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 (Velan 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
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 (CAF’s) 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, 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.
such as IL-10 (Savill et al., 2002). The universality of this concept, phagocytes triggers the production of anti-inflammatory cytokines, and ionizing radiation, was found to be inflammatory (Casares and other chemotherapeutic agents, such as anthracyclines, however, has been challenged because apoptosis induced by cation (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 conse-
quent 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-1\(\alpha\), “danger-associated molecular patterns” (DAMPs) such as calreticulin, HMG-1, and S100A8 and 9 proteins (Ghir- inghelli 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 (Scalfi 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. Pyroptic 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-1\(\alpha\) 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

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 (M\(\theta\)), 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, M\(\theta\) 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 conse-

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case, activation of inflammatory pathways either parallels cell death or can be triggered by cell stress in the absence of death. Oncogene death can be activated (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 (Grievnikov 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 (Grievnikov 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 (Grievnikov 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 ApcMin 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 prosurvival cytokine, renders metastatic colon cancer cells susceptible to the cytotoxic 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 methylicholanthrene 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
 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 G0 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 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...
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 (CCl₄) (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 CCl₄, 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-kB 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 (Dajeel 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 (Nickloff 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 (Siegel 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 dextran 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; Schiechtl 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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