Immune Dysfunction in Cancer Patients

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Immune deficiency in cancer patients is well documented, and tumor cells have developed a variety of cellular and molecular mechanisms to avoid antitumor immune responses. These mechanisms include defective presentation of tumor antigens on the cell surface and/or an inability of the host to effectively recognize these cells and target them for destruction. Tumor-induced defects are known to occur in all major branches of the immune system. The continuous administration of vascular endothelial growth factor (VEGF), a factor produced by most solid tumors, inhibits the functional maturation of dendritic cells, significantly decreases T-cell to B-cell ratios in the peripheral lymphoid organs, and induces rapid and dramatic thymic atrophy in tumor-bearing animals. VEGF is abundantly expressed by a large percentage of solid tumors, and defective antigen presentation, T-cell defects, and premature thymic atrophy are known to occur in cancer patients and tumor-bearing animals. This review will encompass the major mechanisms responsible for tumor evasion of immune surveillance and highlight a role for VEGF as a principal contributor to tumor-associated immune deficiencies. [ONCOLOGY 16(Suppl 1):11-18, 2002]

A n essential function of the immune system is the ability to defend against pathogenic infections. Immune cells can identify foreign antigens expressed on the surface of an infected cell, such as viral or bacterial proteins, and target these cells for destruction. Mutations and/or alterations in normal cellular proteins that arise in a cancerous cell also result in the display of unique antigens on the surface of these cells. When fully functional, the immune system has the capability to identify cancer cells as "non-self" and eliminate them from the body. It is self-evident, however, that clinically apparent tumors avoid effective antitumor immune responses; in fact, cancer patients often exhibit an immune-compromised phenotype that extends beyond an inability to recognize tumor antigens.[1]

Tumor cells have developed a variety of cellular and molecular mechanisms to avoid antitumor immune responses,[2-8] including host alterations in T-cell receptor/CD3 complex expression and function, decreased major and minor histocompatibility complex expression by the tumor, and loss of tumor epitopes. Virtually all branches of the immune system can be affected. Tumor cells also secrete a variety of soluble factors that are capable of inhibiting immune cell function, such as interleukin (IL)-10, tumor necrosis factor (TNF), transforming growth factor-beta (TGF-beta), and vascular endothelial growth factor (VEGF). The effects of these factors appear to be twofold: to inhibit immune cell effector function and to impair the development of immune cells by acting on earlier stages of immunopoiesis.

VEGF and its receptors have profound effects on the early development and differentiation of both vascular endothelial and hematopoietic progenitors.[9] It induces proliferation of mature endothelial cells and is an important component in the formation of tumor neovasculation.[10] VEGF is abundantly expressed by a large percentage of solid tumors; this overexpression is closely associated with a poor prognosis.[11,12] Some of the earliest hematopoietic progenitors express receptors for VEGF[13]; we have demonstrated that VEGF causes a defect in the functional maturation of dendritic cells from progenitors, resulting in defective antigen presentation. This developmental defect is associated with impaired activation of NF-kappaB.[14-17] In addition to defects in the myeloid lineage, VEGF also plays a key role in mediating the development of lymphoid lineage cells. VEGF induces dramatic thymic atrophy resulting in decreased numbers of mature T cells in the periphery, and the loss of the effector cells may also significantly impair an antitumor response (unpublished data).

This article will attempt to provide the reader with an understanding of the major problems that can lead to a failure of antitumor immune induction, with special emphasis on our ongoing research into the important role VEGF plays in mediating this effect. We demonstrate that VEGF is not only important for tumor vascularization, but is also a key factor produced by solid tumors to inhibit recognition and destruction of tumor cells by the immune system.
Defective Antigen Presentation

A primary role of the immune system is to distinguish "self" from "non-self" proteins. Foreign antigens expressed by viruses or bacteria can be presented on the surface of an infected cell, and identify that cell as non-self for destruction by the immune system. Similarly, unique or altered versions of normal cellular proteins produced by tumor cells can be presented to cytotoxic T cells, resulting in a host response against the tumor. Chemical or physical carcinogens can induce tumor antigens[18] or they may originate in spontaneous tumors. To date, a large number of tumor antigens have been identified.[18-23] These endogenous tumor antigens may be derived from fetal or embryonic genes, mutant oncogenes, or oncogenic viral genes such as human papillomavirus. The display of tumor antigens on the cell surface is essential for the recognition and destruction of a tumor cell by the immune system. Tumor or foreign antigens must be degraded, along with normal cellular proteins, into small peptides by the proteosome. These peptides associate with class I MHC (MHC-I) in the lumen of the endoplasmic reticulum and are transported to the cell surface for presentation to CD8-positive cytotoxic T cells. In cases where a structural defect has occurred within the tumor cell, a genetic mutation is often responsible for disrupting the normal display of tumor antigens on the cell surface. These mutations may result in the inability of a cell to produce transporter molecules, such as TAP1, or other molecules essential for this process, such as MHC-I or beta-2-microglobin, and will lead to a failure of the cell to present all antigens. However, structural defects of this nature are only found in approximately 5% to 10% of human tumors, and the majority of human tumors are ineffective at directly inducing an immune response despite adequate display of tumor antigens on their cell surface.

What causes this lack of an antitumor immune response in the remaining 90% to 95% of human tumors? Induction of an effective immune response is a complex process that involves many cell types and cytokine mediators. Tumor-bearing hosts have acquired deficiencies in several of the host elements responsible for this induction. We have found that defects in both myeloid lineage and lymphoid lineage cells are major components of this problem, and the remainder of this article will focus on our studies in this area.

Dendritic Cells in Antitumor Immune Responses

Professional antigen-presenting cells are responsible for the presentation of tumor antigens to both B and T lymphocytes, and can therefore induce both humoral and cell-mediated responses against a tumor (Figure 1). Several studies have described the defects in the function of antigen-presenting cells in tumor-bearing hosts.[24-26] Dendritic cells are the most potent antigen-presenting cells; for this reason, they are potential targets for tumor vaccines and immunotherapies. Because of the central role that dendritic cells play in induction of antitumor immunity, research in our laboratory has focused on the hypothesis that defects in dendritic cell function may potentially account for the immunoresistance of certain tumors.

Tumor-derived factors with the potential to interfere with the development or function of immune cells play an important role in the escape of tumors from normal immune surveillance. We have demonstrated that tumor cells secrete soluble factors that can inhibit the maturation of CD34-positive hematopoietic progenitor cells into functional dendritic cells when cultured in vitro.[14,27] CD34-positive hematopoietic progenitor cells were isolated from human cord blood and cultured in vitro in the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-4, and TNF-alpha.

Tumor-cell supernatants, derived from colon and breast adenocarcinoma cell lines, were added to hematopoietic progenitor cells to determine the effect of tumor-derived soluble factors on dendritic cell maturation in vitro. Dendritic cell function was then measured by two distinct assays: (1) the ability of mature dendritic cells to stimulate proliferation of allogeneic T cells in mixed leukocyte reactions; and (2) the ability to take up fluorescein isothiocyanate (FITC)-dextran. Using both assays, we found that tumor-cell supernatants dramatically reduced dendritic cell function. Dendritic cells obtained after the culture of hematopoietic progenitor cells with tumor-cell supernatants were not only functionally impaired, but also morphologically distinct from mature dendritic cells.

Overall, the number of mature dendritic cells present in the tumor-cell supernatant cultures were reduced two- to threefold. These cells expressed reduced levels of mature dendritic cell surface markers and exhibited several characteristics of immature myeloid cells. Tumor-cell supernatants did not inhibit proliferation of CD34-positive progenitors, nor did they affect the total number of CD34-positive or CD34-positive/CD38-negative progenitor cells, indicating that tumor-cell
supernatant-induced defects did not result from the loss of multipotent progenitor cells. Furthermore, inhibition of dendritic cell function was observed only when tumor-cell supernatants were added within the first 4 days of in vitro culture, indicating an effect on early dendritic cell development.[14] 

Size fractionation experiments demonstrated that dendritic cell-inhibitory action was restricted to the 30 to 50 kD size fraction of tumor-cell supernatants. Neutralizing antibodies to proteins within this size range, and known to be produced by tumor cells, were added to mixed leukocyte reactions in an attempt to identify the dendritic cell-inhibitory factor. Neutralizing antibodies to VEGF, but not antibodies against TGF-beta, IL-10, or c-kit, blocked the ability of dendritic cells to stimulate proliferation of allogeneic T cells[14] (Figure 2). Furthermore, there was a tight correlation between VEGF concentrations and the inhibitory activity of tumor-cell supernatants in 12 tumor cell lines observed. These data indicate that inhibition of dendritic cell function by tumor-cell supernatants is substantially mediated by VEGF.

The Role of VEGF

The VEGF protein (34 to 43 kD) binds specifically to endothelial cells and stimulates angiogenesis and endothelial cell migration in vivo.[28] VEGF is produced by a large majority of solid tumors[28] and is found at elevated levels in the serum of cancer patients.[29] This abnormal VEGF expression plays an important role in the formation of tumor neovasculature, contributing to the growth of tumors.[10] Consistent with these findings, VEGF production by tumors is closely associated with a poor prognosis.[12,30] VEGF binds to two primary receptors—VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1/KDR). VEGF and its receptors have profound effects on the early development and differentiation of both vascular and hematopoietic progenitors.[9] VEGFR-1 expression by CD34-positive hematopoietic progenitor cells has been confirmed by reverse transcription polymerase chain reaction analysis.[14,31] VEGFR-2 is also expressed by hematopoietic progenitor cells,[32] and can be used as a marker for hematopoietic stem cells derived from hemangioblast progenitors.[13] The hemangioblast is an as-yet undiscovered progenitor cell population that is thought to give rise to both the endothelial and hematopoietic lineages.

A functional role for VEGF has been shown in hematopoietic cells as well. The essential role of VEGF in hematopoietic differentiation is underscored by the fact that heterozygous knockouts of VEGF are embryonic lethal and have defective blood island formation.[9] VEGF has also been shown to suppress radiation-induced apoptosis in normal hematopoietic stem cells,[32] suggesting that VEGF may act as a survival factor during hematopoiesis. In addition, VEGF may promote differentiation of certain hematopoietic lineages. Broxmeyer et al have demonstrated that VEGF enhances colony formation by mature subsets of granulocyte-macrophage progenitor cells while inhibiting formation of colonies not stimulated by these factors.[33] Based on these past studies, we hypothesized that VEGF provides dual differentiation signals during hematopoiesis promoting the survival of certain hematopoietic lineages but inhibiting the development and maturation of others.

VEGF Inhibits Development of Dendritic Cells

The above studies suggested that VEGF is a tumor-derived factor at least partly responsible for the defective maturation of dendritic cells in vitro. This finding may provide a mechanism to explain tumor evasion of immune surveillance. In order to confirm the role of VEGF on dendritic cell maturation and function in vivo, mice were given a continuous infusion of VEGF via subcutaneous osmotic pumps (50 ng/h for a period of 28 days). This technique produces steady-state serum concentrations of VEGF between 120 and 160 pg/mL, well within the pathophysiological range observed in advanced-stage cancer patients.[34] Continuous infusion of VEGF into mice resulted in a substantial inhibition of dendritic cell development.[15] The ability of splenic dendritic cells to present antigen to allogeneic T cells was dramatically reduced following 14 days of VEGF infusion. Stimulation of a primary immune response to influenza virus by dendritic cells and the ability to ingest FITC-dextran were also dramatically impaired. There were also decreased numbers of Langerhans' cells—specialized dendritic cells in the skin—which were impaired in their ability to take up antigen and migrate to lymph nodes.[15,16] While defects in dendritic cell function were observed following 14 days VEGF infusion, we only observed significant differences in hematopoietic cell populations following 28 days of VEGF infusion. Fluorescence-activated cell sorting analysis revealed a decreased percentage of CD11c-positive/B7-2-positive dendritic cells in both the spleen and lymph nodes following 28 days of
VEGF infusion. There was a twofold reduction in mature dendritic cells purified from lymph nodes and a more than fourfold reduction in dendritic cells isolated from the spleen. The proportion of lymphocytes in the spleen was also reduced, and despite a fourfold increase in overall splenic cellularity, the number of B cells and T cells was reduced. At the same time, the number of Gr1-positive myeloid cells and Ter119-positive erythroid cells was markedly increased.[15] The fraction of lymphocytes present in the lymph nodes of VEGF-infused mice (28 days) was unaffected, but there was a dramatic shift in B-cell to T-cell ratio, with a greater than threefold increase in the percentage of B cells. Immature myeloid cells and erythroid cells were also increased in the lymph nodes. There was no apparent change in percentage of stem cells or endothelial cells in these tissues.[15] Overall, our data indicate that continuous infusion of VEGF results in the inhibition of dendritic cell function, alterations in lymphocyte numbers, and the accumulation of immature myeloid cells and granulocytes. Similar to what we have observed in vitro, the effects of VEGF on dendritic cell development are evident within the first few days of infusion as monitored by colony-forming assays on Lin-negative hematopoietic progenitor cells.[15]

**Dendritic Cell Defects**

Defective dendritic cell function has been observed previously in both cancer patients and tumor-bearing mice.[24-26] However, the mechanisms that lead to dendritic cell dysfunction, as well as the clinical significance behind this phenomenon, remain unclear. In a study of 93 patients with breast, head/neck, and lung cancer, the clinical correlation between dendritic cell dysfunction and disease progression was observed.[34] Specifically, the number of mature dendritic cells was drastically reduced in the peripheral blood and tumor-draining lymph nodes of cancer patients. These results indicate a systemic immune deficiency in the cancer patients rather than a localized tumor effect.

The dendritic cell decreases were also associated with an increase in immature myeloid cells. The presence of these immature hematopoietic cells correlated closely to the stage and duration of the disease, and defects were partially corrected with successful surgical resection of the tumor. The presence of immature hematopoietic cells in the peripheral blood of cancer patients was also associated with increased plasma levels of VEGF, but not IL-6, GM-CSF, macrophage colony-stimulating factor (M-CSF), IL-10, or TGF-beta. Together these findings suggest that VEGF is one of the primary soluble factors produced by tumors to suppress immune function.

**Antibodies to VEGF Enhance Immunotherapy**

Inadequate function of dendritic cells in tumor-bearing hosts may be one factor that compromises the efficacy of cancer immunotherapy. If VEGF is the primary factor responsible for impaired maturation and function of dendritic cells, then inhibition of VEGF should correct this defect in cancer patients. In addition to their antiangiogenic activities, therapeutic strategies targeting VEGF may lead to improved immune function. We have investigated a novel combination of VEGF-targeted antiangiogenic therapy and immunotherapy using two subcutaneous tumor models in mice: D459 cells, expressing mutant human p53, and MethA sarcoma, with point mutations in the endogenous p53 gene.[35]

Therapy with antimouse VEGF antibody (10 mg intraperitoneally twice a week over 4 weeks) was initiated when tumors became palpable. Anti-VEGF therapy significantly improved the number and function of lymph node- and spleen-derived dendritic cells isolated from these tumor-bearing animals, though treatment of tumors with anti-VEGF antibody alone did not affect the rate of tumor growth. Anti-VEGF antibody therapy also improved the efficacy of cancer immunotherapy when given in conjunction with peptide-pulsed dendritic cells corresponding to the mutation-specific p53 peptides.[35]

Limited data also indicate that antibodies to VEGF are able to substantially correct dendritic cell defects in cancer patients. In a small pilot study, three patients with metastatic lung cancer were given antibodies to VEGF. A complete reversal of all dendritic cell maturation defects was observed in all three patients.[34] Further clinical trials investigating the use of VEGF-targeted therapeutics are ongoing and utilize a variety of different strategies for interruption of VEGF signaling. These strategies include monoclonal antibodies, ribozymes, and specific receptor tyrosine-kinase inhibitors generally in combination with chemotherapy and targeting various disease sites. More pertinent to this discussion, combining anti-VEGF therapies with immunotherapies may dramatically improve their efficacy; several such trials are planned.
T Cells in Antitumor Immune Responses

In addition to defects in dendritic cells and other myeloid cells, tumor-associated immune deficiencies have also been observed in the thymus and T cells.[2-8] While thymic atrophy accompanies normal aging,[36] a high incidence of premature thymic involution is also seen in patients with childhood malignancies[37]; this often rebounds after curative treatment. This can be modeled in mice transplanted with mammary adenocarcinomas, which demonstrate rapid thymic involution associated with depletion and/or alterations of thymocyte subpopulations.[38-41] The mechanism of this cancer-associated thymic atrophy, and more generally the factors responsible for lineage commitment, migration to the thymus, and progression through thymocyte developmental checkpoints, remains poorly understood. In addition to dendritic cell defects, non-tumor-bearing mice treated with a continuous infusion of recombinant VEGF have a decreased number of T cells in their lymph nodes and spleen,[15] and thus VEGF represents a candidate mediator of the tumor-associated thymic defect.

After 3 to 4 weeks of VEGF treatment as described above, we have observed a dramatic reduction in the size of the thymus and a striking decrease in thymocyte cellularity as compared to age-matched, phosphate-buffered saline (PBS)-infused controls (unpublished data). The normally clear distinction between cortical and medullary regions of the thymus is no longer present, and broad hypocellular areas containing collagen, fibroblasts, and dilated blood vessels separated the remaining follicles. The relative percentage of both thymic epithelial cells and vascular structures is increased in VEGF-treated lobes, indicating that cell loss is primarily restricted to the lymphocyte populations. There is no significant difference in thymus size, structure, or cellularity following infusions of less than 14 days or with PBS infusions, suggesting that the observed effects were not due to postsurgical stress.

Thymic atrophy accompanies a dramatic drop in total thymocytes, and this loss is disproportionately seen in the CD4-positive/CD8-positive thymocyte populations. It does not appear to be associated with a significant increase in apoptosis or cell cycle arrest, and VEGF has no effect on thymocyte development in fetal thymic organ culture (unpublished data). All of our data indicate that VEGF acts on thymic progenitors rather than directly on the thymus itself. We propose that treatment with VEGF results in defective seeding of the thymus by bone marrow-derived progenitors, and as these earliest thymocytes fail to replace maturing T cells migrating to the periphery, a depletion of total thymocytes results.

We also demonstrate that hematopoietic progenitor cells from the bone marrow of VEGF-treated mice, when transferred into an irradiated host, reconstitute the thymus 2.5- to 3-fold more efficiently than control hematopoietic progenitor cells. This indicates an increased number of functional thymus-directed progenitors in the marrow of VEGF-treated animals. Thus VEGF appears to induce a block in the differentiation of thymic precursors from lymphoid progenitors in the marrow, resulting in the accumulation of cells upstream from this block. These data are consistent with our dendritic cell data, and strengthen the hypothesis that VEGF affects the development and differentiation of multiple hematopoietic lineages.

VEGF Signaling in Hematopoietic Progenitor Cells

We have demonstrated that VEGF affects the ability of hematopoietic progenitor cells to differentiate into functional dendritic cells during the early stages of hematopoiesis, and induces dramatic thymic atrophy and defective T-cell maturation in vivo. Significant research efforts have been focused on the molecular mechanisms and signaling pathways that are responsible for this effect. We have shown that VEGF binds to specific receptors on the surface of hematopoietic progenitor cells.[17] This binding can be successfully competed by placental growth factor, indicating that signaling is at least in part accomplished by binding of VEGF to the VEGFR-1 (Flt-1) receptor. Additionally, the number of binding sites available for VEGF decreased with dendritic cell maturation and correlated with decreased levels of VEGFR-1 mRNA expression in the late-stage cells. The NF-kappaB signaling pathway has been implicated in the differentiation and function of a variety of immune cell lineages.[42-47] There are five known NF-kappaB/Rel proteins: Rel-A (p65), Rel-B, c-Rel, p50, and p52. Hetero- and homodimers of members of the NF-kappaB family of transcription factors are sequestered in the cytoplasm of cells by inhibitor proteins: I-kappaB-alpha, I-kappaB-beta, I-kappaB-epsilon, I-kappaB-gamma, and Bcl-3. Activation of NF-kappaB is mediated by phosphorylation, ubiquitination, and degradation of I-kappaB, followed by translocation of NF-kappaB to the nucleus. Known signaling pathways demonstrating the importance of NF-kappaB
Immune Dysfunction in Cancer Patients
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signaling in the immune system include TNF-alpha, IL-1alpha, antigen receptors on B and T lymphocytes, and costimulatory molecules such as CD28 and CD40.[45,47-50]
As early as 30 minutes after TNF-alpha induction,[17] VEGF inhibits TNF-alpha-induced binding of NF-kappaB to target DNA sequences in hematopoietic progenitor cells (see Figure 3).[15] VEGF also significantly inhibits NF-kappaB-dependent activation of reporter gene transcription in dendritic cells during the first 24 hours in culture. In addition, VEGF treatment of hematopoietic progenitor cells reduced levels of Rel-B and c-Rel mRNA within 7 to 10 days of culture. To assess the biologic significance of VEGF inhibition of NF-kappaB signaling, we employed an adenovirus that encodes a dominant I-kappaB inhibitor. This inhibitor, termed I-kappaB-DN, effectively blocks NF-kappaB activity in hematopoietic progenitor cells at their early stages of differentiation. Importantly, expression of I-kappaB-DN reproduces the inhibitory effects of VEGF on hematopoietic progenitor cell differentiation. Substitution of VEGF with placental growth factor also resulted in a reduction of NF-kappaB nuclear localization and binding to target sequences.[17] From these data, we conclude that VEGF blocks NF-kappaB activation by TNF-alpha, and NF-kappaB plays a significant role in the maturation of dendritic cells from hematopoietic progenitor cells. These findings also suggest a mechanism by which tumor-derived soluble factors may directly down-regulate immune responses to tumor antigens.

More recent studies in our laboratory have shown that TNF-alpha treatment of dendritic cells induces the nuclear translocation of NF-kappaB complexes containing Rel-A (unpublished results). In contrast, VEGF is able to signal independently through the NF-kappaB signaling pathway, but induction of NF-kappaB signaling is mediated by distinct Rel subunits. VEGF treatment alone induces the translocation of Rel-B-containing complexes. Surprisingly, Rel-B induction was not necessary for VEGF-mediated inhibition of NF-kappaB signaling by TNF-alpha, as similar effects were observed in dendritic cells from Rel-B^−/− knockout mice compared with wild type and heterozygous (Rel-B^+/−) controls.

Nuclear translocation of NF-kappaB is induced by degradation of associated I-kappaB via activation of IKK (inhibitor of -kappaB kinase). Incubation with VEGF decreased TNF-alpha-induced IKK activation, decreased phosphorylation of I-kappaB, and impaired degradation of I-kappaB-alpha and I-kappaB-epsilon in cultured hematopoietic progenitor cells. In the absence of TNF-alpha, VEGF had no effect on I-kappaB phosphorylation or degradation. At present, the mechanisms by which VEGF inhibits TNF-alpha-induced IKK activation remain unknown (unpublished results).

Both VEGFR-1 and VEGFR-2 are members of the fms family of tyrosine kinase receptors. As such, it was surprising that SU5416, a potent inhibitor of VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1/KDR) tyrosine kinase activity, failed to reverse the inhibitory effect of VEGF on NF-kappaB activation. These findings indicate that the effects of VEGF are mediated by a non-tyrosine kinase signaling pathway. The argument for a non-tyrosine kinase pathway for VEGF signaling is further strengthened by knockout studies of VEGFR-1 and VEGFR-2. Null mutations for these receptors are both embryonic lethal,[10,51] whereas mice harboring a deletion in the intracellular domain of VEGFR-1 are viable.[52] The latter mutant strain completely lacks the VEGFR-1 tyrosine kinase domain, but does not display any appreciable defects in development.

In addition, angiogenesis and vascularization during adulthood appears unaffected in VEGFR-1 intracellular domain knockouts, indicating that VEGFR-1 has an essential function in development that is unrelated to its tyrosine kinase activity. Further investigation is necessary to determine whether mice lacking the cytoplasmic domain of VEGFR-1 exhibit defects in hematopoiesis; this information is important in considering the use of anti-VEGFR-1-targeted therapies. The presence of an essential VEG signaling pathway that is independent of VEGFR-1 tyrosine kinase activity may provide a mechanistic explanation for the dual activities of VEGF. One pathway may be responsible for the angiogenic properties of VEGF, while an alternate signaling cascade might mediate the suppression of immune responses to tumors. A dissection of VEGF signaling is an important goal for the development of anti-VEGF adjuvant therapies.

Summary

We have shown that VEGF promotes tumor formation by several modes of action. In addition to its well-documented role in tumor neo-vascularization, VEGF also mediates tumor evasion of normal immune surveillance by inhibiting the development of both dendritic cells and T cells. Other hematopoietic lineages are conversely effected. These defects manifest as an impairment of the immune system to recognize tumor antigens presented on the cell surface, and therefore allow the tumor to avoid destruction by immune effector cells. Suppression of dendritic cell development by
VEGF is observed both in vitro and in vivo and occurs early on in the differentiation of dendritic cells from hematopoietic progenitors. Defects in T-cell development are primarily manifested in a dramatic induction of thymic atrophy and loss of thymocyte cellularity. Development of both lineages appears to be inhibited by activity of VEGF on early hematopoietic progenitor cells in the bone marrow. The importance of VEGF as a tumor-derived soluble factor that is responsible for inhibition of immune cell function is underscored in both the clinical and preclinical experimental models. Antibodies to VEGF rescue dendritic cell maturation defects in cancer patients and tumor-bearing animals, and thymic atrophy associated with malignancy is observed in both systems. Dendritic cell effects are likely mediated by VEGF signaling through VEGFR-1, which is transduced via a non-tyrosine kinase-dependent pathway, and we hypothesize a similar signaling mechanism in lymphoid progenitors. The functional outcome of VEGFR-1 signaling is impaired induction of NF-kappaB, a transcription factor family known to be important for hematopoietic development. Further investigation into the role of VEGF in immune evasion, its mechanisms of action, and clinical significance may provide new insights into the development of novel therapeutic strategies to bolster antitumor immunotherapy.

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