Immunity
Review

Tumor Promotion via Injury- and Death-Induced Inflammation

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Inhibition of programmed cell death is considered to be a major aspect of tumorigenesis. Indeed, several key oncogenic transcription factors, such as NF-κB and STAT3, exert their tumor-promoting activity at least in part through upregulation of survival genes. However, many cancers develop in response to chronic tissue injury, in which the resulting cell death increases the tumorigenic potential of the neighboring cells. In this review, we discuss a resolution to this paradox based on cell death-mediated induction of tumor promoting inflammatory cytokines, which enhance cell survival and trigger compensatory proliferation in response to tissue injury.

Introduction

The idea that tissue injury and cancer are linked is not new. As far back as 1863, Rudolf Virchow hypothesized that previous tissue injury is required for tumor emergence (Mantovani et al., 2008). This hypothesis has gained recent support from clinical data revealing a strong association between chronic injury and subsequent tumorigenesis at the same site. For instance, alcohol abuse causes liver injury and increased risk of hepatocellular carcinoma (HCC). Betel nut chewing, cigarette smoking, and exposure to fine silica dust cause esophageal and lung damage and promote cancer development in these tissues, whereas chronic infection with *Helicobacter pylori* causes gastritis and stomach cancer (El-Serag and Rudolph, 2007; Hecht, 2002; Uemura et al., 2001). How does tissue injury promote tumorigenesis? Certainly mutagenesis, genomic instability, and epigenetic modifications are important in this relationship, but they can be insufficient. Because of strong similarities between key features of wound healing and tumor development, including stem cell and myofibroblast activation, enhanced cell proliferation, inflammation, and neoangiogenesis, it is tempting to postulate that chronic injury can result in an aberrant healing and regenerative response that ultimately promotes the expansion and progression of initiated cells. This idea has already been forwarded by Alexander Haddow who suggested that "tumor production is a possible overhealing" (Haddow, 1972) and Harold Dvorak who stated that "tumors are wounds that do not heal" (Dvorak, 1986).

Can the prevalence of inflammation be the link between tissue injury and cancer? Recent studies have highlighted the particular importance of inflammation in both processes. These studies have indicated that the role of inflammation extends far beyond protection of the injured tissue from infectious agents and removal of damaged cells. In fact, inflammation is critical to almost every phase of tissue repair and tumorigenesis. Thus, we put forth that injury causes inflammation, which in turn orchestrates wound healing and tissue regeneration. If the inflammation cannot be resolved or is chronically provoked by repetitive injury or other factors, the resulting unchecked wound healing process can promote cancer formation. This hypothesis is supported by a large body of data, which is briefly summarized below and depicted in Figure 1.

It should be noted that at least several different types of inflammation associated with tumorigenesis can be delineated (Grivennikov et al., 2010). Certain types of inflammation, such as tumor elicited inflammation, defined as recruitment of immune cells into a growing tumor, occur only in later stages of tumor development. Such inflammation may not be dependent on cell death preceding tumorigenesis and can be elicited by chemokines secreted by the tumor (Karin, 2005), but nonetheless can still influence later aspects of tumor progression. Tumor elicited inflammation may also drive metastatic progress as recent studies of breast and prostate cancers have demonstrated (DeNardo et al., 2009; Kim et al., 2009; Luo et al., 2007; Tan et al., 2011). However, it is entirely plausible that necrosis, resulting from hypoxia at the tumor core may be one type of "injury" signal that triggers, or at least contributes to, tumor-elicited inflammation. Despite the multiple facets of cancer-linked inflammation, this review is focused on the role of tissue injury and cell death as drivers for the inflammation that contributes to tumor initiation and early promotion. Other aspects of inflammation in cancer have been reviewed elsewhere (Grivennikov et al., 2010; Joyce and Pollard, 2009; Mantovani et al., 2008).

After injury, even when no infectious agents are present, immune cells quickly migrate into the injured tissue after vasodilatation and in response to chemokine gradients, classically described as the inflammatory stage of wound healing (Velnar et al., 2009). These cells promote healing by releasing cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6 that suppress further cell death, activate stem cells, and promote epithelial proliferation. For example, depletion of macrophages during the early and middle phases of skin wound repair results in attenuated epithelial proliferation and wound contraction (Lucas et al., 2010). The same cytokines are expressed by tumor-associated inflammatory cells and sometimes by cancer cells themselves and promote cancer cell proliferation while suppressing the death of premalignant cells (see below). Neovascularization during wound healing is critical for providing nutrients and oxygen to the newly remodeled tissue. After

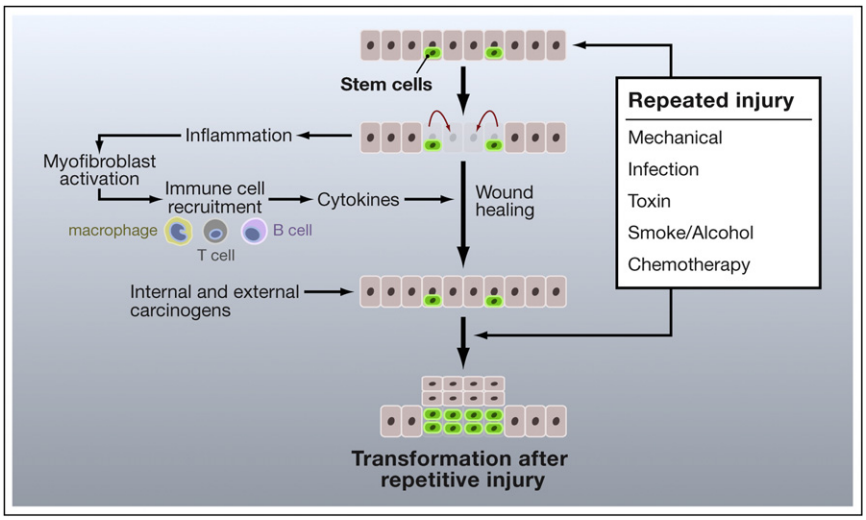

Figure 1. Tumorigenesis in Response to Chronic Tissue Injury of Different Types
Tissue injury and cell death lead to activation of various inflammatory cells that secrete cytokines that promote wound healing. However, if this process is reiterated several times or inflammation fails to resolve, tissue regeneration may be dysregulated and, when combined with carcinogen exposure, can lead to malignant transformation.

recruitment to the site of injury, inflammatory cells including macrophages and neutrophils secrete molecules such as vascular endothelial growth factor A (VEGFA) to promote blood vessel development and tissue remodeling (Bao et al., 2009). In tumors, inflammatory cells play a similar role by promoting neoangiogenesis (Lewis et al., 2000). In particular, VEGF-secreting macrophages are critical to tumor development, given that their depletion reduced vascular density in a breast cancer model (Stockmann et al., 2008). Fibroblast activation or the conversion of tissue fibroblasts into myofibroblasts, which engage in extracellular matrix (ECM) deposition and scar formation, is critical for wound healing (Wynn, 2008). The main activators of fibroblasts after tissue injury are M2-polarized macrophages that are recruited to the site of injury where they secrete factors such as platelet-derived growth factor (PDGF), connective tissue growth factor (CTGF), and transforming growth factor β (TGF-β). In tumorigenesis, cancer-associated fibroblasts (CAFs) have long been thought to promote malignant progression (Orimo and Weinberg, 2006). Although the origin of CAF and their mode of activation remain controversial, immune cell secretion of TGF-β may be instrumental, whereas CAF are essentially identical in their properties to myofibroblasts, especially in their ability to produce a large number of chemokines (Tan et al., 2011).

Not surprisingly, somatic stem cell activation is critical for tissue repair. For example, ablation of hair follicle stem cells leads to a complete hair loss after skin injury (Ito et al., 2005). Furthermore, pathways critical for stem cell maintenance and expansion, such as the Hedgehog and Wnt signaling pathways, are also important for injury repair and tumorigenesis (Beachy et al., 2004). Several studies have implicated inflammation in stem cell function. For example, cytokines such as TNF and IL-6 promote stem cell proliferation (Widera et al., 2006), and their transcriptional effectors NF-κB and STAT3 are involved in stem cell renewal (Matsuda et al., 1999) and cancer (Grivennikov et al., 2010). Much emphasis has recently been placed on cancer stem cells (CSCs), the functional homologs of somatic stem cells that are responsible for tumor initiation and regrowth after debulking (Lobo et al., 2007). Although still poorly explored, inflammation is likely to promote CSC maintenance and proliferation. Reactive oxygen species (ROS), possibly originating from inflammatory cells, can modulate self-renewal of chronic myeloid leukemia stem cells (Miyamoto et al., 2007). Furthermore, macrophages can promote CSC tumorigenicity through IL-6, STAT3, and the Hedgehog pathway (Jinushi et al., 2011) and IL-6, STAT3, and NF-κB can convert non-stem cells to CSCs (Iliopoulos et al., 2011). These findings lend support to the idea that cancer and wound healing progress through similar mechanisms, many of which are affected by inflammatory cytokines. However, an even stronger parallel between inflammation-promoted wound healing and cancer may be the role of inflammation in tumor recurrence. For example, partial hepatectomy, a preferred treatment for localized HCC, is initially successful, but within 5 years, recurrence rates approach 100% (Schwartz et al., 2007). Compensatory hepatocyte proliferation and HCC development depend on similar mechanisms in which IL-6 and STAT3 play key roles (He et al., 2010; Naugler et al., 2007). Similarly, the mainstay of advanced prostate cancer treatment is androgen deprivation therapy, which causes the death of androgen-dependent tumor cells. However, this therapy also promotes the recurrence of castration-resistant cancer (Gulley et al., 2003). We recently found that lymphotoxin (LT), a TNF family member expressed by tumor infiltrating B cells, plays a key role in this process (Ammirante et al., 2010). Thus, therapy-induced inflammation is likely to contribute to tumor recurrence, although it was also proposed to enhance therapeutic outcomes in other cases (Zitvogel et al., 2010).

In summary, although the complete details of the interconnection between injury, inflammation, and cancer are still being unraveled, there is substantial evidence that inflammation is essential in both tissue repair and cancer. In both cases, certain forms of cell death promote inflammation and inflammatory cytokines enhance tissue repair and tumorigenesis, in part, by suppressing the death of remaining neoplastic cells.

Inflammatory versus Noninflammatory Cell Death

The mechanisms by which tissue injury triggers inflammation are complex and not fully understood. Among initial triggers of injury-induced inflammation, necrotic cell death is of particular importance. However, the early distinction between necrotic cell death being inflammatory and apoptosis being an anti-inflammatory form of cell death has become somewhat diffuse. Below, we briefly review mechanisms that link local injury and cell death to induction of inflammation and cytokine production

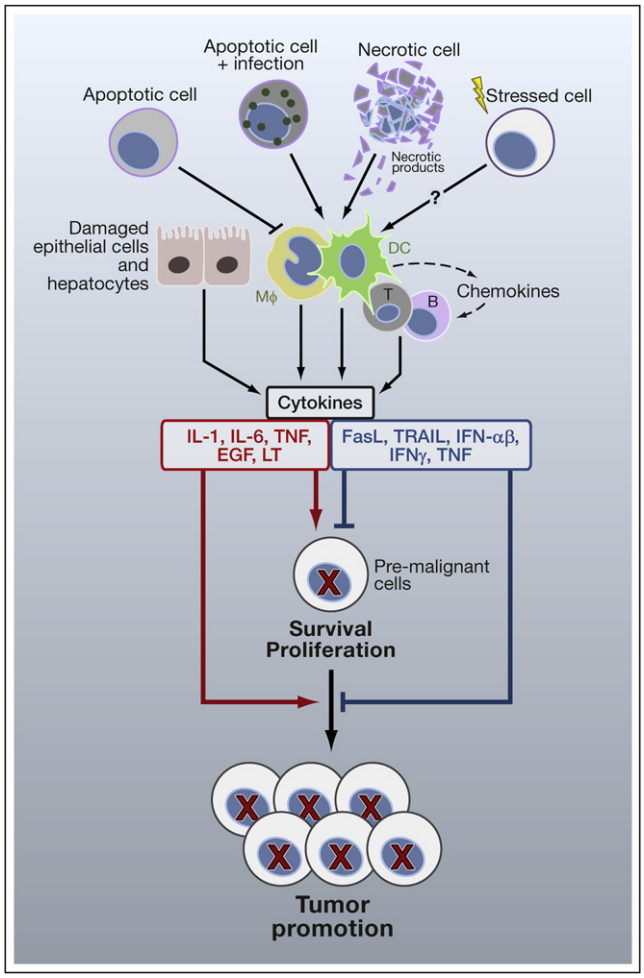

Figure 2. Cell Death and Inflammation

Whereas normal apoptotic cell death inhibits inflammation, apoptotic death of infected cells, necrotic cell death, or factors released by stressed cells lead to activation of different types of immune cells, including T and B lymphocytes, macrophages (MΦ), and dendritic cells (DCs). The latter produce cytokines that have either positive (red) or negative (blue) influences on cell survival and proliferation and regulate different steps of tumorigenesis, including tumor growth and progression. In addition, MΦ and DC may recruit other immune cells into the tumor microenvironment. Damaged or neighboring epithelial cells can also release various cytokines, which further modulate cell survival and growth.

and can thereby impact tumor initiation as well as early tumor promotion (Figure 2).

It was shown that engulfment of apoptotic bodies by macrophages triggers the production of anti-inflammatory cytokines, such as IL-10 (Savill et al., 2002). The universality of this concept, however, has been challenged because apoptosis induced by particular chemotherapeutic agents, such as anthracyclines and ionizing radiation, was found to be inflammatory (Casares et al., 2005; Fucikova et al., 2011). Mechanisms that allow such agents to trigger inflammation include calreticulin translocation (Obeid et al., 2007), heat shock protein 70 and 90 translocation (Udono and Srivastava, 1994), and high mobility group box 1 (HMG1) release (Apetoh et al., 2007). These events result in dendritic cell (DC) and macrophage activation and a consequent inflammatory response (Zitvogel et al., 2010). In addition, recognition of infected apoptotic cells at sites of infection-induced injury culminates in enhanced production of IL-6, which drives differentiation of proinflammatory T cells (Torchinsky et al., 2009). Caspase 3-mediated cell death induced by therapy results in the release of prostaglandins, which are known to promote inflammation, but in this case directly promote the survival of residual tumor cells (Huang et al., 2011).

Unlike apoptosis, necrosis or pyroptosis (defined as cell death that is dependent on inflammatory caspase-1 activity) involve rupture of the plasma membrane and release of the cell's content, making these mechanisms of cell death naturally inflammatory (Bortoluci and Medzhitov, 2010; Zitvogel et al., 2010). Cellular components released during necrotic cell death include IL-1α, "danger-associated molecular patterns" (DAMPs) such as calreticulin, HMG-1, and S100A8 and 9 proteins (Ghiringhelli et al., 2009; Sakurai et al., 2008), and nucleotides and nucleic acids such as ATP, RNA, and DNA, whose recognition leads to DC and macrophage activation (Zitvogel et al., 2010). Although early studies have shown that neutralization of HMG-1 can block cell-death-induced inflammation (Scaffidi et al., 2002), this is not universal and in many cases it has been rather difficult to block the inflammation that follows tissue injury and cancer cell death because of the release of a large number of different inflammatory triggers. Pyroptotic cell death is dependent on activation of caspases, which are also pivotal for the processing and release of IL-1 and IL-18 (Bortoluci and Medzhitov, 2010). For instance, IL-1α released by dying hepatocytes in a liver challenged with the procarcinogen diethyl nitrosamine (DEN) triggers IL-6 production, which activates STAT3 and promotes liver regeneration and tumor growth (He et al., 2010; Sakurai et al., 2008). Various environmental toxins are also capable of triggering cell death-induced inflammation. Components of tobacco smoke, asbestos, and silica particles cause injury and cell death of the lung epithelium, thereby establishing chronic inflammation (Dostert et al., 2008), which promotes the growth of *K-Ras*-induced lung cancer (Takahashi et al., 2010). Lipid accumulation makes hepatocytes within fatty livers more prone to cell death upon exposure to hepatotoxic stimuli (Tuncman et al., 2006) and the ensuing inflammatory response, which involves TNF and IL-6 production, promotes HCC development (Park et al., 2010).

One major factor that determines whether cell death is inflammatory is the rate and the extent of cell death. Slowly occurring physiological cell death may provide phagocytes with enough time to clear the resulting debris, but intense cell death during tissue injury or after cancer therapy may exceed the clearance capacity of tissue macrophages and, even when apoptotic in origin, can trigger inflammation. Indeed, high doses of otherwise noninflammatory genotoxic agents, such as cisplatin and UV irradiation, can induce necrosis and consequent inflammation (Caricchio et al., 2003; Dursun et al., 2006). Furthermore, whereas cell death after androgen withdrawal in prostate cancer is initially apoptotic (McKenzie and Kyprianou, 2006), androgen withdrawal triggers an inflammatory response (Ammirante et al., 2010). Most likely, extensive apoptosis results in secondary necrosis (Zitvogel et al., 2010).

Recent data suggest the involvement of additional cell intrinsic events in the release of cytokines during stress or injury. In this

case, activation of inflammatory pathways either parallels cell death or can be triggered by cell stress in the absence of death. Oncogene activation (Mantovani et al., 2008), inactivation of tumor suppressor p53 (Komarova et al., 2005) and cell senescence induced by extensive DNA damage (Rodier et al., 2009) can all lead to production of the tumor promoting cytokines IL-1, IL-6, and IL-8. Often, stromal cells, such as fibroblasts, sense alterations in tissue homeostasis, which precede injury and tumor development and contribute to inflammation (Bornstein et al., 2009; Stairs et al., 2011). Myofibroblast activation in response to injury results in the production of numerous inflammatory chemokines, including CXCL13, which lead to B cell recruitment into androgen-deprived prostate tumors (Ammirante et al., 2010). Undoubtedly, tissue injury and cell death are important triggers of tumor promoting inflammation (Figure 2).

Inflammation, Cytokine, Cell Death, and Survival

Paradoxically, the inflammatory cytokines that are produced in response to cell death promote tumor development by enhancing the survival of pre-malignant and fully malignant cells (Grivennikov et al., 2010). The mechanisms that lead to the upregulation of inflammatory cytokines in cancer, which can take place both in autocrine and paracrine manners, are diverse and their understanding is still rudimentary. We focus the following discussion on the relationships between cell death, cytokines and cell survival in the context of tissue injury and tumor development.

In many cases, the better understood stimuli that link local injury and cell death to inflammatory cytokine production under cancerous conditions are pathogens or commensals that are recognized by pattern recognition receptors (PRR) on immune or epithelial cells (Medzhitov, 2007). Pathogens that establish persistent infections, such as *Helicobacter pylori* or Hepatitis B and C viruses (HBV; HCV) can lead to the chronic production of pro-tumorigenic cytokines (Grivennikov et al., 2010). In addition to direct PRR activation, certain pathogens, for instance hepatitis B virus (HBV) and hepatitis C virus (HCV), can trigger cytokine production via induction of cell death. As mentioned above, apoptotic cells typically induce expression of IL-10 and TGF-β (Savill et al., 2002), which suppress inflammation and in some cases inhibit tumor development (Grivennikov et al., 2010). However, recognition of infected apoptotic cells results in upregulation of IL-6, which drives differentiation of proinflammatory T helper IL-17-producing (Th17) cells (Torchinsky et al., 2009). Although this response is designed to promote host defense followed by tissue repair, it can also stimulate chronic inflammation and tumor growth, especially in cancers that develop in mucosal surfaces and epithelial barriers populated by bacteria (Torchinsky et al., 2009; Wu et al., 2009). In fact, a Th17-related cytokine signature was recently shown to be a sign of bad prognosis in colorectal cancer (Tosolini et al., 2011). In addition, components of the intestinal microflora promote tumor development in *Il10*$^{-/-}$ mice, which can be prevented by antibiotic treatment (Chichlowski et al., 2008). As discussed above, necrotic cell death caused by hypoxia, nutrient or growth factor deprivation, or cancer therapy can lead to sterile inflammation that, if recurrent, can promote tumor development (Sakurai et al., 2008; Zitvogel et al., 2010).

Inflammatory cytokines are critical regulators of life versus death decisions. IL-1 and IL-6 for instance are potent inducers of cell survival and tumor development, through their ability to activate prosurvival transcription factors, such as NF-κB and STAT3. Other cytokines, such as Fas ligand (FasL) and TNF-related apoptosis-inducing ligand (TRAIL), are potent activators of caspase 8 and therefore are inducers of apoptotic cell death. However, their close relative TNF has both prosurvival and pro-death functions. Other cytokines can exert complex effects on the tumor microenvironment that may affect cell survival and death by more indirect means. According to the cancer immunosurveillance theory (Dunn et al., 2004), death-inducing cytokines (TRAIL, FasL, TWEAK, and occasionally TNF) and cytokines that limit the proliferation of epithelial cells (type I interferon [IFN] and TGF-β) may constitute an important anticancer defense system. This system can eliminate transformed cells and kill metastatic seeds (Swann and Smyth, 2007). Naturally, such cytokines were considered as cancer treatments, but so far success has been rather limited. Nonetheless, genetic or pharmacological blockade of death cytokines often (but not always) increases susceptibility of mice to spontaneous and induced tumorigenesis (Swann and Smyth, 2007). For example, mice lacking membrane-bound forms of FasL or TRAIL develop sarcomas and various blood cancers (Smyth et al., 2003; Swann and Smyth, 2007). TRAIL, in combination with retinoic acid derivatives (required to upregulate TRAIL receptors on cancer cells), can kill tumors by apoptosis and limit growth of microadenomas in *Apc*^{Min} mice (Zhang et al., 2010a). Transgenic mice, which overexpress TRAIL in the skin, exhibit reduced tumorigenicity in the two-step model of skin carcinogenesis (Kedinger et al., 2011). Inhibition of NF-κB activation by TNF, which acts as a pro-survival cytokine, renders metastatic colon cancer cells susceptible to the cytocidal action of TRAIL (Luo et al., 2004). Cytokines such as IFN-γ and IL-12 rarely kill cancer cells directly, but are required for activation of immunosurveillance, including natural killer (NK) cells and cytotoxic T cells (Dunn et al., 2004). Mice deficient in components of IFN-γ signaling are susceptible to induction of sarcomas by methylcholanthrene and other malignancies, including colitis-associated cancer, and also demonstrate increased rates of experimental metastasis (Shankaran et al., 2001; Swann and Smyth, 2007). However, mice lacking both IFN-γ and granulocyte macrophage-colony stimulating factor (GM-CSF) exhibit inflammation and spontaneous development of lymphomas and solid tumors due to chronic bacterial infections (Enzler et al., 2003). Type I IFNs exhibit multifaceted antitumorigenic effects via several distinct mechanisms. First, they restrain proliferation or induce death of premalignant cells, regardless whether such cells are infected with oncogenic viruses or not. Second, type I IFNs upregulate expression of stress-induced surface molecules, such as ligands for γδT cells and NK cells, as well as major histocompatibility complex (MHC) class I molecules, subjecting IFN-exposed cancer cells to enhanced immunosurveillance (Dunn et al., 2005). A third and largely unexplored mechanism of type I IFN action lies in their ability to suppress inflammation, particularly tumor -associated inflammation.

TNF, as its name indicates, was discovered as a death cytokine that induces lysis of sarcoma cells (Carswell et al., 1975). Binding of TNF to its type I receptor (TNFR1) can lead to caspase

8 activation, which can trigger apoptosis, or receptor-interacting protein (RIP) 3 activation, which can lead to necrosis (Kaiser et al., 2011; Oberst et al., 2011). In addition, TNFR1 engagement leads to IκB kinase (IKK) and NF-κB activation, which inhibit apoptosis, as well as c-*jun* N-terminal kinase (JNK) activation, which can potentiate both forms of cell death and stimulate production of ROS (Chang et al., 2006; Ventura et al., 2004). TNF can induce the regression of certain tumors when administered at high doses, most likely through the killing of endothelial cells and thereby starving the tumors of blood supply (Balkwill, 2009). However, there is also ample evidence that TNF is a potent tumor promoter (Balkwill, 2009). Importantly, TNF can directly activate prosurvival NF-κB signaling in cancer cells, as demonstrated in a model of inflammation-dependent cholestatic liver cancer (Pikarsky et al., 2004). A similar effect has been demonstrated for the TNF-related cytokine lymphotoxin (LT), whose overexpression in liver leads to development of HCC in a manner dependent on IKKβ signaling (Haybaeck et al., 2009). TNF can also stimulate the proliferation of premalignant cells, most likely through its ability to activate AP-1 transcription factors (Balkwill, 2009). In addition, TNF has a potent protumorigenic effect in ovarian and colitis-associated cancer, via indirect effects on immune and stromal cells in the microenvironment (Charles et al., 2009; Popivanova et al., 2008). A protumorigenic effect has also been demonstrated for the TNF family member BAFF, whose overexpression in Eμ-Myc transgenic mice leads to rapid development of chronic lymphocytic leukemia (Zhang et al., 2010b). Thus, the protumorigenic effect of antiapoptotic cytokines is not limited to solid malignancies and is also observed in tumors of hematopoietic origin.

Another well-established protumorigenic cytokine is IL-6 (Naugler and Karin, 2008). IL-6 exerts its protumorigenic activities by enhancing the survival and proliferation of premalignant cells, as first demonstrated in colitis associated cancer (Becker et al., 2004; Bollrath et al., 2009; Grivennikov et al., 2009). Most of the pro-tumorigenic effects of IL-6 depend on activation of STAT3, a transcription factor found to be activated in many cancers, including those of the colon, stomach, breast and prostate (Yu et al., 2009). STAT3 exerts its pro-survival and anti-apoptotic activities through transcriptional activation of classical pro-survival genes, such as Bcl-X_L, as well as genes involved in maintenance of epithelial sheet integrity and antimicrobial immunity such as Hsp70 and RegIII (Bollrath et al., 2009). Loss of barrier integrity as demonstrated by the deletion of p120-catenin, an adhesion protein whose expression is downregulated in human gastric cancer, can result in epithelial cell death and formation of a protumorigenic and inflammatory microenvironment (Stairs et al., 2011). Similar effects have been observed during the development of pancreatic cancer (Fukuda et al., 2011; Lesina et al., 2011). The exact mechanisms by which loss of adhesion proteins results in cell death are not entirely clear, but it is tantalizing to speculate that diminished cell adhesion can lead to cell death by anoikis, a type of cell death caused by the loss of cell to cell contact. In summary, cytokines produced in response to injury and cell death have a profound effect on cell death versus survival decisions, thereby contributing to tumor initiation, growth, progression, and metastasis, as well as to the response to antitumor therapy.

Liver Cancer—A Death-Driven Cancer

Two important hallmarks of cancer are uncontrolled cell proliferation and the ability to avoid programmed cell death (Hanahan and Weinberg, 2000). Accordingly, apoptotic cell death is believed to be a major tumor-suppressive mechanism. Indeed, many of the examples outlined above support this concept. However, tumor suppression by apoptosis is not universal and several cancers, especially liver cancer, are caused by cell death. For induction of neoplasia, oncogenic mutations or epigenetic modifications need to be fixed within subsequent cell generations and therefore genetically altered cells have to divide before giving rise to cancer (Figure 3). Although this is not a major obstacle in rapidly renewing epithelia, many tissues, such as the liver, exhibit very low rates of cell proliferation. In fact, adult liver parenchymal cells are synchronized at the G_0 phase of the cell cycle and can be evoked to proliferate only in response to tissue damage or debulking (Luedde and Schwabe, 2011). Not surprisingly, HCC, the major form of adult liver cancer, almost invariably develops in the context of chronic liver inflammation linked to injury and cell death and caused by infection with HBV or HCV, chronic alcohol consumption, excessive hepatosteatosis, or exposure to environmental toxins (El-Serag and Rudolph, 2007). Initially, it was assumed that NF-κB activation may promote the development of chemically induced HCC by suppressing p53-induced apoptosis, as found in tissue culture studies (Tergaonkar et al., 2002). We were therefore surprised to find that inactivation of liver NF-κB through the cell type-specific ablation of IKKβ leads to a marked enhancement of hepatocarcinogenesis in DEN-treated mice (Maeda et al., 2005). Similar observations were made in mice with a hepatocyte-specific deletion of the stress-activated protein kinase p38α (Hui et al., 2007; Sakurai et al., 2008). IKKβ-mediated NF-κB and p38α-regulated Hsp25 expression are critical for prevention of excessive ROS accumulation and thus are important for the survival of pericentral hepatocytes that are engaged in DEN metabolism (Maeda et al., 2005; Sakurai et al., 2008). Thus, in the absence of either NF-κB or p38α, DEN-exposed hepatocytes undergo excessive cell death, resulting in an enhanced regenerative response and compensatory proliferation of surviving hepatocytes. We have therefore proposed that enhanced compensatory proliferation is the major cause of augmented HCC development in both IKKβ- and p38α-hepatocyte-specific knockout mice (Karin, 2006). The regenerative response that leads to compensatory hepatocyte proliferation depends on the release of IL-1α by dying hepatocytes and the activation of the adaptor MyD88-dependent IL-1R signaling in resident liver macrophages (Kupffer cells), leading to IL-6 production by the latter (Naugler et al., 2007; Sakurai et al., 2008). Strikingly, hepatocyte-specific deletion of IKKγ (NEMO), the regulatory subunit of the IKK complex (Luedde et al., 2007) or TAK1, an upstream kinase required for NF-κB activation (Bettermann et al., 2010; Inokuchi et al., 2010), result in spontaneous liver damage, inflammation, and hepatosteatosis, which eventually lead to HCC development in the absence of any exogenous carcinogen. Curiously, tumor development in the absence of TAK1 is reported to be NEMO dependent and TAK1 can gain protumorigenic activity in the absence of NEMO, underscoring their potential role as both tumor promoters and tumor suppressors (Bettermann et al., 2010). These opposing activities of TAK1 and NEMO are

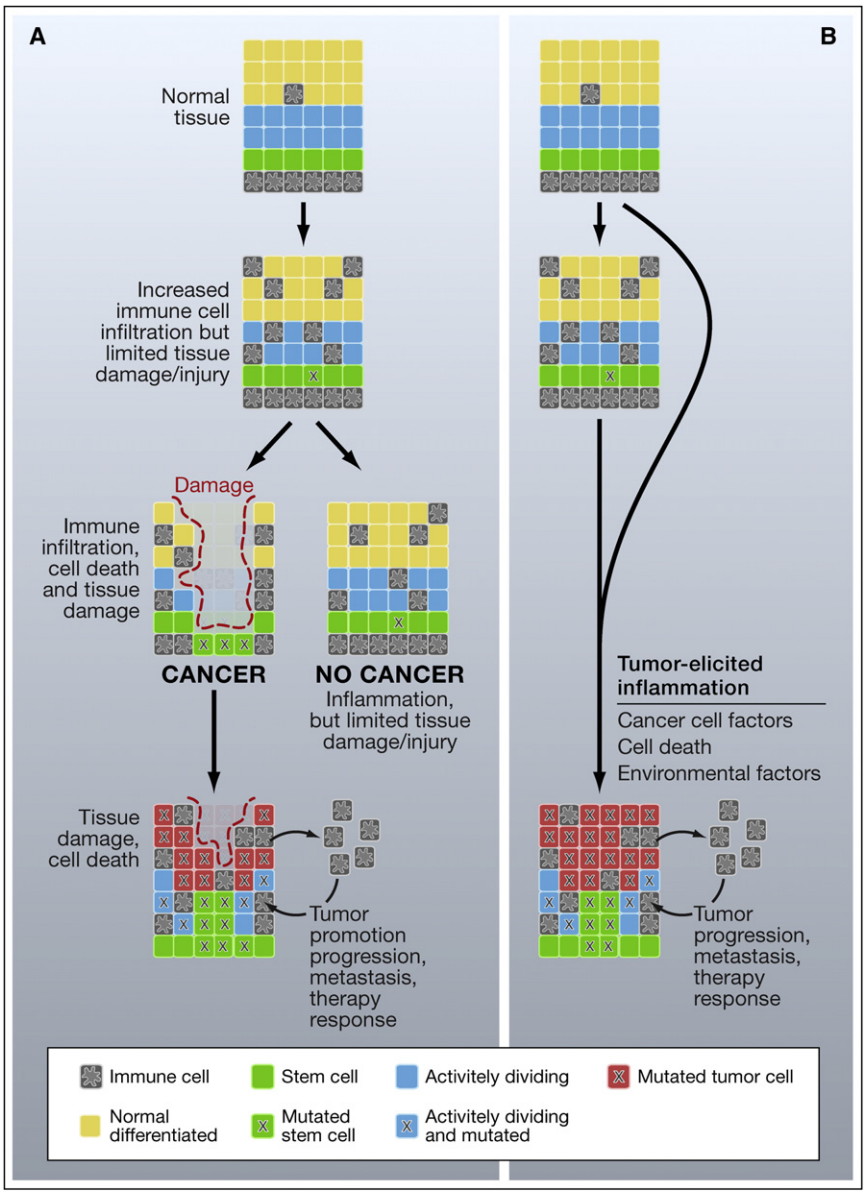

Figure 3. Protumorigenic Function of Cell Death and Tissue Injury

Sentinel immune cells are present in normal tissue, but they do not produce inflammatory cytokines and do not promote tumorigenesis. As shown in (A), inflammation results in immune cell infiltration, but without extensive tissue injury and cell death, tumor promotion typically does not take place, although mutant cells can already be present. Tissue injury and cell death induce additional inflammation, which precedes or accompanies tumor development. Tissue injury and cell death, in combination with inflammation, result in an enhanced regenerative response, leading to the proliferation of stem cells that may harbor oncogenic mutations. Immune cells, in turn, maintain chronic inflammation and may cause additional tissue injury. This altogether leads to tumor initiation, promotion, and further enhancement of tumor progression and metastasis and modulation of antitumor therapy response by inflammation. As shown in (B), inflammation can regulate tumor promotion, progression, and metastasis by other mechanisms, which do not invoke tissue damage and cell death. These mechanisms are present in established tumors and rely on late recruitment of immune cells to the tumor microenvironment as a part of tumor-elicited inflammation. Factors produced by cancer cells, environmental factors, and cell stress and death caused by therapy and/or by hypoxia are responsible for cell recruitment and tumor-associated inflammation in this case.

likely to be NF-κB independent and may involve activation of other transcription factors, such as AP-1 and SMADs.

Consistent with the protumorigenic function of hepatocyte death, mice that are specifically devoid of the death receptor Fas on hepatocytes exhibit a substantial decrease in DEN-induced hepatocarcinogenesis (Chen et al., 2010). So that one could fully appreciate the importance of these findings, it should be noted that in many other cell types, especially in lymphocytes and their precursors, Fas has been shown to act as a tumor suppressor (Peter et al., 2007). It should also be noted that administration of DEN to mice that are older than one month of age does not lead to HCC induction, unless combined with a tumor promoter, such as phenobarbital or carbon tetrachloride (CCl_4) (Maeda et al., 2005). Congruently, feeding of mice with a high fat diet (HFD) for 3 months prior to DEN administration greatly enhanced DEN-induced ROS accumulation and hepatocyte death, resulting in HCC induction in the absence of other tumor promoters (Park et al., 2010). In addition to enhancing DEN-induced liver damage, consumption of HFD results in elevated expression of TNF and IL-6, both of which promote HCC development (Park et al., 2010). Paradoxically, while inducing hepatocyte proliferation, IL-6 also potentiates DEN-induced hepatocyte death (Naugler et al., 2007). The latter effect may be due to IL-6-induced neutrophil recruitment. Such observations may also explain why hepatocyte-specific *Stat3* null mice are protected from DEN-induced HCC (He et al., 2010), but are highly susceptible to HCC induction upon challenge with CCl_4, a liver-damaging agent that does not cause HCC by itself (Wang et al., 2011). A number of retrospective studies suggest that IL-6 is also involved in the pathogenesis of human HCC and inflammatory liver adenomas (Naugler and Karin, 2008; Rebouissou et al., 2009).

As mentioned above, NF-κB signaling has a dual role in hepatocarcinogenesis. While enhancing DEN-induced HCC development, inhibition of liver NF-κB activity can attenuate inflammation-induced HCC that is not accompanied by obvious liver injury (Haybaeck et al., 2009; Pikarsky et al., 2004). Indeed, there is substantial heterogeneity in respect to NF- κB activation in human HCC. Although the majority of HCCs appear to be devoid of nuclear RelA, (a subunit of the NF-κB multiprotein complex) ~25% of such tumors exhibit clear NF-κB activation,

suggesting that even in human liver, NF-κB can assume both antitumorigenic and protumorigenic functions (He et al., 2010).

Cell Death and Skin Cancer

Death-promoted tumorigenesis is not unique to the liver as injury can play both tumor-suppressive and tumor-promoting effects in the skin. Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are the most prominent nonmelanoma forms of skin cancer and two of the most common cancers worldwide (Domingo and Baron, 2008). Inflammatory processes are important for induction, promotion, and progression of both SCC and BCC. However, given that the incidence of these cancers is higher in immunocompromised individuals, the immune system and inflammation may have dual roles in skin carcinogenesis. Death promoting environmental challenges, including UV irradiation, tobacco smoke, and betel nut chewing are major contributors to the etiology of SCC (Rudolph and Zelac, 2004). The skin consists of different cell types and serves as a critical barrier that protects us from microbes, harmful chemicals, and dehydration. Skin integrity is maintained by the ongoing division of stem cells and transient amplifying cells in its basal layer, which give rise to more differentiated cell types that eventually undergo enucleation to form the cornified cell bodies that make up the outermost layer.

As in the liver, chronic stress and injury, as well as defects in normal wound healing, can cause skin cancer (Rudolph and Zelac, 2004). For instance, repetitive exposure to UV radiation causes skin injury and cell death and leads to tumor development. Although UV radiation is a potent DNA damaging agent and a mutagen, not all of its effects depend on DNA damage. The TGF-β-SMAD4 signaling pathway is required for efficient epithelial wound healing and a conditional deletion of SMAD4 in the epidermis results in severe defects in skin wound healing that are accompanied by spontaneous skin lesions, inflammation, and SCC (Owens et al., 2010). Likewise and as seen in the liver, inhibition of epidermal NF-κB activation results in enhanced skin tumorigenesis (Dajee et al., 2003). However, ablation of the NF-κB activating cytokine TNF inhibits two-stage skin cancer carcinogenesis (Moore et al., 1999). As discussed above, TNF is likely to exert its protumorigenic activity through the transcription factor AP-1, as ablation of the transcription factor c-Jun inhibits skin tumorigenesis (Schonthaler et al., 2011). However, ablation of both c-Jun and JunB results in psoriatic inflammation (Schonthaler et al., 2011). Notably, despite being a chronic inflammatory condition linked to increased production of TNF, psoriasis is associated with protection from skin tumorigenesis (Nickoloff et al., 2005), presumably because psoriasis does not cause excessive tissue injury and cell death (see below). Another transcription factor involved in psoriasis is STAT3, which can be activated by a large variety of cytokines, including EGF, HB-EGF, IL-22, and IL-6, which can be particularly induced by stresses and cell injury. STAT3 integrates prosurvival signals from these cytokines and its ablation in the epidermis inhibits two-stage skin carcinogenesis (Kataoka et al., 2008).

Skin damage can result in the release of self-antigens and DAMPs, leading to activation of innate and adaptive immunity and stimulation of T and B cells responses (de Visser et al., 2005). In K14-HPV16 transgenic mice, which overexpress human papilloma virus (HPV) 16 proteins E6 and E7 in keratinocytes and spontaneously develop skin papillomas, antibody-producing B cells lead to activation of mast cells via Fc receptors, thereby triggering a local inflammatory response that stimulates tumor progression (Andreu et al., 2010; de Visser et al., 2005). In a two-step skin carcinogenesis model, B cells producing IL-10 promote papilloma growth by inactivating antitumor immunity represented by cytotoxic T cells and the antitumorigenic cytokine IFN-γ (Schioppa et al., 2011). The DAMPs HMG-B1 and B2 are upregulated during SCC progression and may be required for establishment of chronic inflammation, cancer invasion, and metastasis (Sharma et al., 2008). The identity of the antigens that activate the adaptive immune response in skin injury and cancer remains unknown, although self-antigens, such as chitinase-like proteins (Qureshi et al., 2011) and antigens derived from the skin bacterium *Staphylococcus aureus* (Daniel et al., 2003), have been implicated. T cell responses play a dual role in skin tumorigenesis. Whereas IL-12- and IFN-γ-driven cytotoxic T cells inhibit initiation and progression of skin cancer, IL-23- and IL-17-mediated responses promote skin tumorigenesis (Langowski et al., 2006).

As mentioned above, certain types of chronic skin inflammation, such as psoriasis or atopic dermatitis, do not increase the risk of skin cancer development. It is tempting to speculate that they fail to do so because no prominent tissue damage and subsequent regeneration are inflicted under these conditions. It is also plausible that chronic injury also increases the exposure of normal cells to environmental mutagens and carcinogens, which are normally kept at bay by the skin's barrier function. Given the physiology and anatomy of the epidermis, which consists of stem cells, rapidly dividing basal cells and differentiated cells, which eventually undergo enucleation and death, a key question is when and not whether these keratinocytes will eventually die. Therefore, keratinocyte death is probably not a major suppressor of skin tumorigenesis. Rather, the continuous death of differentiated keratinocytes results in expansion of transient amplifying cells, some of which may harbor oncogenic mutations, thereby promoting tumorigenesis. Thus, unless cell death is restricted to transformed cells harboring oncogenic mutations, it is not universally tumor suppressive. In the case of melanoma, tumor development does not seem to depend on earlier tissue injury and cell death while tumor-cell specific NF-κB activation promotes tumorigenesis (Yang et al., 2010). On the other hand, activation of melanocyte precursors by UVB light, a typical stress stimulus, and IFN-γ, promotes the recruitment of immune cells and enhances melanoma development in an animal model (Zaidi et al., 2011). Here, IFN-γ provides prosurvival and protumorigenic signals to initiated melanocytes.

Concluding Remarks

Chronic tissue damage and inflammation have long been suspected for their ability to promote cancer development and progression, but only recently was the incriminating "smoking gun" identified through the extensive use of physiologically relevant mouse models. Importantly, the experimental evidence obtained in mice is strongly supported by correlative and retrospective analysis of human clinical and epidemiological data. One of the earliest experiments that underscored the importance

of tissue injury and cell death in tumorigenesis was the demonstration that v-Src oncogene cannot induce cancer unless accompanied by tissue injury and subsequent regeneration (Sieweke et al., 1990). Likewise, experimental pancreatic injury is required to unravel the oncogenic potential of activated K-Ras in the postnatal pancreas (Guerra et al., 2007). In lung cancer, tissue injury inflicted by tobacco smoke contributes to disease development, and inhibition of cell death related pathways (JNK) or death-induced proinflammatory cytokines (TNF and IL-6) dampens tumor progression (Takahashi et al., 2010). Disruption of epithelial homeostasis by deletion of p120 catenin induces esophageal cancer (Stairs et al., 2011). An inflammatory bowel disease, such as ulcerative colitis (UC), which is characterized by massive epithelial damage and inflammation, is known to elevate colon cancer risk (Saleh and Trinchieri, 2011). Likewise, mucosal injury induced by dextrane sulfate sodium (DSS) or by oxazolone is required for induction of colitis-associated cancer in mice treated with the procarcinogen azoxymethane (AOM) (Greten et al., 2004; Schiechl et al., 2011). Taken together, these and many other experiments illustrate the protumorigenic activity of cell death and together with clinical and epidemiological findings support the notion that a substantial fraction of all cancer cases are likely to be initiated and promoted by chronic tissue injury (Figure 3). These conclusions also suggest that therapeutic approaches that minimize injury and restore normal tissue homeostasis can be used in cancer prevention.

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REFERENCES

Ammirante, M., Luo, J.L., Grivennikov, S., Nedospasov, S., and Karin, M. (2010). B-cell-derived lymphotoxin promotes castration-resistant prostate cancer. Nature *464*, 302–305.

Andreu, P., Johansson, M., Affara, N.I., Pucci, F., Tan, T., Junankar, S., Korets, L., Lam, J., Tawfik, D., DeNardo, D.G., et al. (2010). FcRgamma activation regulates inflammation-associated squamous carcinogenesis. Cancer Cell *17*, 121–134.

Apetoh, L., Ghiringhelli, F., Tesniere, A., Criollo, A., Ortiz, C., Lidereau, R., Mariette, C., Chaput, N., Mira, J.P., Delaloge, S., et al. (2007). The interaction between HMGB1 and TLR4 dictates the outcome of anticancer chemotherapy and radiotherapy. Immunol. Rev. *220*, 47–59.

Balkwill, F. (2009). Tumour necrosis factor and cancer. Nat. Rev. Cancer *9*, 361–371.

Bao, P., Kodra, A., Tomic-Canic, M., Golinko, M.S., Ehrlich, H.P., and Brem, H. (2009). The role of vascular endothelial growth factor in wound healing. J. Surg. Res. *153*, 347–358.

Beachy, P.A., Karhadkar, S.S., and Berman, D.M. (2004). Tissue repair and stem cell renewal in carcinogenesis. Nature *432*, 324–331.

Becker, C., Fantini, M.C., Schramm, C., Lehr, H.A., Wirtz, S., Nikolaev, A., Burg, J., Strand, S., Kiesslich, R., Huber, S., et al. (2004). TGF-beta suppresses tumor progression in colon cancer by inhibition of IL-6 trans-signaling. Immunity *21*, 491–501.

Bettermann, K., Vucur, M., Haybaeck, J., Koppe, C., Janssen, J., Heymann, F., Weber, A., Weiskirchen, R., Liedtke, C., Gassler, N., et al. (2010). TAK1 suppresses a NEMO-dependent but NF-kappaB-independent pathway to liver cancer. Cancer Cell *17*, 481–496.

Bollrath, J., Phesse, T.J., von Burstin, V.A., Putoczki, T., Bennecke, M., Bateman, T., Nebelsiek, T., Lundgren-May, T., Canli, O., Schwitalla, S., et al. (2009). gp130-mediated Stat3 activation in enterocytes regulates cell survival and cell-cycle progression during colitis-associated tumorigenesis. Cancer Cell *15*, 91–102.

Bornstein, S., White, R., Malkoski, S., Oka, M., Han, G., Cleaver, T., Reh, D., Andersen, P., Gross, N., Olson, S., et al. (2009). Smad4 loss in mice causes spontaneous head and neck cancer with increased genomic instability and inflammation. J. Clin. Invest. *119*, 3408–3419.

Bortoluci, K.R., and Medzhitov, R. (2010). Control of infection by pyroptosis and autophagy: Role of TLR and NLR. Cell. Mol. Life Sci. *67*, 1643–1651.

Caricchio, R., McPhie, L., and Cohen, P.L. (2003). Ultraviolet B radiation-induced cell death: Critical role of ultraviolet dose in inflammation and lupus autoantigen redistribution. J. Immunol. *171*, 5778–5786.

Carswell, E.A., Old, L.J., Kassel, R.L., Green, S., Fiore, N., and Williamson, B. (1975). An endotoxin-induced serum factor that causes necrosis of tumors. Proc. Natl. Acad. Sci. USA *72*, 3666–3670.

Casares, N., Pequignot, M.O., Tesniere, A., Ghiringhelli, F., Roux, S., Chaput, N., Schmitt, E., Hamai, A., Hervas-Stubbs, S., Obeid, M., et al. (2005). Caspase-dependent immunogenicity of doxorubicin-induced tumor cell death. J. Exp. Med. *202*, 1691–1701.

Chang, L., Kamata, H., Solinas, G., Luo, J.L., Maeda, S., Venuprasad, K., Liu, Y.C., and Karin, M. (2006). The E3 ubiquitin ligase itch couples JNK activation to TNFalpha-induced cell death by inducing c-FLIP(L) turnover. Cell *124*, 601–613.

Charles, K.A., Kulbe, H., Soper, R., Escorcio-Correia, M., Lawrence, T., Schultheis, A., Chakravarty, P., Thompson, R.G., Kollias, G., Smyth, J.F., et al. (2009). The tumor-promoting actions of TNF-alpha involve TNFR1 and IL-17 in ovarian cancer in mice and humans. J. Clin. Invest. *119*, 3011–3023.

Chen, L., Park, S.M., Tumanov, A.V., Hau, A., Sawada, K., Feig, C., Turner, J.R., Fu, Y.X., Romero, I.L., Lengyel, E., and Peter, M.E. (2010). CD95 promotes tumour growth. Nature *465*, 492–496.

Chichlowski, M., Sharp, J.M., Vanderford, D.A., Myles, M.H., and Hale, L.P. (2008). Helicobacter typhlonius and Helicobacter rodentium differentially affect the severity of colon inflammation and inflammation-associated neoplasia in IL10-deficient mice. Comp. Med. *58*, 534–541.

Dajee, M., Lazarov, M., Zhang, J.Y., Cai, T., Green, C.L., Russell, A.J., Marinkovich, M.P., Tao, S., Lin, Q., Kubo, Y., and Khavari, P.A. (2003). NF-kappaB blockade and oncogenic Ras trigger invasive human epidermal neoplasia. Nature *421*, 639–643.

Daniel, D., Meyer-Morse, N., Bergsland, E.K., Dehne, K., Coussens, L.M., and Hanahan, D. (2003). Immune enhancement of skin carcinogenesis by CD4+ T cells. J. Exp. Med. *197*, 1017–1028.

de Visser, K.E., Korets, L.V., and Coussens, L.M. (2005). De novo carcinogenesis promoted by chronic inflammation is B lymphocyte dependent. Cancer Cell *7*, 411–423.

DeNardo, D.G., Barreto, J.B., Andreu, P., Vasquez, L., Tawfik, D., Kolhatkar, N., and Coussens, L.M. (2009). CD4(+) T cells regulate pulmonary metastasis of mammary carcinomas by enhancing protumor properties of macrophages. Cancer Cell *16*, 91–102.

Domingo, D.S., and Baron, E.D. (2008). Melanoma and nonmelanoma skin cancers and the immune system. Adv. Exp. Med. Biol. *624*, 187–202.

Dostert, C., Pétrilli, V., Van Bruggen, R., Steele, C., Mossman, B.T., and Tschopp, J. (2008). Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. Science *320*, 674–677.

Dunn, G.P., Old, L.J., and Schreiber, R.D. (2004). The immunobiology of cancer immunosurveillance and immunoediting. Immunity *21*, 137–148.

Dunn, G.P., Bruce, A.T., Sheehan, K.C., Shankaran, V., Uppaluri, R., Bui, J.D., Diamond, M.S., Koebel, C.M., Arthur, C., White, J.M., and Schreiber, R.D. (2005). A critical function for type I interferons in cancer immunoediting. Nat. Immunol. *6*, 722–729.

Dursun, B., He, Z., Somerset, H., Oh, D.J., Faubel, S., and Edelstein, C.L. (2006). Caspases and calpain are independent mediators of cisplatin-induced endothelial cell necrosis. Am. J. Physiol. Renal Physiol. *291*, F578–F587.

Dvorak, H.F. (1986). Tumors: Wounds that do not heal. Similarities between tumor stroma generation and wound healing. N. Engl. J. Med. *315*, 1650–1659.

El-Serag, H.B., and Rudolph, K.L. (2007). Hepatocellular carcinoma: Epidemiology and molecular carcinogenesis. Gastroenterology *132*, 2557–2576.

Enzler, T., Gillessen, S., Manis, J.P., Ferguson, D., Fleming, J., Alt, F.W., Mihm, M., and Dranoff, G. (2003). Deficiencies of GM-CSF and interferon gamma link inflammation and cancer. J. Exp. Med. *197*, 1213–1219.

Fucikova, J., Kralikova, P., Fialova, A., Brtnicky, T., Rob, L., Bartunkova, J., and Spísek, R. (2011). Human tumor cells killed by anthracyclines induce a tumor-specific immune response. Cancer Res. *71*, 4821–4833.

Fukuda, A., Wang, S.C., Morris, J.P., 4th, Folias, A.E., Liou, A., Kim, G.E., Akira, S., Boucher, K.M., Firpo, M.A., Mulvihill, S.J., and Hebrok, M. (2011). Stat3 and MMP7 contribute to pancreatic ductal adenocarcinoma initiation and progression. Cancer Cell *19*, 441–455.

Ghiringhelli, F., Apetoh, L., Tesniere, A., Aymeric, L., Ma, Y., Ortiz, C., Vermaelen, K., Panaretakis, T., Mignot, G., Ullrich, E., et al. (2009). Activation of the NLRP3 inflammasome in dendritic cells induces IL-1beta-dependent adaptive immunity against tumors. Nat. Med. *15*, 1170–1178.

Greten, F.R., Eckmann, L., Greten, T.F., Park, J.M., Li, Z.W., Egan, L.J., Kagnoff, M.F., and Karin, M. (2004). IKKbeta links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. Cell *118*, 285–296.

Grivennikov, S., Karin, E., Terzic, J., Mucida, D., Yu, G.Y., Vallabhapurapu, S., Scheller, J., Rose-John, S., Cheroutre, H., Eckmann, L., and Karin, M. (2009). IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. Cancer Cell *15*, 103–113.

Grivennikov, S.I., Greten, F.R., and Karin, M. (2010). Immunity, inflammation, and cancer. Cell *140*, 883–899.

Guerra, C., Schuhmacher, A.J., Cañamero, M., Grippo, P.J., Verdaguer, L., Pérez-Gallego, L., Dubus, P., Sandgren, E.P., and Barbacid, M. (2007). Chronic pancreatitis is essential for induction of pancreatic ductal adenocarcinoma by K-Ras oncogenes in adult mice. Cancer Cell *11*, 291–302.

Gulley, J., Figg, W.D., and Dahut, W.L. (2003). Treatment options for androgen-independent prostate cancer. Clin. Adv. Hematol. Oncol. *1*, 49–57.

Haddow, A. (1972). Molecular repair, wound healing, and carcinogenesis: Tumor production a possible overhealing? Adv. Cancer Res. *16*, 181–234.

Hanahan, D., and Weinberg, R.A. (2000). The hallmarks of cancer. Cell *100*, 57–70.

Haybaeck, J., Zeller, N., Wolf, M.J., Weber, A., Wagner, U., Kurrer, M.O., Bremer, J., Iezzi, G., Graf, R., Clavien, P.A., et al. (2009). A lymphotoxin-driven pathway to hepatocellular carcinoma. Cancer Cell *16*, 295–308.

He, G., Yu, G.Y., Temkin, V., Ogata, H., Kuntzen, C., Sakurai, T., Sieghart, W., Peck-Radosavljevic, M., Leffert, H.L., and Karin, M. (2010). Hepatocyte IKKbeta/NF-kappaB inhibits tumor promotion and progression by preventing oxidative stress-driven STAT3 activation. Cancer Cell *17*, 286–297.

Hecht, S.S. (2002). Cigarette smoking and lung cancer: Chemical mechanisms and approaches to prevention. Lancet Oncol. *3*, 461–469.

Huang, Q., Li, F., Liu, X., Li, W., Shi, W., Liu, F.F., O'Sullivan, B., He, Z., Peng, Y., Tan, A.C., et al. (2011). Caspase 3-mediated stimulation of tumor cell repopulation during cancer radiotherapy. Nat. Med. *17*, 860–866.

Hui, L., Bakiri, L., Mairhorfer, A., Schweifer, N., Haslinger, C., Kenner, L., Komnenovic, V., Scheuch, H., Beug, H., and Wagner, E.F. (2007). p38alpha suppresses normal and cancer cell proliferation by antagonizing the JNK-c-Jun pathway. Nat. Genet. *39*, 741–749.

Iliopoulos, D., Hirsch, H.A., Wang, G., and Struhl, K. (2011). Inducible formation of breast cancer stem cells and their dynamic equilibrium with non-stem cancer cells via IL6 secretion. Proc. Natl. Acad. Sci. USA *108*, 1397–1402.

Inokuchi, S., Aoyama, T., Miura, K., Osterreicher, C.H., Kodama, Y., Miyai, K., Akira, S., Brenner, D.A., and Seki, E. (2010). Disruption of TAK1 in hepatocytes causes hepatic injury, inflammation, fibrosis, and carcinogenesis. Proc. Natl. Acad. Sci. USA *107*, 844–849.

Ito, M., Liu, Y., Yang, Z., Nguyen, J., Liang, F., Morris, R.J., and Cotsarelis, G. (2005). Stem cells in the hair follicle bulge contribute to wound repair but not to homeostasis of the epidermis. Nat. Med. *11*, 1351–1354.

Jinushi, M., Chiba, S., Yoshiyama, H., Masutomi, K., Kinoshita, I., Dosaka-Akita, H., Yagita, H., Takaoka, A., and Tahara, H. (2011). Tumor-associated macrophages regulate tumorigenicity and anticancer drug responses of cancer stem/initiating cells. Proc. Natl. Acad. Sci. USA *108*, 12425–12430.

Joyce, J.A., and Pollard, J.W. (2009). Microenvironmental regulation of metastasis. Nat. Rev. Cancer *9*, 239–252.

Kaiser, W.J., Upton, J.W., Long, A.B., Livingston-Rosanoff, D., Daley-Bauer, L.P., Hakem, R., Caspary, T., and Mocarski, E.S. (2011). RIP3 mediates the embryonic lethality of caspase-8-deficient mice. Nature *471*, 368–372.

Karin, M. (2005). Inflammation and cancer: The long reach of Ras. Nat. Med. *11*, 20–21.

Karin, M. (2006). Nuclear factor-kappaB in cancer development and progression. Nature *441*, 431–436.

Kataoka, K., Kim, D.J., Carbajal, S., Clifford, J.L., and DiGiovanni, J. (2008). Stage-specific disruption of Stat3 demonstrates a direct requirement during both the initiation and promotion stages of mouse skin tumorigenesis. Carcinogenesis *29*, 1108–1114.

Kedinger, V., Muller, S., and Gronemeyer, H. (2011). Targeted expression of tumor necrosis factor-related apoptosis-inducing ligand TRAIL in skin protects mice against chemical carcinogenesis. Mol. Cancer *10*, 34.

Kim, S., Takahashi, H., Lin, W.W., Descargues, P., Grivennikov, S., Kim, Y., Luo, J.L., and Karin, M. (2009). Carcinoma-produced factors activate myeloid cells through TLR2 to stimulate metastasis. Nature *457*, 102–106.

Komarova, E.A., Krivokrysenko, V., Wang, K., Neznanov, N., Chernov, M.V., Komarov, P.G., Brennan, M.L., Golovkina, T.V., Rokhlin, O.W., Kuprash, D.V., et al. (2005). p53 is a suppressor of inflammatory response in mice. FASEB J. *19*, 1030–1032.

Langowski, J.L., Zhang, X., Wu, L., Mattson, J.D., Chen, T., Smith, K., Basham, B., McClanahan, T., Kastelein, R.A., and Oft, M. (2006). IL-23 promotes tumour incidence and growth. Nature *442*, 461–465.

Lesina, M., Kurkowski, M.U., Ludes, K., Rose-John, S., Treiber, M., Klöppel, G., Yoshimura, A., Reindl, W., Sipos, B., Akira, S., et al. (2011). Stat3/Socs3 activation by IL-6 transsignaling promotes progression of pancreatic intraepithelial neoplasia and development of pancreatic cancer. Cancer Cell *19*, 456–469.

Lewis, J.S., Landers, R.J., Underwood, J.C., Harris, A.L., and Lewis, C.E. (2000). Expression of vascular endothelial growth factor by macrophages is up-regulated in poorly vascularized areas of breast carcinomas. J. Pathol. *192*, 150–158.

Lobo, N.A., Shimono, Y., Qian, D., and Clarke, M.F. (2007). The biology of cancer stem cells. Annu. Rev. Cell Dev. Biol. *23*, 675–699.

Lucas, T., Waisman, A., Ranjan, R., Roes, J., Krieg, T., Müller, W., Roers, A., and Eming, S.A. (2010). Differential roles of macrophages in diverse phases of skin repair. J. Immunol. *184*, 3964–3977.

Luedde, T., and Schwabe, R.F. (2011). NF-κB in the liver—linking injury, fibrosis and hepatocellular carcinoma. Nat. Rev. Gastroenterol. Hepatol. *8*, 108–118.

Luedde, T., Beraza, N., Kotsikoris, V., van Loo, G., Nenci, A., De Vos, R., Roskams, T., Trautwein, C., and Pasparakis, M. (2007). Deletion of NEMO/IKKgamma in liver parenchymal cells causes steatohepatitis and hepatocellular carcinoma. Cancer Cell *11*, 119–132.

Luo, J.L., Maeda, S., Hsu, L.C., Yagita, H., and Karin, M. (2004). Inhibition of NF-kappaB in cancer cells converts inflammation- induced tumor growth mediated by TNFalpha to TRAIL-mediated tumor regression. Cancer Cell *6*, 297–305.

Luo, J.L., Tan, W., Ricono, J.M., Korchynskyi, O., Zhang, M., Gonias, S.L., Cheresh, D.A., and Karin, M. (2007). Nuclear cytokine-activated IKKalpha controls prostate cancer metastasis by repressing Maspin. Nature *446*, 690–694.

Maeda, S., Kamata, H., Luo, J.L., Leffert, H., and Karin, M. (2005). IKKbeta couples hepatocyte death to cytokine-driven compensatory proliferation that promotes chemical hepatocarcinogenesis. Cell *121*, 977–990.

Mantovani, A., Allavena, P., Sica, A., and Balkwill, F. (2008). Cancer-related inflammation. Nature *454*, 436–444.

Matsuda, T., Nakamura, T., Nakao, K., Arai, T., Katsuki, M., Heike, T., and Yokota, T. (1999). STAT3 activation is sufficient to maintain an undifferentiated state of mouse embryonic stem cells. EMBO J. *18*, 4261–4269.

McKenzie, S., and Kyprianou, N. (2006). Apoptosis evasion: The role of survival pathways in prostate cancer progression and therapeutic resistance. J. Cell. Biochem. *97*, 18–32.

Medzhitov, R. (2007). Recognition of microorganisms and activation of the immune response. Nature *449*, 819–826.

Miyamoto, K., Araki, K.Y., Naka, K., Arai, F., Takubo, K., Yamazaki, S., Matsuoka, S., Miyamoto, T., Ito, K., Ohmura, M., et al. (2007). Foxo3a is essential for maintenance of the hematopoietic stem cell pool. Cell Stem Cell *1*, 101–112.

Moore, R.J., Owens, D.M., Stamp, G., Arnott, C., Burke, F., East, N., Holdsworth, H., Turner, L., Rollins, B., Pasparakis, M., et al. (1999). Mice deficient in tumor necrosis factor-alpha are resistant to skin carcinogenesis. Nat. Med. *5*, 828–831.

Naugler, W.E., and Karin, M. (2008). The wolf in sheep's clothing: The role of interleukin-6 in immunity, inflammation and cancer. Trends Mol. Med. *14*, 109–119.

Naugler, W.E., Sakurai, T., Kim, S., Maeda, S., Kim, K., Elsharkawy, A.M., and Karin, M. (2007). Gender disparity in liver cancer due to sex differences in MyD88-dependent IL-6 production. Science *317*, 121–124.

Nickoloff, B.J., Ben-Neriah, Y., and Pikarsky, E. (2005). Inflammation and cancer: Is the link as simple as we think? J. Invest. Dermatol. *124*, x–xiv.

Obeid, M., Tesniere, A., Ghiringhelli, F., Fimia, G.M., Apetoh, L., Perfettini, J.L., Castedo, M., Mignot, G., Panaretakis, T., Casares, N., et al. (2007). Calreticulin exposure dictates the immunogenicity of cancer cell death. Nat. Med. *13*, 54–61.

Oberst, A., Dillon, C.P., Weinlich, R., McCormick, L.L., Fitzgerald, P., Pop, C., Hakem, R., Salvesen, G.S., and Green, D.R. (2011). Catalytic activity of the caspase-8-FLIP(L) complex inhibits RIPK3-dependent necrosis. Nature *471*, 363–367.

Orimo, A., and Weinberg, R.A. (2006). Stromal fibroblasts in cancer: A novel tumor-promoting cell type. Cell Cycle *5*, 1597–1601.

Owens, P., Engelking, E., Han, G., Haeger, S.M., and Wang, X.J. (2010). Epidermal Smad4 deletion results in aberrant wound healing. Am. J. Pathol. *176*, 122–133.

Park, E.J., Lee, J.H., Yu, G.Y., He, G., Ali, S.R., Holzer, R.G., Osterreicher, C.H., Takahashi, H., and Karin, M. (2010). Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. Cell *140*, 197–208.

Peter, M.E., Budd, R.C., Desbarats, J., Hedrick, S.M., Hueber, A.O., Newell, M.K., Owen, L.B., Pope, R.M., Tschopp, J., Wajant, H., et al. (2007). The CD95 receptor: Apoptosis revisited. Cell *129*, 447–450.

Pikarsky, E., Porat, R.M., Stein, I., Abramovitch, R., Amit, S., Kasem, S., Gutkovich-Pyest, E., Urieli-Shoval, S., Galun, E., and Ben-Neriah, Y. (2004). NF-kappaB functions as a tumour promoter in inflammation-associated cancer. Nature *431*, 461–466.

Popivanova, B.K., Kitamura, K., Wu, Y., Kondo, T., Kagaya, T., Kaneko, S., Oshima, M., Fujii, C., and Mukaida, N. (2008). Blocking TNF-alpha in mice reduces colorectal carcinogenesis associated with chronic colitis. J. Clin. Invest. *118*, 560–570.

Qureshi, A.M., Hannigan, A., Campbell, D., Nixon, C., and Wilson, J.B. (2011). Chitinase-like proteins are autoantigens in a model of inflammation-promoted incipient neoplasia. Genes Cancer *2*, 74–87.

Rebouissou, S., Amessou, M., Couchy, G., Poussin, K., Imbeaud, S., Pilati, C., Izard, T., Balabaud, C., Bioulac-Sage, P., and Zucman-Rossi, J. (2009). Frequent in-frame somatic deletions activate gp130 in inflammatory hepatocellular tumours. Nature *457*, 200–204.

Rodier, F., Coppé, J.P., Patil, C.K., Hoeijmakers, W.A., Muñoz, D.P., Raza, S.R., Freund, A., Campeau, E., Davalos, A.R., and Campisi, J. (2009). Persistent DNA damage signalling triggers senescence-associated inflammatory cytokine secretion. Nat. Cell Biol. *11*, 973–979.

Rudolph, R., and Zelac, D.E. (2004). Squamous cell carcinoma of the skin. Plast. Reconstr. Surg. *114*, 82e–94e.

Sakurai, T., He, G., Matsuzawa, A., Yu, G.Y., Maeda, S., Hardiman, G., and Karin, M. (2008). Hepatocyte necrosis induced by oxidative stress and IL-1 alpha release mediate carcinogen-induced compensatory proliferation and liver tumorigenesis. Cancer Cell *14*, 156–165.

Saleh, M., and Trinchieri, G. (2011). Innate immune mechanisms of colitis and colitis-associated colorectal cancer. Nat. Rev. Immunol. *11*, 9–20.

Savill, J., Dransfield, I., Gregory, C., and Haslett, C. (2002). A blast from the past: Clearance of apoptotic cells regulates immune responses. Nat. Rev. Immunol. *2*, 965–975.

Scaffidi, P., Misteli, T., and Bianchi, M.E. (2002). Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. Nature *418*, 191–195.

Schiechl, G., Bauer, B., Fuss, I., Lang, S.A., Moser, C., Ruemmele, P., Rose-John, S., Neurath, M.F., Geissler, E.K., Schlitt, H.J., et al. (2011). Tumor development in murine ulcerative colitis depends on MyD88 signaling of colonic F4/80+CD11b(high)Gr1(low) macrophages. J. Clin. Invest. *121*, 1692–1708.

Schioppa, T., Moore, R., Thompson, R.G., Rosser, E.C., Kulbe, H., Nedospasov, S., Mauri, C., Coussens, L.M., and Balkwill, F.R. (2011). B regulatory cells and the tumor-promoting actions of TNF-α during squamous carcinogenesis. Proc. Natl. Acad. Sci. USA *108*, 10662–10667.

Schonthaler, H.B., Guinea-Viniegra, J., and Wagner, E.F. (2011). Targeting inflammation by modulating the Jun/AP-1 pathway. Ann. Rheum. Dis. *70* (*Suppl 1*), i109–i112.

Schwartz, M., Roayaie, S., and Konstadoulakis, M. (2007). Strategies for the management of hepatocellular carcinoma. Nat. Clin. Pract. Oncol. *4*, 424–432.

Shankaran, V., Ikeda, H., Bruce, A.T., White, J.M., Swanson, P.E., Old, L.J., and Schreiber, R.D. (2001). IFNgamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity. Nature *410*, 1107–1111.

Sharma, A., Ray, R., and Rajeswari, M.R. (2008). Overexpression of high mobility group (HMG) B1 and B2 proteins directly correlates with the progression of squamous cell carcinoma in skin. Cancer Invest. *26*, 843–851.

Sieweke, M.H., Thompson, N.L., Sporn, M.B., and Bissell, M.J. (1990). Mediation of wound-related Rous sarcoma virus tumorigenesis by TGF-beta. Science *248*, 1656–1660.

Smyth, M.J., Takeda, K., Hayakawa, Y., Peschon, J.J., van den Brink, M.R., and Yagita, H. (2003). Nature's TRAIL—on a path to cancer immunotherapy. Immunity *18*, 1–6.

Stairs, D.B., Bayne, L.J., Rhoades, B., Vega, M.E., Waldron, T.J., Kalabis, J., Klein-Szanto, A., Lee, J.S., Katz, J.P., Diehl, J.A., et al. (2011). Deletion of p120-catenin results in a tumor microenvironment with inflammation and cancer that establishes it as a tumor suppressor gene. Cancer Cell *19*, 470–483.

Stockmann, C., Doedens, A., Weidemann, A., Zhang, N., Takeda, N., Greenberg, J.I., Cheresh, D.A., and Johnson, R.S. (2008). Deletion of vascular endothelial growth factor in myeloid cells accelerates tumorigenesis. Nature *456*, 814–818.

Swann, J.B., and Smyth, M.J. (2007). Immune surveillance of tumors. J. Clin. Invest. *117*, 1137–1146.

Takahashi, H., Ogata, H., Nishigaki, R., Broide, D.H., and Karin, M. (2010). Tobacco smoke promotes lung tumorigenesis by triggering IKKbeta- and JNK1-dependent inflammation. Cancer Cell *17*, 89–97.

Tan, W., Zhang, W., Strasner, A., Grivennikov, S., Cheng, J.Q., Hoffman, R.M., and Karin, M. (2011). Tumour-infiltrating regulatory T cells stimulate mammary cancer metastasis through RANKL-RANK signalling. Nature *470*, 548–553.

Tergaonkar, V., Pando, M., Vafa, O., Wahl, G., and Verma, I. (2002). p53 stabilization is decreased upon NFkappaB activation: A role for NFkappaB in acquisition of resistance to chemotherapy. Cancer Cell *1*, 493–503.

Torchinsky, M.B., Garaude, J., Martin, A.P., and Blander, J.M. (2009). Innate immune recognition of infected apoptotic cells directs T(H)17 cell differentiation. Nature *458*, 78–82.

Tosolini, M., Kirilovsky, A., Mlecnik, B., Fredriksen, T., Mauger, S., Bindea, G., Berger, A., Bruneval, P., Fridman, W.H., Pagès, F., and Galon, J. (2011). Clinical impact of different classes of infiltrating T cytotoxic and helper cells (Th1, th2, treg, th17) in patients with colorectal cancer. Cancer Res. *71*, 1263–1271.

Tuncman, G., Hirosumi, J., Solinas, G., Chang, L., Karin, M., and Hotamisligil, G.S. (2006). Functional in vivo interactions between JNK1 and JNK2 isoforms in obesity and insulin resistance. Proc. Natl. Acad. Sci. USA *103*, 10741–10746.

Udono, H., and Srivastava, P.K. (1994). Comparison of tumor-specific immunogenicities of stress-induced proteins gp96, hsp90, and hsp70. J. Immunol. *152*, 5398–5403.

Uemura, N., Okamoto, S., Yamamoto, S., Matsumura, N., Yamaguchi, S., Yamakido, M., Taniyama, K., Sasaki, N., and Schlemper, R.J. (2001). Helicobacter pylori infection and the development of gastric cancer. N. Engl. J. Med. *345*, 784–789.

Velnar, T., Bailey, T., and Smrkolj, V. (2009). The wound healing process: An overview of the cellular and molecular mechanisms. J. Int. Med. Res. *37*, 1528–1542.

Ventura, J.J., Cogswell, P., Flavell, R.A., Baldwin, A.S., Jr., and Davis, R.J. (2004). JNK potentiates TNF-stimulated necrosis by increasing the production of cytotoxic reactive oxygen species. Genes Dev. *18*, 2905–2915.

Wang, H., Lafdil, F., Wang, L., Park, O., Yin, S., Niu, J., Miller, A.M., Sun, Z., and Gao, B. (2011). Hepatoprotective versus Oncogenic Functions of STAT3 in Liver Tumorigenesis. Am. J. Pathol. *179*, 714–724.

Widera, D., Mikenberg, I., Elvers, M., Kaltschmidt, C., and Kaltschmidt, B. (2006). Tumor necrosis factor alpha triggers proliferation of adult neural stem cells via IKK/NF-kappaB signaling. BMC Neurosci. *7*, 64.

Wu, S., Rhee, K.J., Albesiano, E., Rabizadeh, S., Wu, X., Yen, H.R., Huso, D.L., Brancati, F.L., Wick, E., McAllister, F., et al. (2009). A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. Nat. Med. *15*, 1016–1022.

Wynn, T.A. (2008). Cellular and molecular mechanisms of fibrosis. J. Pathol. *214*, 199–210.

Yang, J., Splittgerber, R., Yull, F.E., Kantrow, S., Ayers, G.D., Karin, M., and Richmond, A. (2010). Conditional ablation of Ikkb inhibits melanoma tumor development in mice. J. Clin. Invest. *120*, 2563–2574.

Yu, H., Pardoll, D., and Jove, R. (2009). STATs in cancer inflammation and immunity: A leading role for STAT3. Nat. Rev. Cancer *9*, 798–809.

Zaidi, M.R., Davis, S., Noonan, F.P., Graff-Cherry, C., Hawley, T.S., Walker, R.L., Feigenbaum, L., Fuchs, E., Lyakh, L., Young, H.A., et al. (2011). Interferon-γ links ultraviolet radiation to melanomagenesis in mice. Nature *469*, 548–553.

Zhang, L., Ren, X., Alt, E., Bai, X., Huang, S., Xu, Z., Lynch, P.M., Moyer, M.P., Wen, X.F., and Wu, X. (2010a). Chemoprevention of colorectal cancer by targeting APC-deficient cells for apoptosis. Nature *464*, 1058–1061.

Zhang, W., Kater, A.P., Widhopf, G.F., 2nd, Chuang, H.Y., Enzler, T., James, D.F., Poustovoitov, M., Tseng, P.H., Janz, S., Hoh, C., et al. (2010b). B-cell activating factor and v-Myc myelocytomatosis viral oncogene homolog (c-Myc) influence progression of chronic lymphocytic leukemia. Proc. Natl. Acad. Sci. USA *107*, 18956–18960.

Zitvogel, L., Kepp, O., and Kroemer, G. (2010). Decoding cell death signals in inflammation and immunity. Cell *140*, 798–804.