Inflammation and Cancer: A Comparative View

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Rudolph Virchow first speculated on a relationship between inflammation and cancer more than 150 years ago. Subsequently, chronic inflammation and associated reactive free radical overload and some types of bacterial, viral, and parasite infections that cause inflammation were recognized as important risk factors for cancer development and account for one in four of all human cancers worldwide. Even viruses that do not directly cause inflammation can cause cancer when they act in conjunction with proinflammatory cofactors or when they initiate or promote cancer via the same signaling pathways utilized in inflammation. Whatever its origin, inflammation in the tumor microenvironment has many cancer-promoting effects and aids in the proliferation and survival of malignant cells and promotes angiogenesis and metastasis. Mediators of inflammation such as cytokines, free radicals, prostaglandins, and growth factors can induce DNA damage in tumor suppressor genes and post-translational modifications of proteins involved in essential cellular processes including apoptosis, DNA repair, and cell cycle checkpoints that can lead to initiation and progression of cancer.

Key words: Cancer; Comparative; Infection; Inflammation; Tumor.

Epidemiologic evidence suggests that approximately 25% of all human cancer worldwide is associated with chronic inflammation, chronic infection, or both (Tables 1 and 2).[1–5] Local inflammation as an antecedent event to cancer development has long been recognized in cancer patients. Over 150 years ago, Rudolph Virchow speculated on a link between inflammation and cancer based on his observations of finding leukocytes in human breast carcinomas.[1,4,6,7] He suggested that the "lymphoreticular infiltrate" reflected the origin of cancer at sites of chronic inflammation. Since Virchow's observation, a large and growing body of factual, epidemiologic, and circumstantial evidence defining the wide array of inflammatory and infectious conditions that predispose susceptible cells to carcinogenic changes has developed. Chronic inflammation alone is sufficient to cause oncogenesis.[3,6,7] Frequently however, infection is the primary event and chronic inflammation is the result.

Numerous reviews have explored the relationship of inflammation to cancer and the known or postulated mechanisms of malignant transformation in humans and in laboratory animals.[1–64] Although none of the literature to date in domesticated mammals has summarized the evidence for a similar and broad relationship, such a relationship does exist. It is likely that the mechanisms of chronic, local inflammation with or without infection that induces cancer in humans and laboratory animals and those that induce cancer in veterinary patients are similar. This hypothesis is based on a large and rapidly growing library of literature that has documented similar or identical genetic expression, inflammatory cell infiltrates, cytokine and chemokine expression, and other biomarkers in humans and many domestic mammals with morphologically equivalent cancers.[65–78] The author is unaware of reliable estimates of the total percentage of cancer in domestic species that are the result of inflammation, but the economic impact of cancer resulting from infections causing cancer in some domestic animals has been documented.[79] There are numerous examples of inflammation and infection in veterinary patients that can culminate in malignant transformation of susceptible cells (Tables 3 and 4).[80–131] However, many are individual case reports and anecdotal reports, but taken together they reflect a spectrum of disorders that are linked to cancer.

Basic Concepts of Carcinogenesis

The process of carcinogenesis can conceptually be represented in a number of ways. One way is with the classic stepwise evolution of a malignancy in 3 phases that begins with initiation of susceptible normal cells, promotion of accumulated genetic damage, and progression of disorders we collectively refer to as cancer.[7,10] Initiation is characterized by the accumulation of genetic change in a cell such as point mutations, deletions and amplification, methylation of DNA, and rearrangements of genes and chromosomes that fail to be repaired and lead to irreversible changes in cells that survive a critical transforming level of genetic damage. Mediators of inflammation such as cytokines, reactive oxygen and nitrogen species, prostaglandins, and growth factors are capable of initiating these types of DNA mutations within cells that then can experience disruptions of critical signaling pathways responsible for maintaining normal cellular homeostasis. The initiated cell with its permanent DNA mutations is a *sine qua non* for cancer development. Most cells with minor DNA mutations survive because the damaged DNA is repaired, or if the level of damage is incompatible with survival are signaled to die via apoptosis. For cancer to develop, the damage to DNA must persist and resist the many DNA-repair processes and be

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Table 1. Cancers linked to inflammation in humans.

Predisposing Condition	Associated Increased Risk of Cancer
Ulcerative colitis	Colon carcinoma
Crohn's disease	Colon carcinoma
Chronic pancreatitis	Pancreatic carcinoma
Chronic acid reflux	Esophageal carcinoma
Solar exposure and sun burn	Melanoma, basal cell carcinoma
Foreign material	
Implanted medical devices	Breast carcinoma
Metallic implants	Primary bone tumors
Asbestosis	Mesothelioma
Silica	Various pulmonary cancers
Talc	Various pulmonary cancers
Carbon nanotubes	Various pulmonary cancers
Particulate carcinogens	Various pulmonary cancers
Shrapnel and bullet trauma	Various carcinomas and sarcomas
Surgical sponge	Angiosarcoma
Chronic prostatitis	Prostate carcinoma
Thermal burns	Skin carcinoma

readable by DNA polymerase, which creates and maintains the mutation. As genetic changes accumulate in cells, some growth advantage over unaffected cells is conferred and a precancerous lesion can form.[10] Common preneoplastic DNA mutations are those that result in increased expression of oncogenes like myc, ras, abl, and bcl-2 or decreased activity of tumor suppressor genes like Rb and p53.[4] A locked DNA mutation continuously contributes to the propagation of cells with mutated genetic material with each subsequent cell division. Activation of oncogenes, inactivation of tumor suppressor genes, and the influences of other key regulators of cellular proliferation, such as IL-2 and IFN-γ, during initiation lead to changes in the cellular microenvironment that promote tumor cell survival and clonal expansion of "initiated cells" in the phase known as promotion.[10] During tumor promotion, initiated cells interact via secreted factors from normal leukocytes/immunocytes and are further transformed into cancer cells.[4] This process is very complex and less well defined than the process of initiation. Progression involves substantial growth and/or metastasis of the established cancer.

The Relationship of Inflammation to Carcinogenesis

Inflammation is a rapid, multistep, and normal response to acute tissue damage resulting from physical injury, ischemic injury, toxins, or other types of injury. In addition, infection with viral, bacterial, protozoa, mycotic, or parasite pathogens in normal individuals involves a host immune response and, almost universally, inflammation. The normal end result of inflammation is that any damaged tissue or damaged DNA is repaired, the inflammatory response is quenched, and healing takes place. However, during active inflammation the cellular microenvironment is

Table 2. Cancers linked to chronic infection in humans.

Human Papilloma Virus (HPV)–Especially High Risk Types	Cervical, Vulvar, Penile, Anal, and Oral (Head and Neck) Cancers
Herpes family of viruses	
Epstein-Barr virus	Burkitts lymphoma, Hodgkin's lymphoma, nasopharyngeal carcinoma, AIDS associated lymphoma
	Sinonasal angiocentric T-cell lymphoma
	Immunnosuppression-related lymphoma (post-transplantation, AIDS, X-linked lymphoproliferative disorders)
	Hodgkin's lymphoma in immunocompetent individuals
	Undifferentiated nasopharyngeal carcinoma
	Lymphoepithelioma-like gastric carcinoma[a]
	Gastric adenocarcinoma[a]
	Breast cancer[a]
	Leiomyosarcoma in immunocompromised individuals
	Lymphoepithelioma lung cancer
Human herpes virus-8 (HHV-8)	Kaposi's sarcoma, primary effusion lymphoma
	Castleman's disease (angiofollicular hyperplasia)
Human cytomegalovirus (HCMV)	Not regarded as independently oncogenic but has been implicated as a cofactor in colon cancer, malignant glioma, prostate carcinoma, breast cancer
Hepatitis B, C or B + C	Hepatic carcinoma
Human T-lymphotrophic Virus-1 and 2 (HTLV-1 and HTLV-2)	T-cell leukemia, T-cell lymphoma
Helicobacter pylori colonization	Gastric carcinoma, MALT lymphoma, pancreatic carcinoma
Mycobacterium tuberculosis colonization	Lung cancer
Human JC polyoma virus	Merkel cell carcinoma
Shistosoma hematobium	Bladder cancer, prostate carcinoma,[b] squamous cell carcinoma of cervix[b]
Shistosoma mansoni	Hepatocellular carcinoma, colorectal carcinoma[b]
Shistosoma japonicum	Hepatocellular carcinoma,[b] colorectal carcinoma[b]
Opisthorchis viverrini	Cholangiocarcinoma
Clonorchis sinensis	Cholangiocarcinoma

[a]Although EBV is frequently present in these tumors it is unclear if EBV plays a pathogenic role in their development.
[b]Possible association.

highly reactive and unstable attributable to the combined effects of the many and abundant reactive oxygen and nitrogen species, cytokines, chemokines, eicanosoids, reactive aldehydes, and growth factors that are present.[1,2,4–18] Any disturbance in normal

Table 3.   Cancers linked to chronic inflammation in domestic mammals.

Species	Primary Event	Cancer Type
Cat	Ocular trauma/chronic uveitis	Ocular sarcoma
Dog, horse	Thermal burns	Carcinoma
Dog, horse	Chronic bacterial infection and inflammation	Various
Dog	Foreign material	
	Implanted medical device	Myxosarcoma, osteosarcoma, other malignancies
	Asbestosis	Mesothelioma
	Surgical sponge	Osteosarcoma
Dog, cat, cow (white-haired areas)	Prolonged solar exposure	Squamous cell carcinoma
Horse (white and part white-haired areas)	Prolonged solar exposure	Melanoma, squamous cell carcinoma
Cat, dog	Inflammatory bowel disease	Lymphosarcoma (suspected)
Dog	Chronic myositis	Lymposarcoma
Dog	Chronic cystitis (cyclophosphamide administration)	Carcinoma of urinary bladder
Cat, dog, ferret	Vaccination or other injection	Sarcoma
Cat	Ingestion of coat-associated particulate carcinogens (tobacco smoke and flea collar exposure)	Oral squamous cell carcinoma
Cow	Bracken fern ingestion	Enzootic hematuria progressing to vascular, fibrous, and epithelial tumors of the bladder and esophagus

Table 4.   Cancers linked to chronic infection in domesticated mammals.

Species	Infectious/Infective Agent	Cancer Type
Cat	FeLV	Lymphosarcoma
	FeSV	Sarcoma
Sheep	Jaagsiekte sheep retrovirus	Pulmonary adenocarcinoma
	Enzootic nasal tumor virus (ENTV-1) from sheep	Nasal adenoma and adenocarcinoma
Cow	Bovine leukemia (leukosis) virus	Lymphosarcoma
Cow	Bovine papilloma virus (often with bracken fern ingestion)	Oral, pharyngeal, and rostral esophageal papillomas (warts) and esophageal cancers, bladder carcinoma
Horse	Bovine papilloma virus	Sarcoid (fibropapilloma)
Cat	Bovine papilloma virus	Sarcoid (fibropapilloma)
Dog	*Spirocirca lupi*	Esophageal osteosarcoma/fibrosarcoma
		Pulmonary fibrosarcoma with ectopic migration
Dog	Transplanted cells from a transmissible venereal tumor during copulation	Transmissible venereal tumor
Dog, cat	Papilloma virus	Initial papillomatous lesions may progress to squamous cell carcinoma
Goat	Papilloma virus	Initial papillomatous lesions may progress to squamous cell carcinoma
	Enzootic nasal tumor virus (ENTV-2) from goats	Nasal adenoma and adenocarcinoma

tissue homeostasis will activate innate immune cells (macrophages, mast cells, dendritic cells, and natural killer cells) as a first line of defense that can initiate an inflammatory response by releasing cytokines that signal cellular proliferation, chemokines that attract additional inflammatory cells, matrix-remodeling proteases, and reactive oxygen and nitrogen species that lead to the destruction of pathogens and then finally the repair of tissue damage.[1,2]

Macrophages in particular are important tumor-infiltrating cells that affect tumor growth and metastasis. They are found in 2 different polarization states known as M1 and M2. M1 macrophages produce interleukin 12 and promote tumoricidal responses, while M2 macrophages produce interleukin10 and promote tumor progression. The mechanisms governing macrophage polarization are unclear.[132] There can also be an adaptive immune response to inflammation mediated largely by T lymphocytes.[4]

Any failure in the control of the components of the immune response can lead to chronic inflammation and the generation of a microenvironment that might favor the initiation and progression of cancer.[4] The longer the inflammation persists the higher the probability of genomic instability and mutations that lead to cancer.[4,5,7–9] Normal cells possess intrinsic mechanisms to prevent unregulated proliferation or the accumulation of DNA mutations. These include the intervention of tumor suppressor genes like *p53* that direct DNA repair, apoptosis, cell cycle arrest, and senescence. Failure of these mechanisms also contributes to cancer development.

The mechanism by which inflammation causes cancer can be modeled as consisting of an intrinsic and extrinsic pathway.[4] The intrinsic pathway is activated by genetic alterations like oncogene activation and tumor suppressor gene inactivation. Cells transformed by the intrinsic pathway produce inflammatory mediators that change the tumor microenvironment to an inflammatory microenvironment in which there is no underlying inflammatory condition. An example of this is the inflammatory infiltrate noted in human breast cancer described by Virchow in 1863. The extrinsic pathway is one of inflammation that increases the risk of cancer at certain anatomical sites such as the colon, pancreas, prostate, or esophagus. The combined effects of these 2 cooperative pathways propel cells toward a malignant phenotype by the activation of additional transcription factors that coordinate the production of additional inflammatory mediators. These factors continue to recruit and activate leukocytes and macrophages that compound and reinforce the inflammatory microenvironment to produce a smoldering inflammation that has many tumor-promoting effects.[4]

Many of the signaling pathways involved in inflammation and normal healing also play a dual role in providing survival and proliferative signals to initiated cells that lead to cancer promotion and progression.[15] For example, nuclear factor-kappa B (NF-kB), a family of transcription factors central to the induction of inflammation, has been found to send important survival signals to initiated cells and is considered to be a critical link between inflammation and cancer.[2,4,7,10,12,15,133] NF-kB are ubiquitous transcription factors that regulate over 100 target genes involved in inflammation and proinflammatory cytokines as well as adhesion molecules and apoptosis.[134] NF-kB activation has been observed in many human solid tumors and is the result of underlying inflammation or secondary to the formation of an inflammatory microenvironment during progression of a malignancy. NF-kB links inflammation to cancer through its ability to target genes associated with tumor progression and to up-regulate the expression of tumor-promoting cytokines, and survival genes (Table 5).[2,133–135]

The Mitogen Activated Protein Kinase (MAPK) pathway also has a well-recognized dual role in cancer development and in inflammation. In both events, MAPK mediates external signals such as proinflammatory cytokines from cell surface receptors to downstream transcription factors that lead to cellular responses such as proliferation, growth, motility, survival, or apoptosis. The current consensus is that MAPK signaling touches on all of the characteristics of a surviving and proliferating cancer cell such as independence of proliferation signals, evasion of apoptosis, insensitivity to antigrowth signals, a capacity for invasion and metastasis, and angiogenesis to secure nutrient acquisition and growth.[136]

When a cause and effect relationship between chronic inflammation and cancer development exists most of the literature agrees that the sustained generation of free radicals such as the reactive oxygen species hydroxyl radical (OH·) and superoxide ($O_2-·$) and the reactive nitrogen species nitric oxide (NO·) and peroxynitrite (ONOO−) causes oxidative damage and nitration of DNA bases, which increases the risk for DNA mutations that may be nonrepairable and persist in subsequent generations (Fig 1). In addition, alterations in DNA methylation patterns, especially hypermethylation of DNA, can be a result of inflammation and is common in a variety of human cancers. Hypermethylation of DNA leads to transcriptional silencing of several tumor suppressor genes that can lead to cancer.[2,4,47]

It is important to note, however, that the construct of chronic inflammation leading to cancer is not absolute because some highly inflammatory disorders like rheumatoid arthritis in humans are not associated with an increased cancer risk.[2] Nevertheless, the relationship between inflammation and many cancers is so strong that it is common to find phrases such as "chronic inflammation is essential for cancer growth and metastasis," and "inflammation functions at all three stages of tumor development" and that inflammation is a "key event" in cancer development, published in respected journals.[7,9,18]

Primary Inflammatory Disorders and Human Cancer

Many associations between what are primarily inflammatory disorders and human cancer have been documented. For example, individuals affected with Crohn's disease have 3 times the risk of developing colon cancer and patients with ulcerative colitis have 19 times the risk of developing colon cancer as do individuals without the underlying inflammatory disorder.[2] Humans with chronic acid reflux of the esophagus have 50–100 times the risk of developing esophageal cancer as do humans without the underlying risk of chronic inflammation of the esophagus.[2] Even metabolic disorders such as hemochromatosis (an iron overload disorder of diverse cause) that ultimately results in inflammatory liver damage increases the risk of developing subsequent liver cancer by an astonishing 219 times the risk of humans without hemochromatosis.[2]

Table 5. NF-kB target genes that support tumor progression.[134]

Activity	Genes
Inflammation	TNF, IL-1, chemokines
Cellular immortality	Telomerase
Cell survival	BCL-X$_L$, and various inhibitors of apoptosis
Angiogenesis	VEFG, TNF, IL-1, IL-8
Proliferation	TNF, IL-1, IL-6, Cyclin D1, c-MYC
Tumor promotion	COX2, matrixmetalloproteinase-9, inducible nitric oxide synthase, urokinase plasmingen activator
Metastasis	Intracellular, vascular, and endothelial-leukocyte adhesion molecules
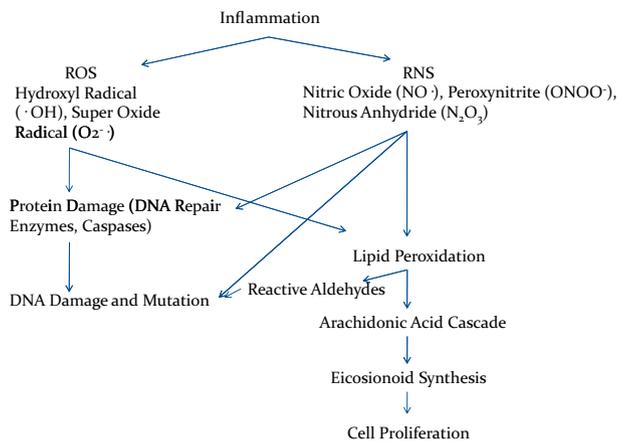
Fig 1. Inflammation and cancer initiation depicted show how inflammation can contribute to DNA damage, mutation, and carcinogenesis. Reactive oxygen and nitrogen species can react with and damage DNA in cancer-related genes and modifications in cellular proteins essential for DNA repair, apoptosis, and normal cell cycle activity either directly or indirectly through lipid peroxidation and generation of reactive aldehydes.

Foreign material either deliberately or accidentally implanted (medical devices, surgical sponges) or accidental or occupational exposure to foreign materials (asbestos, silica, talc, carbon nanotubes, other particulate carcinogens, bullet and shrapnel injury) is also linked to inflammation-based cancer.[3,53,60,63,64] Of interest is that the nature of the foreign materials themselves is unrelated to cancer risk, but their common connection to cancer is their ability to induce an inflammatory reaction and especially stromal proliferation, where those exogenous materials are incorporated and undigested.[3]

Asbestos fibers when inhaled and deposited in the lung of humans can cause mesothelioma. Asbestos is the commercial name for a group of hydrated magnesium silicate fibrous minerals. In the case of asbestos inhalation caused cancer, the shape of the crystal might be related to cancer risk.[57,110] The main crystals types of asbestos are serpentine shaped that consist of long curly fibers primarily of chrysotile and the amphibole group that consists of 5 asbestiform varieties: anthophyllite, amosite, crocidolite, tremolite, and actinolite that are long and thin and needle-like.[110] Each main crystal form has different industrial applications. Some sources report that crocidolite is the most toxic form of asbestos, but all forms of asbestos are dangerous when inhaled because they cannot be eliminated by pulmonary macrophages and result in dose-dependent chronic inflammation of the lung.[110] Asbestos fibers are known to be able to translocate to other organs after inhalation and increase cancer risk in nonlung organs with increased concentrations of asbestos fibers.[52,110]

Thermal burns produce intense inflammation and sites of burn injury can progress to carcinoma years after the initial burn has healed. Burn scar carcinomas were first reported in humans in 1828.[55–57] The pathogenesis of a burn scar carcinoma is obscure, but could involve the secretion of growth factors by cells within the scar matrix that stimulates mutated cells within the scar itself to form a cancer. In this way the scar and the cancer coevolve.[56,57] Another possibility is that foreign material has been incorporated into the scar (encapsulation) and that the stromal proliferation central to encapsulation progresses to cancer.[56,57]

That excessive sunlight exposure could cause skin cancer was suspected as early as 1894.[58,118,119] It is now known that there is a clear and dose response relationship between accumulated solar ultraviolet light exposure and skin cancer. In humans, melanotic skin cancer risk is more related to the frequency and severity of sunburns in childhood and adolescence, while nonmelanotic skin cancer (primarily squamous cell carcinoma and basal cell carcinoma) is related more to cumulative long-term sun exposure.[58,118] Ultraviolet B (ultraviolet light in the range of 280–320 nm; UV-B) is probably the portion of the ultraviolet spectrum that is involved most in nonmelanoma skin cancer in humans and animals.[58,118] The carcinogenic action of UV-B is believed to be associated with the formation of pyrimidine dimers, which when repaired incorrectly result in point mutations.[119]

Infections, Inflammation, and Human Cancer

Chronic viral, bacterial, and parasite infections are common causes of cancer in humans and together are responsible for 15–18% of all human cancers. Many of these infectious agents produce inflammatory reactions that drive cancer development by mechanisms previously discussed that involve oxidative stress. Many viruses cause cancer by mechanisms unrelated to inflammation, although for many of these viruses, nonviral infectious agents that do cause inflammation serve as cofactors that together increase the risk of or cause cancer. Even when viruses do not directly cause cancer by first establishing an inflammatory environment they may activate some of the final signaling pathways such as MAPK and NF-kB that are also found in an inflammatory microenvironment.

Papilloma Viruses

Chronic infection in immunocompetent individuals with human papilloma virus (HPV) can lead to oral and genital (penile, vaginal, cervical, and anal carcinoma) cancer.[19–23] Persistent infection with HPV may occur without inflammation or there may be dramatic inflammation associated with the virus alone or with potential cofactors such as *Chlamydia trachomatis, Neisseria gonorrhoeae*, or herpes simplex virus-2 (HSV-2).[19–23] Among the more than 100 HPV types, high risk type-16 (HPV-16) and high risk type-18 (HPV-18) are the varieties usually detected in genital cancers (there are at least 10 other less common high risk types of HPV).[20,23] There is also weaker evidence that mucosal papilloma viruses are responsible for oral squamous cell carcinoma.[20] Infectious cofactors and other

cofactors such as smoking are thought necessary for HPV infection to progress to cancer.[19,20,23] In total, papilloma viruses are estimated to cause 5.2% of all human cancer and almost 12% of all cancer in women worldwide.[24]

Herpes Viruses

Herpes viruses are widely disseminated in nature. In humans the oncogenic herpes viruses include human herpes virus-8 (HHV-8) and the Epstein-Barr virus (EBV) and perhaps human cytomegalovirus (HCMV).

EBV was the first human virus to be directly implicated as a cause of cancer and is associated with a surprising variety of cancers in humans. The final step in the EBV transformation of cells to cancer is achieved by activation of intracellular signaling pathways like NF-kB and MAPK that also have central roles in the normal response to inflammation.[29,30]

HHV-8 infection has been conclusively linked to Kaposi's sarcoma, primary effusion lymphoma, and Castleman's disease, a rare and clinically aggressive proliferative disorder of lymph nodes that is sometimes referred to as angiofollicular hyperplasia of lymph nodes. In the case of Kaposi's sarcoma, HHV-8 stimulates the production of vascular endothelial growth factor (VEGF), a critical factor for the development of Kaposi's sarcoma. VEGF-A is the best characterized member of the VEGF family and is the primary mediator of pathologic angiogenesis including angiogenesis associated with cancer and chronic inflammation. In addition to its well-known role in cancer angiogenesis, VEGF-A also appears to directly foster inflammation.[137,138] In many of the inflammatory disorders in humans where VEGF is known to be increased before and or during angiogenesis, VEGF increases vascular permeability and the resulting leak of proinflammatory mediators and cytokines causes inflammation that precedes angiogenesis.[138] The complexity of the expression of VEGF family is only now being elucidated and in part involves the signaling pathways NF-kB and MAPK.[25–27]

HCMV is generally not regarded to be a directly oncogenic virus, but it has been implicated as a likely cofactor in different human cancers (Table 2). HCMV is a persistent virus that induces a permanent activation of the immune system and inflammation that may initiate or accelerate a malignant process.[31,139]

Hepatitis Viruses B and C

Hepatitis B virus (HBV) is the cause of 80% of cases of hepatocellular carcinoma in humans.[32] Approximately 2 billion people are infected with this virus and 300,000–500,000 of them die annually from hepatocellular carcinoma.[32] Coinfection with hepatitis B and C viruses roughly doubles the risk of hepatocellular carcinoma.[32] Two major mechanisms of carcinogenesis are likely. The first is that HBV causes chronic inflammation and necrosis of liver cells that is followed by fibrosis, and liver cell regeneration. Repetitive cycles of this process lead to the accumulation of oncogenic mutations. HBV may also have direct oncogenic effects through chromosomal integration or transactivation of host genes that suppress p53 or activate proto-oncogenes that ultimately lead to hepatocellular carcinoma. About 70% of HBV associated hepatocellular carcinomas produce a viral transcriptional transactivating protein known as HBx.[32] The HBx protein upregulates the expression proto-oncogenes such as c-myc and c-Jun, suppresses p53 activity, induces signaling pathways MAPK and NF-kB, and induces angiogenesis that all accelerate cancer formation, invasion, and metastasis.[32]

Human T Lymphotrophic Virus

Human T-lymphotrophic virus type -1 (HTLV-1) is an oncogenic retrovirus that is the cause of T-cell leukemia/lymphoma in human adults.[33,34] HTLV-1 is also associated with a nonmalignant lymphocyte-mediated inflammatory disorders known as tropical spastic paraparesis/HTLV-1 associated myelopathy, HTLV-1 uveitis, HTLV-1 arthropathy, and rheumatoid arthritis.[33,34,134] The pathogenesis of diseases caused by this virus differs from that of other known retroviruses in that it does not encode an oncogene that is transduced from a hosts genome.[33] Instead, this virus encodes an oncoprotein known as Tax that promotes inflammation and inappropriate cellular proliferation, repression of multiple DNA-repair mechanisms, and deregulation of cell cycle checkpoints, and induces genomic instability largely through NF-kB pathways.[33,35,134] Whereas it is not completely understood how HTLV-1 infection causes chronic inflammation, it is believed that the robustness of the host's CD8+ cytotoxic T cell response to HTLV-1 plays an important role in determining the outcome of the inflammatory response.

Helicobacter pylori

Helicobacter pylori infection plays a crucial role in the development of human gastric cancer.[36–38] The 2 major mechanisms of oncogenesis from this organism are first indirectly as the result of chronic inflammation, and second by a more direct effect of the bacteria on epithelial cells through induction of protein modulation and gene mutation.

Helicobacter pylori positive-gastric cancer is invariably associated with gastritis and the severity of the gastritis is proportional to the risk for gastric cancer development.[37] Proinflammatory cytokines are produced, and among them are the cytokines IL-1β and TNF-α that together enhance NF-kB signaling that once again is believed to be the link between inflammation and gastric cancer (NF-kB signaling is also considered to be a key factor for colitis-associated cancer development).[37] In addition, *H. pylori* infected patients with and without cancer show abnormal DNA methylation patterns of the gastric mucosa that may contribute to carcinogenesis by silencing tumor suppressor genes.[36,37]

There is also considerable evidence that *H. pylori* can act directly on gastric epithelial cells by causing mutations to genes within gastric epithelial cells that then modulate cellular functions such as growth, apoptosis, or cell migration.[37] Strains of *H. pylori* that secrete a protein known as *CagA* are invariably associated with gastric cancer.[36–38] The *CagA* protein is believed to act directly on gastric epithelial cells and contribute to cancer formation by inducing NF-kB activity.[37,38]

Inflammation resulting from *H. pylori gastritis* is the cause of 75% of cases of gastric mucosa-associated lymphoid tissue (MALT) lymphoma, a subtype of low-grade B-cell lymphoma in humans. As a result, the majority of gastric MALT lymphomas in man are successfully treated with antibiotic eradication of *H. pylori* alone.[140–143] Paradoxically, the normal human stomach lacks organized MALT tissue within which lymphoma can develop. Lymphoid tissue is acquired in the stomach in response to antigenic stimulation after colonization by *H. pylori*.

Conflicting reports exist concerning the risk for pancreatic cancer development after *H. pylori* colonization of the pancreas.[39,40]

Schistosomiasis

Shistosoma hematobium, Shistosoma mansoni, and *Shistosoma japonicum* are the major species associated with human schistosomiasis and they are found in fresh water snails throughout Sub-Saharan Africa, and variably in Asia, the Middle East, and South America.[41–43] Schistosomiasis affects approximately 200–250 million individuals globally.[41,42] *Schistosoma* infection results in inflammation, granuloma formation, and squamous metaplasia in infected tissues, and chronic infection with schistosoma organisms can promote carcinogenesis by any of 3 mechanisms. One path to cancer is through chronic inflammation and the persistent effects of reactive oxygen and nitrogen species on host DNA. Another mechanism of carcinogenesis could be through the insertion of an active oncogene into host DNA when coinfected with a virus such as hepatitis B or C virus.[41] The last potential mechanism of malignant transformation is as the result of reduced immunosurveillance secondary to immunosuppression.[41]

Infection with *S. haematobium* is considered a definitive cause of squamous cell carcinoma of the urinary bladder that is a relatively uncommon histologic type of bladder cancer in nonendemic areas.[41–43] A possible causal relationship could also exist with prostate carcinoma and with squamous cell carcinoma of the vagina and cervix.[41,43] In addition to the potential mechanisms of carcinogenesis noted above, bladder carcinogenesis can result from concurrent chronic urinary bacterial infection and the production of nitrosamines from their precursors in urine that are well-known bladder carcinogens[41] In addition, multiple mutations of critical cell regulators such as p53, Rb, epidermal growth factor receptor, and c-erbB-2 proteins are frequently found in invasive squamous

cell carcinoma of the bladder from *S. haematobium* infected patients.[41]

The evidence supporting a role in cancer for *S. japonicum* is weaker than for *S. haematobium*; however, infection with *S. japonicum* has been associated with both liver and colorectal cancer. Some investigators think of *S. japonicum* as more of a risk factor than a cause for hepatocellular carcinoma in addition to other risk factors such as hepatitis B and C and alcohol abuse that might be more relevant.[41–43]

The relationship between infection with *S. mansoni* and hepatocellular carcinoma is probably as more of a cofactor that potentiates the effects of hepatitis B or C virus infection.[41] There is also a possible association with *S. mansoni* infection and colorectal cancer.[41]

Opisthorchis viverrini

Endemic to parts of East Asia is the liver fluke *Opisthorchis viverrini* that causes cholangiocarcinoma in humans who consume infected raw fish. Of the many millions of infected individuals, 10–20% of them have advanced hepatic periportal fibrosis, caused by the flukes, that progresses to cholangiocarcinoma.[44,45] Clinical trials, sponsored by the National Institute of Allergy and Infectious Diseases, are currently in progress to better define the inflammatory response and mechanisms of oncogenesis associated with this parasite.[45]

Clonorchis sinensis

Occupying the same geographic distribution of *O. viverrini* is a similar liver fluke known as *Clonorchis sinensis*. *C. sinensis* flukes reside primarily within the gall bladder and the bile ducts and cause inflammation that can lead to cancer probably in similar fashion to *Shistosoma* and *Opisthorchis*.[46]

Primary Inflammatory Disorders and Cancer in Domestic Mammals

As in humans, a variety of what are primarily inflammatory disorders can result in cancer in domestic mammals. For example, similar to humans with Crohn's disease or ulcerative colitis, dogs and cats with inflammatory bowel disease may have an increased risk for cancer. Inflammatory bowel disease (IBD) in dogs is a group of disorders that are classified by the predominant type of inflammatory cell present and the area of the gut affected.[120,121] The importance of genetic factors in IBD of dogs is implied by the fact that certain breeds appear to be predisposed to certain forms of IBD and that some forms only occur in single breeds or pedigree lines. Veterinary clinicians have long observed an apparent overlap between IBD in dogs and cat and subsequent diagnoses of lymphoma.[120] In some of these cases the apparent overlap occurs because the diagnosis of IBD is made from small and superficial endoscopically obtained biopsies that missed the deeper residing malignant tissue when

inflammation and cancer occur concurrently. Alternatively, because a host of inflammatory cytokines have been identified in dogs with IBD and there are clinical and mechanistic similarities between IBD in dogs and humans, chronic bowel inflammation in dogs and cats can be the antecedent event to malignant transformation as it can be in humans.[120,121]

Like humans exposed to asbestosis, dogs exposed to asbestosis can have a similar dose-dependent risk of mesothelioma. In a study of 18 urban dogs with mesothelioma, asbestos bodies were identified in substantially higher numbers in the lungs of 3 dogs when compared with those found in the lung tissue from controls.[108] Although asbestosis can be found in the lungs of the general urban human and canine populations, it is the number of asbestosis bodies per gram of lung tissues that separates occupational/causal exposure from casual environmental exposure.[57,109,110]

As in humans, the development of carcinomas subsequent to thermal burns has also been reported in domestic mammals. There are case reports of dogs and horses that developed squamous cell carcinoma at the site of a burn injury from years earlier.[62,116,117]

Similar to humans, exposure to sunlight can lead to cancer formation in some domestic mammals. However, in many of these cases, chronic inflammation can drive the malignant process as much as incorrectly repaired UV-B solar-induced mutations as is the likely situation in humans. One of the best examples of this is the development of squamous cell carcinoma after exposure to solar UV-B irradiation in white cats, white-faced cattle, and possible Collies and Shetland sheep dogs.[118,119] White cats and white-haired areas (especially the ear tips and nose) of cats are susceptible to a chronic inflammatory dermatitis that is exacerbated by exposure to direct sunlight. These inflammatory lesions can evolve to squamous cell carcinoma.[118,119] Poorly pigmented skin posterior to the planum nasale in dogs is susceptible to a similar progression of a focal chronic inflammatory dermatitis to squamous cell carcinoma.[118,119]

Perhaps the poster-child example in veterinary medicine of inflammation leading to malignancy is sarcoma development after vaccine or nonvaccine injections in cats.[96–101] Most of these tumors develop subsequent to vaccination, but isolated cases have been reported after injections of long-acting antibiotics, corticosteroids, the benzoylurea pesticide lufenuron,[a] nonabsorbable suture material, and microchip implants.[100,101] Although mechanisms are not completely understood, much is nevertheless known.[96–101] Injection site sarcomas in cats often contain a peripheral inflammatory infiltrate consisting of lymphocytes and macrophages. Macrophages in these sarcomas often contain a bluish-gray foreign material, identified by electron probe x-ray microanalysis to be aluminum, presumably remnants of the vaccine adjuvants.[96–101] Transition zones from inflammatory granuloma to sarcoma have been identified and strongly suggest that the inflammatory response to vaccination is antecedent to sarcoma formation.[97,98,100] A similar inflammatory response to

foreign material has been described in inflammatory vaccination-site reactions in dogs, ferrets, and humans, but sarcoma development is exceedingly rare in these species.[102–104]

The unusual relationship of trauma to ocular sarcoma in cats was first published as a case report of a 7-year-old-domestic short hair cat that developed a sarcoma in an eye that had been traumatized 3 years earlier.[127] A review of the literature of other intraocular sarcomas in cats after trauma suggests that trauma to the eye and subsequent uveitis and lens rupture are risk factors for intraocular tumor development. Although the relationship between ocular trauma and tumor development is obscure, released viable lens epithelial cells were suggested as a possible origin of these tumors.[127] We generally think of sarcomas arising from mesenchymal tissues rather than epithelial tissues, but the epithelial origin of feline ocular sarcomas associated with ocular trauma was recently confirmed with immunohistochemistry in 3 of 9 ocular tumors from cats.[128] The morphologic features of feline ocular sarcomas are reminiscent of injection site sarcomas in cats in that they both have a substantial inflammatory component microscopically.

Hemorrhagic cystitis and bladder fibrosis are potential complications of cyclophosphamide treatment.[59,129–131] Acrolein, a metabolite of cyclophosphamide, is believed to be responsible for cystitis complications by acting as a local toxin that causes intense inflammation and bladder hemorrhage. There are multiple reports of hemorrhagic cystitis after cyclophosphamide administration that progressed to transitional cell carcinoma of the urinary bladder in dogs and also in humans.[129–131]

Infections, Inflammation, and Cancer in Domestic Mammals

Similar to the situation in humans, bacterial, viral, and other infectious organisms are occasionally associated with cancer development in domestic mammals. Bacterial infection as a source of chronic inflammation that leads to cancer development in domestic mammals has been reported many times. For example, in one case report a13-year-old Belgian stallion developed squamous cell carcinoma at the site of a laceration that remained infected for 18 months.[111] A different case report is of a squamous cell carcinoma originating from the site of a barbed wire laceration 18 months earlier that had failed to heal properly.[112] In another case report a 5-year-old male Saint Bernard dog developed osteosarcoma after left ulnar ostectomy to correct a valgus deformity of the limb secondary to premature closure of the ulnar physis 4 1/2 years earlier.[113] At the time of presentation of the tumor, a pure culture of *Staphylococcus aureus* was recovered from the former ostectomy and current tumor site suggesting osteomyelitis as a precursor to osteosarcoma.[113] In another report, an aged dog with chronic bilateral otitis external developed bilateral squamous cell carcinoma of the pinnas. The tumors were located

where the pinna would cover the external auditory meatus and were attributed to chronic infection.[114]

The relationship between tumor development and metallic implants used to stabilize fractures in dogs was reviewed in a study in 222 dogs with tumors of any kind that were preceded by a fracture and fixation, and 1,635 dogs who had fractures and fixation without later developing a tumor.[115] The conclusion of this work was that internal fixation with metallic implants is not a risk for bone tumor development.[115] However, because fracture-associated sarcomas develop at previous fracture sites and not at the more usual location of the metaphysis, one can speculate that another factor other than the metallic implant itself may contribute to development of these tumors.[115] Fracture-associated sarcomas in dogs have often been associated with some postoperative complication causing delayed healing. Chronic low-grade bacterial osteomyelitis may play a role in the development of some these tumors.

Bacteria associated with chronic wounds such as those just described often grow as a biofilm that makes eradication of infection very difficult and allows an inflammatory environment to persist.[144–147] Molecular methods of microbial identification have shown that only 1% of all bacteria present in chronic wounds are identified by conventional culture methods so the presence of a biofilm infection may easily go undetected.[146] Biofilms have been confirmed in chronic wounds in horses and pigs, in bovine mastitis, and in experimental infections in dogs.[144,145]

Cats are the natural reservoir for the organism *Bartonella henselae* which is the most important of the pathogenic *Bartonella* species.[148–150] *B. henselae* is relevant to human and animal health because it is the organism responsible for cat scratch disease and the vasculoproliferative disorders bacillary angiomatosis and peliosis hepatis. Peliosis hepatis is a tumorous proliferative disorder of endothelial cells that is characterized by the formation of blood-filled cysts within the parenchyma of the liver in humans and dogs. Although cats are the natural reservoir of *B. henselae*, peliosis hepatis in cats appears to be unrelated to this organism.[150] Bacillary angiomatosis is a similar vasculoproliferative disorder that involves the skin and is similar in appearance to Kaposi's sarcoma caused by HHV-8 infection.[147,148] Similar to the pathogenesis of lesions in humans that are triggered by HHV-8 infection, VEGF plays a leading role in the endothelial cell proliferations induced by *B. henselae*.[148,149]

Polymyositis in dogs may be caused by infectious agent like *Toxoplasma, Borrelia, Leptospira, Neospora, Ehrlichia*, and *Hepatozoon* species.[122] A recent case report of 2 dogs details a complicated relationship between polymyositis and lymphoma in which the dogs reported had a similar course of clinical signs consistent with polymyositis for 2–8 months prior diagnosis. In each case the additional diagnosis of lymphoma was made between 1 and 13 months after the diagnosis and treatment of polymyositis.[122] The lymphoma was multicentric plus muscle infiltration in one case, but limited to muscle infiltration in the other case. The authors concluded that the relationship between polymyositis and lymphoma in these dogs has at least 3 potential explanations. The first is that infiltrating T cells associated with inflammation had undergone malignant change to lymphoma presumably because of the inflammatory microenvironment. Another potential explanation is that the polymyositis was a paraneoplastic syndrome secondary to a primary lymphoma. The 3rd reason offered was that generalized skeletal lymphoma could have been misdiagnosed as polymyositis.[122] There are 4 additional reports of 4 dogs with similar clinical courses that had polymyositis diagnosed before a diagnosis of lymphoma.[123–126]

Spirocerca lupi is a nematode parasite that is found in tropical and subtropical regions that primarily affects dogs.[95] Adult *S. lupi* usually encyst within the wall of the thoracic esophagus. The maturation process to adulthood is characterized by an intense inflammatory reaction and eosinophilic granuloma formation that can progress to osteosarcoma or fibrosarcoma and is often complicated by distant metastasis.[95] The mechanisms of malignant transformation from granuloma to sarcoma have not been studied extensively but could involve a similar mechanism to that observed in the granuloma to sarcoma transformation noted in cats after vaccination.

Papilloma Viruses

Papillomaviruses (PV) are generally considered to be species specific, but there are numerous examples of some PVs jumping species and causing disease. In the cat and horse there is very strong evidence that bovine papilloma virus (BPV) cause sarcoids (fibropapillomas), lesions that are morphologically identical in these species.[80–82,86] There are also at least 2 reports of epithelial lesions in cats that are associated with a HPV. One report is of a cutaneous papilloma in a cat from which HPV type 9 was isolated. The other report documents isolation of HPV types 9, 38, 76, and 80 from a variety of feline cutaneous lesions including squamous cell carcinoma (SCC), squamous cell carcinoma *in situ*, and dysplasia. Both reports support the likelihood of transmission of PVs between humans and cats.

The mechanism of progression from papilloma to carcinoma is not definitively established in domestic mammals but it is likely similar to that in humans (promoting epithelial proliferation).[20,23,80] The role, if any, of inflammation in the causation of papilloma disorders or the progression to cancer in domestic mammals is unknown. However, when evaluated, histologically papillomatous lesions often have a background of inflammation that may be marked depending on the immune response and the degree of invasiveness and ulceration that is present.

The proposed progression from asymptomatic cutaneous papilloma virus infection into cutaneous cancers in cats begins with the formation of viral plaques (areas of active local viral replication), progression through Bowenoid *in situ* carcinoma, and finally to

invasive SCC from which PV DNA can be detected in the carcinoma cells.[80,81] Cutaneous SCC caused by PV is rare in cats, but outdoor rural cats and those with known exposure to cattle are reported to be at higher risk. Most cutaneous SCC in cats is UV-B light induced and not related to BPV infection. However, oral squamous cell carcinoma in cats may result more from PV infection because PV DNA has been isolated from SCC of the oral cavity and obviously the oral cavity receives no significant solar exposure.[151]

Like with humans and cats, PV infections in dogs can be asymptomatic or they can induce viral plaques that can then (very rarely) progress to in situ or invasive carcinomas.[80] Histologic evidence of PV infection is often subtle, but PV antigen has been identified within plaque lesions in dogs. Papilloma viruses have also been associated with endophytic papillomas in dogs (rare lesions of the food pads and ventral surfaces).[80]

Urinary bladder tumors are rare in cattle and account for only 0.01% of all bovine tumors. The majority of these tumors are found in cows that have grazed pastures rich with the plant bracken fern (*Pteridium aquilinum*).[80,83,85] The fern contains incompletely defined toxins that in cattle cause a condition known as enzootic hematuria. Some affected cattle will develop carcinomas of the urothelium through the combined effects of the bracken fern toxins plus BPV-2.[80,83,85] Esophageal tumors are also very rare in cattle and they also have been reported after bracken fern ingestion and infection with BPV-2.[84] An interesting comparative observation is that high-risk HPVs are also associated with esophageal squamous cell carcinomas in humans.[48]

Retroviruses

There are a number of important retroviruses that cause cancer in domestic mammals.[87–94] Jaagsiekte sheep retrovirus (JSRV) is an acute transforming type of retrovirus that can induce lung tumors in sheep known as ovine pulmonary adenocarcinoma (OPA).[87–89,92] Not only is OPA a substantial economic problem in many countries where the prevalence rate can be as high as 30%, but this tumor morphologically resembles bronchogenic carcinoma in humans.[87–89] The structural envelope (env) protein of JSRV is itself an active oncogene and is believed to directly mediate the process of malignant transformation of epithelial cells by activating the necessary signaling pathways (not fully defined at this time, but transformation involves in part the activation of the PI$_3$K/Akt and MAPK signaling cascades).[87] A closely related retrovirus of sheep and goats is known as enzootic nasal tumor virus (ENTV) is believed to cause nasal carcinomas in sheep and goats through a similar signaling pathway where the env protein acts as an oncogene.[90,91]

Bovine leukemia virus (BLV) is a transmissible retrovirus that has enormous economic consequences to beef and dairy cattle worldwide (dairy industry losses alone in 2002 were estimated at $525 million).[79,92,93]

Prevalence rates of infection of cattle herds in the United States range from 0 to 100%. There are 2 main types of clinical expression of BLV infection.[79] The first is known as enzootic bovine leukosis (multicentric lymphoma/leukemia), a disease characterized by widely disseminated accumulations of transformed B lymphocytes and a minor variant known as sporadic bovine leukosis. The second clinical expression is a persistent lymphocytosis that is characterized by a permanent and relatively consistent increase in the number of B lymphocytes in peripheral blood. Persistent lymphocytosis affects approximately one-third of infected animals and is considered to be a benign expression of disease.[79] Infection is not the same as clinical disease and the majority of BLV-infected cattle are asymptomatic with fewer than 1% of peripheral blood cells in animals found to be infected by the virus. The mechanisms preventing viral expression in a larger proportion of cells containing an integrated virus is poorly understood, but may involve inhibition of the Tax protein.[93,152]

Feline leukemia virus (FeLV) is a highly studied oncogenic retrovirus of cats, and it is responsible for a spectrum of clinical disorders including lymphoma and leukemia in infected individuals. The pathogenesis of FeLV-caused disorders does not appear to involve inflammation. For a comprehensive review of FeLV see Hardy (1981).[94]

One cause of sarcoma in cats is the feline sarcoma virus (FeSV). However, this virus is incomplete in the sense that it does not possess a complete viral genome. Because it is missing the *env, pol,* and part of the *gag* viral genes, it cannot replicate or infect a cell without the integration of additional genes from either the host or a helper virus such as FeLV or both (oncogene capture).[94] Because it is a defective virus it is of little relative clinical importance.

Summary

Why does chronic inflammation cause cancer in some individuals but not in others? The answer might lie in the relative ability of the individual to repair accumulated DNA damage. This hypothesis was confirmed in a recent publication that proved that there is a link between DNA damage induced by chronic inflammation and colon carcinogenesis and *H. pylori* induced gastric carcinoma in mice and that individuals with a greater ability to repair DNA damage have a lower cancer risk.[36]

Carcinogenesis and inflammation are complex processes that result from the combined influences of many immunologic and cell signaling forces. That a cause and effect relationship exists between inflammation and cancer development is accepted, but many questions remain. Because the types of inflammation associated with different tumors vary enormously, finding a common mechanism connecting inflammation to cancer would aid understanding of the overall process. Certainly, signaling pathways and factors like NF-κB and MAPK and VEGF that promote both

inflammation and angiogenesis are central to cancer development caused by inflammation, but they are probably not the entire explanation. Other questions remain unanswered such as what controls the relative influences of cancer promoting inflammation versus an inflammatory response that inhibits cancer. Finally, the big question is just how do we use this information therapeutically?

Footnote

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