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Abstract

Although inflammation is primarily a homeostatic response of tissues to damage by infectious, physical, or chemical agents, its persistence in a chronic form generates a profoundly modified environment that favors the occurrence of transformed cells and their progression to malignant cancer. Chronic inflammation is one of the hallmarks of most solid tumors and is a precursor condition in a wide range of pathologies including cancers of the colon, esophagus, stomach, or bladder. Chronic inflammation is characterized by persistent attraction of immune cells secreting specific mediators at the site of the lesions. These mediators include DNA-damaging radicals and cytokines and chemokines that enhance proliferation, stimulate the development of stromal cells, downregulate apoptosis, increase neo-angiogenesis and facilitate cell motility and invasion. Cytokines are produced in a large variety of forms with overlapping biological effects, operating within complex signaling networks. Of particular importance in cancer are interleukin-1 (IL-1), IL-6, tumor necrosis factor α (TNFα), chemokines and their receptors, as well as receptors of the death domain family. Resident cells at inflammatory sites adapt by producing factors that enhance their survival. One of these factors is cyclooxygenase-2 (COX-2), which is controlled by the interplay between p53 and nuclear factor kappa B (NFκB), two factors with broad roles in inflammatory responses. Thus, cancer may be seen as the consequence of a failure of a response primarily geared at wound healing. The mediators of inflammation offer a wide range of potential targets for preventive or therapeutic interventions.

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14.20 Inflammation in Carcinogenesis

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Abbreviations

5mC	5-methylcytosine
ADA	adalimutab
APP	acute phase protein
CLL	chronic lymphocytic leukemia
COX	cyclooxygenase
ETA	etanercept
FAP	familial adenomatous polyposis
FasL	FAS ligand
GCSF	granulocyte colony-stimulating factor
GMCSF	granulocyte-macrophage colony-stimulating factor
gp130	glycoprotein 130
H_2O_2	hydrogen peroxide
HPA	hypothalamic–pituitary–adrenal
IL	interleukin
INF	infliximab
IκK	IκB kinase
KSHV	Kaposi sarcoma-associated herpesvirus
LPS	lipopolysaccharide
MBV	mixed bacterial vaccine
MMP	matrix metalloproteinase
NFκB	nuclear factor kappa B
NO	nitric oxide
NOS	nitric oxide synthase
NSAID	nonsteroid anti-inflammatory drug
RA	rheumatoid arthritis
TAM	tumor-associated macrophage
TNF	tumor necrosis factor
TRAIL	tumor necrosis factor-related apoptosis-inducing ligand

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14.20.1 Introduction

p0005 Cancer develops as the consequence of complex interactions between genes and environment, during which mechanisms regulating DNA repair, cell proliferation, survival, metabolic autonomy, and invasiveness are altered in a coordinated manner (Hanahan and Weinberg 2000). This process is opposed by natural, physiologic responses. At the cellular level, these responses include cell detoxification which eliminates potential mutagens, DNA repair, and cell proliferation control, which effectively protect genetic and genomic

integrity. At the tissue and organ level, inflammation acts as the physiological response to injury caused by wounding, chemical or physical agents, or by infection, stimulating healing processes and facilitating the elimination of damaged cells. At the body level, immune responses act as barriers preventing the breakthrough of foreign biological agents as well as forces limiting the dissemination of modified cells.

p0010 Although primarily an acute and healing natural response, inflammation may become chronic and damaging in a number of pathological circumstances. It then induces DNA damage and mutagenesis, deregulated cell proliferation responses, and profound modifications of tissue architecture and angiogenesis fuelling cancer progression. It is considered that inflammation contributes to about 15% of the global cancer burden but this figure should be seen as an underestimate since inflammation is a component of a large proportion of many cancers caused by infections or exposure to chemical and physical agents (**Table 1**). In general, independently of the site of chronic inflammation, the longer it persists, the higher the risk of cancer.

p0015 Chronic inflammatory diseases are not automatically the precursors of cancer. Rheumatoid arthritis (RA), for example, is a chronic inflammatory condition which causes destruction of the joints through excessive growth and invasion of synovial tissues. RA synoviocytes exhibit many features of transformed fibroblasts, such as enhanced proliferation, deficient apoptosis, increased DNA damage, and loss of contact inhibition. They may even harbor mutations in cancer-related genes such as TP53. However, despite these cancer-like features, they do not become malignant and do not give rise to cancer.

p0020 This chapter provides an overview of how chronic inflammation contributes to cancer. First, it discusses the central concept of cancers as wounds that do not heal, illustrating how carcinogenesis arises as the consequence of the deregulation of processes that are geared toward healing. Second, it summarizes the role of inflammation in tumor initiation, and we provide an overview of the cytokine networks that are the main effectors of the effects of inflammation in tumor promotion and progression. Next, this chapter explains how cells react to their chronically inflamed environment and how the signaling pathways of inflammation response interfere with those of cell growth and survival control. Finally, a discussion is developed on inflammation control as target for cancer prevention and therapy.

14.20.2 Cancer as Wounds That Do Not Heal: Acute Versus Chronic Inflammation

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p0025 Over a century and a half ago the German physician Rudolf Virchow (1858) observed that cancers develop more frequently at the sites of chronic inflammation. A few years later he postulated that cancer develops as a result of the tissue inability to get rid of certain classes of irritants that cause tissue injury and inflammation (Virchow 1863). Over a century passed before Dvorak (1986) reformulated this concept as cancers are the wounds that fail to heal. Comparing the processes of wound healing and those of tumor stroma formation, Dvorak pointed out many similarities. In wound healing, platelets are the source of angiogenic factors and extracellular matrix components that reshape the environment to

t0005 **Table 1** Inflammatory conditions associated with cancer development

Malignancy	*Inflammatory stimulus/condition*
Bladder cancer	Schistosomiasis
Cervical cancer	Infection by Papilloma viruses
Ovarian cancer	Pelvic inflammatory disease
Gastric cancer	*Helicobacter pylori* induced gastritis
MALT lymphoma	*H. pylori*
Esophageal adenocarcinoma	Barrett's mucosa
Colorectal cancer	Inflammatory bowel disease, ulcerative colitis
Hepatocellular carcinoma	Chronic Hepatitis (B and C viruses); cirrhosis
Cholangiocarcinoma (biliary system)	Liver flukes
Bronchial cancer	Cigarette smoke
Mesothelioma	Asbestos
Kaposi's sarcoma	Human herpesvirus type 8

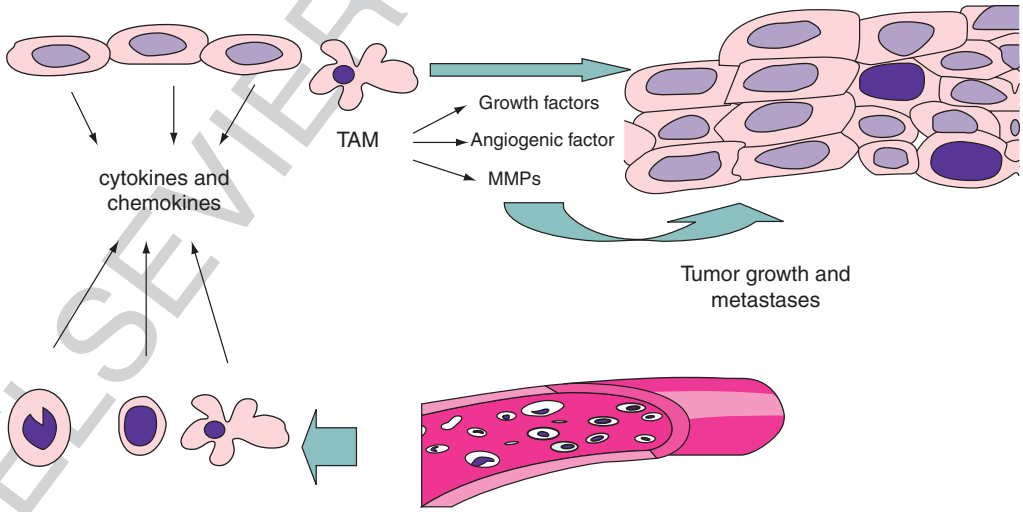
Balkwill, F.; Mantovani, A. *Lancet* **2001**, *357*, 539–545.

facilitate recovery. Similarly, tumor stroma forms a complex environment containing not only immune cells but also newly formed blood vessels, connective tissue, and extracellular matrix. The same cells provide growth, remodeling, and angiogenic factors in both processes. However, in cancer, this process is deregulated in a persistent and sustained way through the fact that malignant cells themselves secrete many of these factor ones to stimulate their continued growth and proliferation (Dvorak 1986).

p0030 Inflammation is essentially mediated by the attraction of cells secreting mediators from the circulation to the wounded sites (**Figure 1**). Two main types of inflammatory responses, acute and chronic, can be distinguished. They differ by their nature, duration, and long-term impact at cell and tissue levels.

p0035 Acute inflammation is an immediate emergency response that participates to safeguard and healing mechanisms. In response to physical or chemical irritants or to infection, acute inflammation initiates a cascade of cytokines and chemokines that attract immune and nonimmune cells, mainly neutrophils, to infiltrate disrupted and damaged tissue. Acute inflammation is usually self-limiting since proinflammatory cytokines stimulate counteracting anti-inflammatory responses as the initial irritant or infection threat recedes. Chronic inflammation develops as the consequence of persistent cell and tissue injury (Philip *et al.* 2004). The sustained infiltration of tissues by mononuclear cells, macrophages, lymphocytes, and plasma cells in addition to neutrophils generates a situation in which tissue destruction is partially compensated by cell renewal and proliferation, and accompanied by profound changes in tissue structure and vascularization. Although acute inflammation is an essentially protective response, chronic inflammation is one of the leading factors that cause cancer. This distinction between the role of chronic and acute inflammation in cancer has been recognized from the very beginning. In the footsteps of Virchow's initial insight that chronic inflammation can drive cancer development, Fehleisen (1882) and Bruns (1887) showed that acute inflammation may instead lead to tumor regression. A decade later, William Coley (1893) in the United States developed cancer therapeutic approaches using highly virulent strains of the bacteria *Streptococcus pyrogenes* to induce skin infection and acute inflammation. The Coley's toxins or similar combinations contained in mixed bacterial vaccines (MBV) became a standard treatment into the first half of twentieth century, only progressively phased out by the development of radiation and cytotoxic therapies.

p0040 In contrast to early recognition of different roles of chronic and acute inflammation in cancer development, it was more recently recognized that tumors may cause systemic immunosuppression. This is in



AU2 f0005 **Figure 1** Cells secreting inflammatory mediators and their role in cancer development. Tumor tissue secretes cytokines and chemokines, and the latter attract immune cells (neutrophils, monocytes, and macrophages) from blood vessels to the site of inflammation. Once monocytes reach the tissue, they differentiate into tumor-associated macrophages (TAMs), which secrete growth factors, angiogenic factors, and matrix metalloproteinases (MMPs) to promote tumor growth and progression to cancer by induction of angiogenesis and metastases. Balkwill, F.; Mantovani, A. *Lancet* **2001**, *357*, 539–545.

apparent contradiction to the fact that tumors often are highly reactive inflammatory sites in which high quantities of proinflammatory signals are produced. Such a systemic anti-inflammatory effect may be explained by several factors. First, increased number of receptors may either decoy or buffer the effect of proinflammatory mediators. Second, high levels of chemokines may lead to desensitization of immune cells normally responsive to such chemoattractants, or by increased amounts of anti-inflammatory mediators produced by tumors (Baniyash 2006). These mechanisms result in a continuous recruitment of leukocytes to tumor sites with a concomitant, decreased capacity to mount systemic inflammatory response. This decrease, in turn, may contribute to reduce tissue barriers to cell invasion and metastasis (Baniyash 2006).

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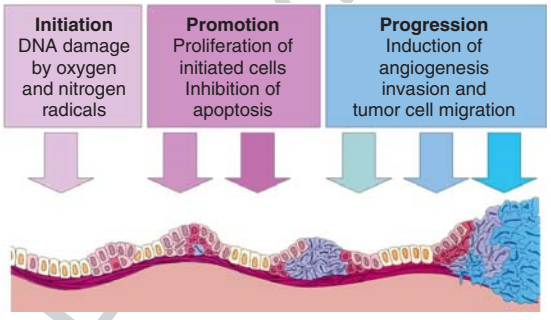
14.20.3 Inflammation, DNA Damage, and Mutagenesis

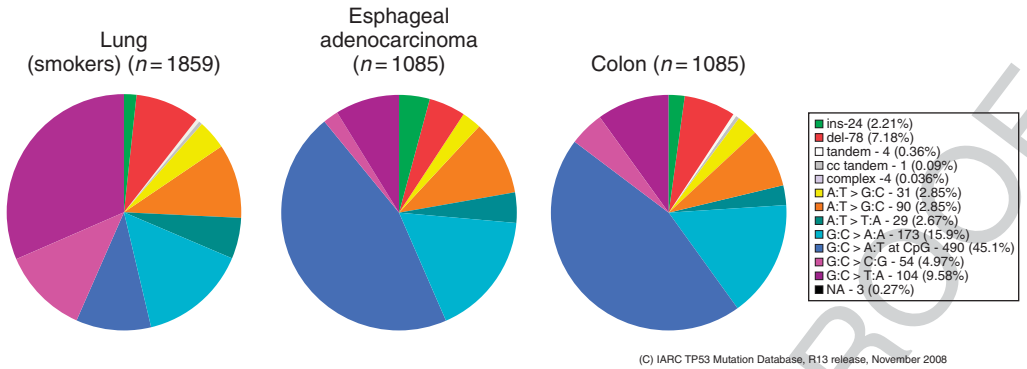
p0045 Studies on mechanisms of chemical carcinogenesis have led to the concept that cancer arises through three main mechanistic steps (Weinberg 2007), namely initiation (the process of acquisition of genetic and epigenetic changes that sets the cell on path to cancer), promotion (a step during which the primed cells express altered responses that provide a selective advantage allowing them to survive and develop locally), and progression (a series of steps during which the now established cancer cells accumulate further changes on the path to malignancy (**Figure 2**). Chronic inflammation contributes to each of these mechanisms. First, inflammation generates



f0010 **Figure 2** The role of inflammation in initiation, promotion, and progression stages of cancer development. The sequence of development of an epithelial tumor is represented and divided in three steps: initiation, promotion, and progression. The contribution of inflammatory mechanisms to each step is summarized.

an overload in reactive oxygen species (ROS) and reactive nitrogen species (RNS) that damage DNA and enhance several mutagenic processes, thereby accelerating the acquisition of mutations that drive the cancer process. Second, chronic inflammation involves the production of a complex combination of factors, some of which promote cell proliferation and survival, while others induce cell death. As a consequence of the effects of these factors, inflammation completely perturbs the normal patterns of cell differentiation, renewal, and replacement. Third, inflammation profoundly alters the relationships between cells and their stroma, and also enhances angiogenesis, thus facilitating local invasion and distal dissemination of cancer cells. In short, inflammation provides a biological context in which cells acquire mutations at a higher rate, while being submitted to intense biological pressure that eventually results in the selection of highly resistant, proliferative, and immortal cancer cells.

p0050 The main DNA-damaging reactive species produced during inflammation are hydrogen peroxide (H_2O_2), nitric oxide ($NO^{\cdot}$), and reactive intermediates such as hydroxyl radicals ($OH^{\cdot}$), superoxide ($O_2^{-\cdot}$), and peroxynitrite ($ONOO^-$). These radicals are released by neutrophils and macrophages. They act both as chemoattractants for other inflammatory cells and for vascular endothelial cells involved in neo-angiogenesis, as well as locally active toxicants which effectively destroy infectious agents and attack physical irritants. During inflammatory response, $NO^{\cdot}$ is also produced inside cells through the activation of the transcription of inducible nitric oxide synthase (NOS)-2 in response to cytokines. The promoter of NOS2 contains binding sites for nuclear factor kappa B (NFκB). Overproduction of $NO^{\cdot}$ causes two main mechanisms of mutagenesis. One is direct DNA damage through radical attack of DNA (generating DNA strand break, base damage, and chromosome damage). The second is enhanced deamination of 5-methylcytosine (5mC), the most common methylated form of cytosine representing about 3% of all cytosines in the genome. Deamination of 5mC into thymine generates a DNA mismatch (G:T) which, if not repaired, may result in a mutation (from a G:C base pair to an A:T base pair). Since 5mC preferentially occurs at CpG dinucleotides, this type of mutation is often found within this particular sequence context. Mutations at CpG dinucleotides are the most frequent form of single base substitutions in inflamed tissues and in cancers arising in an inflammatory context. For



f0015 **Figure 3** TP53 mutation patterns in carcinomas of the lung (smokers), esophagus, and colon. The high proportion of C:C to A:T transitions in esophageal and in colon adenocarcinoma is thought to reflect the role of hyperproduction of NO in enhancing the spontaneous deamination of methylated cytosine into thymine at CpG sites. In contrast, in lung cancers from smokers, a large proportion of the mutations are thought to result from DNA damage by tobacco carcinogens, as for example G:C to T:A transversions induced by polycyclic aromatic hydrocarbons. Data from IARC TP53 mutation database, http://www-p53.iarc.fr.

example, about 50% of mutations in the TP53 tumor suppressor gene occur at CpG dinucleotides in colon cancer and in adenocarcinoma of the esophagus – two cancers with well-defined inflammatory precursors. In contrast, in lung cancers of smokers where most of the DNA damage is thought to be caused by tobacco carcinogens, mutations at CpG sites represent only 15% of all mutations (**Figure 3**). The instability of 5mC has led to its counter-selection during evolution: this motif occurs in the genome five times less frequently than expected (Simmen 2008).

s0020 14.20.4 Proinflammatory Cytokines in Cancer Promotion and Progression

p0055 Inflammation induces deregulated cell growth conditions which operate both to promote and to select for cells that may have acquired oncogenic DNA damage, thus providing a mechanism for cancer progression. These deregulated conditions are set and developed through complex signaling processes mediated by proinflammatory cytokines. Cytokines are soluble factors that regulate all aspects of immune responses including homeostasis, lymphoid development, differentiation, tolerance, and memory. Cytokine signaling is initiated by binding to specific cell-surface receptors which triggers downstream intracellular signaling cascades resulting in activation of genes mediating the above responses. During inflammation, affected tissue (including stromal cells, endothelial, immune, and epithelial cells) produces specific cytokines and receptors, establishing complex signaling networks that determine the manifestation and symptoms of inflammation. Paracrine/autocrine signaling, affecting cytokine secreting cells (autocrine effect) or nearby tissues (paracrine effect), is characteristic for all cytokines. Very few, however, display endocrine signaling by activating the hypothalamic–pituitary–adrenal (HPA) axis, most notably IL-1β (Dinarello 2003). It has been proposed that systemic elevation of corticosteroids in response to such activation of HPA provides a negative feedback to limit excessive inflammatory stimulus, but the physiologic significance of this endocrine action may extend beyond this (Dinarello 2003).

p0060 Proinflammatory cytokines contribute to cancer promotion by acting as growth factors for initiated cells either directly or indirectly by recruitment of immune cells which in turn provide additional growth factors. Conversely, some cytokines act as antiapoptotic agents thereby prolonging survival of initiated cells. A critical mechanism in this process is activation of the transcription factor NFκB, which promotes cell proliferation and survival in conditions of DNA damage (Lin and Karin 2003). Furthermore, proinflammatory cytokines also play essential roles in cancer progression. In particular, tumors require formation of new blood vessels to sustain their growth in hypoxic conditions. Inflammatory cells infiltrating tumors, particularly tumor-associated macrophages (TAMs), contribute to tumor angiogenesis (Balkwill and Mantovani 2001; Leek *et al.* 1998). These cells also secrete matrix metalloproteinases (MMPs), enzymes that degrade extracellular matrix and release the initiated cells from their

anchorage in the surrounding tissue, thereby supporting migration (**Figure 1**). Angiogenic chemokines, predominantly by outweighing the balance with antiangiogenic chemokines, induce the formation of new blood vessels. Chemokines also support tumor cell migration and it has been suggested that tumor cells use chemokine gradients to spread either locally or around the body (Wang *et al.* 1998).

s0025 14.20.5 Signaling through Proinflammatory Cytokine Networks

p0065 Cytokines and their receptors display features that add to the complexity of cytokine signaling networks. In particular, they are pleiomorphic, redundant, and multifunctional (Vandenbroeck 2006). Their pleiomorphic nature helps them fulfill different roles. For example, interleukin-2 (IL-2) is a growth factor for T lymphocytes, B lymphocytes, and also NK cells (although at high, nonphysiological levels) (Nelson and Willerford 1998). In contrast, it also acts as suppressor of immune responses through its sensitization of activated T lymphocytes to undergo apoptosis (Chan *et al.* 2003). Many individual cytokines can bind to several related receptors, with the selection of the receptor depending on the presence of other cytokines in the microenvironment. Such flexibility can result in the ability of same cytokine to exert opposite effects, depending on the microenvironment. An even greater level of complexity is illustrated by the example of TNFα: this cytokine can achieve opposing effects (promote or suppress cell growth) by binding to the same receptor (TNFRI) (van Horssen *et al.* 2006), as discussed in detail below.

p0070 The redundant nature of cytokines is manifested by the fact that many of them can induce the same biological effects. Most often these cytokines are structurally related (belonging to the same cytokine family) and therefore may activate the same or similar receptors (examples in **Tables 2** and **3**). In addition, cytokine receptors are often composed of several subunits and one or several of these subunits may be shared among different receptors. For example, IL-6 signals through a receptor that contains gp130 as a subunit (Taga and Kishimoto 1997). Other cytokines including IL-11, IL-27, LIF, OSM, CNTF, CT-1, and NNT-1/BSF-3 also signal through receptors in which gp130 is a critical component. This shared component is responsible for overlapping biological effects between these cytokines.

p0075 A further degree of complexity arises from the fact that some cytokine receptors can exist in a cell-membrane-free form. In some instances, such soluble receptors participate in signaling. For example, IL-6Rα exists both as membrane bound and in soluble form. Upon binding of IL-6, to the membrane-bound form of the receptor, signaling is initiated through gp130. However, when soluble form of IL-6Rα is present, it can bind IL-6 and initiate signaling by using gp130 as cell-surface receptor, thereby enabling IL-6 signaling even in cells that do not express IL-6Rα on their surface (Taga and Kishimoto 1997). In many other instances, receptors can shed their extracellular (ligand binding) domains, thus producing soluble factors which act as decoys to capture cytokines and prevent their binding to the actual receptor. For example, IL-1 receptor I and II (Mantovani *et al.* 2001) can both have their extracellular domains cleaved and act as decoy. Even in its membrane-bound form IL-1RII is a decoy since its intracellular

t0010 **Table 2** Cytokine knock-out mice and cancer development

Cytokine/receptor	*KO and cancer risk*
TNFα	10 $\times$ fewer skin tumors than normal mice (Moore *et al.* 1999b)
TNFαRI	Resistant to skin carcinogenesis (Moore *et al.* 1999b), fewer hepatic metastasis, attenuated lymphoma development in lpr mice, fewer skin tumors after induction by UVB (Starcher 2000)
TNFαRII	Fewer skin tumors after induction by UVB (Starcher 2000)
IL-1β	IL-1β deficient mice do not develop metastases (Voronov *et al.* 2003)
IL-6	Both tumor growth and cachexia were attenuated in IL-6 KO mice (Cahlin *et al.* 2000) Knock in of human IL-6 in Balb/c mice leads to plasmacytomas (Woodroofe *et al.* 1992) and accelerated plasmacytomas in case of KI of both IL-6 and sIL-6R. This also leads to increased hepatic proliferation and may contribute to hepatocellular carcinoma development (Maione *et al.* 1998)
MCP-1/CCL2	Knock out in mice genetically prone to mammary carcinoma delayed tumor appearance, decreased tumor growth, and prolonged survival

domain is not coupled with intracellular signaling (Mantovani *et al.* 2001). Interestingly, the IL-1 family includes also a natural antagonist, IL-1RA.

p0080 Yet another important feature of these multifunctional cytokines is that they can be induced by a variety of different stimuli. For example, IL-6 can be induced by trauma, injury, infection, inflammation, as well as a consequence of a disease, such as rheumatoid arthritis (RA) or cancer (Nishimoto and Kishimoto 2004). Therefore upregulation of circulating levels observed in many types of cancer should be interpreted with caution. In contrast, individual susceptibilities, depicted as single nucleotide polymorphisms in cytokine genes that affect the expression of their respective proteins, tend to reflect a life-long exposure and may serve as a better estimate of cancer risk.

s0030 14.20.6 Major Cytokines Involved in Cancer Development

p0085 The importance of cytokines in cancer development is underlined by the consequences of their functional inactivation by homologous recombination in mice (**Table 2**). This section briefly describes the roles and relevance to cancer of several major cytokine players.

s0035 14.20.6.1 Tumor Necrosis Factor Alpha

p0090 TNFα is a pleiomorphic cytokine involved in inflammation, apoptosis, cell survival, and immunity. It exerts its effects through two receptors, TNFRI and TNFRII. While TNFRI is present on almost all cells, TNFRII is mainly confined to immune and endothelial cells (Aggarwal 2003). The major difference between the two receptors is that TNFRII lacks the so-called death domain of TNFRI, which mediates apoptosis, and is therefore unable to induce this particular response (Ashkenazi and Dixit 1998). These receptors are also used by lymphotoxin, a cytokine also known as TNFβ. TNFRI is the prototype of a family of proapoptotic receptors that include, among others, FAS/CD95 receptor and KILLER/DR5.

p0095 TNFα was named after its discovery in serum of animals treated with lipopolysaccharide (LPS) (Carswell *et al.* 1975), in which such treatment induced necrotic lesions of tumors and was associated with cancer-related cachexia. While named for its antitumor activity, subsequent studies revealed the AU3 TNFα paradox – that when TNFα is chronically produced, it causes proliferation, invasion, and metastasis of tumor cells. The two opposing effects, proliferation and apoptosis, are mediated via TNFRI. Despite well-characterized intracellular signaling leading to either activation of NFκB and cell proliferation or activation of caspases and apoptosis, the molecular basis of such life–death signaling decisions remain poorly understood (van Horssen *et al.* 2006). The path that each cell takes depends on which type(s) of TNF receptor is expressed at the cell's surface as well as on which accessory proteins are present, either as the result of normal tissue-specific gene expression patterns or as the consequence of mutations (Caligiuri and Lotze 2007). Locally, AU4 TNFα stimulates its own synthesis as well as the production of other inflammatory cytokines including IL-1, IL-6, and chemokines that contribute to sustain proinflammatory signals. In addition to paracrine/autocrine signaling, TNFα is one of the few cytokines with endocrine function. Its systemic effects induce systemic signs of inflammation including fever and production of acute phase proteins (APPs) in the liver. Administration of high levels of TNFα to animals leads to a state similar to septic shock.

p0100 In cancer, TNFα is thought to be one of the key mediators of cachexia, a wasting condition associated with anorexia and establishment of a net catabolic state. Also, it is widely accepted that TNFα secreted by tumors and TAMs promotes cell growth. Mice deficient in TNFα are resistant to chemically induced skin carcinogenesis (Moore *et al.* 1999b). Overall, the dose of TNFα is critical for distinguishing between tumor promoting and tumor regression effects: the tumor promoting effect is achieved at much lower doses than the tumor regression effect (Caligiuri and Lotze 2007). Both the FAS ligand (FasL) and its receptor (FAS/CD95) are extensively deregulated in many carcinomas, with increased expression of the ligand and downregulation of the receptor (GRATAS).

14.20.6.2 Interleukin-1 s0040

p0105 IL-1 shares many biological effects with those of TNFα. There are two forms of IL-1: IL-1α and IL-1β, both synthesized as precursors that are cleaved by caspase-1 to yield functional proteins. IL-1α is predominantly intracellular, while IL-1β is secreted and exhibits paracrine/autocrine effects, as well as endocrine effects similar to TNFα. There are

also two types of IL-1 receptors, IL-1RI and IL-1RII. However, only IL-1RI is capable of active signaling, while IL-1RII appears to serve as a decoy. In addition, each receptor can shed its extracellular portion, producing a soluble form also acting as decoy receptor (Mantovani *et al.* 2001). IL-1 is the only cytokine with a natural antagonist, IL-1 receptor antagonist (IL-1RA). Like TNFα, IL-1β is induced by bacterial products (LPS), induces proinflammatory cytokines and APPs in the liver, as well as systemic effects through HPA activation. In addition, nonmicrobial factors such as cytokines and irradiation can also induce IL-1β (Vandenbroeck 2006). However, unlike TNFα, IL-1β does not directly induce apoptosis but interferes with TNFα signaling in certain conditions (Dinarello 1996; Last-Barney *et al.* 1988; LeGrand *et al.* 2001; McGee *et al.* 1995; Wankowicz *et al.* 1988). In particular, IL-1β downregulates and stimulates shedding of TNFRI, thereby indirectly interfering with activation of intracellular signals leading to apoptosis (Brakebusch *et al.* 1994; Caligiuri and Lotze 2007; Holtmann and Wallach 1987).

p0110 In cancer, IL-1 may contribute to tumor promotion by its indirect antiapoptotic effects as well as by its direct effect as an autocrine growth factor (Caligiuri and Lotze 2007). These effects are mediated by its induction of granulocyte colony-stimulating factor (GCSF) and granulocyte-macrophage colony-stimulating factor (GMCSF) (Neta *et al.* 1987). Further support comes from the observation that IL-1β is not produced by peripheral blood cells of healthy individuals (Mileno *et al.* 1995), but is detectable in leukemic cells, including AML and CML (Kurzrock *et al.* 1993). A similar constitutive expression of IL-1α and IL-1β has also been observed in many different types of cancer (Alexandroff *et al.* 1994; Burger *et al.* 1994; Castelli *et al.* 1994; Tyler *et al.* 1995; von Schweinitz *et al.* 1993). As opposed to such chronic expression, it has been shown *in vitro* that acute stimulation by IL-1β leads to growth inhibition of many different types of cancer cells (Hanauske *et al.* 1992; Herzog and Collin 1992; Kilian *et al.* 1991; Lachman *et al.* 1986; Onozaki *et al.* 1985). Evidence from a mouse model suggests that IL-1 is required for tumor invasiveness and angiogenesis: mice deficient in IL-1 have greatly impaired neo-angiogenesis after injection of several different types of cancer cells (Voronov *et al.* 2003). Its central role in metastases is underlined by evidence suggesting that IL-1 primes animals for metastasis after injection of exogenous tumor cells (Bani *et al.* 1991; Giavazzi *et al.* 1990), primarily through the induction of adhesion molecules facilitating stromal invasion and entry of tumor cells into the vascular circulation (Bevilacqua 1993; Lauri *et al.* 1991).

14.20.6.3 Interleukin-6 s0045

p0115 IL-6 is predominantly considered as a growth-promoting and antiapoptotic factor (Ishihara and Hirano 2002). It is induced by TNFα and IL-1β. Conversely, IL-6 strongly inhibits TNFα, forming a negative feedback loop which inhibits excessive activation of proinflammatory cascades (Ferra *et al.* 1998). Therefore, IL-6 can exhibit both pro and anti-inflammatory effects and does not conform to strict classification into either proinflammatory or anti-inflammatory cytokine groups (Moller and Villiger 2006). Similar to its inducers, IL-6 has a broad range of biological activities on a wide range of target cells. This cytokine was discovered as a factor that induces antibody production in B cells. Circulating levels of IL-6 rise in response to infection, trauma, inflammation as well as in patients with chronic inflammatory diseases (Crohn's disease, Castleman's disease, rheumatoid arthritis) (Nishimoto and Kishimoto 2004). IL-6 receptor is a heterodimer consisting of IL-6Rα and the glycoprotein 130 (gp130). Some of the features of IL-6 receptor have been discussed above.

p0120 In cancer, IL-6 is involved in cell cycle progression and inhibition of apoptosis (Haura *et al.* 2005) and has been suggested to play a pivotal role in pathogenesis of Kaposi sarcoma, multiple myeloma, as well as Hodgkin lymphoma (Bommert *et al.* 2006; Cozen *et al.* 2004; Osborne *et al.* 1999). In multiple myeloma, the level of expression of IL-6 correlates with the severity of the disease and myeloma cells often display a strict dependence upon IL-6 to grow in culture. The Kaposi sarcoma-associated herpesvirus (KSHV) encodes a viral form of IL-6 (Aoki *et al.* 2001) that is thought to play a key role in the pathogenesis of Kaposi syndrome pathogenesis. This observation has led to speculation of a possible role of KSHV in the etiology of multiple myeloma. However, most studies addressing this question have reported negative results.

14.20.6.4 Chemokines s0050

p0125 Chemokines are a subset of cytokines with a property to attract immune cells. Thus far, the human chemokine system includes over 50 chemokines and 18

chemokine receptors (Moser and Loetscher 2001). They are classified into four subfamilies based on their NH_2-terminal cysteine motifs: C, CC, CXC, and CXXXC. Recently, a physiological classification emerged taking into account conditions of chemokine secretion and cellular distribution of their receptors. This classification distinguishes between inflammatory (or inducible) and homeostatic (or constitutive) chemokines, although discrimination between the two groups is not absolute, with three chemokines belonging to both groups (Zlotnik and Yoshie 2000). The major inflammatory chemokines and their receptors are listed in **Table 3**.

p0130 Inflammatory chemokines are produced by inflamed tissue, including resident cells and infiltrating immune cells upon induction by proinflammatory cytokines or following a contact with pathogens. They attract effector cells such as monocytes, granulocytes, and effector T cells to the site of inflammation. CXC chemokines can be further divided based on the presence of ELR (glutamine–lysine–arginine) motif into angiogenic and angiostatic chemokines (**Table 4**). As previously described for cytokines, different chemokines can act through the same receptors, as well as use multiple receptors and thereby activate distinct pathways (**Tables 3** and **4**). For example, angiogenic signals are achieved via CXCR2, but not CXCR1 receptor (Addison *et al.* 2000).

p0135 In cancer, angiogenic chemokines are critical for tumor growth and metastasis, since they provide signals for development of new blood vessels. This has been shown for prostate cancer: growth of prostate cancer cells injected into SCID (immunotolerant) mice was significantly attenuated if the angiogenic chemokines (CXCL1 or CXCL8) were blocked (Moore *et al.* 1999a). Likewise, prostate cancer cells engineered to overexpress CXCL8 (also known as

t0015 **Table 3** Inflammatory chemokines and their receptors

Current nomenclature	*Old nomenclature*	*Receptor(s)*
CCL1	I-309	CCR8
CCL3	MIP-1α	CCR1, CCR5
CCL4	MIP-1β	CCR5
CCL5	RANTES	CCR1, CCR3
CCL2	MCP-1	CCR2
CCL8	MCP-2	CCR2, CCR3, CCR5
CCL7	MCP-3	CCR2, CCR5
CCL13	MCP-4	CCR2, CCR5
CCL11, CCL24, CCL26	Eotaxin-1, -2, and -3	CCR3
CCL28	MEC	CCR5
CXCL9	MIG	CXCR3
CXCL10	IP-10	CXCR3
CXCL11	I-TAC	CXCR3
CXCL16	SCYB16	CXCR16
CX_3CL1	Fractalkine	CX_3CR1

t0020 **Table 4** Chemokines with angiogenic and angiostatic activities and their receptors

Angiogenic CXC chemokine	*Old nomenclature*	*Receptor(s)*
CXCL1	GROα	CXCR1, CXCR2, DARC
CXCL2	GROβ	CXCR2, DARC
CXCL3	GROγ	CXCR2, DARC
CXCL5	ENA-78	CXCR2
CXCL6	GCP-2	CXCR1, CXCR2,
CXCL7	NAP-2	CXCR2, DARC
CXCL8	IL-8	CXCR1, CXCR2, DARC
CXCL4	PF4	CXCR3, integrins
CXCL9	MIG	CXCR3
CXCL10	IP-10	CXCR3

IL-8; see **Table 4**) were significantly more tumorigenic and metastatic as compared to controls (Inoue *et al.* 2000). CXCL8/IL-8 was initially described as neutrophil chemoattractant (Matsushima *et al.* 1988) and was subsequently shown to possess mitogenic and angiogenic properties (Koch *et al.* 1992). Overexpression of CXCL8 correlates with tumor stage, tumor progression, and recurrence in many different cancers (Yuan *et al.* 2005). In addition, many chemokines have antiapoptotic effects, as for example CXCL8 in chronic lymphocytic leukemia (CLL) (Francia di Celle *et al.* 1996) and ovarian cancer (Abdollahi *et al.* 2003); CXCL12 in glioblastoma (Zhou *et al.* 2002), pancreatic adenocarcinoma (Marchesi *et al.* 2004), CLL (Burger *et al.* 2000), and small cell lung carcinoma (Hartmann *et al.* 2005); and CCL25 in T cell acute and CLL (Qiuping *et al.* 2004).

s0055

14.20.7 Inflammation Signaling and Subversion of Growth Control: Interactions between NFκB and p53

p0140 Resident cells caught in a chronic inflammatory environment are submitted to an onslaught by cytokines, chemokines, and reactive oxygen and nitrogen species that stimulate a wide range of intracellular signaling cascades and counteracting cellular responses. Two ubiquitous transcription factors emerge as central contenders in mediating, integrating, and balancing these signals: NFκB and p53. Both factors have a remarkable number of common molecular and biochemical features. Although these two factors are not related at the gene level, they share similar molecular architectures and DNA-binding patterns, striking rapid induction in response to a wide number of extracellular and intracellular stress signals, and capacity to transactivate large repertoires of genes that regulate stress responses, growth control, and cell survival, including several genes common to both NFκB and p53 repertoires. They may be seen as sister molecules. To a large degree, the molecular mechanisms by which chronic inflammation causes cancer are rooted in the deregulation of the delicate balancing act by which they cooperate in the control of cell death and regeneration (de Moraes *et al.* 2007; Lee *et al.* 2007).

p0145 NFκB is a dimeric factor composed of subunits belonging to a family of molecules including p65 (Rel A) and p50, p68 (Rel B) and/or p75 (c-Rel), and p52 subunits (Miyamoto and Verma 1995; Verma *et al.* 1995). The canonical NFκB factor is composed of the p65/p50 heterodimer and the alternative form involves p68/p52. In the absence of inducing stimuli, the p65/p50 homodimer is retained in the cytoplasm by the inhibitory subunit IkappaB (IκB), acting as an anchor. Upon exposure to various inflammatory and oxidative stress signals, activation of the IκB kinase (IκK) leads to the sequential phosphorylation and degradation of IκB to release of p65/p50 for translocation to the nucleus where it exerts its transcriptional control activities (Baldwin 1996; Karin and Greten 2005).

p0150 The p53 tumor suppressor assembles as a homotetramer which also accumulates in the nucleus in response to many stress signals. The mechanism of accumulation, however, differs from that of NFκB. In the absence of inducing signals, p53 protein constitutively relocates to the nucleus but undergoes rapid nuclear export and proteosomal degradation mediated by the Mdm2 protein. In response to formation of DNA damage and to multiple other physiological stresses such as hypoxia or depletion of ribonucleotides, p53 becomes phosphorylated and acetylated, leading to its release from Mdm2-mediated nuclear export degradation and its accumulation as an active transcription factor in the nucleus.

p0155 Many of the signals that induce NFκB also induce p53. Activation of NFκB enhances proliferation and AU6 expression of antiapoptotic genes, thus mediating a survival response which is essential for maintaining the viability and regeneration of cells exposed to chronic inflammation. In contrast, activation of p53 results in the transcriptional regulation of genes collectively involved in cell cycle arrest, DNA repair, apoptosis, and differentiation. The consequences of p53 induction may depend upon the nature and intensity of the signals, the cell type, and the cell's particular history. While stem and progenitor cells with high proliferative potential tend to undergo apoptosis, cell cycle arrest (perhaps coupled with DNA repair) is the primary response in differentiated cells. Inactivation of p53 by mutation or deletion of TP53 (the gene encoding p53, located on chromosome 17p13), or by other mechanisms is one of the hallmarks of cancers.

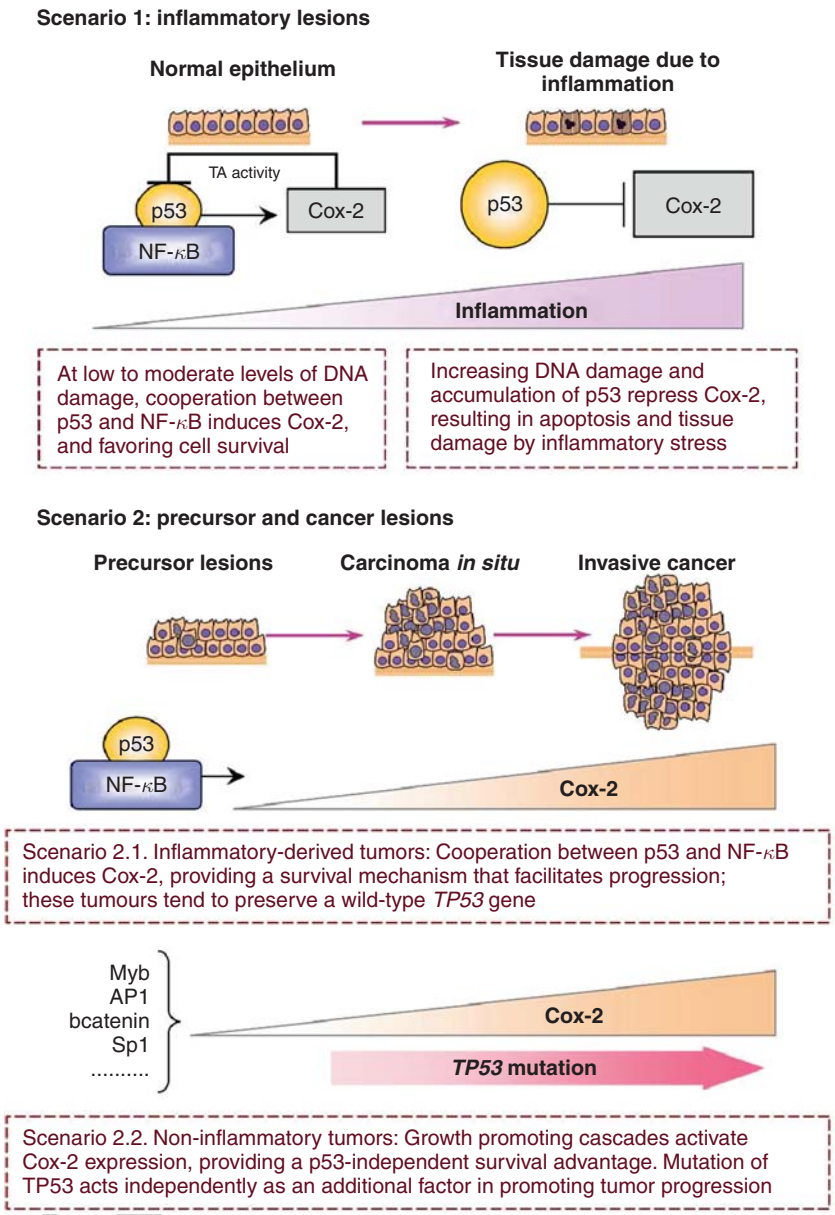
p0160 To a large extent, the NFκB and p53 pathways mediate opposing effects, the balance of which determines cell decisions between life and death. Mutation of TP53 by radical species produced during inflammation may break this balance, thus leaving NFκB run the show to push the cells toward uncontrolled proliferation. However,

NFκB and p53 are not simply acting to counteract one another; they also cooperate in the regulation of genes involved in specific aspects of inflammatory responses, as for example the gene encoding cyclooxygenase-2 (COX-2). There is evidence that p53 can transactivate COX-2 by recruiting NFκB onto its cognate response element in the COX-2 promoter (which does not contain a typical p53 response element). Whether the mechanism involves direct complex formation between the two factors or indirect interactions through common coactivators of transcription is still an open and controversial issue.

p0165 COX-2 is the inducible member of a family of closely related genes encoding heme-containing glycoproteins that catalyze the conversion of arachidonic acid to precursors of prostaglandins, prostacyclins, and thromboxanes. The COX-2 protein is the main pharmacological target of nonsteroidal anti-inflammatory drugs (NSAIDs). The mechanisms by which COX-2 contributes to cell proliferation include (1) synthesizing prostaglandins acting as antiapoptotic, survival factors (Tsujii and DuBois 1995); (2) metabolizing arachidonic acid, a proapoptotic substrate that activates caspase-3 and modulates mitochondrial permeability (Scorrano *et al.* 2001); (3) increasing the expression of the antiapoptotic protein Bcl-2 (Liu *et al.* 2001; Tsujii and DuBois 1995); (4) activating the serine threonine kinase Akt (Arico *et al.* 2002). In contrast, COX-2 also induces the expression of the suppressive factors Gadd153 (Kim *et al.* 2006) and Fas (Ivanov and Hei 2006), sensitizes cells to the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) (Martin *et al.* 2005), and decreases the levels of survivin, a protein that inhibits apoptosis by interfering with the function of caspases 3 and 7 (Ferreira *et al.* 2002; Krysan *et al.* 2004). Overexpression of COX-2 is a common feature in many epithelial tumors and is generally associated with poor prognosis, although its value as an independent marker of prognosis is not established.

p0170 **Figure 4** illustrates several scenarios by which p53 and NFκB may cooperate in the regulation of COX-2 in inflammatory or in cancer cells. In inflammatory lesions, both NFκB (mainly in response to inflammatory cytokines) and p53 (mainly as a consequence of DNA damage by reactive oxygen and nitrogen species) may be activated simultaneously. Cells faced with such conditions need to keep p53 in check to prevent excessive apoptosis, which would result in acute cell and tissue destruction. Cooperation between p53 and NFκB to upregulate COX-2 thus provides a failsafe mechanism by which cells protect themselves against p53-induced apoptosis (**Figure 4**). It should be noted that NFκB can fully activate COX-2 in the absence of p53; thus, the role of p53 in this partnership may be to connect NFκB to pathways that do not by themselves activate it, namely the pathways of response to DNA damage. In precursor and cancer lesions that arise in a chronic inflammatory background, this delicate balance may be upset by mutations. At least two distinct mechanisms of upregulation of COX-2 expression may operate in such lesions (**Figure 4**). In precursor lesions such as Barrett's esophagus or ulcerative colitis, cells may retain a functional regulatory cross talk between wild-type p53 and COX-2 as survival mechanism that tone down p53 and facilitates progression toward neoplasia. Cancers occurring in this context may, in their early stages, retain wild-type *TP53* in conjunction with high COX-2 expression, as observed for example in adenoma of the colon. At later stages of tumor progression, however, wild-type p53 may not be required to maintain a COX-2-dependent protection against apoptosis, either because COX-2 becomes activated by mechanisms independent of p53 and NFκB, or because cells have acquired other modifications allowing them to escape apoptosis.

p0175 Given the powerful role of COX-2 as a survival factor in cells exposed to stress, it is not surprising that its expression may be constitutively activated in many cancers where inflammation does not play a significant role as precursor but may nevertheless arise as a consequence of cancer development. In such cancers, increased expression of COX-2 may occur in response to promoter activation by growth promoting signaling cascades involving genes often mutated in cancer cells such as Wnt/βCatenin, KRAS, or c-MYB. In this case, COX-2 activation appears to be independent of NFκB and may coexist with *TP53* mutation in the same cell, contributing synergistically to the inhibition of apoptosis. Indeed, a review of the literature on COX-2 expression in relation with TP53 mutation suggests that tumors in which both events occur often have very poor prognosis. These cancers include squamous cell carcinomas of the upper airways and digestive tract.



f0020 **Figure 4** Cross talks between p53 and nuclear factor-kappaB (NF-κB) in the regulation of cyclooxygenase-2 (Cox-2) inflammatory lesions and in cancer. Different scenarios are represented to account for Cox-2 overexpression in inflammatory lesions and in cancer cells. See text for detailed explanations. Scenario 1: inflammatory lesions. Scenario 2: precursor and cancer lesions. De Moraes, E.; Dar, N. A.; de Moura Gallo, C. V.; Hainaut, P. *Int. J. Cancer* **2007**, *121*, 929–937.

s0060 14.20.8 Inflammation as Target for Cancer Prevention and Treatment

p0180 The mechanisms of inflammation are a rich source of potential targets to control cancer occurrence and development. Two main mechanisms have been the focus of much attention: the first is the blockade of specific components of the cytokine and chemokine networks and the second is the pharmacological inhibition of COX-2 using nonsteroidal anti-inflammatory drugs (NSAIDs).

s0065 ### 14.20.8.1 Antagonists of TNFα and Other Components of Cytokine Networks

p0185 Since their first licensing for clinical use in 1998, TNFα antagonists have shown remarkable efficacy in the treatment of several chronic inflammatory diseases such as RA or Crohn's disease. Three such antagonists have been extensively tested in randomized trials on large groups of patients with chronic inflammatory disease. Two of them, Infliximab (INF) and Adalimutab (ADA), are monoclonal antibodies. The third, Etanercept (ETA) is a soluble receptor antagonist consisting of a dimmer of extracellular domains of the human p75 type II TNFα receptor (TNFRII), linked to the Fc portion of a human IgG1. These antagonists operate through their ability to bind and neutralize soluble TNFα and to prevent ligand binding by TNFR. Recently, it has also been shown that these antagonists may also work by affecting intracellular signaling, increasing cell cycle arrest and apoptosis, downregulating the production of other cytokines, and reducing angiogenesis. These effects may be useful in cancer therapy at three levels. First, in precursor inflammatory lesions, they may decrease the promoting effect of inflammatory stress and thus prevent the emergence of malignant lesions. Second, in cancer patients, they may effectively reduce cancer growth and tumor angiogenesis. Third, at the systemic level, they may contribute to reduce or limit cachexia. There are, however, considerable variations in the effects of these antagonists according to inflammatory diseases, as well as individual variations among patients and further studies are needed to establish the impact and place of TNFα antagonist in multimodal cancer therapy. Other components of the cytokine/chemokine networks are promising targets for cancer therapy, including in particular IL-6 and death receptor ligands other than TNFα such as FasL and TRAIL. Recombinant forms of these ligands have shown their capacity to potentiate chemotherapeutic drug effects in preclinical models. Thus, one of the applications of such molecules would be to limit or overcome resistance to cytotoxic therapies using either conventional or targeted drugs. NFκB inhibition, due to its central role in cytokine signaling, has also been an interesting target to induce apoptosis (Karin 2006). However, mere inhibition of NFκB proved inefficient in inducing apoptosis, unless combined with other apoptosis-inducing drugs or radiation as is now considered as an adjuvant therapy along other cancer therapies (Karin 2006). Many specific NFκB and IκB inhibitors are currently being tested.

14.20.8.2 Inhibitors of Cyclooxygenase 2 s0070

p0190 The role of NSAIDs, either selective for COX-2 inhibition or nonselective, has been examined as chemopreventive agents in colorectal cancers in many large prospective studies. However, gastrointestinal side effects limit their use as chemopreventive agents in inflammatory bowel disease, a disease increasing the risk of colorectal cancer development. In contrast, patients with familial adenomatous polyposis (FAP), another CRC predisposing condition, tolerated COX-2 specific inhibitor Celecoxib very well. The initial clinical trial using Sulindac, a nonselective COX-1 and COX-2 inhibitor, showed a significant reduction in polyp number and size (Waddell *et al.* 1989), sparking a large multicenter study to examine its efficacy in the secondary prevention of polyps. Indeed, Sandler *et al.* (2003) showed that high dose aspirin was effective in preventing adenoma in patients previously treated for CRC. Sulindac was also used successfully in treating adenomas in FAP (Giardiello *et al.* 1996). This success opened the way to examining its use in ongoing multicenter trials in secondary prevention of other premalignant lesions, including oral leukoplakia, Barrett's esophagus, and actinic keratosys. There is strong evidence that a protective effect also exists in the case of several other cancers in which chronic inflammation plays a causal role. However, recent randomized study on Celecoxib for the prevention of sporadic adenoma curbed the enthusiasm showing that high dose of Celecoxib increased mortality from cardiovascular events (Solomon *et al.* 2005). Therefore, routine use of NSAIDs for prevention of CRC in the general population is not recommended (Dube *et al.* 2007). More recent trials are focusing on using NSAIDs in combination with other chemopreventive agents for CRC prevention (Barry *et al.* 2006; Meyskens and Gerner 1999; Nie *et al.* 2005).

14.20.9 Conclusions and Perspectives s0075

p0195 The frequent occurrence of cancer at sites of chronic inflammation can be interpreted as an application at the tissue level of the Darwinian theory of natural selection. Chronic inflammation may be compared to a tissue's ecological catastrophe in which a highly perturbed environment results in enhanced mutagenesis and in strong selection pressure to favor the emergence of cells having acquired the capacity to survive and proliferate in a perturbed environment. Cancer cells that

occur and develop in such conditions thus illustrate the principle of the survival of the fittest. However, a further twist in the story of inflammation and cancer is that cancer cells become themselves the source of mediators of inflammation, resulting in profound modification of tissue architecture and angiogenesis that facilitates invasion and dissemination of cancer. Thus, if inflammation is one of the main causes of cancer, it is also an extremely common consequence of the development of cancer. The complex networks of signals that regulate inflammatory responses still hold many secrets. During the past 25 years, considerable progress has been made in identifying cytokines and their receptors and in understanding the basic components of their signaling cascades. However, the interconnections, feedbacks, and cross talk between these cascades are still largely unknown. One of the most challenging questions is to identify the detailed cross talk between signaling by cytokines, by receptors involved in innate and acquired immune responses, and by growth factors. Another critical aspect will be to understand the mechanism by which inflammation modifies epithelium–mesenchyme interactions, as well as its impact on progenitor and stem cells which may be at the origin of the transformation process.

p0200 Together with control of cancer-causing infections, control of inflammation represents the most promising approach for pharmacological prevention of cancer. The chemopreventive effect of NSAIDS in colorectal carcinogenesis and other common cancers provide a proof of this principle. Another important aspect will be to understand and assess the impact of individual variations in inflammatory responses and their impact on cancer risk. Finally, the fine variations in inflammatory responses may provide tools to better understand the impact of environmental factors in causing cancer, in particular in a context of persistent infections, which form the underlying condition in about 15% of all cancers worldwide.

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