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Chronic inflammation and immunologic-based constraints in malignant disease

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Abstract

Acute inflammatory reactions benefit the host by supporting the effective clearance of pathogens and fostering wound healing, in addition to other self-preservative processes. However, when the inflammatory program is not resolved, becoming chronic in nature, it creates an environment conducive to cancer development and progression. Therefore, minimizing exposure to risk factors that contribute to chronic inflammation and reconditioning the host towards a state of (at least locoregional) acute inflammation would meaningfully impact cancer incidence and its treatment, respectively. Regarding cancer therapy, combinational treatments that both disrupt chronic inflammation and install specific adaptive type I immunity are predicted to enhance quality of life and extend the overall survival of patients.

Keywords

cancer; chronic inflammation infection; immunotherapy; metastatic renal cell carcinoma; sunitinib; wound healing

Inflammation serves as the host's natural response to alleviate infection and promote tissue healing, among other processes in the body. However, in cases where acute inflammation turns into a state of chronic persistence, consequences such as cancer can result. Chronic inflammation plays an instrumental role in promoting all phases of tumorigenesis, from initiation to metastasis, as this article will discuss. The article will focus primarily on inflammation-driven phenomena associated with solid malignancies, although chronic inflammatory responses may similarly advance the severity and worsen the prognosis of hematological cancers.

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Developing a state of chronic inflammation

The most significant numbers of deaths associated with cancer worldwide involve the lung, stomach, liver, colon/rectum and breast, in decreasing order of magnitude [101]. Although the incidence of cancer continues to rise, particularly in low-/medium-income countries [1], a majority of these malignancies are now considered as preventable owing to the so called 'avoidable' risk factors that comprise environmental exposure (e.g., arsenic and tobacco smoke), infectious organisms and dietary behavior (e.g., obesity and alcohol consumption) [2].

In the case of lung, stomach, liver, colorectal and breast cancers, a variety of dietary and/or environmental agents have been reported as cofactors that increase the risk of tumorigenesis [1]. Notably, chronic infections with microbial pathogens are second only to tobacco usage and exposure, with regard to risk factors to develop cancer, accounting for 15–20% of the global cancer burden [3]. The bacterium *Helicobacter pylori* is typically implicated as a causative agent in stomach cancer cases [4], while approximately 80% of hepatocellular carcinomas can be linked to chronic infections with hepatitis B and C viruses (HBV and HCV), respectively [1,3]. In the case of cervical cancer, the fourth leading cause of cancer death in women worldwide, human papillomavirus-16 and -18 infections determine the onset of 70% of total cases [1]. Other notable malignancies such as Burkitt's lymphoma, Hodgkin's disease [5] and adult T-cell leukemia/lymphoma [6] can also be directly attributed to viral infections.

Aside from chemical carcinogens and some viruses (i.e., human papillomavirus, human T-lymphotropic virus-1, HBV, HCV and Epstein–Barr virus), there is little convincing evidence that the major risk factors directly initiate cell transformation. It appears that prolonged exposure eventually helps to contribute to the onset of the malignant cell phenotype, through a number of proposed mechanisms that include inflammatory-mediated effects [7–9]. In the case of viral and bacterial agents, chronic inflammation owing to infection is indicated as a predominant but indirect carcinogenic mechanism [3,10]. In an attempt to rid the body of pathogenic organisms, host cells synthesize and release a number of antimicrobial factors, which include reactive oxygen and nitrogen species, cytokines (e.g., IL-1, IL-6 and TNF-α) and chemokines (e.g., CCL2 and CXCL8), which foster the recruitment and activation of protective immune effector cells such as macrophages and neutrophils. The inflammatory response is intended to quickly resolve infection with minimal harm evolved against the host. However, in cases of unresolved infections such as those observed for *H. pylori* or HBV/HCV, the sustained assault of infected tissues by host immune cells results in an overwhelmingly negative condition, in which beneficial immunologic effects are limited and cancer promotion may ensue [11,12]. A similar program may also be initiated by extrinsic factors that contribute to procancerous inflammation, such as processes involved in normal tissue repair [13]. For example, surgical resection of primary tumors in patients leads to increased levels of systemic growth and angiogenic factors such as VEGF and cytokines such as TGF-β, which underlie the normal tissue repair process; however, such factors may favor the outgrowth of residual/occult tumor cells, as will be discussed [14,15]. Chronic inflammation therefore plays a decisive role as a rheostat in all stages of tumor development; initiation, progression and metastatic spread (particularly when combined with intrinsic cell factors driven by oncogenes) (Figure 1) [14,16].

Chronic inflammation enforces malignancy

Regardless of the host's underlying condition that contributes to chronic inflammatory reactions, the continued onslaught of the affected cells/tissues by inflammatory mediators

has been demonstrated to enhance neoplastic cell growth and proliferation. On the whole, these inflammatory-based mechanisms either directly impact cell mutational rates or indirectly induce molecular effects that favor tumorigenesis, as summarized in Figure 2.

High levels of host-derived reactive oxygen and nitrogen compounds damage DNA and RNA through nucleotide modifications that include deamination, oxygenation and adduct formation, with oxidized products such as lipids, carbohydrates and DNA [17]. These major effects instigate carcinogenesis by modulating the downstream functions of proto-oncogenes and tumor suppressor genes via a number of pathways [18]. For example, the direct oxidation by reactive oxygen species in the cell can lead to the reduced expression and enzymatic activity of DNA mismatch repair genes, resulting in increased cell mutagenesis and probability of tumor initiation [14,18]. The induction and direct effects of reactive oxygen and nitrogen species by inflammatory stimuli, however, do not follow a linear fashion; reactive oxygen and nitrogen species can also be regulated upon oncogene activation, as observed in the case of increased RAS-mediated signaling [18]. Recently, mitochondrial-derived reactive oxygen species have been reported to enhance the intracellular expression of proinflammatory cytokines such as IL-1 and IL-6 although the precise molecular mechanisms of this mode of control are presently unclear [19].

Host-derived proinflammatory cytokines induce the release of reactive oxygen and nitrogen species, which further the development of mutational effects and cooperate to induce epigenetic changes that promote tumorigenesis at the cell level [14]. IL-6 is capable of mediating modifications to the methylation status of genes associated with (tumor) cell growth and migration [20–22]. For example, by utilizing primary patient and established colonic cell lines *in vitro*, IL-6 was observed to negatively impact the expression of genes associated with tumor suppression and anchorage dependence [21]. These epigenetic silencing events were a result of IL-6 upregulating DNA methyltransferase levels in the cell. Inflammatory cytokines can also shape a cell's self-sufficiency, largely through transcriptional factor control. A classic function of the proinflammatory cytokine, TNF-α, is to activate the transcriptional factors NF-κB and AP-1, which serve as regulators of premalignant cell proliferation and survival under conditions of chronic inflammation [23]. IL-6, among other proinflammatory cytokines, is also capable of driving transcription factors that control oncogene expression [24]. In a mouse model of colitis-associated cancer, myeloid expression of IL-6 stimulated the survival and proliferation of pre-malignant intestinal epithelial cells [25]. These protumorigenic effects were largely the result of IL-6-activated STAT3 signaling in intestinal epithelial cells.

Inflammatory stimuli also differentially modulate miRNAs associated with disease pathogenesis. miRNAs are single stranded RNA molecules that regulate gene translation and can induce a malignant phenotype at the cell level [26]. For example, the miRNA miR-21 is upregulated under conditions of chronic inflammation and in the case of a diverse array of solid and hematological human cancers [18,26]. IL-6 can induce the expression of *miR-21* via STAT3 signaling. This induces downstream effects that enhance cell proliferation and prevent cellular apoptosis, by regulating oncogene and tumor suppressor gene (e.g., programd cell death 4, tropomyosin 1, phosphatase and tensin homolog and BTG family member 2) expression [18,27]. In settings where miR-21 has been functionally blocked, tumor cells have increased sensitivity to therapeutic assaults such as chemotherapy while tumor growth is inhibited in xenograft animal models [27]. However, the detailed carcinogenic role of miRNAs in cancer patients has been more difficult to assess since patient specimens are typically obtained from well-established tumor lesions. Such samples are less likely to yield information related to the early cell events that ultimately lead to tumorigenesis [26]. In the case of miR-21, non-small-cell lung cancer and colorectal patients with increased miR-21 sample expression have a worse prognosis and disease progression

status compared with control cohorts [27,28]. Therefore, owing to the relative molecular ease of miRNA detection; miRNA status may serve as a preferred mode of cancer detection and prognosis (i.e., likelihood of response to an indicated therapy) in affected patients [29–31].

Chronic inflammation facilitates & sustains primary tumor growth

Progressive tumor cell proliferation eventually exceeds the capacity of the local tissue micro-environment to provide/exchange proper nutrients and oxygenation, necessitating the process of neoangiogenesis and/or neovascularization [32]. Tumor-associated blood vessels, however, are commonly observed to be functionally impaired, based on their inefficient structure (i.e., being composed of poorly-organized and interconnected, leaky vascular endothelial networks that are only loosely decorated with supportive pericytes) that fails to develop hierarchical transitions from arterioles-to-capillaries-to-venules. Such blood vessel deficiencies lead to increased interstitial fluid pressure, hypoxia and low pH within the tumor microenvironment (TME) [32–34], which negatively impacts protective lymphocyte homing, extravasation and function into/within the TME [33].

Cancer cell hypoxic signals induce the expression and release of VEGF and PDGF (rendered through HIFα signaling), among other factors, and cause a number of immediate effects that contribute to the instillation of a chronically inflamed microenvironment, which potentiates tumor growth and progression [35]. VEGF and PDGF bind their cognate receptors, expressed by endothelial cells and pericytes respectively [36,37], and initiate angiogenesis by recruiting endothelial precursor/pericyte cells, promoting endothelial/pericyte cell proliferation and generating capillaries [37]. Tumor cell hypoxia can also promote the immigration of inflammatory cells, such as tumor-associated macrophages (TAMs) into cancer lesions [38,39]. TAMs, in turn, encourage angiogenesis further by secreting proangiogenic factors such as VEGF [40]. This is consistent with the correlation between high TAM content and poor clinical prognosis in cancer patients [14]. Nevertheless, there is considerable cell plasticity in TAMs, regarding exposure to factors derived from tumor and infiltrating cells. Most TAMs isolated from human cancers display a M2-like phenotype, which drives tumorigenesis by promoting Th2-based reactions and dampening cells mediating cytolytic functions against tumor cells [16,40]. For instance, macrophages exposed to type 2 cytokines such as IL-4 or IL-10 can be polarized to an M2 phenotype, and in this functional state, contribute to support the development of regulatory T cell (Treg) function(s), which serve to limit protective immunity. M2-polarized TAMs may also promote tumor infiltration of Treg and Th2 cells via locoregional production of chemokines, such as CCL17, CCL22 and CCL24. Likewise, Tregs and Th2 cells in the TME may drive or sustain M2-like macrophage activity by elaborating IL-10 and IL-4, respectively [40].

Cancer cells are also adept at secreting chemokines and expressing chemokine receptors that function to support tumor-derived blood networks and to recruit tumor-promoting cells [41]. For example, endothelial cell production of chemokines such as CXCL1 and CXCL8 promotes angiogenesis through ligation with CXCR2 expressed by tumor cells. Interestingly, a variety of human carcinomas overexpress CXCL8, which further drives cancer cell establishment and spread. In the case of non-small-cell lung cancer, tumor secretion of CXCL8 contributes to such protumorigenic effects as angiogenesis, progression, and neutrophil infiltration [42,43]. TAMs and myeloid-derived suppressor cells (MDSCs) may also infiltrate tumor lesions, based on cancer cell-derived gradients of CCL2, which conditions functional M2 TAMs [40,41].

In addition to TAMs, both neutrophils and MDSCs recruited into the primary mass appear to contribute to and maintain an overall ‘suppressive’ TME. In turn, local inflammatory

conditions sustain these infiltrating cell types in a reinforced feedback loop. Typically, poor prognosis in cancer patients correlates with high neutrophil volume, although the specific mechanism of action for how these cells promote malignant growth remains incomplete [44,45]. It is known that neutrophils induce the accumulation of inflammatory cells within the TME via production of IL-1, IL-6 and TNF-α, and that neutrophils may modulate cell mutational frequencies as a consequence of elaborating reactive oxygen species [45]. However, MDSCs are composed of a heterogeneous population of cells that express both monocytic and granulocytic markers [46]. Cancer patients typically present with elevated levels of MDSCs (in tumors and in blood), and the main apparent function of MDSC subsets in the setting of established tumor growth is to negatively regulate type 1 T and natural killer cell responses, via mechanisms that involve reactive oxygen and nitrogen species, arginase (i.e., depleting T cells of L-arginine and promoting their apoptosis), and immunosuppressive cytokines such as IL-10, which notably promotes Treg function [47,48].

In summary, the physical constraints and immunosuppressive properties of the TME serve to limit concurrent protective (proinflammatory) immune reactions (i.e., a concept broadly defined as immunosurveillance), whereby, immune effector cells such as $CD8^+$ T and NK cells provide systemic protection against host cells exhibiting aberrant phenotypes (e.g., pre-malignant and cancerous cells). What emerges then is the concept that chronic inflammation helps to drive the creation of an early primary tumor lesion that is less receptive/responsive to spontaneous and therapeutically-induced type 1 immunity, allowing the lesion to progress and develop into an advanced mass containing cells with increased propensity to metastasize.

Cancer metastasis is impacted by inflammation

There exists much debate about how precisely metastasis occurs. Considering that over 90% of patients die from systemic disease to organs such as the brain, lung and liver, as opposed to a primary lesion, understanding the steps of metastasis more clearly allows the opportunity to develop interventional treatment strategies [49]. Overall, successful cancer metastasis is believed to involve a two-stage process: tumor cell emigration from the primary lesion into the circulation (intravasation) and corollary colonization of a distant tissue site (extravasation).

In terms of the first phase, there are competing hypotheses that describe precisely which types of tumor cells are involved in traversing the extracellular matrix (ECM) of the TME in order to access blood vessels. The cancer stem cell (CSC) hypothesis is a newly appreciated observation stipulating that only a few tumor cells maintain the self-renewal and growth potential of the solid cancer mass [49]. At some point during the development of the primary lesion (possibly even at a stage of occult disease), a CSC reaches and enters the local blood supply. To further support this metastatic potential, CSCs maintain inherent qualities that would predispose them to successful intravasation and extravasation processes, namely a perivascular location, in conjunction with enhanced properties of motility, invasiveness and resistance to apoptosis [49]. As an alternatively described phenomenon, the CSC phenotype may be ‘plastic’ in nature and rely upon environmental cues within the TME to induce ‘non-CSC’ tumor cells to evolve CSC characteristics. Although both hypotheses have been experimentally supported to certain degrees, neither has been fully described within the clinical setting, and the models are also not mutually exclusive. Both scenarios may exist at any given time *in vivo*, and there may be variance in the importance of the type of CSC (i.e., intrinsic vs induced) in founding distant metastatic niches, which would be based on the type of cancer involved [49,50]. For example, tumor cells induced to become CSC-like may play a more decisive role in the metastatic spread of cancers via the vasculature.

In addition to inflammatory infiltrates and a deviant vasculature network, the TME contains an altered ECM and an assortment of other cancer-associated stromal cell types, including fibroblasts that serve to further potentiate angiogenesis and metastasis [38]. The tumor-derived ECM is significantly remodeled (relative to its architecture among normal cells) during tumorigenesis, in order to allow for processes such as invasion and metastasis [38,39]. Structural alterations in the ECM are largely carried out by stromal-elaborated matrix metalloproteinases, which degrade ECM substrates such as collagen. However, inflammatory cells such as TAMs and neutrophils are also important contributor sof matrix metalloproteinases within the TME [16,40,45]. ECM expression of integrins and other cell surface receptors also provide tumor cells with survival/proliferative signals, along with the impetus for increased migratory capacity. In the end, such TME properties foster successful epithelial-to-mesenchymal transition in tumor cells, a proposed process that would hold key for the induced CSC hypothesis [49]. In this scenario, which could help explain intravasation, nonmotile epithelial tumor cells take on a morphological invasive switch to motile mesenchymal cells, owing to a variety of epithelial-to-mesenchymal transition-inducing signals that include TGF-β and FGF [39,49]. Although local sources for these molecules vary, inflammatory infiltrates such as TAMs, MDSCs, and cancer-associated fibroblasts could provide significant levels of TGF-β. Tumor cell hypoxic signaling in the TME would also induce the expression of and supply FGF [38,47].

We are still deficient in having a detailed understanding of the steps involving cancer cell entry into the blood circulation in order to colonize a distant site [49]. Mechanisms could certainly include cancer cells becoming trapped in capillary beds based on size (i.e., emboli), as well as being recruited into distant tissue sites owing to chemokine gradients originating at such sites. In the case of the latter, systemic or locoregional chronic inflammation may cause an upregulation of adhesion ligands, specific to cancer cell integrins, expressed by the blood vessel endothelia within target organs [14,51,52]. What follows upon homing is extravasation into the tissue, and the ability of malignant cells to quickly adapt to a foreign environment that is likely to be very dissimilar from the primary tumor site. A state of chronic inflammation may provide a hospitable environment to founder cancer cells; by preventing apoptosis and inducing epigenetic and mutational effects that would favor cancer progression within the distal tissue location (as detailed in Table 1). In addition, the aforementioned factors (see Table 1) secreted by locally recruited inflammatory cells, such as TAMs, could provide the protumorigenic support of neoangiogenesis essential to tumor growth of macrometastases.

Clinical intervention

Controlling chronic inflammation remains a logical step toward preventing many types of malignant disease (i.e., circumventing the ‘avoidable’ factors). For example, in the case of *H. pylori* infections, improvements to hygiene and the use of antibiotics are thought to have contributed towards the 80% lower incidence rates of stomach cancer in the USA since 1950 [1]. Reduced rates of liver cancer have also been reported in countries that have established infant vaccine campaigns against HBV compared with high incidence areas in the world (e.g., sub-Saharan Africa and many parts of Asia) where such programs do not exist [1,2]. As an additional proof-of-principle, individuals who prophylactically take NSAIDs such as aspirin have reduced incidence of breast cancer and decreased risks of prostate and colon cancer [14,53]. Although there are risks of side effects from long-term administration of such agents, the potential benefits far outweigh the risks for most individuals, except those with a genetic or environmental predisposition to develop cancer [14].

In cases of established malignant disease, rigorous therapeutic strategies will be required to combat the effects of inflammatory-based reactions that sustain and potentiate

tumorigenesis. A number of single modality agents targeting various aspects of chronic inflammation (with specific focus on the TME) have entered clinical trials and have been recently reviewed [38,54]. Examples of these targets include inhibitors of angiogenesis, cytokines, ECM degradation and hypoxia. More generally, however, these experimental therapies alone have not resulted in significant long-term improvements in the quality of life and survival of patients with cancer. It appears likely that patient-specific combinational strategies will have to be developed and implemented, in order to mediate therapeutic efficacy in the clinic. A multipronged attack would be required to first abrogate the downstream effects of chronic inflammation, allowing cancer cells to become more effectively targeted by alternate methods. One such secondary approach that holds considerable promise involves immunotherapeutic strategies, with its ability to specifically target malignant growth and generate long-lasting immunity through memory recall responses. What follows is an example from our laboratory where the use of a pharmacological drug, targeting chronic inflammatory-induced angiogenesis, and a tumor cell-specific vaccine are utilized concurrently to mediate more effective inhibition of cancer progression than either agent can provide alone.

Administration of the US FDA approved receptor tyrosine kinase (RTK) inhibitor sunitinib in individuals with metastatic renal cell carcinoma (mRCC) mediates clinical responses by improving overall survival and time to progression, compared with standard protocols [55,56]. Sunitinib, therefore, remains a first-line treatment for good and intermediate-risk mRCC patients, as recommended by the National Comprehensive Cancer Network [57,58]. However, most patients will develop resistance to the drug with a median time to progression of 6–15 months post-treatment [59]. Sunitinib works by primarily disrupting the ATP binding site within the kinase domain of the VEGF and PDGF receptors, in addition to negatively regulating other RTKs, blocking the ensuing downstream signaling pathways [36,60,61]. Although there is no convincing evidence that sunitinib destroys renal cell carcinoma cells directly, much of the drug's actions appear to mediate tumor lysis indirectly, by affecting the maturation of the tumor stroma as a result of locoregional chronic inflammation [62].

Normalization of the tumor vasculature through antiangiogenic strategies is hypothesized to help restore proper blood flow and vessel integrity within the tumor mass, and aid in improving the delivery and efficacy of co-applied cancer therapies [33,63,64]. In the case of sunitinib, the RTK inhibitor is observed to be adept at impacting immature endothelial cells [65], which serves to normalize the renal cell carcinoma vasculature by 'pruning' vessels that have not yet been fully stabilized by pericytes [65–68]. Indeed, several reports have documented the increased uptake of chemotherapeutic drugs, following sunitinib treatment in mouse models of cancer [66,68].

As mRCC patients are administered sunitinib, Treg levels diminish via an as-yet-undetermined mechanism of action [69,70]. The RTK inhibitor also normalizes the progeny of the myeloid lineage, effectively reducing MDSCs, while promoting the differentiation of mature immunostimulatory DCs [70,71]. In addition, T cells from mRCC patients treated with sunitinib exhibit a preferential capacity to secrete Th1 (over Th2) cytokines after mitogenic stimulation *in vitro* [69,70]. These drug functions appear to ultimately restore the beneficial properties of acute inflammation in the host, from the suppressive aspects of chronic inflammation that have rendered traditional treatment approaches such as surgery and cytokine therapy to mRCC unsuccessful. Sunitinib may, therefore, represent a suitable sensitizing therapy in patients to improve, for example, TME targeting/delivery of immunotherapeutic moieties (as similarly observed with other combination regimens [63,72]), which target associated antigens of the renal cell carcinoma stroma, based on the drug's propensity to lessen chronic inflammation by normalizing the tumor vasculature and

restoring type 1 immunity. To support this hypothesis, we have recently reported on the ability of sunitinib to work in concert with a specific immunotherapeutic approach to targeting malignant growth [73]. Combination therapy employing sunitinib plus specific vaccination resulted in a significant reduction in mean tumor size and increased long-term survival, when compared with either monotherapy. Tumor infiltrating lymphocytes harvested from animals treated with sunitinib/vaccine cotherapy also produced superior levels of IFN-γ *in vitro* in response to vaccine-associated peptide epitopes. Such responses appear to be facilitated by the coordinate loss of immunosuppressive MDSCs and Tregs from the TME in mice receiving the combined therapy. Overall, these studies highlight the ability of sunitinib to work effectively in concert with a specific immunotherapy, in order to initiate and sustain heightened Th1 reactions in the TME (at the expense of suppressive mechanisms), and these data support the translational evaluation of sunitinib/vaccine combinational strategies against solid vascularized lesions such as mRCC in pilot clinical trials.

Conclusion

Under conditions of pathogenic infection or tissue regeneration, the host immune system may productively mediate a state of acute inflammation. In the absence of event closure (i.e., episodes of chronic infection or wound healing), the benefits of such immune responses may become deviated towards a protumorigenic state, in which inflammatory mediators promote all stages of the malignant process, from the initiation of cancerous cells to their systemic dissemination. Although our understanding of the molecular/mechanistic underpinnings of cancer progression has advanced significantly over the last decade, the complexity and redundant biology of the TME presents a formidable challenge to therapeutic intervention for patients with established disease. It appears all but certain that combinational strategies will have to be incorporated clinically, in order to combat the multiple levels at which inflammation contributes to the malignant process. Considering that chronic inflammation plays such a vital role in tumorigenesis, particular attention should be devoted to first alleviating inflammatory-based constraints, so that additional strategic efforts can become increasingly efficacious *in vivo*.

Future perspective

Our understanding of the basic tenets governing inflammation-driven tumorigenesis has grown considerably over the last 10 years, and will continue to do so over the next decade. Our major challenge remains the translation of laboratory findings into the clinic (and corollary reinvestment in translational studies to better understand mechanisms of action and to refine systems-biology approaches applied in the clinic) where more effective treatments may be developed for cancer patients in randomized clinical trials. To date, single modality strategies targeting various aspects of chronic inflammation have failed to advance the long-term quality of life and survival of patients. We hypothesize that combinational therapies, incorporating targeted anti-(chronic)inflammatory strategies, may improve the objective clinical response rate of treated patients by attacking regulatory aspects that currently serve to limit the effectiveness of combined therapeutics such as chemo-/radio-/immuno-therapies.

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Executive summary

- Chronic inflammation favors cancer initiation, progression and dissemination.
- Dysregulated host inflammatory reactions induce the elaboration of reactive oxygen/nitrogen species and cytokines, which contribute to carcinogenesis through mutational and epigenetic effects.
- Primary tumor growth and neoangiogenesis is supported by tumor microenvironment (TME) infiltrating immune cells, including tumor-associated macrophages, myeloid-derived suppressor cells, neutrophils and regulatory T cells.
- Chronically activated proinflammatory cells in the TME contribute to the metastatic potential of cancer.
- In order to decrease cancer incidence, known risk factors that induce chronic inflammation should be avoided (i.e., exposure to environmental hazards, infectious organisms and diet).
- Targeted disruption of chronic inflammation should be addressed in the setting of established cancers – particularly as part of a combined therapeutic strategy – in order to yield more effective treatment options for patients; improving their quality of life and increasing overall survival. For example, the abrogation of inflammation in the TME may allow for additional successful clinical interventions that include chemotherapy, immunotherapy and/or radiotherapy.

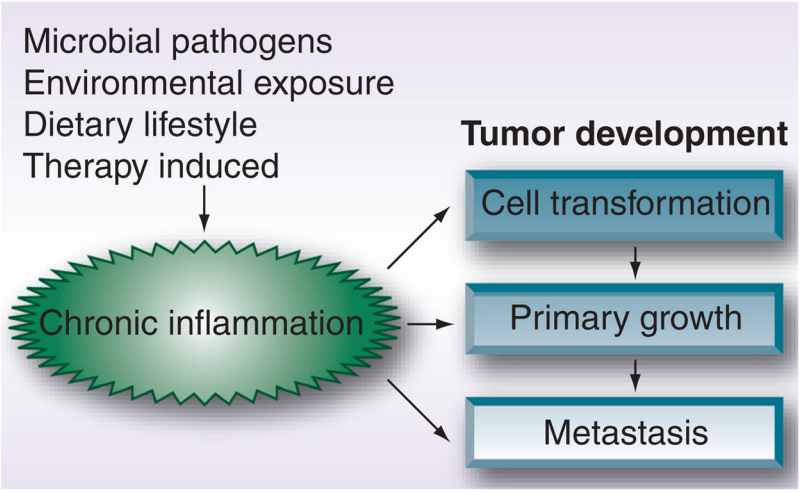

Figure 1. Role of chronic inflammation in cancer development

Chronic inflammation initiates and impacts all major stages of tumor progression, from cell transformation to widespread metastasis. The cause of chronic inflammation varies by individual and includes exposure to infectious microorganisms and harmful chemicals.

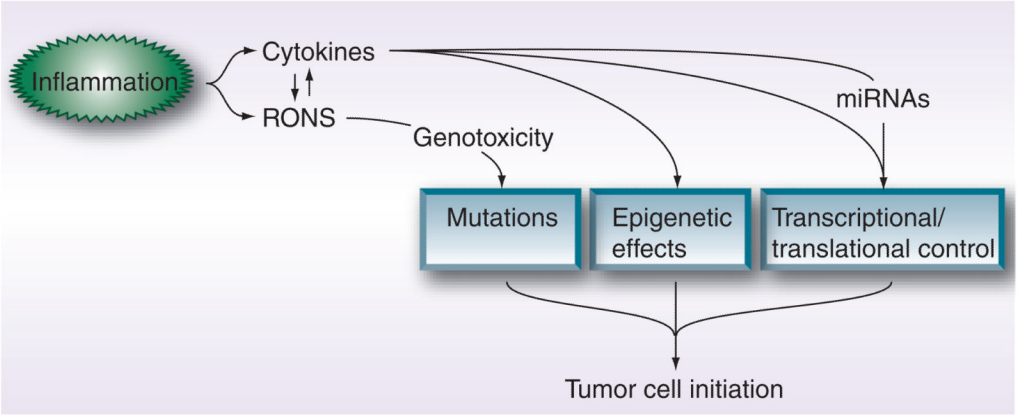

Figure 2. Chronic inflammation drives tumor cell initiation through direct mutational and indirect molecular effects

Cytokines such as IL-6 promote cell transformation by modifying gene expression profiles, through mechanisms that include epigenetic effects and transcriptional factor control, as well as inducing protumorigenic miRNAs. RONS, on the other hand, serve to directly instigate gene mutations by damaging DNA and RNA. Interestingly, a positive feedback loop appears to exist between the ability of inflammatory cytokines to induce the synthesis of RONS and *vice versa*.

RONS: Reactive oxygen/nitrogen species.

Table 1

General inflammatory-associated factors involved in cancer development.

Inflammatory-induced agents	Representative protumorigenic effects
Cytokines	
IL-1	Mediates inflammatory cell accumulation in the TME
IL-6	Modifies gene expression through epigenetic effects, transcription factor control and miRNA induction; involved in promoting inflammatory cell migration into the TME
TNF-α	Activates transcription factors that mediate tumor cell proliferation/survival; promotes immune cell infiltration into the TME
TGF-β	Helps promote EMT in cancer cells
IL-4	Polarizes macrophages to an M2 phenotype
IL-10	Supports immunosuppression by sustaining M2-driven macrophages and Tregs
Chemokines	
CCL2	Tumor-derived chemotactic factor for infiltrating TAMs and MDSCs; Helps promote the M2 phenotype in TAMs
CXCL8	Instigates angiogenesis, tumor cell progression, and neutrophil migration
CCL17, CCL22, CCL24	Migratory factors for Tregs and Th2 cells in the TME
CXCL1	Promotes tumor angiogenesis through ligation with CXCR2
Other factors	
RONS	Damages DNA/RNA resulting in cell mutagenesis
miRNAs	Regulates key genes involved in cancer cell proliferation/apoptosis
VEGF & PDGF	Angiogenic factors that promote tumor vascularization
FGF	Induces EMT in tumor cells

EMT: Epithelial-to-mesenchymal transition; MDSC: Myeloid-derived suppressor cell; RONS: Reactive oxygen/nitrogen species; TAM: Tumor-associated macrophage; TME: Tumor-associated microenvironment; Tregs: Regulatory T cells.