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Review

REVIEW

The effect of environmental chemicals on the tumor microenvironment

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Abstract

Potentially carcinogenic compounds may cause cancer through direct DNA damage or through indirect cellular or physiological effects. To study possible carcinogens, the fields of endocrinology, genetics, epigenetics, medicine, environmental health, toxicology, pharmacology and oncology must be considered. Disruptive chemicals may also contribute to multiple stages of tumor development through effects on the tumor microenvironment. In turn, the tumor microenvironment consists of a complex interaction among blood vessels that feed the tumor, the extracellular matrix that provides structural and biochemical support, signaling molecules that send messages and soluble factors such as cytokines. The tumor microenvironment also consists of many host cellular effectors including multipotent stromal cells/mesenchymal stem cells, fibroblasts, endothelial cell precursors, antigen-presenting cells, lymphocytes and innate immune cells. Carcinogens can influence the tumor microenvironment through effects on epithelial cells, the most common origin of cancer, as well as on stromal cells, extracellular matrix components and immune cells. Here, we review how environmental exposures can perturb the tumor microenvironment. We suggest a role for disrupting chemicals such as nickel chloride, Bisphenol A, butyltins, methylmercury and paraquat as well as more traditional carcinogens, such as radiation, and pharmaceuticals, such as diabetes medications, in the disruption of the tumor microenvironment. Further studies interrogating the role of chemicals and their mixtures in dose-dependent effects on the tumor microenvironment could have important general mechanistic implications for the etiology and prevention of tumorigenesis.

Abbreviations

AhR	aryl hydrocarbon receptor
BPA	Bisphenol A
DC	dendritic cell
ECM	extracellular matrix
EDC	endocrine-disrupting chemical
EMT	epithelial–mesenchymal transition
ER	estrogen receptor
IFN	interferon
IGF	insulin-like growth factor
IL	interleukin
MeHg	methylmercury
MMP	matrix metalloproteinase
NF-κB	nuclear factor-kappaB
NK	natural killer
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
PAH	polycyclic aromatic hydrocarbon
ROS	reactive oxygen species
TBT	tributyltin
TGF	transforming growth factor
TNF	tumor necrosis factor
Treg	regulatory T cell
VEGF	vascular endothelial growth factor

Introduction

Carcinogens can cause cancer through direct effects on DNA, leading to genetic mutations or genomic damage, as well as indirectly through the perturbation of cellular regulatory processes, and also through the host microenvironment that thereby facilitates tumor progression and the acquisition of additional genetic events (1). Confirmed and possible carcinogens have many different chemical properties; they are derived from a multitude of different sources and they can interact with each other *in vivo* in a complex manner (1). Understanding how known and possible carcinogens cause cancer requires insight from many different fields on multiple scales including chemistry, endocrinology, toxicology, pharmacology, cell biology, oncology, genetics, epigenetics, immunology, inflammation and environmental health (2). Disruptive chemicals contribute to the evolution of tumorigenesis during cancer initiation, progression and maintenance, but also therapeutic response and resistance. Importantly, many of these effects of carcinogens occur through modulation of the tumor microenvironment. Finally, established and putative carcinogens can come from the environment but also can be endogenously produced by cells and tissues. However, in this review, we have generally focused on exposure to exogenous and environmental compounds.

The microenvironment is integral to the process by which known and possible carcinogens contribute to tumorigenesis (Figure 1). Tumor initiation is associated with the recruitment and activation of multipotent stromal cells/mesenchymal stem cells, fibroblasts, endothelial cell precursors, antigen-presenting cells (APCs), such as dendritic cells (DCs), and other hematopoietic cells (3). These non-tumor host cells recruit stroma and immune cells and produce cytokines that collectively contribute to the tumor microenvironment (4). Chemicals often modulate these cellular host effectors, including epithelial cells, stromal cells, extracellular matrix (ECM) components or immune cells, can influence the generation of stroma (5) and may modulate the production cytokines (6) (Figure 1). Known and potential carcinogens mediate these effects directly or indirectly through immunological activation, chronic inflammation and endocrinological mechanisms (4). Moreover, combinations of chemicals with different biological activities may potentiate each other's tumorigenic effects (Figure 1). Further, some of these changes could be caused by the influence on tumor cells alone or in concert with environmental exposures. Correspondingly, mixtures of even low doses of disruptive compounds are likely to contribute to tumorigenesis through many effects, including the modification of the microenvironment. By understanding how these chemicals influence the microenvironment, it should be possible to predict which disruptive compounds will cooperate and thereby anticipate preventive and therapeutic strategies to mitigate chemical-induced tumorigenesis.

The microenvironment could also be key to identifying the earliest influences of known or putative carcinogens in promoting tumorigenesis. Specific changes in the microenvironment could be used as biological markers of chemical exposure. This could be particularly useful in discriminating when complex mixtures and in particular low-dose combinations of chemicals may contribute to tumorigenesis.

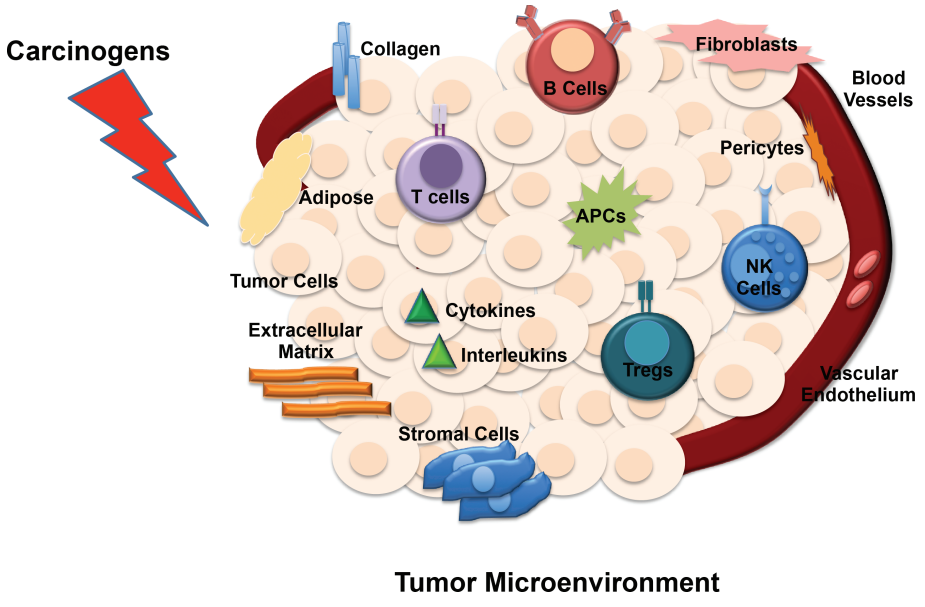

Figure 1. Carcinogens promote tumorigenesis by targeting multiple components in the tissue, and subsequently, the tumor microenvironment. First, carcinogens may exert preneoplastic influences on various cell types within the tissue, such as stromal cells, fibroblasts and endothelial cells. Carcinogens may also affect the innate (antigen-presenting cells) and adaptive (B, T lymphocytes) immune system, as well as secreted molecules. Carcinogens may encourage angiogenesis and chronic inflammation, which fuel the growth and evolution of the neoplastic cells.

The origins of a neoplastic-prone tissue landscape

Neoplastic cell populations interact with their surroundings by continuously emanating and receiving stimuli, resulting in an ever-changing biological landscape. The significance of this concept was illustrated several decades ago when it was noted that most carcinogens are toxic to their target tissue, despite the fact that their long-term effect is the induction of a hyperproliferative disease that can culminate in cancer (7). A landmark study showed that chemical carcinogenesis could foster the growth of preneoplastic lesions through an indirect mechanism by limiting the proliferative capacity of surrounding normal tissue (8). Such a seemingly paradoxical circumstance could only be explained by carcinogens exerting their effects by suppressing growth in the bulk of normal cells, but resulting in the activation of the proliferation in a rare population of cells that eventually leads to neoplastic lesions. Hence, the initial global effects of a carcinogen can be to restrain growth, but this can result in an environment that selects for rare cells that escape and in fact benefit from this constraint, leading to tumorigenesis.

Many chemicals can profoundly modulate the tumor microenvironment. By using adoptive transplantation approaches, it has been demonstrated that a growth-constrained tissue microenvironment could provide a powerful driving force for the rapid expansion and progression of transplanted, preneoplastic cells (9). Exposure to retrorsine, a naturally occurring pyrrolizidine alkaloid, induces a persistent block in hepatocyte cell cycle. When rats that were pretreated with retrorsine were then orthotopically transplanted with syngenic hepatocytes isolated from liver nodules, they developed preneoplastic and neoplastic lesions that were clearly from donor origin. However, the same nodular cell preparations were unable to grow and progress to cancer following injection into normal, untreated host liver. These findings underscore the role of the microenvironment in the pathogenesis of neoplastic disease (10). Further, they suggest that an altered tissue landscape might in fact represent a rate-limiting step during carcinogenesis, at least in some cases. Indeed, most cancers in humans arise in a background of chronic disease that affects the target tissue (11).

One could use the transplantation system as a tool toward the identification of disease risk factors affecting the tissue microenvironment. In fact, it has several features that make it particularly attractive to analyze the impact of complex combinations of chemical exposures including (i) it is an *in vivo* orthotopic and syngeneic transplantation system, implying that cells are injected in the homotypic tissue of a living animal, without the need for immune suppression, (ii) the fate of transplanted cells can be easily followed in the recipient animal through the use of simple immunohistochemical techniques and (iii) cells isolated from the earliest possible stages of carcinogenesis can be transplanted, allowing for a stepwise analysis of any role of the microenvironment in their phenotypic behavior. Furthermore, (iv) the biological continuity of the neoplastic process is essentially maintained, since cell transplantation is performed soon after isolation; however, *in vitro* culture and manipulation of isolated cells is possible and (v) this transplantation system can dissect alterations induced on the host (surrounding) tissue from those exerted on focal cell populations, which can be used to facilitate the mechanistic analysis as well as to identify counteracting therapeutic strategies. Thus, a transplantation system could be used as a specific and sensitive biological test to identify risk factors for neoplastic disease that may exert their effect by inducing a neoplastic-prone tissue landscape (12).

A transplantation system could be used to interrogate the role of more recently identified biological programs that may regulate the tumor microenvironment. Cellular senescence acts as a fail-safe mechanism with the potential to direct the terminal differentiation of transformed cells. This may suppress carcinogenesis both by directly blocking individual cells from progressing to a malignant state, but also by altering the local

microenvironment through the production of cytokines and growth factors and recruitment of immune cells (13).

Transplantation enables the dissection of how the tumor and host interact in the tumor microenvironment with discrete roles in the pathogenesis of cancer (14). An altered tissue microenvironment may be particularly important during the earliest stages of carcinogenesis, when focal proliferative lesions emerge such as nodules/adenomas, polyps and papilloma. Once these focal lesions are formed, a unique tumor microenvironment appears, characterized by defective oxygen and nutrient supply, resulting in altered growth. The biochemical and metabolic consequences of transient hypoxia on tumorigenesis include the induction of genetic instability (15) and changes in tissue pattern formation (16,17). Accordingly, single cancer-causing agents and mixed exposures may interfere with the fine-tuned mechanisms overseeing tissue architecture and may have the potential to add to the carcinogenic risk. Similarly, the role of endocrine programs could be studied (18). Hormones can follow a non-monotonic curve, and this adds to the complexity of the relationship (19). Biologically integrated model systems could be used to address the role of these various biological programs.

The general understanding of how carcinogens alone and in concert cause tumorigenesis requires insight into the tumor microenvironment. In addition to defining specific cellular effectors and cytokines, the role of other cellular programs such as cellular senescence and endocrine programs can be studied. Measurements in the microenvironment may be useful as biomarkers to predict as well as therapeutic targets to prevent carcinogenesis.

Preneoplastic changes in the microenvironment caused by carcinogens

Genetic, epigenetic or transcriptomic changes within a cell that possesses clonal lineage potential can become fixed within that lineage and enable the first steps toward oncogenesis. Once fixed, further oncogenic change can accumulate within a clone until oncogenic transformation occurs. This process likely follows a complex evolutionary pathway as a result of Darwinian competition within the clonal microenvironment. In normal homeostasis, this pathway displays a pattern of neutrality resulting in survival and expansion of a clone as a result of stochastic dynamics within the clonal microenvironment. However, in the presence of a carcinogen, this balanced competition can become skewed to favor the survival of a clone that possesses an advantageous oncogenic change. Interaction of these clonal units with various environmental carcinogens, particularly in exposed epithelia such as the skin, lungs and gastrointestinal tract, can lead to diverse heterogeneity of clones within a single individual as well as increase the rate at which divergence of clonal heterogeneity occurs.

Exposure to known and potential carcinogens influences the microenvironment. Field cancerization refers to the widespread premalignant changes in the microenvironment of an organ or tissue, potentially as a result of a carcinogenic insult. Effects, such as increased inflammatory cytokine production and aberrant cell-to-cell signaling, then predispose the population of cells within that 'field' to the development of, sometimes multiple, premalignant foci as demonstrated in prostate cancer and colonic aberrant crypt foci (20). The progression from normal to premalignant to cancer, with field cancerization, can be seen in progression from benign adenomatous polyps preceding colorectal cancer, intraepithelial neoplasia progressing to cervical carcinoma and benign monoclonal plasma cell proliferation in individuals who later develop multiple myeloma (21,22). An understanding of the early changes in the progression of these diseases could aid prevention policies and early detection systems.

There are many mechanisms through which tissue-wide changes could contribute to tumor formation. These include direct modification of gene expression, epigenetic alterations and chromosomal aberrations. DNA double-strand breaks occur largely as a result of damage caused by ionizing radiation, a topic discussed later in this review. Aberrant repair of these lesions can lead to chromosomal translocations, which potentially results in the overexpression of oncogenic loci and deregulation of key signaling networks. Chromosomal aberrations are reported in the majority of solid and myeloproliferative neoplasms (23). Interestingly, early field aneusomies have also been reported in benign adjacent parenchyma and contralateral breast biopsies (24), adjacent normal mucosa from head and neck carcinomas (25) and show an accumulation in normal colonic epithelial tissue with age (26). These early-stage changes suggest a role of chromosome aberration in preneoplasia and not only in malignancy.

Many environmental compounds, including known and possible carcinogens, can lead to cellular stress directly resulting in gene expression changes. In prostate, adjacent 'normal' mucosa has been shown to have an altered gene expression profile more similar to that of the primary tumor than mucosa from unaffected controls (27) suggesting field cancerization effects to be present in histologically normal tissue. Mesenchymal-specific changes in *Notch* signaling networks in the skin lead to stromal atrophy, inflammation and formation of actinic keratosis lesions, which are believed to be precursors of squamous cell carcinoma (28). Importantly, it was demonstrated that this effect could be recapitulated through UVB exposure. Furthermore, nickel exposure has been shown to induce increased levels of reactive oxygen species (ROS) that, besides their direct mutagenic effect, can directly lead to alterations in specific gene expression programs that potentially drive oncogenesis (29,30). In particular, the upregulation of a gene network involving c-Myc following nickel exposure has been hypothesized to drive oncogenesis. Importantly, the effect of nickel was shown to be passage-dependent *in vitro*, indicating the importance of cumulative and prolonged cellular stress in the progression of a preneoplastic state to cancer (29). Low-level, prolonged exposure to such agents can induce and maintain altered gene expression networks within long-lived clonal lineages, and their local environment, that can predispose such populations to subsequent oncogenic transformation.

Furthermore, epigenetic modifications are also involved in carcinogenesis. Cancers display global hypomethylation combined with specific regions of hypermethylation within tumor suppressor gene promoter elements such as *p16INK4a*, *hMLH1* and *BRCA1* (31). The impact of various environmental, non-genotoxic carcinogens in inducing methylome changes associated with oncogenic progression has been shown in lung, colorectal and liver oncogenesis as well as leukemogenesis (32). Strikingly, the hypermethylation of promoter elements of tumor suppressor genes such as *MGMT* and *SFRP* in the histologically normal mucosa surrounding colon cancer indicates the role of epigenetics in field cancerization in this malignancy. Similar findings have been shown in the surrounding tissue of breast, prostate and certain squamous cell

carcinomas (20). These changes have been suggested to relate to non-genotoxic agent exposure leading to key methylome changes in the supporting stroma. For example, low-level benzene exposure has been associated with global hypomethylation as well as hypermethylation of the *p15* tumor suppressor gene promoter element associated with acute myeloid leukemia progression (33). Determining how disruptive chemicals are associated with epigenetic modifications would help further understand cancerization.

Chronic inflammation is associated with an increased risk of cancer formation in many tissues. It has been estimated that 20% of cancer deaths are caused by chronic inflammation (34). For example, it has been well established that people suffering from inflammatory bowel disease have, on average, a 2-fold higher risk of developing colon carcinomas (35). Similarly, lung cancer is much more common in patients with idiopathic lung fibrosis, an inflammatory lung disease (36). Furthermore, a direct relationship between the duration of chronic inflammatory processes and the likelihood of developing cancer exists (35). Therefore, it is pivotal to our understanding of environmental- and lifestyle-induced cancers to appreciate the potential pro-inflammatory and resulting pro-carcinogenic properties of substances to which we are exposed.

The mechanisms by which an inflammatory microenvironment promotes carcinogenesis are multifold. Chronic inflammatory processes attract activated immune cells that then produce a plethora of cytokines of which some have pro-tumorigenic properties such as interleukin (IL)-6 and transforming growth factor (TGF)-β. These signaling molecules activate intracellular signal transduction cascades in the preneoplastic cells such as nuclear factor-kappaB (NF-κB) and Wnt that promote proliferation and decrease the susceptibility to apoptosis (37). Additionally, chronic inflammation is associated with chronic oxidative stress and elevated levels of ROS that have a direct mutagenic impact on cells in the environment. This has been speculated to contribute to the development of solid malignancies (38) and myeloproliferative neoplasms (39). More recently, it was established that an inflammatory environment renders differentiated cells more susceptible to oncogenic transformation, something that under normal conditions happens much more efficiently in the stem cell compartment (40,41). Therefore, inflammation expands the pool of potential cancer cells of origin within a tissue and subsequently enhances the chance of tumor development.

Asbestos is an example of an environmental agent that induces inflammation associated with tumorigenesis. Asbestos fibers are long, thin crystalline structures that upon inhalation can lead to a variety of lung diseases including lung cancer and mesothelioma. In addition to direct effects on lung epithelial cells, asbestos fibers are ingested by macrophages where they activate the Nalp3 inflammasome that subsequently leads to IL-1β production (42). IL-1β, in combination with other growth factors and cytokines such as TGF-β and tumor necrosis factor (TNF)-α, triggers a fibrotic response in the lung, mediated by activation of local fibroblasts that promotes collagen deposition. This fibrotic condition, known as asbestosis, is characterized by the presence of asbestos bodies, which are asbestos fibers covered in collagen deposits and are a continuous stimulant for further inflammation. Interestingly, the number of asbestos bodies detected directly relates to the risk of lung cancer (43). An additional consequence of increased IL-1β levels in asbestosis is that it has the ability to activate the NF-κB cascade in lung epithelial cells that has direct pro-tumorigenic properties similar to that seen in the intestine (44).

Methylmercury (MeHg), a ubiquitous pollutant, is known to induce changes in cellular enzymes and cellular functions and mitochondrial dysfunction, as well as disorders relating to microtubule composition and cellular migration (45). Of particular note, MeHg can induce oxidative stress, which promotes carcinogenesis via mechanisms discussed above. Similarly, paraquat, the second most widely used herbicide worldwide, can induce mitochondrial damage, oxidative stress and oxidative injury (46). Other compounds can cause an equivalent sequence of events in the lung leading from a chronic, fibrotic inflammatory state toward cancer, usually after long-term exposure. These include tobacco smoke, petroleum fumes and perhaps nanoparticles. Additional examples of non-infectious inflammatory conditions induced by recognized agents and associated with cancer formation include alcohol, leading to cirrhosis and liver cancer, pancreatitis and pancreatic carcinoma, and chewed tobacco, which is associated with lichen planus and oral cancers. These agents are complex mixtures of chemicals of which some also have clear and direct mutagenic effects.

Hence, mixtures of some chemicals may work in concert on both incipient tumor cells as well as the host to induce genetic and/or epigenetic changes that contribute to carcinogenesis. This likely occurs in a temporal sequence that imposes evolutionary selection. Chronic inflammation may be one of the critical drivers in the initiation and maintenance of tumorigenesis through an influence *in situ* in the tumor microenvironment.

Matrix metalloproteinases and carcinogens

There are many specific factors in the pre-tumor microenvironment that can be affected by known and possible carcinogens, including matrix metalloproteinases (MMPs), vascular cells, stromal fibroblasts, infiltrating immune cells and specific chemokines. The MMP-1 was identified as a collagenase derived from human fibroblasts (47). Currently, the MMP family consists of well over 20 zinc-containing endopeptidases that degrade various components of the ECM, many of which were first identified by their overexpression in tumor cells (47,48). MMPs are regulated by cytokines (e.g. IL-1), TNF-α, growth factors, bacterial components, hormones and mechanical stress (49). MMPs also exhibit pro- and anti-angiogenic functions via the respective release of growth factors and angiogenic inhibitor peptides from the ECM (48). Tumor cells and fibroblasts are cell types that contribute to the production of MMPs in the tumor microenvironment.

Tumor cells undergo a developmental process called epithelial–mesenchymal transition (EMT) whereby cells become invasive and favor cell–ECM rather than cell–cell adhesions (50). Evidence has indicated that MMP-2, MMP-3, MMP-7, MMP-9, MMP-28 and membrane type 1-MMP are involved in EMT (51). The aryl hydrocarbon receptor (AhR) is also implicated in EMT whereby AhR expression in skin and mammary epithelial cell lines inhibits basal and TGF-β-induced EMT as characterized by changes in epithelial and mesenchymal markers and by increased cell migration (52). AhR is a member of a family of orphan nuclear receptors, including the pregnane-X-receptor and the constitutive androstane receptor, which mediate the accumulation and clearance of xenobiotic carcinogens, pollutants and drugs (53). Activation of AhR in breast (54), prostate

(55), melanoma (56), gastric (57) and urothelial (58) tumor cell lines induces the production of MMP-1, MMP-2 and MMP-9. Thus, differences in the tumor type, the carcinogen or the MMP produced may affect the EMT process. Of interest, the expression and activity of these MMPs has been reported to be mediated through AhR-induced activation of human epidermal growth factor receptor-1 (54). AhR is also known to alter the activity of cytokine (IL-1, TNF-α) receptors that activate MMPs (49,59). Moreover, various murine models have shown that these cytokines are essential for chemical carcinogen-induced tumor development and promotion (60–63), suggesting that cytokine-induced MMPs via tumor cells may play a role in chemical-based tumorigenesis.

In addition, hormone receptor activation induces MMP production and exhibits cross talk with AhR. Immunoblot analysis revealed that AhR expression increases in androgen-independent (C4-2) prostate cancer cells when compared with androgen-sensitive human prostate adenocarcinoma cell line (LNCaP) cells (64). In ZR-75, T47D and MCF-7 human breast cancer cells, dioxin treatment induces proteasome-dependent degradation of endogenous estrogen receptor α (ERα) (65). Various studies have also linked ERα and ERβ transcriptional activity with the expression and activity of AhR and AhR co-activators (66). Thus, the invasive phenotype of hormone-related cancers may be associated not only with MMP production but an altered status of AhR expression or function. Carcinogens, particularly endocrine-disrupting chemicals (EDCs), may act through this pathway.

Fibroblasts are a pervasive and diverse population of cells that produce and maintain the ECM in normal tissue homeostasis, the wound/repair response and tumorigenesis (67). In the wound/repair response, quiescent fibroblasts transform into myofibroblasts, subsequently encourage healing via the release of various molecules (ECM proteins, growth factors, stress fibers), and then undergo programmed cell death upon successful wound closure (68). In the stroma of various tumors (breast, pancreas, prostate, ovary, skin, colon, esophagus), fibroblasts transform into myofibroblasts that release wound/repair molecules, but the process of programmed cell death does not occur (68,69). The mechanisms involved in the generation of cancer-associated fibroblasts are not clearly understood but may include the transdifferentiation from various cell types (carcinoma, epithelial, resident fibroblast, endothelial, mesenchymal, pericytes), the increased production of MMPs as well as cytokines (IL-1, TNF-α, IL-6, TGF-β) and growth factors [stromal-derived factor-1, hepatocyte growth factor, vascular endothelial growth factor (VEGF)] (68).

Interestingly, immortalized primary mammary gland fibroblasts in an immunodeficient murine xenograft model demonstrated similar proliferation and myofibroblast transformation in the presence or absence of the AhR but the ability of $AhR^{-/-}$ fibroblasts to induce subcutaneous tumors was significantly reduced. This difference in tumorigenesis may, in part, be attributed to the reduced MMP-9 activity and VEGF receptor-1 expression in the $AhR^{-/-}$ fibroblasts (70). Although MMP-2 levels were not affected by AhR status in mammary gland fibroblasts, the absence of AhR in mouse embryo fibroblasts did result in reduced MMP-2 activity (70,71). Additional *in vitro* studies using the AhR agonist, tranilast, indicated that in nasal fibroblasts, TNF-α-induced MMP-2 and MMP-9 production are inhibited by tranilast. In a human fibroblast cell line from gastric carcinoma, MMP-2 and TGF-β production are inhibited by tranilast (72,73). These data indicate a complex interplay between MMPs and carcinogens in fibroblasts that may depend on the chemical structure, type of fibroblast and the presence of additional cytokines or cell types. Thus, additional study of carcinogen-induced ECM responses in fibroblasts seems warranted.

Carcinogens, tumor microenvironment and the tumor vasculature

Chronic low-level exposure to disruptive chemicals can promote oncogenesis (74,75), as previously discussed. The cell types in the tumor microenvironment that are known to contribute to tumor progression include fibroblasts, endothelial cells and pericytes, all of which may be targeted by carcinogens. Endothelial cells, which are the cells that line the vasculature, are activated during tumor growth undergoing an angiogenic switch, a prerequisite for the onset of tumor angiogenesis, which is necessary to support the expansion of the tumor mass (76). Although few studies have examined the effect of carcinogens specifically on endothelial cells during tumor angiogenesis, there have been studies investigating how environmental toxins disrupt embryonic development and affect vasculogenesis.

The process of vasculogenesis is the differentiation and formation of blood vessels from progenitor cells during development leading to the formation of a vascular network in the embryo (77). This is different from that of angiogenesis, which remodels and expands the vascular network and relies on existing endothelial cells to proliferate, migrate and form new vessels occurring during both physiologic and pathologic processes. Studies have shown unique gene expression patterns during normal versus pathologic angiogenesis influenced by tumor-associated factors in the microenvironment such as hypoxia, alteration in blood flow and infiltration by immune cells. For example, inflammatory cells, such as macrophages, are abundant in the tumor microenvironment but are not detected in the corpus luteum, where high levels of normal physiological angiogenesis occur. Macrophages and other immune cells secrete soluble factors, which then influence endothelial gene expression. One well-characterized endothelial mitogen known to be critical for both physiological and pathological angiogenesis is VEGF (78).

Studies examining the effects of carcinogens and environmental toxins on vasculogenesis and angiogenesis have revealed significant changes in VEGF expression levels. For example, treatment of pregnant mice with the environmental toxicant herbicide Nitrofen leads to pups born with airway vascular abnormalities along with numerous other defects that mimic the newborn condition, congenital diaphragmatic hernia. VEGF levels were significantly lower in lungs during early stages of embryogenesis in Nitrofen- versus vehicle-treated mice (79). At embryonic day 14, high levels of VEGF are required for normal lung development since endothelial cells are the most abundant cell type in the differentiated lung and vessel formation in the developing lung requires VEGF-mediated endothelial cell differentiation, migration and tube formation to form a complex organized network (80).

In a murine lung tumor xenograft model, exposure to either estradiol or nicotine led to a significant increase in VEGF expression with a concomitant increase in tumor growth. Although both estrogen and nicotine are known to be carcinogenic, causing genotoxic mutations triggering initiation and promotion of cancer, their effects on angiogenesis and endothelial cells are less well understood (81). In another study using the known carcinogen *N*-nitrosobis(2-hydroxypropyl) amine, expression of VEGF and its receptors were examined upon euthanization of rats at 20–28 weeks after drinking *N*-nitrosobis(2-hydroxypropyl)amine-containing water for the

first 12 weeks of life after weaning. At killing, mice harbored lung adenocarcinomas, squamous cell carcinomas, adenomas and alveolar hyperplasias with VEGF expression and its receptors most highly upregulated in adenocarcinomas and squamous cell carcinomas implicating the importance of increasing VEGF levels in malignancy (82).

Further studies are necessary to understand the mechanism by which prolonged exposure to carcinogens and environmental toxins regulates VEGF expression as well as the expression of other angiogenic regulators. However, it is becoming increasingly evident that long-term low-dose exposure to carcinogens promotes tumor growth through their effects on the tumor microenvironment and tumor angiogenesis.

Effects of carcinogens on ECMs and implications for the tumor microenvironment

Little is known about the impact of known and potential carcinogens on the stroma, an important component of the tumor microenvironment. Specifically, the effects of carcinogens on the amount and composition of ECMs in tissues is unclear, and how tissue-remodeling genes may impact carcinogenesis is poorly understood. Many cancers emerge in the setting of chronic tissue inflammation and remodeling; the latter is characterized by alterations in the expression, deposition and degradation of ECMs leading to dramatic changes in matrix composition and tissue architecture (83). For example, subjects with liver cirrhosis are at increased risk of developing hepatocellular carcinoma, while most lung cancers develop in patients with chronic lung disorders like emphysema and lung fibrosis (84,85), as discussed earlier in this review. Interestingly, new data have revealed activation of tissue remodeling in the lungs of aging animals, which is intriguing since there is increased incidence of cancer in the elderly (86).

The predilection for cancer development in the setting of chronic inflammation and tissue remodeling suggests that the tumor microenvironment plays important roles in carcinogenesis. Some of the best data available implicating carcinogens in tissue remodeling and increased incidence of tumors exist for lung cancer. In lung, chronic exposure to asbestos, beryllium, heavy metals, silica, radiation and organic agents are all associated with higher incidence of chronic lung disease characterized by tissue remodeling. Similar changes have been found in animal models of lung injury caused by exposure to heavy metal, radiation, cadmium chloride, crocidolite, ozone, carbon tetrachloride and residual oil fly ash, among others (43,87). Chronic tobacco smoke with nicotine exposure is also associated with activation of tissue remodeling leading to increased deposition of matrices and, ultimately, loss of lung structure and function (88). However, little is known about the effects of mixtures of low-dose chemicals on tissue remodeling or if these mixtures have additive or synergistic effects on carcinogenesis.

Some chemicals may promote tissue remodeling by stimulating host cells to express pro-fibrotic growth factors, cytokines and chemokines, to deposit excess matrix glycoproteins and collagenous proteins implicated in lung injury and repair and to release matrix-degrading proteases. These products may originate in activated resident cells as well as incoming inflammatory cells. These alterations in tissue remodeling genes may lead to alterations in tissue architecture and it is within this abnormal inflamed and remodeled tissue that tumors develop and confront innate immunity. Many mechanisms may be involved in tissue remodeling. First, the disruption of basement membranes can occur during tissue injury exposing transitional matrices like fibronectin and fibrin, which alters cell–cell interactions and promotes epithelial cell proliferation and/or decreased apoptosis (89). Growth factors embedded in the matrix are released during tissue remodeling and can become activated during injury and repair. Newly deposited matrices and/or their fragments may stimulate chemotaxis and immune cell activation through pathways such as activator protein 1 and NF-κB, promoting inflammation (90).

Tissue remodeling has implications for both host cells and tumor cells alike since both express a repertoire of integrins and other receptors capable of recognizing the newly deposited matrix and activating intracellular pro-oncogenic signals, such as Ras signaling, Erk activation, and decreased tumor suppressors. These pathways can participate with and even collaborate with pathways triggered by known or possible carcinogens in tumor cells. Such collaborative interactions are likely to exist for many chemical mixtures even at doses considered below their 'no observable adverse effects levels', but further investigation is needed.

Dissecting the pathways through which environmental exposures promote tissue remodeling might be fruitful. For example, nicotine and ethanol (recently associated with increased incidence of lung cancer) were shown to interact with lung fibroblasts (and tumor cells) through nicotinic acetylcholine receptors to promote fibroproliferation and matrix expression. The availability of new technology capable of developing anti-nicotinic receptor agents might allow for the targeting of these pathways. Another approach would be to target tumor cell–stromal interactions through downregulation of integrins or integrin-mediated signals. Recently, decreased tumor growth and lung metastasis were observed in an experimental model of lung cancer where non-small cell lung carcinoma cells silenced for α5β1 fibronectin integrin receptors were injected (89). Strategies designed to modulate tissue remodeling and/or influence tumor cell–matrix interactions may be beneficial to ameliorate or inhibit the pro-oncogenic effects of specific chemicals, but further exploration into the true role these interactions play in carcinogenesis will be required.

Carcinogens and immune effectors within the tumor microenvironment

Known and potential carcinogens may exert a role on the tumor microenvironment through infiltrating immune effectors. The role of these disruptive chemicals on immune cells has been documented in the literature, particularly for suppressive regulatory T cells (Tregs), APCs and natural killer (NK) cells. It is likely that disruptive chemicals that are associated with tumorigenesis may cause cancer at least in part through disturbance of immune effectors.

Urethane-induced lung tumors have elevated levels of myeloid-derived suppressor cells along with Tregs. These suppressor cells ($CD11b^+$, $GR\text{-}1^+$) infiltrated the tumor, whereas there was an increase in interferon (IFN)-γ-producing effector immune cells in the periphery (91). Bisphenol A (BPA), commonly used in a variety of chemical products such as epoxy resins and polycarbonate, is known to possess estrogen-like activity (92). It has been found to have immunomodulatory activity and can influence the maturation and polarization of DCs. DCs in the presence of TNF-α secrete additional CC chemokine ligand 1 and higher levels of the immunosuppressive cytokine IL-10; these DCs were preferentially induced in favor of Th2 (92). These findings could have implications for DCs recruited to the tumor microenvironment to present

tumor-associated antigens during cancer therapy. BPA, as well as other EDCs such as diethyl stilbesterol, bis(2-ethylhexyl) phthalate and *p*-nonylphenol, can also stimulate the macrophages to produce cytokines (93).

Other chemicals have been found to modulate $CD8^+$ T cells and NK cells, as well as the expression of IL-10 and TGF-β. NK cells function as an early protection against tumor cells and may secrete large quantities of TNF-α. In chemically induced neoplasias in a rat model, increased numbers of NK cells were observed in colon, lung and kidney tumors, and fewer $CD8^+$ T cells were observed in intestine and lung tumors. Additionally, immunosuppressive IL-10 was elevated in select tumors, such as kidney, and elevated TGF-β was found in liver and kidney tumors (94). NK cells can also be affected by EDCs such as butyltins, including dibutyltin and tributyltin (TBT). TBT and dibutyltin may inhibit the ability of NK cells to kill target tumor cells and may do so by reducing the cytokine secretion of the NK cells (95). Moreover, the effects of dibutyltin and TBT were found at biologically relevant concentrations (that are normally seen in human blood) (95). Consequently, carcinogens may exert at least some of their effects through diminished NK cell activity via diminished cytokine and/or IL secretion. Mechanistically, TBT may lead to a decrease in adenosine triphosphate levels, which can lower the tumor-lysing function of NK cells (96). Thus, although TBT may not induce DNA damage, it may very possibly play a major role in diminishing the antitumor activity of cytotoxic immune cells within the tumor microenvironment. Exposure to such chemicals may encourage the growth of tumors or may render select therapeutics less powerful, as they cannot harness the antitumor capabilities of NK cells.

Other chemicals may also dampen NK cell activity. For example, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), the most potent carcinogen found in tobacco and tobacco smoke, has been found to suppress the activity of NK cells in a mouse model (97). Killing and clearance of tumor cells was reduced in the lungs of mice treated with NKK while the total number of NK cells remained the same, indicating that only their function had been compromised (97). Furthermore, the tumor cells were more likely to metastasize (97), indicating that carcinogens can modulate the tumor microenvironment not just in the initiation of lung cancer but also in its progression.

Carcinogens can modulate other immune cells in the tumor microenvironment, such as T cells. It is not surprising that carcinogens can affect T cell populations, as effector and Tregs are influenced by the tumor microenvironment (98), which can in turn be influenced by carcinogens. In a mouse study, exposure to a tobacco carcinogen tripled $FoxP3^+$ Tregs in the lung in measurements taken before tumor development (99). Similarly, mice lacking $FoxP3^+$ T cells developed 75% fewer lung tumors as compared with control animals (99). These data indicate that $FoxP3^+$ Tregs are necessary for K-Ras-mediated lung tumorigenesis and also suggests that in addition to targeting the proto-tumor cells, carcinogens may be targeting lymphocytes in the proto-tumor microenvironment, such as Tregs, and generating a pro-tumor microenvironment. Data in human patient samples have supported work from animal models. Smokers with lung cancer have been found to have a lower proportion of helper T cells and a higher proportion of suppressor T cells/cytotoxic cells (100), indicating that carcinogens in tobacco may encourage the recruitment of suppressive lymphocytes to the tumor microenvironment.

Carcinogens may also affect other lymphocytes that play a role in the antitumor immune response. Polycyclic aromatic hydrocarbons (PAHs) are frequently found in the environment and are well known to be immunosuppressive. PAH exposure leads to pre-B cell apoptosis via inhibition of the NF-κB pathway (101). Exposure to chemicals that inhibit this pathway may lead to a reduction in B cell precursors in the bone marrow and consequently in the periphery and in the antitumor immune response.

Known and potential carcinogens can contribute to both the initiation of cancer as well as the microenvironmental immunosuppression that can lead to its progression; chemicals either alone or in mixtures may shift the balance of the local immune milieu. In order to better understand the role of cancer-causing agents, assays other than traditional mutagenic assays are needed, particularly to characterize the long-term, low-dose effects of non-genotoxic agents. Alternative screening strategies (102) could help categorize exposure threats and reduce cancer risks (103).

Carcinogens and activation of the innate immune system

The innate immune system can both suppress and/or promote carcinogenesis. Dimethylbenz(a)anthracene is commonly utilized as a tumor initiator and organ-specific laboratory carcinogen and provides a good example of an immune suppressive agent. Dimethylbenz(a)anthracene, for instance, is able to efficiently induce rat mammary tumors, where it has been shown that, besides its mutagenic effect on tumor cells themselves, it also suppresses both cell-mediated and humoral immune responses (104). One central reason for this immunosuppressive activity is the inhibition of IL-2 receptor expression in lymphocytes of dimethylbenz(a)anthracene-treated animals (104), a receptor that is essential for their activation and expansion.

Splenic macrophages also play an important 'cleaning' role against foreign substances carried in the blood and in major sites where antibodies are produced and released into circulation. Lead and arsenic are environmental agents that macrophages attempt—but fail—to clear. It has been reported that lead acetate has, in fact, a profound effect on cell adhesion and morphology of splenic macrophages, which, as a consequence of exposure, have reduced capacity to produce alkaline phosphatase (105). Similarly, sodium arsenite impairs their phagocytic activity and the production of nitric oxide and induces a degree of apoptosis (105).

Macrophages are sensitive to ozone (O_3), a well-characterized toxic gaseous pollutant known to have damaging effects on lung (106). Indeed, their viability is reduced as a consequence of exposure to the gas (107). The migration of macrophages is first reduced, while their chemotactic migration is then increased 24 h after the exposure (107). Most importantly, their cytotoxicity toward tumor cells is significantly reduced, indicating that O_3 could lead to a deficiency in tumor surveillance that can increase the host susceptibility to pulmonary cancer (107).

The cytolytic activity of macrophages can also be affected by diterpene esters (organic compounds of fungal or plant origin, very often used in the past for caulking of boats and waterproofing ropes), which are widely recognized tumor promoters (108). Probably the best-known and utilized in cancer research is the phorbol ester TPA. Such esters can both prevent the lymphokine-induced enhancement of natural cytolytic activity of resting macrophages and suppress the cytotoxicity of activated ones. Therefore, diterpene esters both stimulate directly the growth of transformed cells and interfere with the natural antitumor immune response (109).

Another example of immunosuppressive activity by carcinogens has been observed in smokers. More than 20 carcinogens have been identified in cigarette smoke. One of the most

abundant is NNK. It has been shown that in addition to its carcinogenic effect, NNK is immunosuppressive in tobacco smokers, acting on alveolar macrophages in addition to its previously discussed effects on NK cells. Macrophages in turn produce cyclooxygenase-1 and -2, which are involved in the bioactivation of NNK to electrophilic mutagenic intermediates. Data suggest that ROS are generated during pulmonary metabolism of NNK and cause NF-κB activation with consequent activation of cyclooxygenase-1 and production of prostaglandin E_2 (110). Concomitantly, NNK also reduces the production of TNF, macrophage inflammatory protein-1α, IL-12 and nitric oxide (111).

Exposure to chemicals, such as alpha-naphthylamine and *N*-methyl-*N*-nitrosourea, can render macrophages themselves tumorigenic. Indeed, peritoneal murine macrophages exposed to these chemicals can give rise to immortal cell lines with tumorigenic activity in athymic nu/nu mice (112). But other agents, besides chemical ones, can also promote the tumorigenic activity of macrophages. Ionizing radiation, which will be discussed later in this review, is ubiquitous in the environment and comes from naturally occurring radioactive materials and cosmic rays. Common artificial sources are industrially produced radioisotopes, X-ray tubes and particle accelerators. It has many practical uses in areas such as medicine, research and construction, but presents a health hazard if used improperly, resulting in genetic mutation, radiation sickness, cancer and even death. One common target of ionizing radiation is hematopoietic tissue, in which increased macrophage infiltration, followed by neutrophil recruitment, has been observed (113). This inflammatory response is unsurprisingly first triggered by the presence of radiation-induced apoptotic cells, but it persists long after apoptotic bodies have been removed (113). At this point, macrophages stay active and continuously produce nitric oxide and clastogenic factors, providing a bystander effect that contributes to long-term genomic instability and potentially to leukemogenesis (113).

Macrophages are involved in the carcinogenic response to asbestos fibers in lung and pleural tissue. When they attempt to engulf and digest the fibers, they cause formation and release of ROS, namely hydrogen peroxide and super oxide radical anion (114). ROS then initiate a reaction (Haber–Weiss reaction) catalyzed by the iron present on the surface of the asbestos fibers leading to production of hydroxyl radicals, which are even more potent oxidizers (115). The presence of asbestos fibers also causes alveolar macrophages to release leukotrienes, prostaglandins and TNF-α, all contributing to inflammation, further macrophage recruitment, cell and DNA damage, proliferation and apoptosis (115,116). Macrophages are not the only culprits. Neutrophils can alter their functions following chronic inhalation of environmental particles. Indeed, neutrophils normally exert a protective activity against ROS, and specifically against H_2O_2, thanks to the production of myeloperoxidase (117). However, in the presence of nitrite, consumption of H_2O_2 by myeloperoxidase is inhibited and neutrophil-induced DNA strand breakage in pulmonary epithelial cells is increased, contributing to pulmonary carcinogenesis (117). Furthermore, some carcinogens require metabolic activation by immune cells themselves to become fully mutagenic and cytotoxic, and neutrophils can, for instance, perform peroxidative oxidation of *N*-arylhydroxamic acids generating the potent mutagen 2-nitrosofluorene (118,119).

Finally, neutrophils have been shown to have a clear role in methylcholanthrene-inititated butylated hydroxytoluene-promoted lung carcinogenesis (120). Methylcholanthrene is a highly carcinogenic PAH produced by burning organic compounds at very high temperatures, whereas butylated hydroxytoluene is a lipophilic organic compound used commonly (yet controversially) as an anti-oxidant in food, cosmetics, pharmaceuticals, rubber, electrical transformer oil and as a fuel additive. Indeed, depletion of neutrophils in BALB mice treated with these two carcinogens resulted in significant reduction in tumor multiplicity (120), indicating the crucial role of neutrophils as permissive—if not promoting—players in the tumorigenic process.

Carcinogens deregulate soluble factors and promote local inflammation

Known and possible carcinogens may also modulate their effects via deregulation of soluble factors and the local inflammation that these factors can generate. Carcinogens can include chemical endocrine disruptors such as BPA, bisphenol S (BPS), metal contaminants such as arsenic, beryllium and nanoparticles among many others (121).

Inflammation can be induced by chelating agents that change the equilibrium in Zn^{2+} and Ca^{2+} ions in renal cells, and metal contaminants such as beryllium in lung cancer that induce an immune response identified by an accumulation of CD4+ T lymphocytes (121). IL-6 secretion has been shown to be affected by different types of chemicals, such as BPA (122) or cadmium-containing silica nanoparticles, thus leading to a local increase of immunoreactive cells (123). Some disrupting chemicals such as BPA are lipogenic. In the context of breast cancer, BPA displays genotoxic effects well described on mammary epithelial cells but it has also been reported to accumulate in adipose tissue (124). This is particularly interesting as adipose tissue is a highly dynamic tissue and chemicals may be stored in microenvironment tissue and then released a long time after the initial exposure. IL-6 induction following nanoparticles exposure and modification of the local stroma (such as a stromal fibrogenic reaction) has been observed (123). This can induce an immunosuppressive microenvironment favoring cancer development.

Known and potential carcinogens also induce other key cytokines such as TGF-β and bone morphogenic proteins (BMPs). TGF-β expression is modified upon exposure to carcinogens as demonstrated, for example, upon exposure to silica nanoparticles and magnetite nanocrystals mainly associated with pulmonary disorders (123). Interestingly, not only a modification of the expression of TGF-β as well as the major actors of downstream signaling elements such as SMAD6/7 and DNA-binding protein inhibitor (ID) genes (125) may be induced. Furthermore, TGF-β induction by nanoparticles is associated with modifications of the tissue structure through the induction of a fibrotic process mediated by tissue inhibitors of metalloproteinases (TIMPs) MMP proteins (126). In human breast, BPA and its substitute bisphenol S are able to affect the microenvironment equilibrium of the naturally present soluble BMPs (BMP2/4) (127). BMPs and TGF-β molecules are often described to have contradictory effects, especially regarding stem cell regulation and cancer. Carcinogens are likely to affect either the stem cells directly and/or their microenvironment by perturbing the TGF-β/BMP balance.

The exposure to a combination of pollutants could result in amplifying effect driven by one specific agent. In pulmonary disease, both the IL-6 and TGF-β pathways are altered upon exposure to select nanoparticles (123). Benzene has been shown to directly affect hematopoietic stem cells by inducing their cytotoxicity (128). Regulation of hematopoietic stem cell key features is known to be highly dependent upon their interactions with their microenvironment, also called a niche (129). Benzene indirectly affects hematopoietic stem cells by modulating their microenvironment through the modulation of the

differentiation of microenvironmental cells such as mesenchymal stem cells. This ultimately leads to increased risk of leukemia (130). BPA induces the differentiation of mesenchymal stem cells into the adipogenic lineage (131). This is of particular interest, as previously discussed; BPA likely accumulates in adipose tissue through time, thus contributing to conditions that favor cancer emergence and progression. Indeed, hormonal disruptors (BPA/bisphenol S) alter the secretion of BMPs that leads to the initiation of the transformation process by affecting mammary stem cells in the presence of IL-6 (127).

Some chemicals may disturb major functions involved in tissue homeostasis, leading to cancer initiation, immune evasion, angiogenesis and tumor dissemination. This results from the environment perturbation through induction of soluble factors (TGF, BMPs and IL-6) and modification of tissue integrity (stromal cell content, matrix remodeling) (Figure 2).

Metabolic perturbators and the tumor microenvironment

Metabolic disorders are associated with an altered risk for developing malignancies. In particular, subjects with type 2 diabetes mellitus are at increased risk of a wide range of malignancies, including breast, endometrial, bladder, kidney, colorectal, pancreatic and liver cancer, as well as hematologic malignancies such as non-Hodgkin's lymphoma (132), whereas the risk of prostate cancer is reduced (133). The mechanisms underlying connection of these two largely heterogeneous and chronic disease states are incompletely understood. Hyperinsulinemia and enhanced insulin-like growth factor-1 (IGF-1) activation are among the most likely causal links (134). Insulin resistance and subsequent hyperinsulinemia in type 2 diabetic subjects may promote proliferation and survival of cancer cells and premalignant lesions since they frequently express high levels of insulin receptor. Insulin may also act as a mitogen by activating the IGF-1 receptor (135). Excessive insulin decreases the IGF-1 binding protein production by the liver, which increases the availability of free IGF-1, and thus stimulates its mitogenic and antiapoptotic activity (136). Thus, treatment of diabetic subjects with exogenously added insulin and related compounds harbors potential risk of promoting cancer. Consequently, the use of insulin may contribute to effects of other disrupting chemicals in the tumor microenvironment, and there may be synergy between insulin and these chemical mixtures.

A vast array of antidiabetic drugs have been developed, including biguanides, sulfonylureas, meglitinides, α-glucosidase inhibitors, insulin and its analogs, thiazolidinediones, gliptins, analogs of amylin and analogs of glucagon-like peptides. Biguanides are insulin sensitizers that were first discovered in 1920s, when guanidine compounds were isolated from *Galega officinalis* (*Fabaceae*). Metformin (*N*,*N*-dimethylbiguanide) is currently the most widely prescribed drug to treat hyperglycemia in type 2 diabetics and is recommended as a first-line oral therapy by the American Diabetes Association and European Association of the Study of Diabetes (137). Current evidence suggests its role as an insulin sensitizer (since it facilitates insulin receptor expression and activity), modulator of the incretin axis (via peroxisome proliferator-activated receptor-α or glucagon-like peptide 1) and inhibitor of hepatic gluconeogenesis (138), thus potentially implicating metformin in xenobiotic metabolism. A case–control study with a cohort of 12 000 type 2 diabetes subjects (139) revealed that metformin therapy is associated with a reduced risk of cancer (odds ratio 0.79), whereas the prolonged metformin therapy further increased the inhibitory effects on cancer incidence. Similar effects were observed with a wide range of cancer types, while only a few studies suggested that metformin does not affect cancer incidence (Table 1).

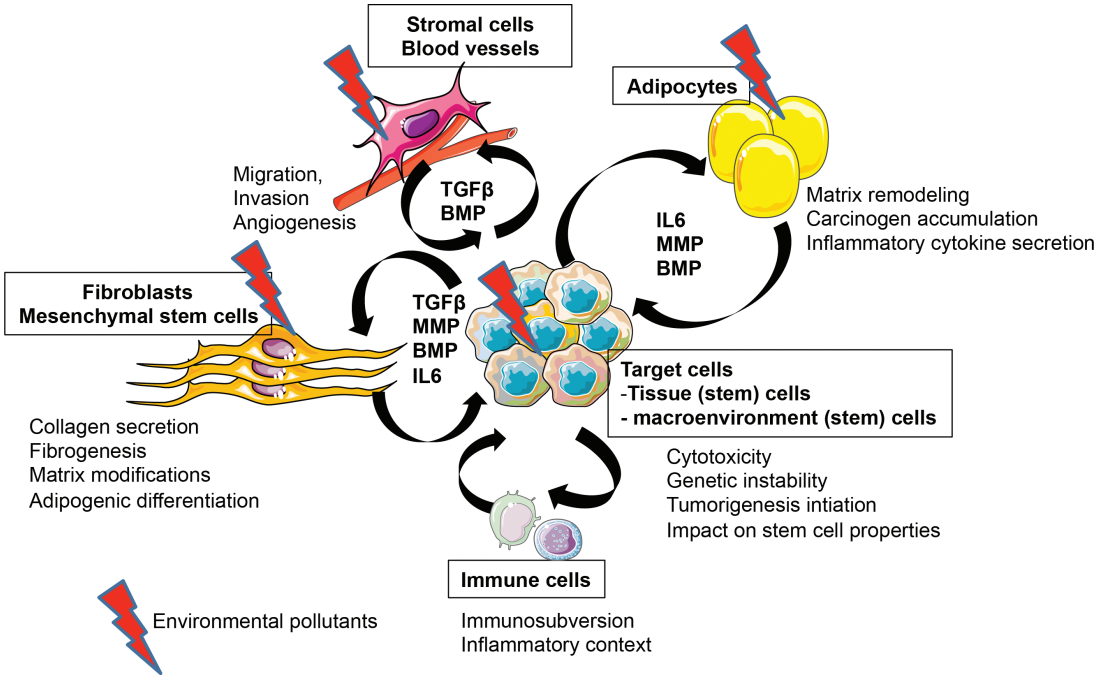

Figure 2. Environmental pollutant target resident cells and their local environment thus affecting key parameters of tissue homeostasis. Environmental pollutants target tissue resident cells, thus changing their intrinsic properties, and also affect their environment, in particular changing soluble factors available. All these events can lead to modifications of tissue homeostasis and emergence of cancer. During our lifetime, we can be exposed to different types of carcinogens at different times and the consequences of combinatorial exposure remain poorly deciphered. Environmental pollutant seems to induce both short- and long-term effects, which together with our own history (aging, genetic predisposition and/or cancer history) creates a context that may promote the development of cancer, long after the initial parameters. All these complex and person-dependent parameters raise challenging issues for public health to overcome cancer induced by carcinogens.

Table 1. Changes in cancer risk associated with administration of metformin and sulfonylureas

	Group	Relative risk (RR)	95% CI	$n_{\text{total treated}}$	$n_{\text{events treated}}$	$n_{\text{untreated}}$	$n_{\text{events untreated}}$
Metformin cohorts	Total: fixed effect model	0.70	0.67; 0.73	152910	4652	202510	4468
	Total: random effect model	0.85	0.65; 1.11				
Metformin case–control studies	Total: fixed effect model	0.90	0.84; 0.98	12469	1749	12360	2113
	Total: random effect model	0.71	0.57; 0.88				
Metformin randomized control trials	Total: fixed effect model	1.01	0.81; 1.26	2576	137	4000	194
	Total: random effect model	1.01	0.80; 1.27				
Sulfonylureas cohorts	Total: fixed effect model	1.55	1.48; 1.63	109220	3634	187684	3012
	Total: random effect model	1.19	0.88; 1.62				
Sulfonylureas case–control studies	Total: fixed effect model	1.02	0.93; 1.13	5881	1194	6159	1277
	Total: random effect model	1.05	0.82; 1.35				
Sulfonylureas randomized control trials	Total: fixed effect model	1.17	0.95; 1.45	2546	153	4027	189
	Total: random effect model	1.17	0.95; 1.45				

Results of the meta-analysis (52).

Metformin-induced improvement of blood glucose and insulin levels seems to be complemented by yet unknown insulin-independent anticancer effects as shown in phosphatase and tensin homolog (PTEN)$^{+/-}$, Her-2/neu and APC$^{Min/+}$ mouse models (140–142) and later by the follow-up experiments utilizing small interfering RNA and inhibitor-based approaches. Metformin decreases adenosine triphosphate synthesis via disruption of complex I of the mitochondrial respiratory chain, thus inhibiting mitochondrial respiration and leading to the rise in intracellular adenosine monophosphate: adenosine triphosphate ratio, which activates the liver kinase B 1/AMP-activated protein kinase pathway. Activation of the liver kinase B 1 AMP-activated protein kinase pathway (or alternative metformin-induced mechanisms such as modulation of the RAG GTPase) leads to the inhibition of mammalian target of rapamycin complex 1 signaling and thus to the inhibition of protein synthesis and cellular proliferation (139). The antidiabetics thiazolidinediones activate AMP-activated protein kinase and inhibits mammalian target of rapamycin activity downstream of the IGF-1 and insulin receptors (143). The disruption of mammalian target of rapamycin signaling is in part associated with metformin-induced dysregulation of micro RNA-mediated control of messenger RNA transcripts, involving micro RNAs of the let-7 and miR-200 families, and the messenger RNAs for Nanog, Oct4, Notch1 and EZH2 in cancer stem cells, all of which are crucial regulators of the cancer stem cell survival and proliferation. Additionally, metformin was shown to decrease Fas expression, which leads to the attenuation of *de novo* fatty acid biosynthesis (144). Metformin can modulate the cancer inflammatory microenvironment (145,146), inhibit neoplastic angiogenesis, decrease VEGF and plasminogen activator inhibitor-1 levels (147,148), inhibit human epidermal growth factor receptor-2 expression via p70S6K1 activity inhibition (149), induce cell cycle arrest (150), promote both caspase-dependent and caspase-independent apoptosis (151,152) and block p53-dependent autophagy and glycolysis. In prostate cancer cells, metformin inhibits mitochondrial respiration and promotes apoptosis in a p53-dependent manner in the presence of 2-deoxyglucose (153). Metformin induces the sensitization to energy stress, under conditions of nutrient deprivation, typically at low glucose concentration (153–156). In humans, the metformin therapeutic plasma levels ranging between 0.465 and 2.5 mg/dm^3 (2.8–15 μM; maximum safety dose 42.5 mg/kg/day) were shown to inhibit proliferation of various histological types of lung cancer cell lines (157), but most of the *in vitro* experiments utilized higher dosage at 165–6600 mg/dm^3 (158).

Among another biguanides, phenformin (phenethyl biguanide) was reported to display more potent anticancer activity than metformin in colon cancer cells and in a triple-negative breast cancer xenograft model (159,160) and was shown to be equal to metformin in studies of other malignancies. However, phenformin (previously used as an antidiabetic drug) is out of the clinical market due to frequent adverse events of lactic acidosis. Anticancer effects of phenformin, buformin and metformin on animal models of spontaneous and induced carcinogenesis were recently summarized (161).

Biguanides play a role in the cancer-associated inflammatory processes and in the association with cellular matrix. Metformin inhibits TNF-α production in vascular endothelial cells and in human monocytes (162,163) and is suggested to improve the efficacy of experimental anticancer vaccines by modulating fatty acid metabolism of CD8$^+$ memory T cells (164). In neurons, metformin interferes with cellular polarization (165). In the model of endometrial cancer and fibrosarcoma, a metformin-induced decrease of MMP-2 and MMP-9 and associated inhibition of the cell invasiveness were recorded (166,167). Somewhat related to the effects on cancer environment is also the recent report claiming that in breast cancer stem cells, metformin alters the initial transient inflammatory signal initiating the epigenetic switch from non-transformed to cancer cells via the mechanism involving IL-6 secretion and the cancer stem cell transcriptional regulatory circuit. In a Src-inducible model of cellular transformation, metformin induces anti-inflammatory stimulus by blocking NF-κB nuclear translocation and signal transducer and activator of transcription 3 phosphorylation, thus preventing the cancer onset and progression (168). Further examination of the effects of biguanides on the tumor microenvironment is needed to establish its potential beyond affecting the levels of glucose and insulin and beyond the changes induced by altered mitochondrial respiration.

Various human insulin analogs have been shown to have growth effects. The first of the insulin analogs developed, insulin B10Asp, was based on a single amino acid substitution, which alone was sufficient to induce 10-fold increase in mitogenicity compared with the wild-type human insulin. Later, insulin B10Asp was withdrawn from the pipeline based on the carcinogenicity study showing excessive formation of mammary tumors in rats (169). The increased mitogenicity of insulin B10Asp can be explained by multiple binding mode of insulins differing in the length of binding and also in the downstream effects (metabolic × mitogenic). The widely used insulin glargine (A21Gly, B31Arg, B32Arg human insulin) stimulates a 6- to 8-fold increase in receptor affinity and mitogenicity when compared with human insulin (170,171). Outcomes of clinical studies on cancer risk and mortality associated with various insulin

analogs are inconclusive, showing either no effects or slight pro-carcinogenic effects [such as shown for insulin glargine (172–175)]. Only improvement of the study designs (sensitivity, focus on narrowly specified cancer types) may lead to more consistent results in a near future.

Metabolic adaptations are critical for cancer cell survival and propagation. Neoplastic cells are often under a broad range of stress stimuli, including hypoxia and lack of nutrients. Antidiabetics have a strong potential to alter the preexistent adaptive responses of cancer cells and thus to affect the outcomes of cancer treatment. As claimed recently by Lewis Cantley, 'Metformin may have already saved more people from cancer deaths than any drug in history' (176). Both positive (e.g. metformin) and negative effects (insulin analogs) can be experienced and may exacerbate the effects of other disrupting compounds to which one is exposed.

Ionizing radiation and its effects on the tumor microenvironment

Ionizing radiation is one of very few environmental exposures unequivocally associated with increased cancer risk in humans (177), particularly in thyroid and breast cancer following exposure at a young age (178,179). Excess cancers are observed in populations acutely exposed to high doses. For example, elevated rates of cancer are found in the Japanese atomic bomb survivors at doses of 0.1–4 Gy, which are between 40 and 1600 times the average yearly background levels in the USA (180). A 2006 review study of the National Academy of Sciences (Committee on the Biological Effects of Ionizing Radiations) contends that human health risks continue in a linear fashion from high doses, where harm is evident, to very low doses without a threshold, such that the smallest dose has the potential to increase risk in humans. As a consequence, radiation risk models use an assumption of linearity to extrapolate in the region below which epidemiological data are robust. This linear-no-threshold regulatory paradigm is based in large part on observations that cancer incidence increases with increasing dose above 0.1 Gy, as well as pragmatic, regulatory and societal considerations to protect the population.

However, neoplastic transformation, often ascribed to unrepaired DNA damage, is both non-linear and susceptible to the influences from the microenvironment. The frequency of neoplastic transformation in cultured irradiated tracheal epithelial cells (181,182) or C3H 10T1/2 cells (183) is inversely correlated to the number of cells seeded, i.e. the fewer cells seeded the more transformed colonies are produced, suggesting that cell density/interactions suppress this supposedly mutagenic consequence. Bauer and colleagues showed that the frequency of radiation, chemical and virally mediated transformation of cultured human and rodent fibroblasts is actively suppressed by non-transformed cells by a process called intercellular induction of apoptosis. The decreased transformation in the presence of normal cells is ascribed to induction of selective apoptosis of transformed cells. If this control system acts *in vivo* as efficiently as it does *in vitro*, tumor formation should require the establishment of resistance mechanisms directed against intercellular induction of apoptosis. Indeed, transformed foci from cells cultured from established tumors are not influenced by the presence of normal cells (184). Bauer identified TGF-β as a key signal in this process. TGF-β produced by the differentiated normal epithelial cells inhibits the growth and phenotype of radiation-transformed cells (185). Bauer and colleagues showed that there are three distinct, but competing, roles for TGF-β during transformation [reviewed in (186)]: TGF-β actually helps maintain the transformed state of mesenchymal cells, enables non-transformed neighbors to recognize transformed cells and triggers an apoptosis-inducing signal. The latter two processes are enhanced following very low radiation doses (187).

Biological responses to radiation damage that evolve quickly and amplify in a non-linear manner, particularly following low doses, have been broadly documented both in cell culture and *in vivo*. Experimental studies show that low-dose radiation alters the response to subsequent challenge doses (i.e. adaptive responses), affects daughter cell fates such as differentiation and senescence, induces long-range signals that affect non-irradiated cells and generates a state of chronic genomic instability. This class of radiation effects is called 'non-targeted' and encompasses bystander phenomenon and those that are exhibited in the daughters of irradiated cells that are not mediated by a mutational mechanism, including radiation-induced genomic instability and persistent phenotypic changes. Although the extent to which these phenomena reflect different molecular mechanisms is not clear, experimental results to date suggest that systemic and microenvironmental effects of radiation mediate its carcinogenic potential.

Ionizing radiation is a complete carcinogen that is able to both initiate and promote cancer. A study by Kaplan *et al.* dating back >50 years demonstrates that radiation carcinogenesis is complex. These studies used C57BL mice, which are very susceptible to thymic lymphomas after radiation exposure. Young mice underwent thymectomy and 2–7 days later they received the first of four consecutive doses of 168 cGy. Several hours after the last irradiation, a single thymus from a non-irradiated mouse was transplanted subcutaneously under the right chest or upper abdomen of each of the previously thymectomized, irradiated hosts. Surprisingly, thymic lymphoma incidence and latency arising from the grafts matched that observed in irradiated, intact mice. Furthermore, the tumors were histologically identical to those found in the intact mice and exhibited a similar pattern of metastasis (188). This study showed that radiation-induced thymic lymphomas occur even when the grafted thymus was never exposed to radiation, suggesting a systemic effect of radiation in the host that controls tumor initiation and progression in the microenvironment.

In a similar type of study, Morgan *et al.* showed that an immortal myogenic cell line formed tumors far more rapidly in irradiated compared with non-irradiated host muscle. The accelerated tumor phenotype was a direct effect of irradiation on the stroma, rather than due to systemic effects, because tumors did not form in distant muscle sites (189). Interestingly, when transplanted to normal mice, these tumors formed large amounts of muscle. Likewise, irradiated pancreatic fibroblasts mixed with pancreatic carcinoma cells formed more aggressive and invasive cancer than when the pancreatic cancer cells were mixed with non-irradiated pancreatic fibroblasts (190). These authors further demonstrated that an antagonist of hepatocyte growth factor completely blocked the increased invasiveness of pancreatic cancer cells that was induced by coculture with irradiated fibroblasts.

A radiation chimera model was developed to evaluate the contribution of the irradiated microenvironment in breast cancer. This model consists of surgically removing the endogenous mammary parenchyma, irradiating the mouse, and several days later transplanting the cleared mammary fat pads with syngeneic mammary tissue, oncogenically primed by deletion of *Trp53*. Even though hosts were irradiated many months before tumor development and the mammary epithelium was never irradiated, the course of *Trp53* null carcinogenesis is significantly

altered by host irradiation as evidenced by decreased tumor latency and more rapid tumor growth rate. Unexpectedly, host irradiation also increased the development of aggressive tumors. Expression profiles of *Trp53* null tumors arising in an irradiated host compared with those arising in non-irradiated hosts were distinct, suggesting that the biology elicited by radiation has long-lasting effects on tumor development. Tumors arising in an irradiated mouse are characterized by a gene signature of chronic inflammation, enriched in genes involved leukocyte chemoattraction, transendothelial migration and monocyte maturation (191).

A complete understanding of radiation systemic and microenvironment effects are important because they act to promote cancer, are persistent but are not permanent, may contribute to other health risks and/or interact with other environmental exposures, such as to mixtures of chemicals. Of particular importance is that general responses, like chronic inflammation, which has been discussed at length in other sections, may be suitable as targets for prevention. Wang and colleagues proposed that chronic inflammation, whether induced by chronic infection or by carcinogen exposure, results in a myriad of effects that produces an environment conducive for the emergence of cancer (192). Agents that suppress inflammation, like aspirin, might reduce cancer risk following radiation.

Disrupting chemicals in the aquatic environment

One of the most significant exposures to disruptive chemicals is through contamination of the coastal environment. Even very low concentrations of these contaminants detected in water or bottom sediments may result in fish or shellfish tissue concentrations high enough to pose health risks to seafood consumers. Elevated concentrations of confirmed or possibly carcinogenic chemicals, including trace metals (arsenic, cadmium, nickel and lead), PAHs and polychlorinated biphenyls, have been often reported in marine organisms, especially shellfishes from coastal waters at several locations across the globe (193,194). Marine bivalves, especially mussels, are widely used as sentinel organisms for coastal biomonitoring programs due to their sessile nature, mode of feeding, ability to accumulate contaminants from the environment and availability for human consumption (195). Under the mussel watch program, high concentrations of xenobiotics were reported in samples collected from several urban-associated sites across the world (193–197). A significant proportion of the chemicals detected in mussel samples were carcinogenic and likely to cause public health risk, if transferred to the human consumers.

Although over 1 billion people all over the world rely on seafood as their primary source of animal protein, seafood are vulnerable to contamination with persistent organic pollutants in concentrations that are somewhat higher than in other nutritious food items like milk, meat and egg (198). In general, organochlorine levels in fish intended for human consumption are low and probably below levels likely to adversely affect human health (199,200). However, they are of potential concern for two groups: populations for whom seafood forms a major part of the diet and infants and young children who consume substantial quantities of oily fish. There have been a number of studies that have investigated chemical concentrations of persistent organic pollutants in human populations in relation to diet (201,202). In a recent study, concentrations of PAHs, OCPs, polychlorinated biphenyls and PBDEs in human blood plasma collected from Hong Kong residents were correlated with seafood diet (202). Several quality control measures and guidelines are implemented across the world (203–205) to control and regulate the marketing and consumption of seafood contaminated with disruptive chemicals (see Table 2).

Human activities resulting in the chemical contamination of the environment have increased the potential stresses on marine organisms in most of their exposed habitats. Even at very low concentrations, toxic contaminants can have drastic effects on their physiology, immunology and ecology, and an increase in number and extent of disease outbreaks in marine organisms was reported (206). Occurrences of cancers and preneoplastic conditions initiated and promoted by contaminant exposure have been observed in marine taxa ranging from invertebrates to marine mammals (207,208). Diseases caused by pathogenic agents and liver histopathology associated with cancer were reported in marine fishes for several years (209). The occurrence of neoplasia in flatfish liver has been reported as a direct evidence of contaminant exposure and indicates historic exposure to carcinogenic chemicals that initiate and promote cancer-like diseases (210,211).

Neoplastic conditions called disseminated neoplasia or hemic neoplasia have been reported worldwide in 15 species of marine bivalves, including 4 species of oysters, 6 species of clams and 5 species of mussels (212). The disease is characterized by proliferation of enlarged circulating hemocytes with a large lobate nucleus, one or more nucleoli, a high frequency of mitotic figures and a high nuclear to cytoplasmic ratio (213). The etiology of molluscan neoplasia remains uncertain, and several researchers have suggested possible causes ranging from carcinogenic chemicals to involvement of a c-type retrovirus (212). In a recent study, neoplastic cockles (bivalves) showed significantly higher transcription levels of p53 and ras than healthy animals and mutational alterations in ras gene sequence were detected (214). When exposed to the environmental genotoxicant, benzo(a)pyrene, induction of tissue-specific expression of p53 and ras genes was reported in marine mussels (215). Others (216) showed that marine bivalve hemocyte cancer can provide excellent *in vitro* and *in vivo* models for transcriptional and non-transcriptional outcomes reflecting those seen in similar human cancers under stress and with similar malfunctions in p53 functionality.

The bioaccumulation of environmental contaminants in the tissue of marine mammals due to their position at the top of the aquatic food chain and their rather long life span is well established (217). High tissue concentrations of

Table 2. Regulatory threshold for consumption of potential carcinogenic chemicals in seafood commodities (204,205)

	Maximum levels (mg/kg wet weight)		
Contaminant	USA	European Union	Seafood item
Arsenic	86	—	Molluscs and crustaceans
Cadmium	3–4	0.05–1.0	Fish, molluscs
Lead	1.5–1.7	0.2–1.0	Fish, molluscs
Methylmercury	1	1	All fish
PCB	2	0.000008	All fish
DDT, TDE	5	—	All fish
Diedrin	0	—	All fish
Dioxin	—	0.000004	All fish
PAHs–benzo(a) pyrene	1	0.01	All fish

DDT, dichlorodiphenyltrichloroethane; PCB, polychlorinated biphenyl; TDE, 1,1-bis(p-chlorophenyl)-2,2-dichloroethane.

persistent organic pollutants and inorganic contaminants were observed in marine mammal tissue samples from coastal regions associated with dense human populations (218). Elevated levels of organic and inorganic contaminants apparently resulted in high prevalence of tumors in beluga populations from the St. Lawrence estuary (219). Studies also indicated that endogenous hormones and environmental contaminants that interact with steroid hormone receptors acted as causative agents for urogenital carcinogenesis in California sea lions (219).

Various types of neoplastic changes were reported in marine organisms from urban-associated coastal sites across the globe and linkages have been established between the xenobiotic exposure and neoplastic changes in most of the cases. Thus, this evidence demonstrates not only that carcinogens exert their effects on a multitude of species but also that we are also exposed, on a global basis, to carcinogens and/or EDCs via the diet and water. Surveillance and monitoring of fish and wildlife populations at all levels of biological organization are essential tools for documenting the presence and severity of the risks of modernity.

Cross talk between carcinogens that affect the tumor microenvironment and the hallmarks of cancer

Given that the carcinogenicity of low-dose exposures to chemical mixtures in any given tissue will likely depend upon simultaneous activation of several important tumor promotion mechanisms and the disruption of several important defense mechanisms, it is likely that a better way of visualizing the potential synergies of combinations of chemicals will ultimately involve a thorough review of disruptive actions across the full range of mechanisms that are known to be relevant in cancer biology. Accordingly, we undertook a thorough cross-validation activity to illustrate the importance of the prioritized target sites for disruption that this team has identified (across multiple aspects of cancer biology) and to illustrate the seriousness of the prototypical chemical disruptors that we identified (i.e. also disruptive to other mechanisms that are relevant to carcinogenesis). All validation data are summarized in Tables 3 and 4.

The tumor microenvironment influences inflammation process associated with the onset and progression of tumors (37). Through the production of inflammation-associated molecules, including cytokines, ROS and reactive nitrogen species, the tumor microenvironment may affect several mechanisms of the carcinogenesis process. Inflammation contributes to tumor initiation by inducing DNA damage and chromosomal instability and through the production of ROS (292). Besides their adverse effect in inducing cell and tissue injury, ROS are now regarded as second messengers that can stimulate the induction of angiogenesis growth factors, such as VEGF, promote cell proliferation and immune evasion and play a role in cell survival (221,222,224). The mechanism through which the tumor microenvironment may interplay with cell survival and death signaling is quite complex. The production of ROS may induce as well as prevent cell apoptosis (223). Even if the production of ROS is recognized as an early step in tumor progression, through which the transformed cells acquire the energy for metabolism reprogramming (220), oxidative stress and specifically ROS produced within the tumor microenvironment may directly affect the production of metalloproteinases in transformed cells, which acquire invasive properties (226). Changes in mitochondrial function, which is

Table 3. Cross-validation of target pathways

Tumor microenvironment priority targets	Deregulated metabolism	Evasion of anti-growth signaling	Angiogenesis	Genetic instability	Resistance to cell death	Immune system evasion	Replicative immortality	Sustained proliferative signaling	Tissue invasion and metastasis	Tumor-promoting inflammation
ROS and cellular stress	+ (220)	+/– (221)	+ (222)	0	+/– (223)	+ (224)	+/– (225)	+ (221)	+/– (226)	+ (37)
IL-6 expression, improper dendritic cell maturation and polarization	0	+ (227)	0	0	– (228)	+ (229)	+/0 (230)	– (231)	+ (232,233)	+ (234)
NK cell inhibition	0	– (235)	– (236)	0	+ (237)	+ (238)	0	+ (239)	– (240)	+ (241)
Chronic oxidative stress	+/– (242)	+ (243)	+ (244)	+ (245)	– (246)	0	+ (246)	+ (221)	0	+ (247)
Oxidative stress and IL-6 production	+ (248)	0	+ (249)	0	– (228)	+ (250)	+/– (251,252)	0	0	0

(+): Targets and chemicals those were not only relevant for tumor microenvironment but also relevant for other areas of cancer biology (i.e. pro-carcinogenic). (–): Targets and chemicals that were found to have opposing actions (i.e. anti-carcinogenic). (+/–): Instances where reports on relevant actions in other aspects of cancer biology were mixed (i.e., reports showing both pro-carcinogenic potential and anti-carcinogenic potential). (0): Instances where no literature support was found to document the relevance of a target site or chemical in a particular aspect of cancer biology.

Table 4. Cross-validation of disruptors

Tumor microenvironment prototypical disruptors	Deregulated metabolism	Evasion of anti-growth signaling	Angiogenesis	Genetic instability	Immune system evasion	Resistance to cell death	Replicative immortality	Sustained proliferative signaling	Tissue invasion and metastasis	Tumor-promoting inflammation
Nickel	+ Not known	+ (30)	+ (253)	+ (254)	0	+/– (255,256)	– (257,258)	+ (259)	+ (260)	+ (261)
BPA	+ (262)	+ (92)	+ (227)	+ (263)	0	+/– (264,265)	+ (266)	+ (267)	+ Not known	+ (268)
Butyltins (such as TBT)	+ (269)	+ (270)	0	+ (271)	0	– (272,273)	0	– (274)	0	+ (95)
MeHg	+ (275)	+ (276,277)	– (278)	+ (279)	0	– (280–283)	0	+ (284)	0	+ (285,286)
Paraquat	+, 0	+ (287)	0	+ (288)	0	– (289,290)	0	– (225)	0	+ (291)

(+): Targets and chemicals those were not only relevant for tumor microenvironment but also relevant for other areas of cancer biology (i.e. pro-carcinogenic). (–): Targets and chemicals that were found to have opposing actions (i.e. anti-carcinogenic). (+/–): Instances where reports on relevant actions in other aspects of cancer biology were mixed (i.e., reports showing both pro-carcinogenic potential and anti-carcinogenic potential). (0): Instances where no literature support was found to document the relevance of a target site or chemical in a particular aspect of cancer biology.

associated with the production of ROS, are involved in the process of cellular senescence (293).

IL-6 is a pleiotropic cytokine that can activate various cell types and it is recognized to play a master role in tumor-associated inflammation (234). Most IL-6 target genes are involved in cell cycle progression and suppression of apoptosis. However, some reports suggest that by activating specific IL-6-related target, such as NF-IL6, it may induce apoptosis in some cell types but inhibit apoptosis in others (228). An increase in IL-6 secretion, together with that of TGF-β, may be responsible for immunosuppression as a consequence of a reduction in circulating DCs, eventually resulting in a possible mechanism of immune evasion (229). IL-6 decreases senescence while increasing telomerase activity (230). IL-6 has been described as a novel target of non-canonical Notch signaling and its regulation depends on the status of p53 in the cell. This could explain IL-6's multiple roles in cell proliferation (294). Both IL-6 secretion and tumor-associated DCs sustain tumor progression, by increasing cell growth, migration, invasion and EMT (232,233).

NK cells can regulate cell survival both directly due to their ability to induce cytotoxicity and by triggering the secretion of cytokines, such as IFN-γ, that stimulate apoptosis. The secretion of IFN plays a central role to control cancer growth and it represents one of the main pathways through which NK cells may control cell proliferation and angiogenesis (235,236,239) as well as induce inflammatory and adaptive immune response (241). However, NK cells may affect several cancer hallmarks through a variety of pathways. Molecules that can bind NK receptors may be responsible of immune evasion of tumor cells (238). NKs ability to induce cell cytotoxicity is jeopardized by tumor microenvironment hypoxia that is a pressure factor for metastatic spread (240).

Evidence confirms that oxidative stress is the master key through which tumor microenvironment interplays with almost all other tumor hallmarks, although its primary role is promoting tumor inflammation (247). Oxidative stress can lead to metabolism reprogramming (242), stimulate cell growth and proliferation (221,243), trigger angiogenic signals (244), induce DNA damage (244,245) and influence senescence (295). Chronic oxidative stress, however, at low level may induce apoptotic cell death by activating the caspase-3-dependent PKC-delta (246). The combination of oxidative stress and IL-6 production may also contribute to tumor onset and progression affecting metabolism (248) and angiogenesis (249). It is also a mechanism for immune evasion (250) while playing a dual role in cell senescence (251,252) and it is even able to counteract tumor growth by inducing apoptotic cell death (228). Thus, chemicals that affect oxidative stress in the tumor microenvironment may have enormous consequences on tumorigenesis and tumor maintenance.

All chemicals that are able to induce oxidative stress through the production of ROS may equally play a role in the pathway leading to tumor promotion and progression. The exposure to nickel chloride has been associated with the generation of ROS as a possible mechanism of action through which several nickel compounds exert carcinogenic activity.

For example, nickel chloride has been found to inhibit (255) or induce apoptosis (256), induce DNA damage and epigenetic modifications (254), regulate inflammation (261), sustain proliferation through the alteration of miR-222 and its target genes CDKN1B and CDKN1C (259) and modulate cell senescence, through the stabilization of G-quadruplex DNA (257), leading to antiproliferative activity coupled with telomerase inhibitory activity (258). Cell proliferation due to nickel exposure has been associated with mutagenic activity against p53 and the

activation of several transcription factors (30). Nickel can also trigger pleiotropic effects through the induction of hypoxia inducible factor-1, which, in turn, can activate the transcription of a variety of genes involved in angiogenesis, including glucose transporter and glycolytic enzymes involved in the upregulation of metabolism (253). Nickel chloride can induce EMT, which is considered a key event in the acquisition of the metastatic phenotype, through the downregulation of E-cadherin by ROS generation and E-cadherin promoter hypermethylation (260).

BPA is a plasticizer used for manufacturing polycarbonate plastics and epoxy resins. Due to its use, the safety of BPA is under examination by several regulatory agencies and authoritative scientific bodies around the world with the goal of addressing the concern about possible presence of BPA monomer leaching into baby and children products, such as baby bottles, sippy cups, baby food containers and food packaging. BPA is concerning because of developmental effects observed in some animal studies and it is actually under scrutiny as possibly toxic for reproduction. These effects may be related to the ability of BPA to interact with the ER. No carcinogenic activity has been associated with BPA according to the guideline-compliant assays or scientifically acceptable studies that could be considered for BPA classification as a carcinogen.

However, BPA is a paradigmatic compound for which mechanistic studies suggest that it can hit targets that may play a role in tumor onset and progression. Prenatal exposure to BPA in experimental animals disrupts ERα and triggers angiogenesis (227). The weak estrogenic activity, exerted through the binding to ERs and G-protein-coupled receptors, may be responsible for triggering cell proliferation (92,267). The antiestrogenic activity is thought to be responsible for impairing the DNA double-strand break repair machinery in the germ line by downregulating DNA double-strand break repair genes and resulting in chromosomal aberrations accumulation in *Caenorhabditis elegans* model (263). BPA toxicity has been explained as related to the production of ROS and downregulation of genes involved in anti-oxidant pathways (268) possibly playing a role in inflammation, while a ROS-independent mechanism is thought to be responsible for the induction of apoptosis in HL-60 cells treated with BPA (264). BPA was found to induce apoptosis and cell cycle arrest in ovarian granulose cells (265). BPA has also been reported as capable of increasing hTERT expression, thus suggesting a role in cell immortalization (266).

The whole picture offers an interesting point of view of BPA behavior, through which BPA hits those hallmarks that are common traits to the cancer process and reproduction adversity. Microenvironment plays a main role during pregnancy and delivery. So it is not surprising that BPA interplays with cell proliferation, genomic instability, inflammation, metabolism and cell immortalization, which are related to cell differentiation (262). Errors in these mechanisms lead to problems in developing organs. However, BPA does not have characterized roles in invasion and metastasis, which are considered the specific markers of malignant disease.

Butyltins, and specifically TBT, an endocrine disruptor, have been found to inhibit the cytotoxic activity of NK cells (269). This effect is accompanied by the activation of the MAPK pathway, which allows the cell to evade growth control (270). This result is confirmed by other studies showing the downregulation by TBT oxide of MAPKs and other proteins, such as matrin-3 and ribonucleotide reductase, subunit RRM2, which are implicated in cell proliferation (274). Butyltins can induce chromosomal aberrations in an *in vitro* model (271), play a role in promoting inflammation by altering TNF-α secretion and increasing TNF-α levels as well as by affecting the function of membrane metalloproteinases (95). Activation of TNF-α is also a mechanism that supports TBT-induced apoptosis (272). However, TBT can induce apoptosis through different mechanisms according to the chemical concentration (273), a behavior that has been often observed for compounds acting as endocrine disruptors.

MeHg is a neurotoxic compound deriving from metallic mercury through bacteria-supported metabolism in aquatic environments. Bioconcentration in fish and shellfish may pose risk for sensitive population categories such as pregnant women and infants. MeHg is regarded as a possible carcinogen on the basis of a single animal study that is not considered sufficient to support a regulatory classification of carcinogenicity. MeHg can induce apoptotic cell death through the oxidative stress-mediated pathway (285). Several reports confirm the apoptotic effect of MeHg at low doses of treatment and this can occur through different pathways, involving both mitochondria- and endoplasmic reticulum-supported processes, almost always related to the initial oxidative stress following MeHg exposure (280–282). Interestingly, at high concentration of MeHg, the non-apoptotic pathway of cell death becomes predominant (283). A complex pathway has been described, involving the activation of phospholipase A2, as a consequence of MeHg-induced ROS production and as the first step of a cascade leading to endothelial cell cytotoxicity (278). MeHg can increase macrophages and cachectins (TNF-α and IFN-γ) in inflammatory heart lesions at subacute concentrations (286). MeHg may affect cell proliferation through its antimicrotubule activity that could be responsible for the antimitotic effects of MeHg (284). Sporadic genotoxic activity has been reported (279) that has not been confirmed in other studies in the same model. MeHg is not known to play a role in cell immortalization or the metastasis process.

Paraquat is a reference compound for experimental neurodegenerative models and for understanding the mechanisms leading to chronic neurodegenerative diseases, such as Parkinson's disease. To date, only the United States Environmental Protection Agency has classified it as a possible carcinogen, and its use is authorized only under certain conditions. Paraquat metabolism generates superoxide radicals and other ROS giving evidence that oxidative stress-mediated pathway is the main mechanism of paraquat toxicity, leading to adverse effects on cell survival and proliferation (225,287). Paraquat is able to modulate the expression of genes involved in the inflammatory process, including CXCL10, CXCL11, IL-10, and in cell death, such as BCL2, MMP-9 and BAK-1 (291). Paraquat can induce apoptosis also through the mitochondrial pathway associated with p53 (289). Expression of p53 and p21 is altered in cells treated with paraquat (225). Transcriptional factors and caspase-3 activation was also observed in paraquat-induced apoptosis (290). Thus, Paraquat may have a multitude of molecular targets involved in tumorigenesis and tumor maintenance, securing its role as a disruptor of the tumor microenvironment.

Concluding remarks

Known and possible carcinogens play a role in the initiation, progression, growth and relapse of cancer. However, less is understood about the effects of long-term, low-dose exposure of environmental toxins in promoting tumorigenesis. Importantly, some investigators have examined in animal models the effects of these low-dose exposures of environmental carcinogens in promoting tumorigenesis (296–299). Importantly, these studies suggest that the carcinogenic effects clearly occur through not only effects on the incipient tumor cells but also on the host, in

a dose-dependent manner (300). These effects occur in a temporal trajectory, which can be influenced by evolutionary pressure. They are realized through both genetic and epigenetic changes. Changes in the microenvironment are causally related to carcinogenesis through effects on inflammation, the vasculature, stromal matrix, innate and adaptive immunity and specific cytokines. Carcinogenesis is also mediated through modulation of proliferative, senescence, endocrine and metabolic programs. Carcinogenic exposure occurs through ionizing radiation and contamination of marine and other environments. The measurement of these carcinogens in the environment and the effects of these carcinogens on the tumor microenvironment will be important not only for developing experimental strategies to uncover the mechanisms of carcinogenesis but also for preventing and therapeutically intervening against carcinogenesis.

One of the hallmarks of cancer is the tumor microenvironment. This refers to specialized cell populations in a tumor independent of the cancer cells themselves. A tumor is a complex entity, composed of different types of cancer cells as a result of a multistep process. The microenvironment that plays a crucial role in tissue homeostasis is also likely to be affected and involved in the pathology (129). One way of generally organizing our understanding of the tumor microenvironment and its role in carcinogenesis is to think of this on three scales. First, field cancerization may occur after exposure to carcinogens, generating premalignant changes in the pre-tumor microenvironment. This is often accompanied by the induction of inflammation, pro-tumorigenic cytokines and immunosuppressive cytokines, which encourage cancer development and promote its growth. Second, MMPs may be deregulated as tissue remodeling goes askew, and fibroblasts and vasculogenesis may also be affected. Third, immune cells, such as macrophages, NK cells and T cells may be affected by carcinogens, suggesting that carcinogens and/or its resulting inflammation has a hand in both the innate and the adaptive arms of the immune system.

Cancer-causing agents may range from 'classic' carcinogens, such as ionizing radiation, to 'modern' carcinogens, such as the presence of metabolic syndrome provoked by diabetes, to endocrine-disrupting compounds, such as BPA, which we may be exposed to via the food chain and increasingly contaminated water sources. However, many carcinogens may act at very low concentrations, such as the picomolar to nanomolar range, and generate non-monotonic (or 'U' or 'inverted U' shape) dose responses (301); furthermore, the end points observed at lower doses may be different than those observed at higher doses (302). For example, the breast cancer cell line 'MCF-7' proliferates when exposed to estrogenic compounds at very low doses (10^{-12} to 10^{-11} M), but the opposite is observed at higher, pharmacological and toxicological doses (10^{-11} to 10^{-6} M) (303). Disruptive chemicals may exert their role on the biochemical, cellular or tissue level of biological organization.

As studies that examine risk assessment move forward, they will ideally include the study of chemicals at a safe reference dose, a dose relevant to actual human exposure, and an ability to detect a non-monotonic dose–response curve (302). Additionally, further work needs to be done to examine the mixtures of the hundreds of environmental chemicals (304) that are found in human samples. The combinations in which these chemicals appear may dramatically affect proto-tumor cells, the establishment and maintenance of tissue patterns, recruitment of immune cells, stromal cells, secreted factors, vasculature and other cells in the tumor microenvironment; the position of each carcinogen on its respective non-monotonic dose–response curve may dictate the position of another and/or their synergistic effect. Chemical carcinogens may also confound the effect of non-chemical carcinogens, such as radiation, and affect the tumor microenvironment through mechanisms that are not currently well understood.

Ideally, steps will continue to be taken to remove existing carcinogens from the environment in as much as is feasible, and 'green chemistry' will be used to obtain information about dangerous effects of chemicals earlier in the design process (305) using a series of tests ranging from *in silico* assessment up to individual cell- and whole animal-based assays. Molecular modeling and docking can now be used to help predict endocrine-disrupting potential by identifying potential binding, biological or physiological activity of chemicals to one specific or an ensemble of targets of interest (306–308) Lastly, multiple modes of action of potential carcinogens must be examined; for example, BPA exhibits estrogenic activity through genomic and non-genomic mechanisms, is anti-androgenic, antagonizes the thyroid hormone and activates members of the peroxisome proliferator-activated receptor family (305). Consequently, it may be somewhat complex to identify the many possible roles and mechanisms of each existing and newly identified carcinogens on the many cells and factors that together make up the tumor microenvironment.

Finally, the primary prevention of cancer requires insights into the mechanisms of carcinogenesis and, in particular, recognition of how combinations of carcinogens can cooperate to induce microenvironmental changes that culminate in tumorigenesis. Experimental methods that can interrogate these microenvironmental changes, such as using transplantation-based model systems, could be employed, to dissect the role of known and possible carcinogens acting alone, in concert, in low doses on incipient tumors as well as in host cells and to define their role in tumorigenesis. Then, the identification of specific microenvironmental changes, strongly associated with carcinogenic influences that promote tumorigenesis, could then be used to monitor patients for exposures to potential carcinogens.

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