The association between inflammation and cancer was identified in the 19th century. Initially, it was believed that leukocyte infiltrates in tumors represented an attempt by the host to eradicate malignant cells. It was later demonstrated that several chronic inflammatory conditions, such as inflammatory bowel disease, Helicobacter pylori infection, hepatitis B or C infection, and prostatitis, predisposed people to cancer of the colon, stomach, liver, and prostate, respectively. In addition, malignant tissues that contain inflammatory cells such as macrophages in breast cancer or neutrophils and mast cells in lung cancer are associated with an unfavorable outcome.

Lung cancer risk is clearly enhanced by cigarette smoking, and chronic inflammation associated with chronic obstructive pulmonary disease probably enhances this risk, although an increase is difficult to demonstrate. Some lung cancers that occur in association with scars could have no relationship with smoking habits. In patients with idiopathic fibrosis, lung cancer incidence is much higher than in the general population. Oncogene activation is often associated with inflammatory response. For example, scar-associated cancers seem to more often have KRAS (codon 12) mutations. Further, a transgenic mouse model of lung cancer generated by KRAS activation showed a robust inflammatory response compared to the wild-type mice. Lastly, in several mouse models, this inflammatory response has been demonstrated to be not only associated with but also required for tumor initiation or growth.

The tumor microenvironment is composed of structural (extracellular matrix [ECM]), soluble (growth factors, chemokines, cytokines, proteases, and hormones, among others), and cellular components (tumor cells, fibroblasts, inflammatory cells, vascular and lymphatic endothelial cells, and vascular smooth muscle cells and pericytic cells, among others). Characterization of the inflammatory cells within tumors has revealed both the adaptive and innate arms of the immune response. For example, dendritic cells (DCs) present tumor antigens to T lymphocytes (CD4 and CD8, and natural killer [NK]), promoting an antitumor cytotoxic T-cell response. This response is negated by a population of immature myeloid cells called myeloid-derived suppressor cells that promotes the development of FOXP3+ CD4+ T cells or Tregs, which suppress the antitumor cytotoxic T-cell response and induce polarized differentiation of monocytes into tumor-associated macrophages (TAMs or M2 macrophages). TAMs, vascular endothelial cells, and fibroblasts within the tumor stroma secrete a number of growth factors and chemokines that promote tumorigenesis. Thus, conflicting immunologic forces fight for supremacy in the tumor microenvironment. This chapter will deal with recent research on the tumorigenic and antitumorigenic effects of the immune system on the lung. The latter was discussed fully in a recent review.

**ANGIOGENESIS**

Angiogenesis is the growth of the new blood vessels, necessary for cancerous tumors to keep growing and spreading (see Chapter 8). Many proteins and other smaller molecules have been identified as angiogenic, particularly vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and CXC chemokines, among others. The binding of these molecules to their appropriate receptor activates a series of relay proteins that transmits a signal into the nucleus of the endothelial cells. The nuclear signal ultimately prompts a group of genes to make products needed for new endothelial cell growth. First, the activated endothelial cells produce matrix metalloproteinases (MMPs), a class of degradative enzymes that break down the extracellular matrix, thus permitting the migration of endothelial cells that had been tethered to the matrix. As they migrate into the surrounding tissues, activated endothelial cells begin to divide. Soon they organize into hollow tubes that evolve gradually into a mature network of blood vessels. Cancer cells originating in a primary tumor can spread to another organ and form metastases that can remain dormant for years. The induction of this vasculature in primary tumor or in metastases, termed angiogenic switch, can occur at various stages of tumor progression, depending on the tumor...
type and the environment (see Chapter 8). In many studies, angiogenic switch has been reported to be closely associated with malignant transition. Cancer cells themselves could release molecules to activate this process, as could cells from the tumor microenvironment. This review will describe effects of the cells from the tumor microenvironment on angiogenesis.

**FIBROBLASTS**

Normal stroma contains fibroblasts in association with physiological extracellular matrix. Reactive stroma is associated with an increased number of fibroblasts, enhanced capillary density, and type I collagen and fibrin deposition. In chickens that are cancer-prone because they have been infected with Rous sarcoma virus, wounding leads to invasive carcinoma, demonstrating that reactive stroma provides oncogenic signals that facilitate tumorigenesis. Fibroblasts are associated with cancer cells (tumor-associated fibroblasts [TAFs], carcinoma-associated fibroblasts [CAFs]) at all stages of cancer progression. The growth factors, chemokines, and extracellular matrix—these fibroblasts produce facilitate angiogenic recruitment of endothelial cells and pericytes. They are phenotypically and functionally distinct from fibroblasts that are not in the tumor microenvironment. The modified phenotype they acquire is similar to that of fibroblasts with normal tissue fibroblasts associated with wound healing. Smooth muscle differentiation (myofibroblasts) is prominent in stromal cells of malignant breast tissue but rarely seen in normal breast tissue. The signals that mediate the transition of normal fibroblasts into TAF or CAF are not fully understood, but transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), and fibroblast growth factor 2 (FGF2) are the main mediators to induce fibroblast activation. TGF-β induces the acquisition of activated phenotype of fibroblasts in culture and has been shown to be correlated with desmoplastic reaction and poor prognosis in breast cancer. PDGF induces the proliferation of fibroblasts and has been shown to be associated with cancer progression in breast cancer. FGF2 also stimulates proliferation of fibroblasts and is also recognized for its potential to induce angiogenesis.

The fact that fibroblasts contribute to tumor initiation, growth, and metastasis have been demonstrated by both in vivo and in vitro study. Whereas normal fibroblasts are required to maintain epithelial homeostasis, CAFs probably initiate and promote tumorigenic alterations in epithelial cells. Fibroblasts cultured from malignant tumors have stimulatory effects on breast tumor cell lines, whereas fibroblasts cultured from normal tissue are inhibitory. If CAFs are coinoculated with prostate, breast, or bladder tumor cell lines into nude mice, tumor latency is shortened and tumor growth increased, whereas normal fibroblasts do not have this effect. Increased cell proliferation and angiogenesis also result. Lastly, fibroblasts could promote metastasis by secreting growth factors that create a niche that promotes the growth of cancer cells at distant sites.

CAFs could also modulate the immune response. CAFs isolated from primary non–small cell lung cancers (NSCLCs) were able to enhance or suppress tumor-associated T-cell function. The epithelial-to-mesenchymal transition (EMT) might be an additional source of fibroblast-like cells (with an altered genome). In EMT, epithelial cells lose cell–cell contacts and acquire mesenchymal properties. Cancer cells undergoing EMT develop invasive and migratory abilities and express EMT markers (E-Cadherin, Vimentin) that have been shown to be markers of tumor progression. This phenotype has also been shown to be associated with resistance to certain therapies such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) in NSCLC.

**MACROPHAGES**

Most solid tumors are abundantly populated with TAMs. These cells can compromise clinical outcome. Clinical studies have shown a correlation between TAM density and poor prognosis for several types of cancer, an association that is particularly strong for breast, prostate, ovarian, and cervical cancers. For NSCLC, TAM density correlated significantly and negatively with overall survival or relapse-free survival in two of three published studies.

Macrophages are recruited to tumors by a wide variety of growth factors—granulocyte colony-stimulating factor (G-CSF), granulocyte-monocyte colony-stimulating factor (GM-CSF), macrophage-stimulating protein (MSP), VEGF, TGF-β—and chemokines, which include CC chemokines, monocyte chemoattractant protein family, macrophage inflammatory protein-1 (MIP-1), and macrophage migration inhibitory factor (MIF). Tumor-derived molecules probably influence TAM phenotype. Exposure to IL-4 and IL-10 in tumors may induce TAMs to develop into M2 macrophages, which are characterized by poor antigen-presenting capacity and production of factors that suppress T-cell proliferation and activity and induce angiogenesis, whereas M1 macrophages are efficient immune cells.

Macrophages induce angiogenesis. Correlations between number of macrophages and microvessel count have been observed for many tumor types including lung cancer. Macrophage infiltration into tumor is not homogeneous: studies using hypoxic markers have shown that TAMs accumulate in hypoxic and necrotic areas. Hypoxia induces synthesis of macrophage chemoattractants such as VEGF by upregulating hypoxia-inducible factor (HIF), which recruits and immobilizes macrophages in such areas. Here, these cells synthesize angiogenic regulators, which results in formation of new blood vessels. These regulators are angiogenic factors (VEGF, PDGF, IL-8) and angiogenesis-modulating enzymes (MMPs and cyclooxygenase-2 [COX-2]). In vitro studies, based on coculture experiences, showed that exposure of macrophage to tumor cells increases synthesis of angiogenic factors. In transgenic...
mice susceptible to mammary cancer (PyMT mice), malignant transition was demonstrated to be regulated by infiltrated macrophages in primary mammary tumors. Inhibition of macrophage recruitment into the tumors delayed the angiogenic switch and malignant progression, while genetic restoration of the macrophage population rescued angiogenesis.3\textsuperscript{3}

Macrophages have been shown to stimulate proliferation of tumor cells. In K-ras\textsuperscript{A1} mice, which develop lung adenocarcinoma through somatic activation of a K-ras allele, intraepithelial and airspace macrophage infiltration is observed beginning at the earliest stage of neoplasia and increasing with malignant progression.\textsuperscript{3} In this model, inhibition of malignant progression by a targeted treatment directed against the mTOR pathway was accompanied by macrophage loss. Conditioned media from primary cultures of macrophages stimulated the proliferation of lung tumor cells, which was consistent with previous reports demonstrating a stimulatory effect of alveolar macrophages on the proliferation of normal and distal airway epithelial cells in other animal models.\textsuperscript{34–36} In a transgenic mouse model of preneoplastic progression in the mammary gland, conditional depletion of macrophages inhibited epithelial cell proliferation and lateral budding.\textsuperscript{37}

Macrophages are involved in invasion and metastasis. In the PyMT mouse model of breast cancer progression, leukocytic infiltrates were present in areas of basement membrane breakdown\textsuperscript{38} suggesting their involvement in tumor invasion; macrophage depletion resulted in reduced formation of lung metastases.\textsuperscript{4} In coculture experiments, interaction between macrophages and tumor cells facilitated invasion of tumor cells into a collagen matrix.\textsuperscript{39} In a chemotaxis-based in vivo invasion assay, a paracrine loop involving macrophages and tumor cells was essential for motility and invasion of tumor cells in mammary tumor.\textsuperscript{40} Colony-stimulating factor-1 (CSF-1) secreted by carcinoma cells leads to the activation of macrophages to secrete EGFR ligands, leading to stimulation of carcinoma cell movement.\textsuperscript{40}

**NEUTROPHILS**

Neutrophil infiltration has been described in NSCLC, and particularly in the bronchioalveolar subtype.\textsuperscript{41,42} Recent studies support the fact that this could be induced by Ras activation, one of the most common oncogenic events in pulmonary adenocarcinoma.\textsuperscript{3} Neutrophils could be recruited to tumors by CXC chemokines with an N-terminal Glu-Leu-Arg (ELR) motif. These chemokines are also autocrine growth factors for certain types of cancer cells.\textsuperscript{43–45} Mutations in the proto-oncogene KRAS occur in 10% to 30% of lung adenocarcinomas,\textsuperscript{46} and expression of mutant KRAS in the alveolar epithelium leads to the development of lung adenocarcinoma in mice.\textsuperscript{45–50} In addition to its role in the transformation of alveolar epithelial cells, the presence of KRAS mutations is a predictor of shorter survival in NSCLC patients\textsuperscript{51} and of resistance to therapy.\textsuperscript{52} Sparmann et al.\textsuperscript{53} demonstrated that the CXC chemokine CXCL8 (interleukin-8) is a transcriptional target of Ras signaling and is required for the initiation of tumor-associated inflammation and neovascularization in xenograft models. In this model, neutralization of CXCL8 in RasV12-expressing subcutaneous tumors attenuates neoplastic growth; CXCL8 inhibition does not affect tumor cell proliferation but leads to an increase in tumor cell death and an impairment of tumor vascularization coincident with an impairment of stromal infiltration of neutrophils. In the heterotopic and orthotopic Lewis lung cancer models, tumor growth is associated with enhanced neovascularization, neutrophil inflammation, and expression of CXC chemokines. Neutralization of CXC chemokine receptor decreases tumor size and increases tumor necrosis.\textsuperscript{53}

In Kras\textsuperscript{A1} mice, a mouse model in which lung adenocarcinoma develops through somatic activation of a KRAS allele carrying an activating mutation in codon 12 (G12D),\textsuperscript{54} neutrophils, and vascular endothelial cells infiltration increased during malignant progression, and the murine functional homologues of human CXCR2 chemokines (KC, MIP-2) and their receptor CXCR2 are highly expressed.\textsuperscript{54} CXCR2 inhibition blocks the expansion of early alveolar neoplastic lesions, but this antitumor effect does not occur outside the presence of the tumor microenvironment.

In humans, adenocarcinomas with bronchoalveolar features are also characterized by an intense inflammatory reaction, predominantly consisting of alveolar neutrophils and macrophages. Increased numbers of tumor-infiltrating neutrophils are linked to poorer outcome in these patients.\textsuperscript{41} The tumor environment drives local neutrophil recruitment and activation via CXC chemokine release, but it also prolongs alveolar neutrophil survival through the production of soluble antipapoptotic factors GM-CSF and G-CSF. The mechanisms by which neutrophils influence the prognosis of adenocarcinomas with bronchoalveolar features could be multiple. It has been postulated that the persistence of neutrophil alveolitis would result in persistent release of proinflammatory mediators such as cytokines, proteases, and reactive oxygen and nitrogen species that can damage DNA and activate oncogenes.\textsuperscript{46,57} Among these factors released by neutrophils, hepatocyte growth factor (HGF) seems to be particularly involved in the progression of these types of tumors, especially through its mitogenic and scattering properties, favoring c-Met–expressing tumor cell migration along the alveolar basal membrane.\textsuperscript{58} Lastly, neutrophils might be involved in luminal tumor spread by promoting tumor cell shedding,\textsuperscript{59} which is described pathologically as the presence of micropapillary clusters that are also involved in the mechanism of aerogenous progression.\textsuperscript{60}

**MAST CELLS**

Several different studies showed a significant association between mast cell density, angiogenesis, and poor prognosis in NSCLC.\textsuperscript{61–64} Using monoclonal antibodies for tryptase—a specific marker for mast cells—and for endothelial cell surface
molecules, several studies quantified mast cell and microvessel density in lung cancer tissue. Takamami et al. showed a correlation between mast cell density and microvessel count in a study of 180 patients with resected pulmonary adenocarcinoma. Mast cell density was also associated with N classification and was an independent factor for survival duration. Production of angiogenic factors such as VEGF or other proinflammatory cytokines by mast cells is probably involved in this phenomenon.

DENDRITIC CELLS

Effective antitumor responses require antigen-presenting cells (APCs), lymphocytes, and NK effectors. DCs are bone marrow–derived leukocytes characterized by a high level of expression of major histocompatibility complex (MHC) and costimulatory molecules. They are the most effective APCs. To initiate and maintain an effective antitumor response after antigen uptake, DC should migrate to draining lymph nodes and to prime T cells. This priming reaction is triggered by an activation-driven maturation process of DC characterized by upregulation of costimulatory molecules (CD40, CD80, and CD86), a switch in the chemokine receptor repertoire, and production of immunomodulatory cytokines (IL-12 and IFN-α) necessary for the generation of cytotoxic T lymphocytes. However, immunosuppressive cytokines such as IL-10, TGF-β, prostaglandin E2 (PGE2), and VEGF interfere with DC maturation and migration, altering tumor response. To improve antitumor immunity, tumor cells have been transduced with genes encoding molecules able to attract and to activate DC but with limited efficacy in curing established tumors. To overcome tumor microenvironment–associated suppressive effect on the DC, a recent work used a strategy that incorporates ex vivo–activated DC as the delivery for chemokine expression. The authors transduced the gene of the secondary lymphoid chemokine (CCL21, CCR7 receptor ligand) into DC ex vivo and delivered the gene-modified DC (DC-AdCCL21) in a mouse model of spontaneous bronchoalveolar carcinoma. A single intratracheal administration led to a marked reduction in tumor burden with extensive mononuclear cell infiltration of the tumors. The reduction of tumor burden was accompanied by the enhanced elaboration of type I cytokines (IL-12 and IFN-γ and GM-CSF) and antiangiogenic cytokines and a decrease in immunosuppressive cytokines (IL-10, TGF-β, PGE2) in the tumor microenvironment. Continuous administration of DC-AdCCL21 significantly prolonged survival of mice.

In another study, repeated treatments with a combination of a microbial stimulus (a Toll-like receptor 9 ligand, CpG oligonucleotide) and an antibody blocking the IL-10 receptor reversed the functional paralysis of DC and reestablished IL-12 production. Lastly, a combination of local treatment of CCL16 and CpG together with systemic administration of antibody blocking the IL-10 receptor cured syngeneic tumors in mice.

ADAPTIVE IMMUNITY

Lung cancer cells themselves find a way to avoid activating the adaptive immune system. Although they express tumor antigens, the limited expression of MHC antigens, defective antigen processing, and lack of costimulatory molecules make them ineffective APC. For example, the absence of expression of costimulatory B7 molecules renders tumors invisible to the immune system, whereas enhanced expression of inhibitory B7 molecules protects them from effective T-cell destruction.

Tumor-reactive T cells accumulate in the lung tumor microenvironment but fail to respond because of suppressive tumor cell–derived factors. These factors can reduce T-cell survival. Lymphocytes exposed to lung tumor supernatant undergo enhanced apoptosis with an impairment of nuclear factor κB activation due to reduced IκB kinase (IKK) activity. A high proportion of tumor-infiltrating lymphocytes in the tumor microenvironment are regulatory T cells. The CD4+ CD25+ T regulatory cells found in lung tumors have been shown to selectively inhibit the host immune response and contribute to the progression of lung cancer. They mediate potent inhibition of autologous T-cell proliferation while they fail to inhibit the proliferation of allogeneic T cells.

B cells also play a crucial role in the onset of chronic inflammation associated with epithelial cancer development. In a recent study using a transgenic mouse model of skin carcinoma with the gene of human papillomavirus 16 (HPV-16) expressed under control of the human keratin 14 promoter, B cells were shown to be activated peripherally—with no need to be recruited in neoplastic tissue. They were also shown to initiate immunoglobulin deposition into neoplastic tissue, paralleling the recruitment of inflammatory cells (mast cells and granulocytes) and malignant progression. Antibodies mediate recruitment of innate immune cells via engagement of FcR expressed on immune cells. Other studies have reported that humoral immune responses potentiate in vivo growth and invasion of injected murine and human tumor cell lines via recruitment and activation of granulocytes and macrophages. The authors suggested that pharmaceutical intervention attenuating B cell activation or blocking B cell–mediated recruitment of innate immune cells may be effective in preventing premalignant epithelial progression.

CLINICAL IMPLICATIONS

Ongoing biochemical processes in the tumor microenvironment create new targets for cancer therapy. One advantage of therapies targeting the microenvironment is that these non–tumor cells are presumably genetically stable, whereas tumor cells are genetically unstable and thus can accumulate adaptive mutations and rapidly acquire drug resistance. Several drugs directed against nontumor cells or their soluble mediators have been developed and are now being evaluated in clinical trials.
MMPs that break down the ECM are necessary for angiogenesis and invasion of tumor cells, into both the surrounding normal tissue and the blood and lymphatic systems. ECM is also a rich source of sequestered heparin, binding pro/angiogenic and proangiogenic factors, which are made available following increased production of matrix-degrading enzymes. Clinical trials were undertaken to determine if inhibitors of MMPs (MMPI) improved overall survival in NSCLC or SCLC. Marimastat, a nonselective MMPI, has also been tested in a number of malignancies, including small cell lung cancer and breast, gastric, and pancreatic cancers; the results were negative.74–77 Musculoskeletal toxicity was a significant problem in all studies. The failure of the broad-spectrum MMP inhibitors (MMP-I) in the clinic has been explained by the fact that some MMPs can also release angiogenic proteins. Prinomastat, a more targeted MMPI with activity mainly against MMP2 and MMP9, was given versus placebo in patients with advanced NSCLC in combination with gemcitabine–cisplatin chemotherapy. This study was closed after an interim analysis showed a lack of efficacy.78 A parallel study of similar design found no benefit when prinomastat was administered in addition to paclitaxel and carboplatin in patients with advanced NSCLC.79 Another selective MMPI, BAY 12–9566, has been evaluated in several disease settings, but after disappointing results in studies of SCLC and pancreatic cancer, its development has been suspended.

Fibroblasts might be a novel therapeutic target in cancer. The cell-surface serine protease known as fibroblast activation protein (FAP) is mostly expressed in wound healing and in tumor stroma. A phase I dose escalation study with an antibody directed to human FAP (ibuzumab) in patients with colorectal cancer or NSCLC has shown that the antibody bound specifically to the tumor sites.80 Targeting CAFs as a therapeutic strategy against cancer needs further study.

A plethora of antiangiogenic agents inhibiting either angiogenic growth factors or their receptors have been developed and tested in preclinical experiments. More recent data from the clinical trials of the VEGF–specific antibody, bevacizumab (Avastin), showed that in patients with metastatic colorectal cancer, breast cancer, and NSCLC, there was a significant survival benefit when combined with chemotherapy.81,82 Leading to the Food and Drug Administration (FDA) approval of bevacizumab. Treatment with thalidomide, another antiangiogenic agent, was not associated with a significant improvement in survival of SCLC patients. However, there was pronounced heterogeneity in survival outcomes between groups of patients.83 Some benefit was observed among patients with a performance status (PS) of 1 or 2, showing that angiogenesis deserves further study as a therapeutic target in this disease.

Epidemiological studies have demonstrated that people taking nonsteroidal anti-inflammatory drugs (NSAIDs) have a clear reduction in their risk of developing colorectal cancer,84 and possibly other tumors. As a result, there were high expectations for the next-generation NSAIDs, the selective COX-2 inhibitors, in the prevention and treatment of cancers associated with chronic inflammation. Celecoxib had demonstrated ability to reduce the incidence of colorectal cancer.85 The addition of rofecoxib did not improve overall survival compared with first-line treatment with cisplatin plus gemcitabine in patients with advanced NSCLC in a prospective, open-label, randomized phase III trial.86 Most of the clinical trials have closed early because long-term high-dose COX-2 inhibitor elevates the risk of cardiovascular events87; alternative drugs will need to be identified.

CONCLUSION

A growing body of evidence demonstrates that cancer cells have accomplices. Quite early in tumor development, cancer cells co-opt blood vessels and recruit leukocytes and fibroblasts, reprogramming them to provide nourishment in the form of peptides that support cell proliferation and metastasis. Although their ability to dupe the host into becoming an ally provides cancer cells with a selective advantage, it may also be their Achilles heel. Initial efforts to elucidate the mechanisms by which cancer cells interact with surrounding cells within the tumor has revealed several potential therapeutic opportunities. Future research will better define these bidirectional interactions between tumor and host, and future clinical trials should be designed to capitalize on this understanding.

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