

Inflammation

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Introduction

In 1863, Virchow proposed that cancer originates at sites of inflammatory responses (Virchow 1863a, b; Balkwill and Mantovani, 2001). Based on extensive epidemiological studies in the 20th century (de Martel et al., 2012; Elinav et al., 2013; Okada, 2014), the association between persistent infections, inflammation, and the development of human cancers was conclusively established for several types of carcinomas and lymphomas (Table 17.1 and Table 17.2).

Worldwide, infections have been linked with 16.1% of human cancers, accounting for 22.9% of cancers in developing countries (de Martel et al., 2012). Sterile inflammation associated with inhalation of crystalline silica or asbestos fibres (Volume 100C of the *IARC Monographs*; IARC, 2012a)

has also been associated with development of lung cancer and malignant mesothelioma (Table 17.1). Cancer-related inflammation has been defined as “the seventh hallmark of cancer” (Colotta et al., 2009), and Hanahan and Weinberg (2011) added “tumour-promoting inflammation” as an enabling characteristic of human tumours.

This chapter focuses on the contribution of inflammation to multiple steps during the evolution of cancer, including genetic and epigenetic alterations, disruption of tissue organization and homeostasis, and establishment of a local microenvironment that contributes to tumour growth, invasion, and metastasis (Fig. 17.1). The key mechanistic pathways and mediators involved in inflammation-associated carcinogenesis are summarized.

Intrinsic and extrinsic pathways linking inflammation and cancer

Acute inflammation is a beneficial host response against tissue injury and microbial invasion that usually resolves after killing of the invading organisms, followed by tissue regeneration or repair. Persistent infections or inadequate resolution of acute inflammatory responses perpetuate tissue injury and lead to prolonged chronic inflammation accompanied by fibrosis or scarring (Kundu and Surh, 2012).

Persistent infection and inflammation disrupt local tissue homeostasis and dysregulate cell signalling pathways, leading to recruitment and activation of inflammatory cells (Balkwill, 2012). Persistent inflammatory conditions triggered by infectious or environmental agents are defined

Table 17.1. Human carcinomas associated with infections and chronic or persistent inflammation

Agent	Cancer sites
Hepatitis B and C viruses	Liver
Human papillomaviruses	Cervix, oral cavity, larynx, vulva, penis, anus
<i>Clonorchis sinensis</i>	Bile duct
<i>Helicobacter pylori</i>	Stomach
<i>Opisthorchis viverrini</i>	Bile duct
<i>Schistosoma haematobium</i>	Bladder
Asbestos fibres	Lung, mesothelium, larynx, ovary
Crystalline silica	Lung
Erionite fibres	Mesothelium

Source: Compiled from de Martel et al. (2012), IARC (2012a, b), and Trinchieri (2012).

as extrinsic pathways leading to the development of cancer (Mantovani et al., 2010; Multhoff et al., 2011). Examples of human carcinomas and lymphomas associated with exogenous infections or environmental exposures are listed in Table 17.1 and Table 17.2.

Intrinsic pathways driven by activation of proto-oncogenes and signalling pathways in pre-neoplastic and neoplastic cells also recruit host-derived inflammatory cells that stimulate tumour growth and progression (Grivennikov et al., 2010), changes that may be evident in the absence of any obvious exogenous infectious exposure. For example, the *RAS* oncogene is frequently activated by point mutation in malignant epithelial cells, which leads to activation of intracellular signalling cascades and increased expression of the pro-inflammatory cytokines interleukin 1 alpha (IL-1 α), IL-1 β , and IL-6 (Trinchieri, 2012).

In papillary thyroid cancer, rearrangement of the RET/PTC (rearranged during transfection/papillary thyroid carcinoma) tyrosine

kinase activates expression of the chemokines IL-8, chemokine (C-C motif) ligand 2 (CCL2), and CCL20 that attract inflammatory cells, and induces expression of the chemokine receptor CXCR4 by malignant thyroid epithelial cells (Bozec et al., 2010). In addition to CXCR4, which is overexpressed in many malignant cells as well as in cancer stem cells (Trautmann et al., 2014), multiple chemokine receptors are expressed in leukaemias and lymphomas as well as in cancers of the lung, ovary, stomach, bladder, and prostate, which may contribute to tumour invasion and metastasis (Balkwill, 2012).

The pathways that are activated by persistent or repeated episodes of acute inflammation or by chronic inflammation and that contribute to tumour growth, invasion, and metastasis are illustrated in Fig. 17.1. Continued recruitment of host inflammatory cells to the evolving tumour microenvironment in response to persistent infections, ongoing tissue injury, or upregulated production of cytokines and chemokines drives cancer development (Grivennikov et al., 2010; Chai et al., 2015).

Activated inflammatory cells, including neutrophils and macrophages, produce reactive oxygen species and reactive nitrogen species. These potent chemical mediators are important in killing invading pathogens; however, their prolonged release can cause local tissue injury, damage to proteins, lipids, and DNA (the DNA damage may be mutagenic if not repaired correctly), and upregulation of signalling pathways, especially of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), that amplify pro-inflammatory responses (Lu et al., 2006; DiDonato et al., 2012). Key pro-inflammatory mediators that initiate and amplify tumour-associated inflammation include prostaglandins, cytokines, chemokines, and heat shock proteins (Fig. 17.1).

Prostaglandins are synthesized from arachidonic acid and contribute to tumour cell proliferation, survival, angiogenesis, and invasion. The rate-limiting enzyme in prostaglandin synthesis is prostaglandin-endoperoxide synthase 2 (PGHS-2), also known as cyclooxygenase 2 (COX-2), induced by NF- κ B (Chai et al., 2015). Key cytokines in tumour-associated inflammation are IL-1 and tumour necrosis factor alpha (TNF- α). IL-1 is produced by tumour, endothelial, and inflammatory cells and activates intracellular signalling pathways, including those of NF- κ B, activator protein 1 (AP-1), and p38 mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK), that stimulate production of mediators involved in inflammation, invasion, and angiogenesis (Multhoff et al., 2011). TNF- α is a pro-inflammatory mediator produced by activated macrophages and tumour cells, leading to activation of NF- κ B and signal transducer and activator

Table 17.2. Human lymphomas associated with persistent infections and inflammation

Agent	Malignancy
<i>Borrelia burgdorferi</i>	Cutaneous lymphoma
<i>Chlamydia psittaci</i>	Ocular adnexal lymphoma
<i>Helicobacter pylori</i>	Gastric lymphoma
Epstein–Barr virus	Burkitt lymphoma Large B-cell lymphoma Hodgkin lymphoma
Human T-cell lymphotropic virus type 1	Adult T-cell lymphoma

Source: Compiled from de Martel et al. (2012) and IARC (2012b).

of transcription 3 (STAT3) (Lin and Karin, 2007). IL-6 also promotes tumour angiogenesis and invasion (Multhoff et al., 2011). Constitutive activation of NF- κ B and STAT3 is found in several human tumours, and these factors act synergistically to sustain and enhance tumour-associated inflammation (Chai et al., 2015).

The ultimate impact of intratumoural inflammation on tumour growth is to stimulate proliferation and survival of tumour cells, resistance to apoptosis, evasion of host immune attack, angiogenesis, and invasion, which are all major hallmarks of cancer (Hanahan and Weinberg, 2011). These authors identified tumour-promoting inflammation as an enabling characteristic of cancer, in addition to genomic instability, which is discussed later in this chapter.

How do exogenous infectious agents and environmental exposures trigger tumour-associated inflammation?

Exogenous agents responsible for inflammation cause persistent tissue injury, aberrant tissue regeneration and healing, and a favourable environment for tumour growth (Trinchieri, 2012). Although apopto-

sis is usually not associated with an inflammatory response, extensive apoptosis and necrosis do trigger inflammation by releasing damage-associated molecular factors, including adenosine triphosphate (ATP), nucleic acids, heat shock proteins, S100 proteins, and the high-mobility group box 1 protein (HMGB1) (Pandey et al., 2015).

Pyroptotic cell death – which is similar to apoptosis but is dependent on a different set of initiator caspases – is associated with necrosis and depends on activation of the inflammasome, a multiprotein cytoplasmic complex assembled in response to generation of reactive oxygen species, potassium ion efflux, or permeabilization of lysosomes, resulting in cytoplasmic release of neutral proteases, such as cathepsin B (Kuraishy et al., 2011; Zitvogel et al., 2012).

Environmental exposures to, for example, crystalline silica and asbestos fibres also trigger activation of the inflammasome, which results in lung epithelial injury, release of pro-inflammatory mediators, and lung fibrosis (Fig. 17.2; Dostert et al., 2008, 2013; Luna-Gomes et al., 2015). Crystalline silica and asbestos fibres are phagocytosed

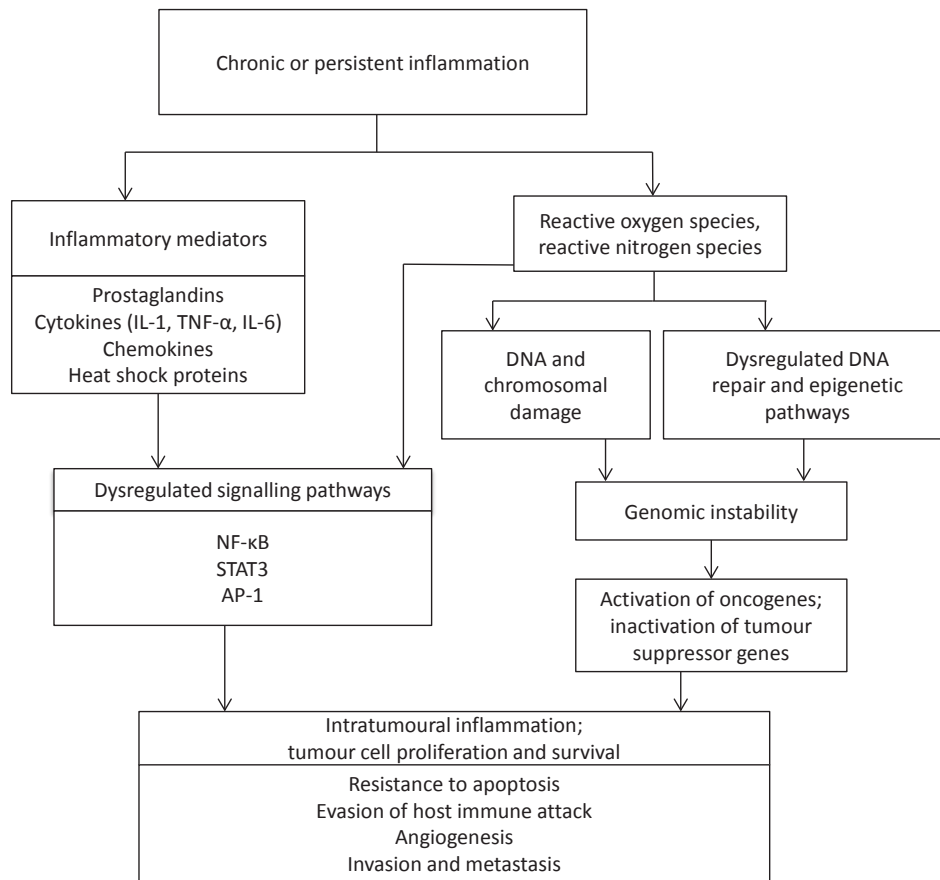
by macrophages, resulting in activation of the NLRP3 inflammasome (Biswas et al., 2011; Li et al., 2012).

Amphibole asbestos fibres, after inhalation into the lungs, translocate to the pleural cavity, where they may also activate the inflammasome in the mesothelial cell lining, leading to sustained inflammation that contributes to the development of diffuse malignant pleural mesothelioma (Broaddus et al., 2011; Mossman et al., 2013). Particles of carbon black have also been shown to induce activation of the inflammasome and pyroptosis of alveolar macrophages at high doses (Reisetter et al., 2011).

After assembly of the inflammasome or release of cathepsin B from lysosomes, pro-caspase-1 is activated by proteolytic cleavage to produce active caspase-1 that cleaves pro-IL-1 β and pro-IL-18 to their active forms, which initiate and amplify inflammation after release in the local environment (Fig. 17.2). Active caspase-1 can also cleave pro-caspase-7, triggering cell death by pyroptosis (Zitvogel et al., 2012). Active IL-1 β and IL-18 can suppress immune surveillance in addition to promoting growth of tumour stromal cells by paracrine signalling pathways (Fig. 17.2). Persistent inflammation and pyroptosis may enhance damage to epithelial barriers and thus contribute to gastric cancer associated with *Helicobacter pylori* infection (Grivennikov et al., 2010). Persistent infection with hepatitis B or C virus can also lead to chronic release of pro-inflammatory cytokines (Grivennikov et al., 2010; Read and Douglas, 2014).

Chronic exposure to irritants present in tobacco smoke, or to acetaldehyde generated by ethanol metabolism after consumption of alcoholic beverages, induces epithelial

Fig. 17.1. Pathways linking inflammation to cancer. AP-1, activator protein 1; IL-1, interleukin 1; IL-6, interleukin 6; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; STAT3, signal transducer and activator of transcription 3; TNF- α , tumour necrosis factor alpha. Source: Compiled from Colotta et al. (2009), Grivennikov et al. (2010), Multhoff et al. (2011), Kundu and Surh (2012), and Cooks et al. (2014).



cell injury in the oral cavity and the upper respiratory tract. These lesions synergize with potent chemical carcinogens in tobacco smoke and smokeless tobacco, thereby increasing the risk of cancers of the oral cavity, larynx, and oesophagus (Smith et al., 2006). Persistent chronic inflammation associated with hepatitis B viral infection acts synergistically with aflatoxin, a genotoxic carcinogen, in the development of hepatocellular carcinoma (Kew, 2003; Cougot et al., 2005).

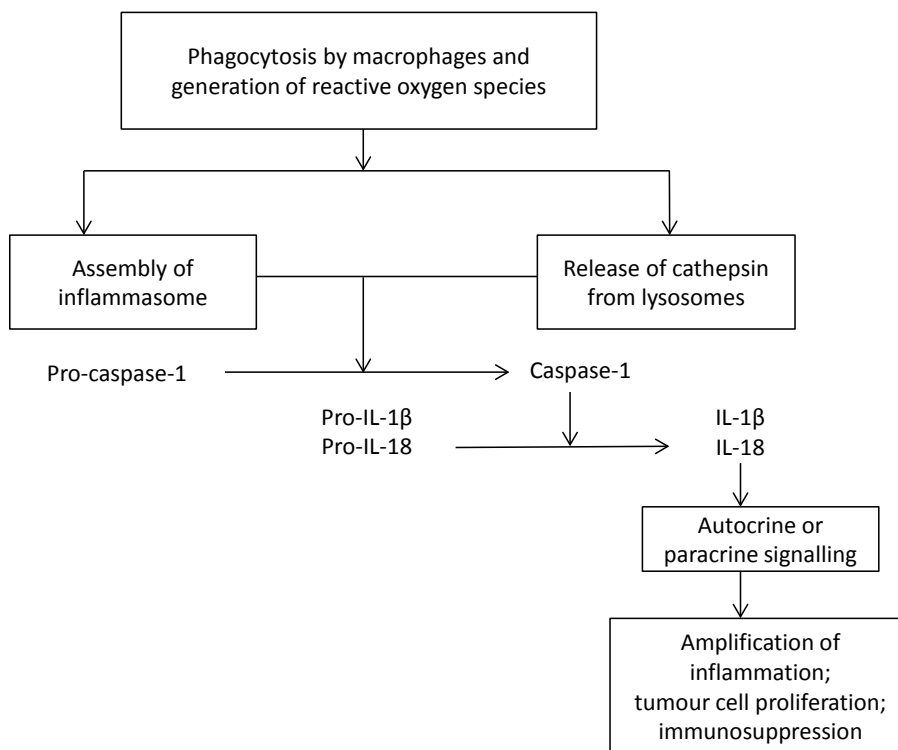
Inflammation and genomic instability

Activation of the NF- κ B and STAT3 signalling pathways and activation of macrophages by TNF- α are the key contributors to sustained generation of reactive oxygen species and reactive nitrogen species in cancer-related inflammation (Colotta et al., 2009). Activated macrophages release large quantities of reactive oxygen species, and NF- κ B upregulates nitric oxide synthase,

which generates excess reactive nitrogen species (Laskin et al., 2011). Constitutive activation of STAT3 in cancers maintains NF- κ B activation, creating a self-sustaining amplification loop (Chai et al., 2015).

NF- κ B activity is prolonged in the presence of mutant p53 protein and upregulates activation-induced cytidine deaminase, an error-prone DNA repair enzyme (Cooks et al., 2014). Reactive oxygen species inactivate mismatch DNA repair enzymes by inducing oxidative damage; although

Fig. 17.2. Crystalline silica and asbestos fibres activate the NLRP3 inflammasome. IL-1 β , interleukin 1 beta; IL-18, interleukin 18. Source: Compiled from Dostert et al. (2008), Biswas et al. (2011), Zitvogel et al. (2012), and Mossman et al. (2013).



reactive oxygen species induce the base excision repair pathway, over-expression of these repair enzymes enhances microsatellite instability (Colotta et al., 2009). Upregulation of NF- κ B and sustained production of cytokines cooperate with mutated p53 protein to enhance genomic instability (Fig. 17.1; Grivennikov et al., 2010; Cooks et al., 2014).

Tumour-associated inflammation is also linked with epigenetic alterations that lead to silencing of key tumour suppressor genes, such as *INK4a* or *p16* in lung cancers and malignant mesothelioma (Blanco et al., 2007; Christensen et al., 2009, 2010; Nelson et al., 2012). Oxidative damage to cytosine and chlorination

or bromination have been proposed to induce heritable epigenetic alterations due to cytosine methylation (Valinluck and Sowers, 2007). Chronic infection with *Helicobacter pylori* is also associated with hypermethylation and silencing of *p16* as well as *E-cadherin* (Kundu and Surh, 2012).

In summary, chronic or persistent inflammation favours accumulation of DNA lesions and chromosomal damage induced by persistent production of reactive oxygen species and reactive nitrogen species, impaired DNA repair pathways, and heritable epigenetic alterations, leading to activation of oncogenes and inactivation of tumour suppressor genes in devel-

oping tumours. Tumour-associated inflammation and genomic instability drive tumour growth and progression, which enable acquisition of the six core hallmarks of cancer (Hanahan and Weinberg, 2011).

Inflammation, fibrosis, and cancer

In 1986, Dvorak described cancers as “wounds that do not heal”, based on evidence of inflammatory cells infiltrating into tumours, accompanied by angiogenesis and fibrosis, similar to wound healing (Dvorak, 1986; see also Dvorak, 2015). Persistent infections accompanied by parenchymal cell injury and chronic inflammation, and fibrosis associated with

inhalation of crystalline silica or asbestos fibres promote tumorigenesis (Kuraishy et al., 2011). For example, persistent infection with hepatitis B or C virus can produce fibrotic scarring or cirrhosis in the liver, accompanied by nodules of regenerating hepatocytes, leading to development of hepatocellular carcinoma (El-Serag and Rudolph, 2007). Nodular fibrotic scarring of the lungs is characteristic of silicosis (Leung et al., 2012), and inhalation of asbestos fibres can cause diffuse fibrosis or asbestosis (Mossman et al., 2011). Pulmonary fibrosis has been associated with development of lung cancer (IARC, 2002; Laskin et al., 2011). Several mechanistic links between fibrosis and tumour development and progression have been proposed (Hanahan and Coussens, 2012).

Tissue fibrosis changes the normal architecture and compliance of the extracellular matrix, resulting in dense cross-linked connective tissue and increased stiffness (Liu et al., 2010). Excess extracellular matrix components, including heparan sulfate proteoglycans that bind to the CD44 receptor, are produced during cancer development and contribute to enhanced growth factor signalling and cell proliferation (Nasser, 2008). Disrupted assembly and disorganization of the extracellular matrix can alter polarity and differentiation of pre-neoplastic epithelial cells, facilitating their proliferation, migration, and invasion through the basement membrane (Lu et al., 2012).

Resident fibroblasts in connective tissues and mesenchymal stem cells, in local stem cell niches or recruited from the bone marrow, secrete epithelial and fibroblast growth factors as well as pro-inflammatory cytokines and chemokines that contribute to the tumour microenvironment

(Hanahan and Coussens, 2012). They are also a source of paracrine growth factors, including insulin-like growth factor 1 (IGF-1) and IGF-2, that promote survival of cancer cells, as well as a source of angiogenic factors that promote tumour angiogenesis (Lu et al., 2012).

Matrix metalloproteinases (MMPs), which accelerate the degradation or remodelling of the tumour stroma and the release of immobilized growth factors and cytokines, are frequently overexpressed in tumours. The gelatinases MMP-2 and MMP-9 are overexpressed by malignant tumour cells or stromal cells in a wide range of carcinomas, as well as by leukaemias and lymphomas. Activation of MMPs in the tumour microenvironment promotes tumour cell migration and invasion, release of sequestered growth factors, and activation of latent forms of cytokines including IL-1 β (Bauvois, 2012).

Tumour-associated macrophages and lymphocytes are major sources of cytokines in the tumour environment (Laskin et al., 2011; Balkwill, 2012). The phenotype of tumour-associated macrophages is shifted to a pro-fibrotic, pro-angiogenic phenotype, M2, characterized by production of arginase, IL-10, and TGF- β (Sica and Mantovani, 2012) as well as IL-23 (Grivennikov et al., 2010). The T-lymphocyte subset TH17 produces IL-17, which upregulates IL-23 expression in the tumour microenvironment. IL-23 is a key cytokine in tumour growth and invasion; it causes upregulation of MMP-9 expression and increases angiogenesis and fibrosis (Langowski et al., 2006). IL-17 also promotes liver fibrosis and activates hepatic stellate cells to produce collagen in murine models of toxic liver cell injury (Meng et al., 2012).

Resident tissue stem cells in adults occupy a specialized niche to maintain their polarity, self-renewal, and differentiation by anchoring to receptors in the basement membrane or in the extracellular matrix. Altered extracellular matrix organization and stiffness may disrupt this contact, allowing local expansion of the stem cell pool (Lu et al., 2012). These locally proliferating stem cells may give rise to cancer stem cells or tumour-initiating cells. Cancer stem cells express cell surface markers, including CD24, CD44, and CD133, which are thought to enhance growth and invasion as well as resistance to apoptosis (Keysar and Jimeno, 2010).

Summary and conclusions

Inflammation has been hypothesized to contribute to multiple stages in cancer development (Trinchieri, 2012). Sustained or persistent inflammation releases mediators that can damage DNA and hamper DNA repair, leading to cell transformation; it establishes a local microenvironment that allows the tumour to grow and metastasize, and to avoid immune destruction, thus preventing an effective immune response against the tumour (Mantovani et al., 2010).

Persistent or chronic inflammation, frequently in association with oxidative stress, is considered to be an established or likely mechanistic event contributing to human cancers associated with exposure to crystalline silica and asbestos fibres (IARC 2002; Shukla et al., 2003; Valavanidis et al., 2013) as well as diesel engine emissions and indoor coal combustion (Sood, 2012; Carlsten and Georas, 2014; Vermeulen et al., 2014). These inhalation exposures

are associated with lung cancer in humans and experimental animals, and asbestos fibres may also induce cancer at distant sites, including the mesothelial lining and the ovary (IARC, 2012a).

Persistent bacterial, viral, and parasitic infections (IARC, 2012b) are also associated with a variety of human carcinomas as well as leukaemias and lymphomas (Table 17.1 and Table 17.2). Persistent or repeated episodes of tissue injury and inflammation may also synergize with viral oncoproteins and the fungal

contaminant aflatoxin in the development of hepatocellular carcinoma (Kew, 2003; IARC, 2012b; Siment et al., 2012). In combination with potent carcinogens in tobacco smoke and smokeless tobacco (e.g. arylamines, polycyclic aromatic hydrocarbons, and nitrosamines), ethanol consumption may increase epithelial permeability and injury, which together with oxidative stress enhance the development of cancers of the oral cavity, larynx, and oesophagus (Bor and Capanoglu, 2009; IARC, 2012c). Exogenous environmental,

occupational, personal, and infectious exposures resulting in persistent or chronic inflammation are preventable, and modifying these circumstances of exposure would diminish the worldwide burden of cancer.

Acknowledgement

The author's research is supported by a National Institute of Environmental Health Sciences (NIEHS) Superfund Research Program grant, P42 ES013660.

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