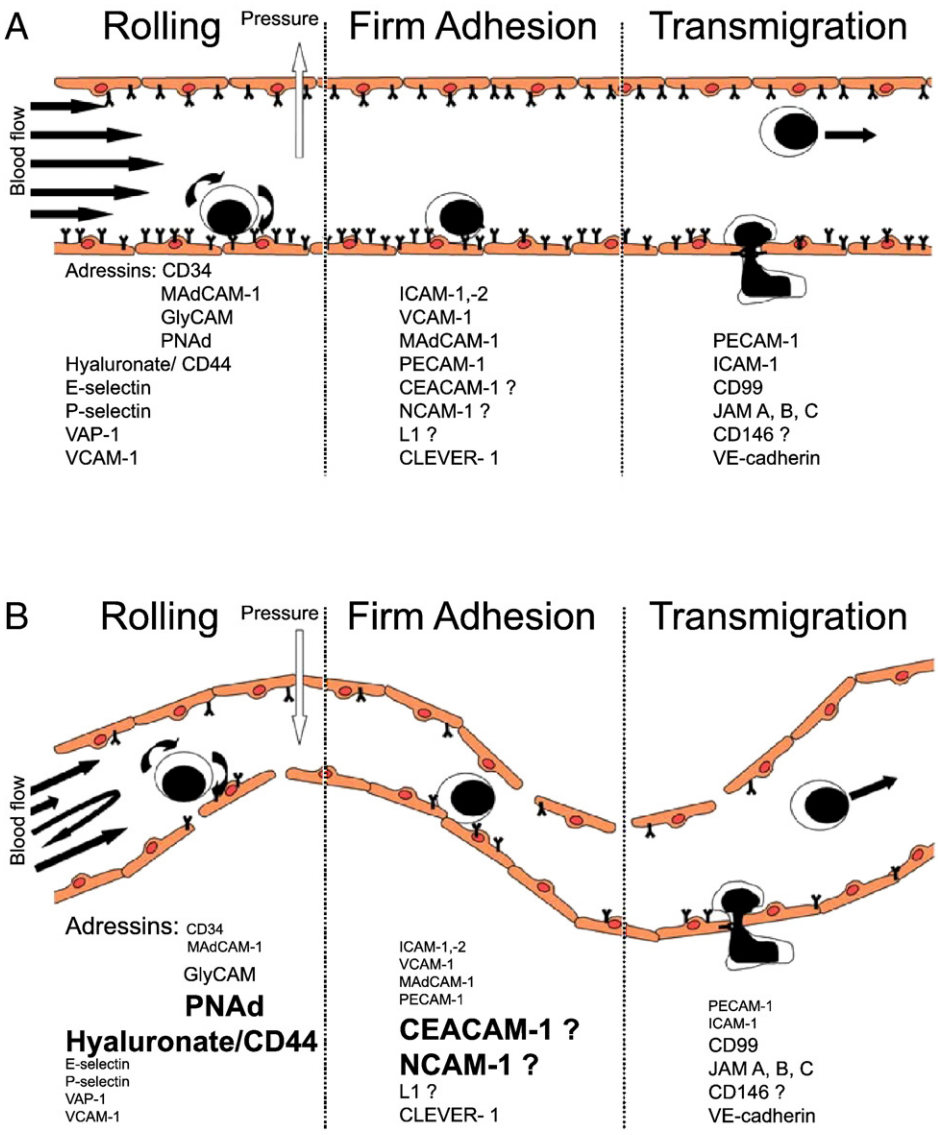

Fig. 1. The leukocyte adhesion cascade is modulated by tumor cells to escape anti-tumor immunity. (A) The recruitment of leukocytes from a normal blood vessels into tissues under shear flow (black arrows) is mediated through a cascade of events that is comprised of the following steps: (i) initial leukocyte tethering and rolling, (ii) firm adhesion and (iii) transmigration through the endothelial cell lining. Every step in this cascade is mediated by specific endothelial cell adhesion molecules (**Y**) as indicated. (B) In order to evoke the anti-tumor immune response, tumors modulate the expression of these adhesion molecules in a specific manner. The size of the font indicates the induction (bold large) or reduction (small) of expression levels on tumor endothelial cells. The amount of expression of a few adhesion molecules is not affected (unchanged size of font) by the tumor microenvironment. In addition, blood flow (black arrows) and interstitial pressure (white arrow) are very irregular and different compared to normal vessels.

2. The adhesion cascade for leukocyte recruitment

Recruitment of leukocytes from the blood into tissues under shear flow is a multistep process, comprised of initial tethering and rolling, activation, firm adhesion, and transendothelial migration of leukocytes [5,6] (Fig. 1A). This adhesion cascade is orchestrated by tissue-specific communication between leukocytes, endothelium, stromal cells and in tumors also by tumor cells, through factors secreted in the microenvironment.

Initial tethering and rolling of leukocytes is predominantly mediated by selectins. Low affinity binding of endothelial (E)-selectin and platelet (P)-selectin on endothelial cells, to leukocyte (L)-selectin, leads to initial rolling of the leukocytes along the endothelium [7,8]. Next to selectins, other adhesion molecules can initiate tethering and rolling of leukocytes on the vessel wall. Vascular addressins, such as peripheral lymph node addressin (PNAd), CD34, GlyCAM and mucosal addressin (MAdCAM-1) [9], all ligands of L-selectin, can also mediate low-affinity binding between endothelial cells and leukocytes. In addition, vascular adhesion protein-1 (VAP-1) [10–14], vascular cell adhesion molecule-1 (VCAM-1) [15,16] and hyaluronate (HA)/CD44 [17] expression on endothelial cells can be involved in such primary adhesion processes of leukocytes as well. Tethering and rolling are processes based on reversible adhesion events. In order to achieve firm and tight binding, these must be replaced by stronger adhesion through other adhesion molecules. This is accomplished during activation of endothelial cells and leukocytes by cytokines, chemokines or chemoattractants excreted by surrounding cells and tissues as well as by the adhesion events itself [5,6,8,18,19]. Upon activation, expression of endothelial ligands for leukocytes is either increased or induced de novo. The specific patterns of endothelial cell adhesion molecules are complex and depend on the combination of cytokines and the type of endothelial cells [6,8]. Activation of leukocytes by chemokines increases the expression and functional activity of leukocyte integrins [20], leading to high-affinity binding with endothelial cell adhesion molecules. An overview of the most well-known and well-described endothelial cell adhesion molecules and their leukocyte counter-ligands is given in Table 1. Firm adhesion of leukocytes to the endothelial wall is mainly obtained by three members of the immunoglobulin gene superfamily: intercellular adhesion molecule-1 (ICAM-1), ICAM-2 and VCAM-1 [21–24] (Fig. 1A). MAdCAM-1 [5,24] and platelet-endothelial cell adhesion molecule-1 (PECAM-1) [25], have also been associated with firm adhesion, although their involvement in this process is less pronounced. The adhesive properties of some immunoglobulin-like adhesion molecules are not yet fully unraveled. L1 adhesion molecule [26–28], neural cell adhesion molecule (NCAM) [29] and carcinoembryonic antigen-related cell adhesion molecule-1 (CEACAM-1) [30,31] are able to mediate cell–cell adhesion, however leukocyte–endothelial cell adhesion has not yet been convincingly demonstrated. Adhesion molecules not related to the immunoglobulin gene superfamily have been associated with leukocyte arrest as well. One of them is the common lymphatic endothelial and vascular endothelial receptor-1 (CLEVER-1 also known as FEEL-1, stabilin-1) which can mediate leukocyte adhesion both on vascular as well as lymphatic endothelium [32].

Table 1
Endothelial cell adhesion molecules implicated in the adhesion cascade and their leukocyte counter-receptors

Endothelial-cell molecule	Leukocyte counter-receptor	Leukocyte-vessel wall interaction	References
CD34	L-selectin	rolling	[24]
MAdCAM	L-selectin, $\alpha_4\beta_7$	rolling, firm adhesion	[24]
GlyCAM	L-selectin	rolling	[24]
PNAd	L-selectin	rolling	[24]
E-selectin	PSGL-1, L-selectin	rolling	[24]
P-selectin	PSGL-1, L-selectin	rolling	[24]
VAP-1	?	rolling	[47,48,91]
VCAM-1	VLA-4, $\alpha_4\beta_7$	rolling,	[24]
HA	CD44	rolling	[17]
CD44	HA/CD44	rolling	[97]
ICAM-1	LFA-1, Mac-1	firm adhesion, transmigration	[24]
ICAM-2	LFA-1, Mac-1	firm adhesion	[24]
PECAM-1	PECAM-1	firm adhesion, transmigration	[43]
NCAM-1	? NCAM-1?	? firm adhesion ?	[29]
L1	VLA5, $\alpha_4\beta_3$, L1	? firm adhesion ?	[26–28]
CEACAM-1	? LFA-1?	? firm adhesion ?	[30]
CLEVER-1	?	firm adhesion	[32]
CD99	CD99	transmigration	[43]
JAM A	LFA-1, JAM A	transmigration	[43]
JAM B	VLA-4	transmigration	[43]
JAM C	Mac-1, JAM C	transmigration	[43]
CD146	?	? transmigration ?	[42]
VE-cadherin	No direct interaction with leukocytes	transmigration	[43]

? indicates unknown and not yet fully proven leukocyte counter-receptors or implications in the vessel wall interactions.

Interestingly, cell matrix adhesion molecule alpha(v)beta(3) integrin ($\alpha v\beta 3$) might be implicated in leukocyte-vessel wall interactions when expressed on endothelial cells [25], since there are reports that show leukocyte adhesion to endothelial cells via $\alpha v\beta 3$–CD31 interaction [33]. Galectins are also suggested to mediate leukocyte-vessel wall interactions. Galectins are a family of carbohydrate binding proteins that has been implicated in cell–cell adhesion interactions. Galectin-1, -3 and -9 are described to be expressed by endothelial cells, of which galectin-3 and -9 might mediate adhesion of neutrophils [34,35] and eosinophils [36,37], respectively.

Firm adhesion is followed by diapedesis of leukocytes through the vessel wall with minimal disruption of the vascular lining. Although it has been reported that a small number of leukocytes transmigrate at non-junctional locations [38], leukocytes mainly cross the endothelium via inter-endothelial junctions. PECAM-1, ICAM-2, CD99, junctional adhesion molecule (JAM)-A, -B, -C and vascular endothelial-cadherin (VE-cadherin) have been predominantly described to mediate this paracellular diapedesis [19,39–45]. CLEVER-1 [46] and VAP-1 [14,47,48] also participate in leukocyte migration. Next to PECAM-1, ICAM-2 and JAMs, a fourth member of the immunoglobulin gene superfamily is enriched at cell–cell

junctions, namely CD146 (Mel-CAM) [42]. Its possible role in transendothelial migration has not yet been described.

The combination of molecules expressed by the endothelium, receptors on leukocytes and tissue-specific microenvironmental factors act together to determine whether a leukocyte is recruited. This intricately regulated process provides numerous events at which diversity can be introduced to regulate tissue-specific recruitment of a diverse and effective leukocyte infiltrate [49–51].

3. Regulation of endothelial adhesion molecule expression by tumor cells

Cytotoxic T cells are, when activated, able to control tumor growth [52], whereas T helper cells also play an important role in regulation of tumor destruction [53]. Nevertheless, many tumors can progress without any signs of attack by immune cells [54]. The reason why immune responses are unable to eradicate the tumor is not fully understood. Several processes have been shown to contribute to the escape of a tumor from the immune system. The expression on tumor cells of MHC/HLA determinants that present tumor antigens can be suppressed [55–57]. Compounds from the tumor microenvironment prohibit effector T cell maturation and function [58,59]. Furthermore, immunosuppressive leukocytes like regulatory T cells and myeloid-derived suppressor cells are preferentially attracted and activated in tumor tissues [60,61]. In addition, it has also been described that tumor-derived VEGF can prevent the proper maturation of dendritic cells. Besides these processes, one other very significant explanation of ineffective immunity is aberrant leukocyte-vessel wall interactions and trans-vessel migration. A prerequisite for anti-tumor immunity is that immune cells actually enter into the tumor. However, the tumor microenvironment modulates leukocyte recruitment in such a way that infiltration of tumor specific effector leukocytes into cancer tissues is inhibited and consequently tumor eradication by the immune system is prevented. As leukocyte recruitment is a multistep process, the tumor can interfere at different levels of this cascade in order to decrease total influx of leukocytes. Tumor vessels differ from normal vessels in their irregular structure, tortuous morphology, leakiness and aberrant blood flow (Fig. 1A, B). Furthermore, rapid proliferation of tumor cells increases interstitial pressure which can lead to collapsed vessels within the tumor tissue [62]. The following section will give an overview of the manipulation of endothelial adhesion molecule expression by the tumor at different steps during leukocyte recruitment (Fig. 1B). Special emphasis will be on the importance of less well known and more recently described adhesion molecules expressed on tumor endothelium.

3.1. Rolling

In blood vessels activated by inflammatory factors, leukocytes are able to roll along the vessel wall before firm adhesion is established. Although a tumor frequently behaves as an inflammation, these interactions in a tumor are much less frequent [63,64]. It has been described that exposure to angiostatic factors, produced by tumor cells to induce angiogenesis, is causally related to a suppressed endothelial adhesion molecule expression and a diminished number of low-affinity interactions. Although angiogenic factors like basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) initially increase expression of E-selectin on endothelial cells in vitro, chronic stimulation as occurs in the tumor microenvironment, leads to a significant decrease of selectins [65–67]. Animal and patient reports confirmed in different tumor types that the expression of E- and P-selectin is decreased on tumor microvasculature as compared to expression in normal vessels in healthy tissues [68–71]. Studies in melanoma and colorectal cancer even showed progressive loss of P-selectin expression with increasing tumor malignancy [72,73]. Furthermore, decreased expression of P-selectin on tumor vessels was correlated with diminished leukocyte tumor infiltration, indicating that tumor lesions can evade inflammatory regression processes via decreasing leukocyte rolling along the tumor vessel wall. On the other hand, there are studies that found high E- and P-selectin expression levels in tumor vessels compared to control. However, in these studies, the expression levels of endothelial adhesion molecules on tumor vessels were very heterogeneous, suggesting an inefficient leukocyte recruitment throughout the tumor tissue. In addition, high levels of E- and P-selectin contribute to the invasive character of the tumor and tumor metastasis [74,75].

PNAd and GlyCAM-1 mainly mediate leukocyte rolling in high endothelial venules in secondary lymphoid tissues, whereas MAdCAM-1 is predominantly present on endothelial cells in the gastrointestinal tract [76–80]. However, they have also been implicated to mediate rolling of leukocytes within tumor vessels [81]. Onrust et al. showed that lack of L-selectin ligand expression on vessels in β cell tumors is associated with diminished leukocyte tumor infiltration [82]. In addition, a recent study with gastric adenocarcinomas by Enarsson and coworkers revealed a shift in the homing mechanisms of T lymphocytes used for migration to normal and tumor gastric tissue. In normal gastric mucosa, T lymphocytes are recruited by MAdCAM-1 whereas the expression of MAdCAM-1 in gastric adenocarcinomas is decreased in favor of PNAd expression, leading to recruitment of a-typical T lymphocytes to the tumor tissue [83]. CD34, also a member of the addressin family, is actively regulated on endothelial cells by angiogenic factors. Furthermore, endothelial CD34 is suppressed in renal cell carcinoma compared to normal renal tissue [84]. These findings suggest that tumors can evade immune-mediated destruction by failure and/or modifications of addressin expression on tumor vessels (Fig. 1B).

Since L-selectin ligands play an important role in leukocyte recruitment to secondary lymphoid tissues, the first stage of tumor metastasis, one can imagine that leukocyte recruitment to these nodes may determine the development of metastatic disease. Indeed, trafficking of effective natural killer cells to tumor draining lymph nodes via L-selectin suppresses tumor formation in these tissues [85].

It is important to mention that the specific composition of integrins, growth factors and chemokines within the tumor

microenvironment also contributes to the recruitment of a-typical T lymphocytes and especially stimulates the attraction of leukocytes that participate in tumor progression. Over-expression of VEGF in tumors is associated with elevated numbers of regulatory T cells within the tumor tissue. The balance between regulatory T / effector T cells is thereby altered and tumor-associated antigen specific immunity is suppressed [60]. The trafficking of regulatory T cells to the tumor site is also partly mediated by the chemokine CCL22 in ovarian carcinoma and reduces patient survival [86]. In addition, stromal-derived factor-1 (SDF-1), expressed at high levels by human ovarian epithelial tumor cells, recruits plasmacytoid dendritic cell precursors. These cells produce high amounts of interleukin 10 into the tumor microenvironment consequently leading to impaired effector T cell function [87].

The most recent endothelial cell adhesion molecule found to be involved in leukocyte recruitment is VAP-1. Besides mediating leukocyte tethering and transmigration, VAP-1 also possesses an enzymatic function [88–92]. However, neither the mechanism nor the ligand by which VAP-1 binds leukocytes is fully elucidated. A few studies have shown that VAP-1 mediates rolling of tumor-infiltrating lymphocytes and proved expression of VAP-1 on tumor vessels although significantly decreased compared to expression in normal vessels [81,93,94]. The degree of VAP-1 expression is correlated with the amount of lymphocytes that infiltrates a tumor, suggesting that a tumor can dodge immune responses by decreasing VAP-1 expression in its vessels [95].

Finally, CD44 is involved in leukocyte endothelium interactions. This molecule, described as a leukocyte homing receptor, is expressed by both leukocytes and endothelium. With its natural ligand hyaluronic acid (HA) as a bridging molecule, CD44 provides a primary adhesion pathway for leukocyte rolling [96]. Cytokine stimulation leads to an induction of HA and CD44 expression [97,98] on endothelial cells derived of microvasculature followed by increased CD44-dependent primary adhesive interactions [17,98]. However, these interactions have not yet been described in tumor vessels. In cancer, HA is mainly studied as a product of tumor cells where, next to an association with tumor aggressiveness and metastatic potential, it has been reported to affect tumor angiogenesis [99,100]. HA has different roles in neovascularization depending on molecular mass [101]. These findings suggest that an increase in HA in tumor vessels would lead to induction of tumor growth rather than an increase of leukocyte influx, nevertheless so far no negative correlation between HA expression and leukocyte infiltration has been shown.

3.2. Firm adhesion

As mentioned before, rolling and tethering are low-affinity interactions and must be replaced by high-affinity ones to make leukocyte recruitment possible. Chronic stimulation of endothelial cells by angiogenic factors, abundantly present in tumor microenvironment, inhibits firm adhesion of leukocytes to endothelial cells in vitro [65,67,102,103]. In addition, intravital microscopy showed that exposure of non-tumor vessels to angiogenic factors, bFGF or VEGF, decreased cytokine-induced leukocyte adhesion [104]. Reduction of leukocyte adhesion was associated with a decrease of ICAM-1 and VCAM-1 expression on endothelial cells (Fig. 2A). Furthermore, firm interactions in tumor vessels (Fig. 2C) in vivo are diminished compared to interactions in normal vessels (Fig. 2B) and once again a positive relationship with ICAM-1 and VCAM-1 expression was observed [64]. Investigation of endothelial cells from different tumor tissues established a decrease in the endothelial cell adhesion molecules ICAM-1, ICAM-2 and VCAM-1 compared to endothelial cells of normal tissues [70,71]. This decrease was positively correlated with decreased leukocyte infiltration and associated with tumor progression [105,106]. To the contrary, tumor angiogenic factors can induce adhesion molecule expression on EC.

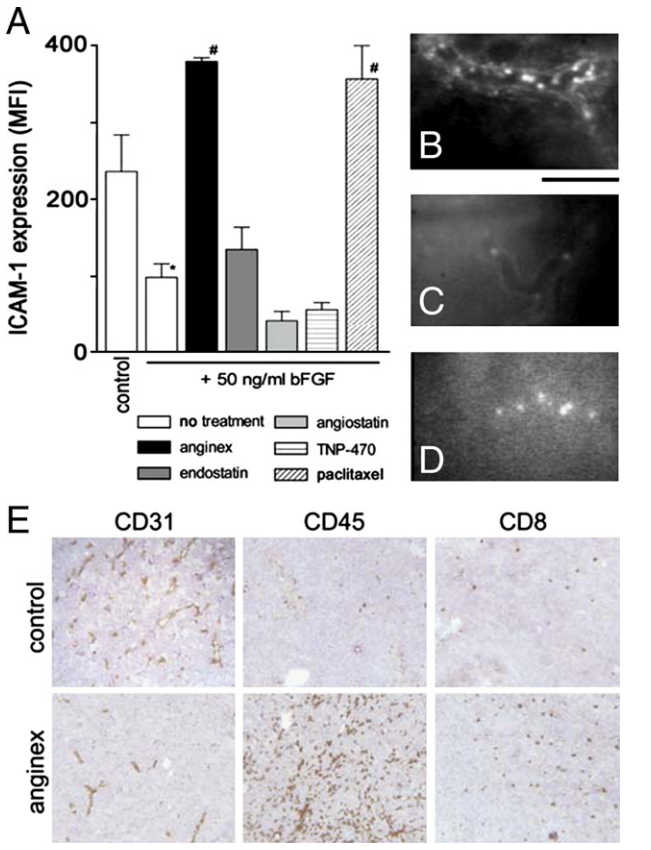

Fig. 2. Suppressed leukocyte recruitment in tumors can be normalized by angiostatic and chemotherapeutic compounds. (A) FACS analysis of ICAM-1 expression in b END5 mouse endothelial cells in the presence or absence of bFGF, and after treatment with angiostatic and chemotherapeutic agents. Data are expressed as mean fluorescence intensity (MFI), ±SEM, 4 independent experiments. $^{*}P<0.05$ vs. cells without bFGF, $^{\#}P<0.05$ vs. untreated cells. (B–D) Typical intravital fluorescence microscopy images of a normal ear skin vessel (B), an untreated tumor vessel (C), and an anginex-treated tumor vessel (D). Leukocytes are fluorescently labeled with Rhodamin 6G. The bar between panels B and C represents 45 μm. Video images can be viewed at www.angiogenesis.nl. (E) Immunohistochemical images of microvessel density (CD31), and infiltration by $CD45^{+}$ leukocytes and $CD8^{+}$ T lymphocytes in B16F10 melanoma of control and anginex treated mice. Bar in upper left panel represents 50 μm. Figure extracted with permission from Dirkx et al. The FASEB J, 20, 621–630 (2006).

Acute stimulation of endothelial cells with VEGF or bFGF induces ICAM-1 and VCAM-1 expression [66,107]. However, this is in conflict with the tumor microenvironmental conditions where prolonged release of angiogenic factors occurs. Bessa and co-workers stated that impaired leukocyte recruitment in tumor vasculature cannot be attributed to suppressed expression of the main endothelial cell adhesion molecules [74]. A recent publication by Bouzin and co-workers may give an explanation for this finding [108]. They found that besides quantity of adhesion molecule expression, the distribution of ICAM-1 and VCAM-1 on the endothelial cells surface determines leukocyte adhesion. Caveolin-1, a caveolar structural protein on EC, is diminished by VEGF stimulation. As caveolin-1 affects ICAM-1 and VCAM-1 clustering, a decrease of this protein leads to ineffective clustering and consequently decreased leukocyte adhesion [108].

Despite the fact that NCAM and CEACAM-1 are able to mediate cell–cell adhesion, they have not yet been implicated in leukocyte-EC adhesion. However, their expression on tumor endothelial cells has been established, suggesting that they could play a role in leukocyte adhesion in tumor vessels. NCAM has been found on tumor endothelial cells of renal cell carcinoma but not on vessels of normal renal tissue [109–111]. The expression of NCAM is associated with an immature phenotype of endothelial cells and tumor neo-angiogenesis. In addition, NCAM was detected on endothelial cells of smooth muscle and peripheral nerve sheath tumors [112]. Presence of NCAM on tumor endothelial cells is positively correlated with metastatic potential, in contrast with leukocyte infiltration which is not affected by NCAM expression [109]. Decreased expression of NCAM on malignant tumor cells increases their invasive capacity [113] as has also been shown for adhesion molecule L1. This neural cell adhesion molecule on tumor cells serves as a potential ligand for αvβ3 integrin during melanoma transendothelial migration suggesting a contribution of L1 to tumor progression by promoting cell adhesion and migration [114,115]. Like NCAM, CEACAM-1 is associated with newly formed immature tumor blood vessels and is positively correlated with aggressiveness of bladder cancer, melanoma and prostate cancer [30,116,117]. Furthermore, VEGF induces CEACAM-1 expression on endothelial cells and constitutive expression of CEACAM-1 in microvascular endothelial cells switches them to an angiogenic phenotype [118–120]. Interestingly, leukocyte adhesion is increased by CEACAM-1 expression on neutrophils, although via modulation of CD18/CD11 on leukocytes [121]. In contrast, CEACAM-1 appears to function as a coinhibitory receptor during T cell activation [122]. These reports show that while ICAM-1, ICAM-2 and VCAM-1 expression are diminished on tumor vasculature, NCAM and CEACAM-1 are upregulated on these vessels (Fig. 1) consequently leading to induction of angiogenesis, decreased leukocyte influx and ultimately tumor progression.

Similarly to NCAM and CEACAM, CLEVER-1 can mediate tumor metastasis. CLEVER-1 expression has been reported on vasculature of melanoma, squamous cell cancer of the head and neck and breast cancer where it might be involved in the adhesive interaction between tumor cells and endothelial cells [123,124]. The role of CLEVER-1 in leukocyte adhesion and migration has been under debate [125,126]. However, treatment with inhibitory antibodies against this molecule showed a decrease in leukocyte adhesion and diapedesis on/through vascular and lymphatic endothelium [32,127]. Since CLEVER-1 expression on tumor vasculature has been determined, CLEVER-1 might mediate leukocyte-tumor vessel wall interactions, although further investigation needs to be performed.

Cell adhesion molecule αvβ3 integrin is involved in many tumor-related processes and is highly expressed on activated endothelial cells, especially tumor EC, whereas it is hardly expressed on resting and quiescent endothelial cells in non-diseased tissues [128]. However, a role for αvβ3 integrin in leukocyte-tumor vessel wall interactions is unlikely considering the low number of interactions in contrast to the high abundance of αvβ3 integrin expression on tumor endothelial cells.

3.3. Transmigration

After leukocytes are firmly bound to the vessel wall, they can cross the endothelial cell barrier. As mentioned before, tumors prevent rolling and firm adhesion of leukocytes partly by decreasing endothelial adhesion molecule expression that mediates these processes. Consequently, only a small number of leukocytes has the opportunity to pass the endothelial lining. The best-described endothelial adhesion molecule that mediates leukocyte migration is PECAM-1 which is expressed by tumor EC. PECAM-1 expression is not affected by tumor growth factors bFGF or VEGF [70,102,129]. Nevertheless, a study by Berger et al. showed a redistribution of PECAM-1 expression from a constitutive circumferential membrane pattern on healthy and inflamed vessels to a pattern restricted to cell–cell junctions in tumor vessels [68]. This suggests a negligible role for PECAM-1 in firm adhesion of leukocytes on tumor EC. Anastassiou et al. showed that high PECAM-1 expression is correlated with extended survival in patients with renal cell carcinoma [130]. In addition, high PECAM-1 expression on vessels of these tumors is associated with stronger leukocyte infiltration within the tumor, proposing that, by reducing PECAM-1 expression on its vessels, the tumor can circumvent leukocyte influx.

CD99 is a type I transmembrane protein that is expressed on most hematopoietic cells and many other cell types [131]. For instance, its expression is characteristic for Ewing sarcomas and is used for differential diagnosis among sarcomas [132,133]. Schenkel et al. demonstrated CD99 expression on endothelial cells and function in the migration of monocytes through endothelial junctions [134]. Furthermore, it has been shown that CD99 is a key player in lymphocyte and neutrophil diapedesis [135,136]. Although CD99 expression has been extensively described on tumor cells, till now, no reports have shown the expression of this adhesion molecule on endothelial cells of tumor blood vessels. However, this does not exclude a role for CD99 in leukocyte transmigration through tumor endothelial cell lining. CD99-mediated transmigration is independent and subsequential to PECAM-1-mediated diapedesis and may

therefore be involved in the final steps of leukocyte migration through tumor vessels [137].

The JAM family members were initially described as adhesion molecules localized in cell–cell contacts and specifically enriched at tight junctions [138]. They are expressed by leukocytes and platelets as well as by endothelial and epithelial cells [137,139,140]. JAMs are suggested to possess dual functions [138]. They appear to regulate on one hand, leukocyte/platelet/endothelial cell interactions in the immune system [141,142], and on the other hand tight junction formation in epithelial and endothelial cells during acquisition of polarity [143,144]. JAMs can undergo homophilic as well as heterophilic interactions with other JAM family members as well as integrins. JAM-A, JAM-B and JAM-C interact with respectively leukocyte function-associated antigen-1(LFA-1) [142,145], very late antigen-4 (VLA-4) and integrin alphaM-beta2 (Mac-1) [146–148] expressed by leukocytes. These interactions can all lead to transmigration of leukocytes through the vessel wall. JAM-A and JAM-C have also been demonstrated to be involved in the process of angiogenesis [149–152]. Inhibitory antibodies of JAM-A decreased neovascularization in different models [153]. Furthermore, Lamagna and coworkers showed that besides tumor growth reduction by angiogenesis inhibition, JAM-C inhibitory antibody treatment in mice also reduces macrophage tumor infiltration, suggesting a role for JAMs in leukocyte recruitment in tumors [149]. Interestingly, angiogenic factors that induce angiogenesis do not decrease protein expression levels of JAM-A, JAM-B nor JAM-C. However, the distribution of JAMs is shifted to a broad zipper-like pattern and appeared to relocalize diffusely along the entire cell membrane, liberated from the tight junctions [154,155]. This finding might explain the decrease of transendothelial migration of leukocytes in tumor vessels.

Similar to a αvβ3 integrin and CD44, galectin-1 has been shown to increase upon angiogenic stimulation of tumor microvessels. Galectin-1 expression on endothelium has been described to hamper transmigration of leukocytes. An increase of this protein might therefore decrease the leukocyte influx in tumor tissues [156,157].

Finally, also VE-cadherin mediates leukocyte migration. In contrast to CD99, PECAM-1 and the JAM family, VE-cadherin does not mediate leukocyte transmigration via direct binding of the immune cells. During leukocyte transmigration, transient and reversible changes in VE-cadherin localization on the endothelium are observed, leading to an increased vascular permeability and a higher influx of leukocytes into inflamed tissues [137,158,159]. Angiogenic factors produced by tumor cells do not affect the expression level of VE-caderin on EC. Interestingly, VE-cadherin blocking antibodies are able to inhibit tumor growth and angiogenesis in a mouse model [152,155,160]. These reports indicate that, despite the fact that tumors are not able to affect VE-cadherin expression, it plays an important role in tumor angiogenesis and tumor progression and most of all operates as a barrier for immune cells.

The above-mentioned studies indicate that tumor cells can display regulatory functions in all sequential steps in the adhesion cascade of leukocytes, in order to diminish exposure to cytotoxic effector cells.

4. Imaging and therapeutic exploitations of endothelial adhesion molecules expression on tumor vessels

Over the last decades, scientists have searched for different strategies in treatment and diagnosis of cancer. One of these strategies is to target the tumor vasculature. By eradicating their vasculature, tumors become deprived of oxygen and nutritional supplies. Consequently, tumor growth decreases, however, in many cases without complete remission. As described previously, the tumor vasculature is modulated in such a way that immune cells can hardly cross the endothelial cell lining. Therapies that increase the distribution and extent of endothelial cell adhesion molecules on tumor EC, thereby augmenting leukocyte recruitment, might improve cancer therapy especially when combined with other strategies like anti-angiogenesis treatment. In addition, the specific composition of adhesion molecules present on tumor vessels (Fig. 1) can be used for different imaging modalities and targeted tumor therapy as will be discussed in the present section.

4.1. Imaging modalities

The in vivo regulation of receptors on vascular endothelial cells at diseased sites represents an attractive marker for visualization, early detection and monitoring of treatment responses, based on a range of important disease processes [128]. In angiogenic tissues such as tumors, blood vessels express a specific composition of adhesion molecules which can be applied in different tumor imaging strategies.

Cell adhesion molecule αvβ3 integrin is a frequently used tool for non-invasive imaging of tumor vessels. As mentioned before, this integrin is involved in many tumor-related processes and is highly expressed on activated endothelial cells, especially tumor EC, whereas it is hardly expressed on resting and quiescent endothelial cells [128]. This finding makes it a suitable marker for angiogenic vessels in malignant tissues. The αvβ3 integrin binds to a wide variety of extracellular matrix proteins, which expose the tripeptide sequence arginine–glycine–aspartic acid (RGD) as a common receptor motif [161]. Therefore, RGD-peptides and -mimetics have become a popular tool for targeting αvβ3 integrin-expressing tumor vasculature and they have been used in different non-invasive tumor imaging modalities like SPECT (single photon emission computed tomography), PET (positron emission tomography), scintigraphic imaging and MRI (magnetic resonance imaging) [162–167]. Recently, Mulder et al. proved that by using RGD-labeled, αvβ3 integrin targeted liposomes for noninvasive MRI utilities, imaging of tumor angiogenesis as well as early in vivo response to angiostatic tumor treatment can be assessed [168,169].

As mentioned before, NCAM is stably expressed by renal tumor-derived endothelial cells but not by normal quiescent ECs. This finding makes NCAM, like αvβ3 integrin, a suitable marker for tumor vascular imaging modalities. Geninatti-Crich et al. showed in a recent paper that a specific NCAM-binding

peptide, the chemoattractant degradation fragment of complement factor 3 (C3d), coupled to a gadolinium-loaded apoferritin is a highly efficient and selective contrast agent for MRI imaging of tumor vessels [170]. Aside from NCAM, CEACAM (CD146) expression has been demonstrated on activated EC. Anti-CD146 antibody showed restricted binding to CD146 expressed in blood vessels of tumors, suggesting potential for CEACAM in different tumor vasculature imaging strategies [171].

Although not yet demonstrated in tumor models, ICAM-1, VCAM-1, VAP-1 and E-selectin expression on endothelial cells can be used for visualization of vasculature as well. E-selectin expression was applied as an endothelial inflammatory marker in MRI studies using in vitro and in vivo models of inflammation and was found to posses an interesting capacity as a diagnostic tool [172–174]. In addition, non-invasive imaging of activated endothelium was obtained by using antibody fragments against VCAM-1 [175]. Even atherosclerosis, with low-grade endothelial activation, can be visualized by VCAM-1 targeted imaging, using MRI techniques [176,177]. In addition, MRI and scintigraphic imaging with respectively ICAM-1 and VAP-1 probes have been performed in different inflammation models in animals [178,179]. These reports indicate that increases of adhesion molecule expression can be visualized in different vessel types, suggesting that induction of adhesion molecule expression on tumor vessels by specific treatment could be assessed.

4.2. Treatment strategies

In addition to imaging modalities, the characteristic composition of adhesion molecules on tumor vessels are also an excellent tool for specific tumor targeted therapy. For instance, αvβ3 integrin is used in different strategies for selective delivery of therapeutics to tumor vasculature. Antibodies, peptides and small molecule peptidomimetics targeted to αvβ3 integrin on tumor endothelial cells via RGD motifs are successfully used in tumor therapies. Furthermore, efficiency of RGD-mediated viral gene delivery was demonstrated. These topics are elegantly reviewed by Temming [180] and Lim [166].

The specific tumor-associated arrangement of endothelial cell adhesion molecules may also be an interesting target for vaccine strategies. Tumor-vessel associated adhesion molecules could be used as tumor-associated antigens to create a selective immune response against tumor endothelial cells. This vaccination approach has already been successfully used for several tumor endothelium related molecules like VEGF, VEGF receptor 2 and angiogenic endothelial-cell growth factor-1 (ECGF-1) [181–183].

As mentioned before, besides αvβ3 integrin, CEACAM-1 is prominently expressed on tumor vessels. Several studies suggest that the constitutive expression of CEACAM-1 on tumor microvascular ECs switches them to an angiogenic phenotype [117,119,120]. Consequently, treatment with an inhibitory antibody for CEACAM-1 reduces tumor angiogenesis, growth and metastatic potential, providing a promising strategy for cancer therapy [171,184,185]. Furthermore, other family members of the immunoglobulin family, JAM-A and JAM-C, participate in angiogenesis and are subsequently interesting targets for anti-angiogenesis tumor treatment [150,155]. Nevertheless, junctional adhesion molecules are implicated in leukocyte transmigration processes, indicating that treatment of cancer with functional inhibitory antibodies of these molecules does not only inhibit tumor angiogenesis but also decreases leukocyte recruitment to tumor tissues [149,153]. Clearly, therapy that inhibits angiogenesis without diminishing leukocyte tumor recruitment would improve disease outcome. Inhibitory antibody against VE-cadherin might be such an agent. Monoclonal antibody to VE-cadherin is a potent inhibitor of angiogenesis, tumor growth and metastasis [160] and has been reported to induce vascular permeability thereby enhancing neutrophil extravasation [158].

Reports from our laboratory and others show that in addition to diminishing tumor vessel formation, a number of angiostatic compounds can also restore the expression of several adhesion molecules on activated endothelial cells (Fig. 2A). ICAM-1, VCAM-1, E-selectin and CD34 expression that are, as mentioned before, substantially decreased on angiogenically stimulated endothelial cells can be normalized after treatment with potent angiogenesis inhibitors like for example platelet factor 4, endostatin, angiostatin, SU6668 and anginex [63,129,186,187]. A recent paper by Hellebrekers et al. indicated the importance of epigenetic mechanisms in the normalization of adhesion molecules expression on tumor vessels, since DNA methyltransferase and histone deacetylase are able to reexpress these molecules on endothelial cells in tumor conditions [188,189]. The restoration of endothelial cell adhesion molecule expression on tumor vessels leads to an amelioration of leukocyte–vessel wall interactions and consequently an induction of leukocyte infiltration in the tumor tissue (Fig. 2C–E) [63,188]. These findings indicate that by using angiogenesis inhibitors, the gate for leukocytes to the tumor can be unlocked and many doors for combinations with modern immunotherapeutic approaches can be opened.

Until now, combination of angiostatic and immunotherapy to treat cancer was performed with the rational that angiostatic therapy reduces tumor growth thereby gaining time for the tumor specific immune response to assess [190–192]. Another combination strategy is immunization of animals against angiogenesis-associated antigens in order to induce anti-angiogenic immunity [193]. However these combination therapies have not fully exploit the dual function (Fig. 2E) of angiogenesis inhibitors namely (i) inhibition of vessel formation and (ii) the induction of adhesion molecule expression and leukocyte–vessel wall interactions in tumors, which might even increase affectivity of cancer treatments.

Interestingly, the endogenous angiogenesis inhibitor endostatin does not only increase expression of endothelial cell adhesion molecules on activated EC, it also requires the expression of E-selectin on endothelial cells in order to perform its angiostatic functions [194]. Furthermore, E-selectin expression might predict the efficacy of endostatin therapy and the modulation of E-selectin expression may improve antiangiogenic therapy mediated by endostatin. In addition

to endothelial cells membrane associated E-selectin, the soluble form of E-selectin (sE-selectin) in the blood circulation possesses prognostic properties, dependently of the tumor type. In breast carcinoma, it has been demonstrated that high serum concentration of sE-selectin in patients is associated with poor survival [195]. However, in patients with renal cell carcinoma, no correlation with prognosis could be assessed [196]. Soluble ICAM-1 (sICAM-1) and soluble VCAM-1 (sVCAM-1) are both important prognostic markers in several malignant diseases. Especially sICAM-1, that besides its diagnostic potential, has been implicated as a marker for treatment response. High serum levels of sICAM-1 and/or sVCAM-1 indicate a poor survival for the patient, whereas decreased concentrations of sICAM-1 after treatment indicate a positive response to therapy [197–201]. The role of soluble adhesion molecules in carcinogenesis is not yet fully unraveled, but it has been suggested that the shedding of sICAM-1 may enhance metastasis by protecting tumor cells from host immune surveillance [202]. Soluble adhesion molecules may bind to and block circulating cytotoxic lymphocytes, thereby helping tumor cells to escape from immune recognition [203]. Because sICAM-1, sVCAM-1 and sE-selectin can also promote angiogenesis [204–207], these soluble adhesion molecules may have a dual role in enhancing tumor growth.

4.3. Paradoxal role of leukocyte infiltration in tumor progression

Infiltration of leukocytes into tumors is not always beneficial to the process of tumor growth inhibition. Various studies report a positive correlation between the amount of tumor-infiltrated leukocytes and tumor growth as well as tumor angiogenesis [208–214]. Tumor-associated macrophages have pleitrophic actions. Macrophages can release growth and angiogenic factors that stimulate tumor cell proliferation, promote angiogenesis, and favor invasion and metastasis. To the contrary, when activated, these tumor-associated macrophages are able to kill neoplastic cells and/or elicit tumor-destructive reactions centered on the tumor vasculature. The outcome depends on the net result of individual functions, dictated by the activation state of the macrophages and the intrinsic properties of the tumor cell [215–217].

Tumor infiltration of T-lymphocytes mainly promotes patient survival [218–223] although there are studies that show the opposite [208,209]. The latter studies suggest that the immune response cannot act to attenuate tumor growth. This apparent paradox may be resolved by assessing the activation status and cytolytic capacity of tumor-infiltrated lymphocytes. In addition, the T-lymphocyte population that decreases patient outcome generally consists of CD4-positive T cells [208,209]. The previous mentioned immune suppressive regulatory T cells are positive for this marker as well as for CD25 and Foxp3. These cells prevent, as stated higher, the induction of tumor-associated antigen specific immunity and inhibit the anti-tumor immune response [224–227].

Furthermore, infiltration of tumor tissues with plasmacytotic dendritic [213] cells as well as myeloid-derived suppressor cells [61] reduces the functions of effector T cells in tumors and promotes tumor outgrowth.

These reports suggest that by increasing leukocyte influx in a tumor, it will expand rather than degrade. However, the effect of the leukocyte infiltrate in tumors on this progression depends on the composition of the leukocyte populations within this tissue and especially their activation status. The tumor microenvironment displays various factors that manipulate the expression of endothelial cell adhesion molecules and cytokines/chemokines in such a way that a-typical and immune suppressive leukocytes are preferentially attracted to the tumor tissue [60,61,83,86,227]. Moreover, different mechanisms provided by the tumor diminish the possibility of the establishment of an effective anti-tumor immune response regardless of the amount of leukocytes that infiltrated in the tumor tissue [55,56,58,59,61]. Therefore, it might be recommended that therapy which increases leukocyte influx in tumors and in several studies shows positive effects [63,72,188] is combined with strategies that stimulate cytotoxic T cell function and eliminates the function and presence of suppressive immune cells. It has already been demonstrated that anti-tumor therapy can be improved by removal of regulatory T cells, which permits a robust and pe\rsistent immune response in the tumor [228,229]. Therapy with immune stimulatory cytokines like interleukin 2 (IL-2), IL-15 and IL-12 has also shown promising results in various mouse models [230–233].

5. Concluding remarks

Taken together, it can be concluded that factors of the tumor microenvironment like bFGF and VEGF modulate the expression of endothelial cell adhesion molecules in such a way that tumor progression is stimulated. The development of an effective immune response is prohibited partly by suppression of endothelial cell adhesion molecule expression and consequently leukocyte–vessel wall interactions and leukocyte tumor infiltration. In addition, modifications of endothelial cell adhesion molecules that mediate leukocyte rolling can lead to an influx of a-typical, less competent T-cells in the tumor tissue. Thus, a tumor can escape eradication by the immune system in part by evoking infiltration of tumor specific immune cells. Moreover, the non-regulation of endothelial cell adhesion molecules that have not yet been implicated in leukocyte–vessel wall interactions in tumors, like CEACAM-1, NCAM-1 and CLEVER-1, contributes to the aggressiveness of the tumor by inducing tumor angiogenesis and tumor cell metastasis.

Scientists have exploited the specific composition of adhesion molecules on tumor vessels for the development of different strategies to visualize tumor vasculature and assess treatment responses. Furthermore, by inhibiting the function of several tumor endothelial specific adhesion molecules, promising therapies have been generated. However, the effects of these treatment procedures are not exclusively positive since leukocyte recruitment is shown to be abolished. Therefore, angiostatic strategies using angiogenesis inhibitors that are able to inhibit angiogenesis as well as expand endothelial adhesion molecule expression and consequently leukocyte recruitment in

the tumor tissue seem a better way to go. The future of cancer treatment might lie in the concept of combining modern immunotherapeutic approaches with these angiostatic therapies.

Unfortunately, there are some pitfalls with this approach that have to be taken into account. Endothelial cell adhesion molecules that have been implicated in leukocyte recruitment also play an important role in tumor cell metastasis. High levels of E-selectin expression can be found on endothelial cells adjacent to primary colorectal cancer nests and is even higher on endothelial cells of small vessels adjacent to the metastatic lesions. This expression appears to be induced through stimuli by cancer cells and is inversely correlated to the distance of the blood vessels from the cancer nests [234]. The common lymphatic endothelial and vascular endothelial receptor CLEVER-1 has been suggested to play a role in directing the traffic of cancer cells within the lymphatic system [124]. Finally, members of the immunoglobulin family have also been implicated in cancer metastasis. A recent paper by Klemke and coworkers showed for human melanoma cells that the interaction of the tumor cells with VCAM-1 expressed by endothelial cells leads to cancer cell migration [235].

Furthermore, CD146 inhibitory antibody decreases metastasis of human melanoma [185]. ICAM-1 also takes part in cancer cell metastasis, although till now, this has only been attributed when ICAM-1 is expressed on tumor cells. Reliant on the tumor type, ICAM-1 expression can inhibit or induce tumor cell invasion. In a model of colorectal carcinoma, ICAM-1 expression was inversely correlated with liver metastasis [236] whereas studies with lung cancer cells [237], breast cancer cells [238] and malignant melanoma cells [239] showed an induction of metastasis when ICAM-1 expression was high. One report in a model of lung cancer demonstrated that treatment with the angiogenesis inhibitor thalidomide decreased the ICAM-1-mediated metastatic potential of these cells [240]. This suggests that ICAM-1 expression on tumor cells is differently regulated as compared to ICAM-1 expression on endothelial cells which is, in contrast to ICAM-1 expressed by tumor cells, increased by angiostatic treatment [63].

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