Virus Infection, Inflammation and Prevention of Cancer

Norman Woller and Florian Kühnel

Abstract

Our molecular understanding of cancer biology has made substantial progress during the last two decades. During recent years it became evident that inflammation is a major driving force in tumor development since chronic virus infection and carcinogenesis are closely correlated. These insights refined our view on the decisive role of persistent virus infection and chronic inflammation in tumor onset, growth, and metastatic progression. Explanations have been delivered how tumor cells interact and correspond with neighbouring epithelia and infiltrating immune cells for shaping the so-called 'tumor-microenvironment' and establishing tumor-specific tolerance. This extended view on malignant diseases should now allow for rational design of interventions targeting inflammation and underlying pathways for prevention and therapy of inflammation-associated cancer. This chapter outlines the role of virus-mediated inflammations in tumorigenesis thereby shedding light on the mechanisms of cancer-related inflammation and on characteristic features of the tumor-microenvironment, which has been recently identified to play a key role in maintenance and progression of tumors. Finally, the chapter discusses latest aspects in prevention of inflammation-related cancer and provides a short outlook on the future prospects of cancer immunotherapy.

N. Woller · F. Kühnel (✉)
Clinic for Gastroenterology, Hepatology, and Endocrinology, Hannover Medical School, Carl-Neuberg-Str. 1, 30625, Hannover, Germany
e-mail: Kuehnel.Florian@mh-hannover.de

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In the 19th century, Rudolph Virchow hypothesized that tissue injury precedes tumor development at the same locus. Observations of leukocyte infiltrations in tumor tissue let him speculate that inflammatory processes of wound healing may be involved in tumor development (Balkwill and Mantovani 2001). Picking up these ideas, tumors have been later described as a result of 'possible overhealing' (Haddow 1972) or as 'wounds that do not heal' (Dvorak 1986) thereby referring to obvious similarities between tumor growth and wound healing such as fibroblast activation, attraction of leukocytes, cell proliferation and angiogenesis. During the last two decades, this notion was supported by molecular evidence confirming that inflammatory processes are essentially involved in the development of tumor and in emergence of metastases (Karin 2006; Guerra et al. 2007). With regard to etiology of cancer, germline mutations play a minor role in the development of cancer whereas up to 90 % of all cancers are associated with acquired somatic mutations, which are mainly acquired by environmental and life style factors. 30 % of global malignancies can be attributed to tobacco smoking and 35 % are due to dietary factors including obesity (Aggarwal et al. 2009). An estimated 20-25 % of the global cancer burden is associated with pathogen inflammations, the vast majority due to unresolved, persistent virus infections that drive inflammation (Hussain and Harris 2007; Parkin 2006). Moreover, an inflammatory component is also present in the microenvironment of tumors that are epidemiologically not related to classical pathogen infections but to other environmental risk factors such as tobacco smoking or inhalation of silica fibres thus illustrating the general role of inflammation in carcinogenesis. In this review, we summarize the key aspects of the role of virus-associated infections and inflammations for tumor development, and discuss applicable measures to prevent infection-associated cancers. Hereby, we will focus on infection-associated inflammatory processes involved in carcinogenesis that may offer attractive molecular targets for pharmacologic means in cancer prevention and therapy. In the following section,

the clinically most relevant virus types that cause chronic tissue inflammation and cancer are briefly introduced.

1 Chronic Virus Infection as a Cause of Cancer

Virus infections belong to the most important causes of cancer (de Martel and Franceschi 2009). Among those tumors that are related to virus infections, solid tumors in the liver and cervix uteri are the most relevant entities in terms of global health burden. These tumors are mainly attributable to hepatitis B and C virus (HBV; HCV) and human papilloma virus (HPV), respectively. HBV is a small DNA virus from the hepadnavirus family which can be transmitted between humans mainly via blood contact or sexual intercourse. Liver infections by HBV frequently lead to severe complications such as acute hepatitis including the risk of liver failure and furthermore to cirrhosis and hepatocellular carcinoma if the infection persists. The causal relationship between HBV and HCC development is well established (Chen et al. 2006) and conservatively estimated 54 % of liver cancer cases are due to HBV infection. Though an effective vaccination is available since more than 20 years, HBV remains a major health problem since approximately 360 million chronic HBV carriers exist worldwide (Shepard et al. 2006; Custer et al. 2004). The risk to develop HCC as a late complication of liver infection is closely linked to the duration of the virus-mediated inflammation. Several pathogenic mechanisms are involved including oncogenic effects mediated by HBV proteins (such as HBx), by mutagenic insertion of parts of the viral DNA into the host cell genome, and by T cell-dependent autoimmunity (Farazi and DePinho 2006).

A second virus that is significantly involved in the development of liver cancer is HCV, a single stranded RNA virus from the flavivirus family. HCV infection is a blood borne disease that chronically infects 3 % of the world's population (Shepard et al. 2005). HCV-positive individuals have a highly significant risk to develop an HCC (Donato et al. 1998) and about 31 % of liver cancer cases are due to chronic HCV infections. The underlying pathogenetic mechanisms are not fully understood. As in case of HBV, HCV can establish persistent infections and malignant transformation results from a longer-lasting process of coincident inflammation, cell death and tissue renewal. Molecular studies have shown that several HCV proteins such as NS3, NS4B, NS5A and core actually have oncogenic potential (Farazi and DePinho 2006; Barth et al. 2008).

A further virus involved in development of infection- and inflammation-associated solid tumors is human papilloma virus (HPV) (Parkin and Bray 2006). HPV is a non-enveloped DNA virus that can induce benign and malignant lesions of skin and mucosa. The course of infection is usually asymptomatic and local immunity leads to virus clearance in most individuals (Plummer et al. 2007). In about 10 % of infected women HPV establishes a persistent infection, which elevates the risk for cervix cancer development. Among 100 different genotypes,

several HPV strains are regarded as high risk strains due to their causal correlation with development of cervix carcinoma. In this context, the most virulent HPV-16 and HPV-18 genotypes account for the majority of cervical neoplasias (Smith et al. 2007). The pathogenic mechanisms underlying HPV-mediated oncogenesis are relatively well studied. Chronic infection with HPV is accompanied by integration of viral DNA sequences into the DNA of the host cell. The expression of early viral genes such as E6/E7 from viral integrates interferes with the activity of the tumor suppressors p53 and Rb, thus activating the cell cycle and inhibiting intrinsic apoptosis. Additional immunological or mutagenic influence factors can further promote cell transformation and tumor growth.

A further example for a clinically relevant oncogenic pathogen is the Epstein-Barr virus (EBV) which has been associated with several hematological malignancies such as Burkitt's lymphoma, Hodgkin- and non-Hodgkin-lymphoma. Further tumor-associated viruses are the human herpes virus 8 (HHV-8), the causal pathogen for Kaposi Sarcoma, the human T cell leukemia virus type 1 (HTLV-1), and Merkel cell polyoma virus.

2 Inflammation and Cancer

2.1 The Interconnection Between Inflammation and Tumor Development

Under steady-state conditions, maintenance of tissue-integrity and cell renewal is tightly regulated by the host. Upon disturbance of tissue-integrity by pathogen infection or tissue damage, an acute inflammation is elicited, a locally and timely limited immune mechanism that enables both effective elimination of the pathogen and wound healing responses. Though the preferential goal of an acute inflammation is the pathogen-free reconstitution of tissue integrity, infection is eventually not completely cleared by acute inflammatory mechanisms. This consequently is leading over to a chronic inflammatory response, which is in coincidental balance with pathogen persistence. Two events appear to be fundamental to establish chronic virus-mediated inflammations. First, tumor-associated viruses must find ways to subvert the host's antiviral immune defense or to retreat into immunoprivileged niches to persist in a latent state. Second, the rigor of antiviral immune responses must be adjusted to levels that outbalance sufficient control of viremia and prevention of severe immunopathology in the infected organ. These persistent infections lead to a mild, but chronic inflammation. In persistent infections, cells are not only subject of transformation by viral oncogenes. Accumulation of tumor-prone genetic alterations is also accelerated by enhanced cell turnover during chronic inflammations. Both features, chronic inflammation and viral transformation of cells, are important events of tumorigenesis (Rakoff-Nahoum and Medzhitov 2009). Moreover, inflammation has been identified to be of utmost importance to promote virtually every step of tumorigenesis (Karin 2006). Even

the involvement of inflammatory processes in initial cell transformation is a matter of discussion. It has been shown that inflammation may increase mutation frequency in tissues even in the absence of defined extrinsic triggers (Sato et al. 2006; Bielas et al. 2006). Inflammatory mechanisms are involved in the process of 'immunosurveillance' which effectively limits tumor development at a very early stage. Triggered by aberrant oncogene activation, induction of cellular senescence in liver cells consequently leads to the elimination of senescent cells, orchestrated by CD4 T cells and M1 macrophages (Kang et al. 2011). On the other hand, immunosuppression or overcoming and escape from senescence further promote tumorigenesis at an early stage by inflammatory mechanisms such as senescence-associated cytokine secretion (Rodier et al. 2009).

Once an early neoplastic nodule is established, several kinds of leukocytes and mesenchymal cells are attracted, which establish the tumor-microenvironment and provide cancer cells with supplemental growth stimuli and cytokines. This smoldering inflammatory tumor-microenvironment is vital for tumor development and has been generally accepted as another hallmark of cancer (Hanahan and Weinberg 2011). These observations also attracted much attention towards the contribution of non-malignant cells to the tumor-microenvironment, their interactions, the released signalling molecules and central molecular pathways.

2.2 Cytokine Signalling and Molecular Pathways in Tumor-Associated Inflammation

Tumor-associated inflammation and tumorigenesis are closely interconnected mechanisms with the inflammatory process as a predominant driver of the malignant disease. Crucial endogenous factors of tumor-associated inflammation have already been identified in numerous studies such as the signal transducer activator of transcription-3 (STAT-3) and the transcription factor NFκB. These transcriptional activators are essentially involved in signal transduction and/or expression of inflammatory cytokines playing a role in tumor-associated inflammation, such as TNF-α, IL-6, IL-1β, IL-11, and IL-23 (Grivennikov et al. 2009; Fukuda et al. 2011; Lesina et al. 2011; Voronov et al. 2003; Langowski et al. 2006). NFκB is a well known key orchestrator in innate immune and inflammatory responses and is activated in both tumor cells as well as in immune cells involved in tumor-associated inflammation. NFκB translates a panoply of extrinsic and intrinsic danger signals into specific gene activation. NFκB lies downstream of toll-like-receptor (TLR)-MyD88 dependent pathways and processes signals from receptors of inflammatory cytokines such as TNF-α and IL-1β. Additionally, NFκB can be upregulated by endogenous genetic alterations in cancer cells. Upon upstream signalling, NFκB activates expression of proinflammatory factors such as cytokines, adhesion molecules, NO-synthase, stimulators of angiogenesis, and COX2, a crucial enzyme in prostaglandin synthesis. NFκB as well as STAT3 promote cell survival by expression of the antiapoptotic mediators Bcl-2, Bcl-XL,

Mcl-1, c-Flip, survivin, and IAPs thereby conferring resistance against antitumoral immune responses in cancer surveillance. Additionally, links between NFκB activation and the hypoxic response have been reported (Rius et al. 2008). Both NFκB and STAT3 also interfere with p53 functions in genome surveillance, DNA damage response and intrinsic apoptosis (Colotta et al. 2009; Ryan et al. 2000).

2.3 The Inflammatory Tumor-Microenvironment

Most prominent cells of the immune system recruited to the tumor-microenvironment are tumor-associated macrophages (TAMs). This cell type reflects a subtype of the monocyte-macrophage lineage and may be obligatory for invasion, metastasis, and angiogenesis (Condeelis and Pollard 2006). Due to the plasticity and diversity of these cells, two fundamental phenotypes are distinguished. The classical M1 activation is mediated by TLR ligands and IFN-γ, whereas alternative M2 activation is stimulated by IL-4/IL-13. The polarization of M1-M2 mirrors the polarization of Th1-Th2 T cells. M1 macrophages promote Th1 responses and release high levels of proinflammatory cytokines, reactive oxygen species and reactive nitrogen intermediates, whereas M2 polarized macrophages display immunoregulatory functions, promote tissue remodeling and display high expression of scavenger receptors (Gordon and Martinez 2010; Biswas and Mantovani 2010; Mantovani et al. 2002). TAMs found in advanced stages during tumor-development generally display an M2-like phenotype, which is characterized by a tumor-promoting activity of tissue-remodelling and angiogenesis together with a high IL-10 expression. These cells are polarized by tumor-resident lymphocytes of different origin, depending on the organ (Biswas and Mantovani 2010). In breast carcinogenesis, plasma cells promote TAM-polarization (DeNardo et al. 2009; Pedroza-Gonzalez et al. 2011) whereas in development of skin tumors IL-4 secreting Th2 cells induce the M2-like phenotype (Schioppa et al. 2011; Andreu et al. 2010). Additionally, tumor cells have the ability to directly influence macrophages towards a cancer-promoting mode by secretion of different components. These include components of the extracellular matrix, the cytokines M-CSF and IL-10, and chemokines like CCL2, CCL17, CCL18, and CXCL4 (Mantovani et al. 2008; Erler et al. 2009; Kim et al. 2009; Roca et al. 2009). It has been shown, that a high TAM infiltration correlates with a poor prognosis (Murdoch et al. 2008).

Besides the central role of TAMs, several other innate and adaptive immune cells are found in the tumor-microenvironment, and for almost all of them a protumorigenic role has been demonstrated. These include T and B cells, dendritic cells, mast cells, myeloid-derived suppressor cells, and neutrophils. Only NK cells lack an established tumor-supporting function so far. Mature T cells present in solid tumors are classically defined as cytotoxic CD8 T cells (CTLs) and CD4 helper cells (Th). The latter are further classified in Th1, Th2, Th17, and regulatory T (Treg) cells. The polarization of these cells dictate, whether T cell subsets (including CD8 T cells) promote tumor development and metastasis (Roberts et al.

2007). Additionally, polarization correlates with survival in some cancers, due to invasion of tumor-specific CTLs and Th1 cells, as shown in melanoma, pancreatic cancer, colon cancer, and multiple myeloma (Galon et al. 2006; Laghi et al. 2009; Swann and Smyth 2007). Moreover, presence of tumor-infiltrating lymphocytes (TILs) with high ratios of CD8/CD4 and Th1/Th2 indicates an improved prognosis in breast cancer (Kohrt et al. 2005). Treg cells are mainly suspected to mediate tumor tolerance by suppression of antitumor immune responses (Gallimore and Simon 2008). However, Erdman and colleagues could demonstrate that Tregs can also inhibit cancer-associated inflammation thereby playing an antitumorigenic role in malignant diseases (Erdman et al. 2005). Myeloid-derived suppressor cells (MDSCs) are often recruited and activated by the inflammatory tumor-microenvironment by multiple factors, such as IL-6, IL-1ß, and VEGF (Gabrilovich and Nagaraj 2009). Activated MDSCs in turn release pro-inflammatory factors which results in a positive feedback loop promoting cancer-associated inflammation. Furthermore, MDSCs are not only capable to suppress adaptive immune responses, but also influence the cytokine production of macrophages (Sinha et al. 2007). Tumor-associated neutrophils (TAN) have been identified to play a role in cancer-related inflammation as well (Cassatella et al. 2009; Mantovani 2009). Their previously unnoticed plasticity can exert tumor-promoting and tumoricidal functions, depending on the polarization by TGF-ß (Fridlender et al. 2009).

Cancer-associated fibroblasts (CAFs) are a major component of the tumor stroma and an integral part of the cancer-related inflammatory environment. They are activated by IL-1 and share many characteristics with activated fibroblasts in wound healing processes. CAFs have a proinflammatory signature and promote tumor growth and angiogenesis (Erez et al. 2010).

During tumorigenesis, malignant cells frequently interact with immune cells resulting in their polarization into a tumor-supportive phenotype. The tumor-microenvironment is to a large extent borne by feedback of these tumor-promoting immune cells finally mediating tolerance by adaptation and manipulation of infiltrating lymphocytes within the tumor-microenvironment.

Many, if not all innate and adaptive immune cells that are involved in tumor development, exhibit a more or less significant plasticity, which can even be reverted under certain conditions (Sharma et al. 2010; Fridlender et al. 2009). Therefore, it can be assumed that cancer-associated inflammation and antitumor immunity are able to coexist simultaneously and thereby mutually affect each other during tumor progression. However, a growing tumor mass might finally quench antitumor immunity, thus achieving the tumor's complete immune escape in advanced stages of tumor development (Koebel et al. 2007).

2.4 Inflammation, Hypoxia and Angiogenesis in Tumor-Growth

Hypoxic conditions generally appear in solid malignancies, when the demand for oxygen and nutrients of a growing tumor is greater, than the blood supply is able to provide. At first, cells respond by induction of hypoxia-inducible factor (HIF1α),

which finally modifies glucose metabolism, angiogenesis and furthermore cell survival and invasion (Staller et al. 2003). Hypoxic conditions also result in necrotic cell death in the core of the tumor. These dying cells induce the proinflammatory mediators IL-1 and HMGB1, which additionally trigger angiogenesis and deliver further growth factors to the tumor environment (Vakkila and Lotze 2004). However, besides hypoxia, tumor neoangiogenesis is moreover driven by TAMs, which recognize hypoxia and respond with the release of angiopoetin 2 and VEGF. It is important to note, that proangiogenic genes in TAMs and other cell types are regulated by AP1, STAT3, and the NF-κB-pathway (Kujawski et al. 2008; Rius et al. 2008). So far, it cannot be finally concluded, whether hypoxia is sufficient to induce neoangiogenesis or whether the inflammatory mediators activated by hypoxia are the key drivers of angiogenesis.

2.5 T Cell Exhaustion in Chronic Viral Infection and Malignant Diseases

CD8 T cells play a pivotal role in antitumoral immune responses. Mature cytotoxic T cells are able to invade infected or tumor tissue and directly lyse target cells in an antigen-specific manner. Specificity is mediated by the $\alpha\beta$T cell receptor recognizing mutated or overexpressed self-antigens or antigens of viral origin presented on major histocompatibility complex (MHC) molecules of the putative target cell. Naïve antigen-specific CD8 T cells proliferate extensively following acute viral infection. First, they are activated by professional antigen-presenting cells (APCs), such as dendritic cells (DCs), which cross-present captured viral peptides and provide all necessary signals of costimulation. The expansion of naïve virus specific T cells after initial antigen stimulation is accompanied by the acquisition of effector functions, chemokine production and the ability to migrate towards the site of infection. The expanded population of pathogen-specific CD8 T cells normally facilitates clearance of the virus and after reaching the peak of clonal expansion, the virus-specific T cell population is subject to a rapid contraction, where most of the T cells undergo apoptosis. A small percentage of this cell population survives and establishes a pool of long-lived memory CD8 T cells that can be subdivided into effector memory (EM) and central memory (CM) T cells, depending on phenotypic markers (CD62L and CCR7). Upon rechallenge, memory cells can rapidly proliferate and exert effector functions thus providing protective immunity.

In contrast to the development of protective CD8 T cell immunity after acute infections, behaviour of CD8 T cells in chronic infections and cancer is dramatically altered. In the early course of chronic diseases, naïve pathogen- or disease-specific T cells are primed and initially gain effector functions. However, they are often incapable to differentiate into functional memory cells and effector functions deteriorate. This loss of function is also called T cell exhaustion. The process follows a hierarchical order, whereby exhausted T cells have impaired IL-2

production and proliferation, then acquiring improper cytolytic function and produce less TNF. Finally, fully exhausted T cells may even lose the ability to secrete IFN-γ (Zajac et al. 1998; Fuller and Zajac 2003; Wherry et al. 2003).

During exhaustion, CD8 T cells continually upregulate inhibitory receptors, including PD-1, Tim-3, LAG3, CD160 and 2B4 (Barber et al. 2006; Blackburn et al. 2009; Fourcade et al. 2010). Commonly, the need of T cell exhaustion is explained by the adjustment of the inflammatory response of the immune system towards viral antigens in order to limit viral replication on the one hand and on the other hand to avoid durable inflammation-mediated tissue damage in permanently infected tissue, if the host cannot fully eliminate the virus.

CD8 T cell responses in malignant diseases, directed against antigens expressed by the tumor, are frequently found in melanoma patients (Boon et al. 2006). The coexistence of spontaneously arising tumor-specific immune responses with progressive disease demonstrates a tumor-induced dysfunction in T cells as well. In cancer patients, the induction of tumor-specific T cells does not follow the mechanisms of acute viral infections. Tumor-tolerance mechanisms actively interfere with antitumoral immune responses and tumor-antigens further lack pathogen-associated molecular patterns (PAMPs) in malignant cells. This might lead to incomplete activation and licensing of cytotoxic T cells. Additionally, the constitutive antigenic challenge and the presence of an inflammatory tolerance-mediating tumor-microenvironment might further contribute to the malfunction of exhausted T cells (Fourcade et al. 2010; Baitsch et al. 2011).

The tumor-associated antigens (TAA) investigated in patients are often cancer-germline antigens (CGAs), which are expressed by tumor cells of different origins, but not by non-malignant cells, except the testis. The CGA NY-ESO-1 is often subject to spontaneous cellular and humoral responses that are detectable in patients with advanced NY-ESO-1-expressing tumors (Stockert et al. 1998; Mandic et al. 2005; Fourcade et al. 2008). Recent studies of spontaneous tumorantigen-specific CD8 T cells revealed upregulation of PD-1 and Tim-3 in mice and melanoma patients (Fourcade et al. 2010; Sakuishi et al. 2010; Baitsch et al. 2011). These two negative regulatory or immune checkpoint molecules are very important markers of T cell exhaustion in malignant diseases. PD-1 abrogates T cell receptor signaling and Tim-3 plays a role in promoting MDSCs and in regulating cytokine responses of myeloid cells (Dardalhon et al. 2010; Zhang et al. 2012).

Furthermore, PD-1 controls expansion of NY-ESO-1-specific CD8 T cells and PD-1/Tim-3 double positive cells have a more exhausted phenotype by production of less IFN-γ, IL-2 and TNF compared to single positive CD8 T cells in patients (Fourcade et al. 2010). Blockade of PD-1 and Tim-3 in animal models has been shown to partially restore T cell function and that combined targeting of Tim-3 and PD-1 pathways is more effective in tumor growth inhibition than either pathway alone (Sakuishi et al. 2010).

Interestingly, coexistence of TAA-specific CD8 cells with an effector profile were found in the circulation and exhausted cells were present in the tumor

environment of metastases from melanoma patients after vaccination with CpG and Melan–A/MART–1 (Baitsch et al. 2011).

3 Inflammation and Metastases

Metastases are a central aspect in clinical oncology because over 90 % of cancer mortality is attributable to metastases. Formation of metastases is a highly complex process including tumor cell motility, intravasation into the circulation, spread through the blood or the lymphatic system, extravasation and finally establishment and outgrowth of tumor-nodules in new tissues and organs. Approximately only 0.01 % of cancer cells that enter the circulation will successfully develop micrometastases (Joyce and Pollard 2009). The initially increased motility and invasiveness of metastatic tumor cells are caused by the epithelial-mesenchymal transition (EMT). In the process of EMT, epithelial cells aquire a fibroblast-like properties that increase their motility and facilitates to invade epithelial barriers and to cross the basal membrane towards the circulation (Kalluri and Weinberg 2009). The extravasation of premetastatic cells is mediated by integrins, followed by crosstalk with immune and stromal cells, which allow them to proliferate (Polyak and Weinberg 2009). It has been shown, that leukocytes pave the way for the construction of a premetastatic niche (Erler et al. 2009; Hiratsuka et al. 2006; Kaplan et al. 2006; Kaplan et al. 2005; Padua et al. 2008) and that the inflammatory stimuli is furthermore mediated by the extracellular matrix component versican, which in turn activates macrophages and leads to the secretion of the prometastatic cytokine TNF-α (Kim et al. 2009). Another prometastatic and anti-inflammatory cytokine is TGF-β. It mediates trans-endothelial migration and metastasis by induction of angiopoietin 4 and is secreted by cancer cells, myeloid cells, and T lymphocytes. Elevated levels of TGF-β therefore often indicate a poor prognosis (Yang and Weinberg 2008).

4 Prevention of Inflammation-Associated Cancer

Cancers that are related to chronic viral infections, can be addressed at different stages during tumorigenesis (feasible interventions are summarized in Fig. 1). First of all, effective vaccinations are fundamental, not only to prevent acute infection-related illness, but also to finally prevent the development of cancer as late complication of the underlying viral infection. Patients that have suffered from an infection once in their life by viruses that are known to cause enhanced cancer risk must be routinely monitored for chronification. Chronically-infected patients need state of the art pharmacologic treatments to reduce viral loads to the most possible extend or, at its best, to finally heal up the infection. Furthermore, patients with chronic infections have to be carefully investigated for signs of precancerous lesions of the affected tissue. In this case, therapeutic interventions to inhibit or

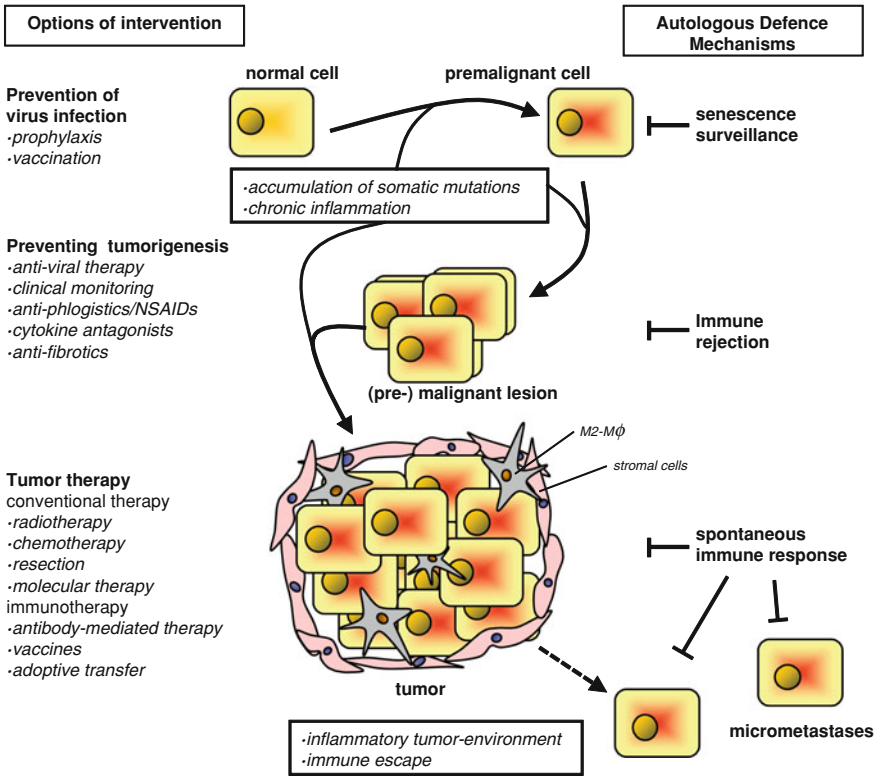

Fig. 1 The figure illustrates different stages of the development of inflammation-associated cancer, the corresponding host's immune defense mechanisms involved in tumor prevention and applicable interventions to prevent or treat cancer

even revert tissue organization should be considered in particular for those individuals that have a genetic predisposition for cancer. Since chronic inflammation promotes carcinogenesis and dissemination, long-term antiphlogistic treatment could represent a suitable cancer-preventive regimen for infected patients. Concrete means to address the above listed options for prevention of virus-mediated cancers are presented in the following section.

4.1 Antiviral Vaccinations and Therapies

HBV, HCV, or HPV are causative for the vast majority of solid cancers that are associated with chronic virus infections and infection-related inflammation.

The options to prevent HBV-related HCC is to ward off acquisition of chronic HBV infection for risk groups like intravenous drug-addicts or recipients of blood-infusions. Furthermore, effective vaccines against HBV exist since more than

20 years. Vaccination programs, including passive immunizations as part of a post-exposition-prophylaxis for children of HBV infected women, have led to a dramatic reduction of HBV carriers, and to a reduction of HCC during childhood (Chang et al. 1997). HBV vaccination is now part of the National Infant Immunization Schedule in 162 countries and represents the first example of cancer preventive vaccination. However, the actual clinical benefit of the ongoing vaccination programs on mortality due to HBV-related HCC will become apparent after further decades (Zanetti et al. 2008). Additionally, routine HBsAg-screening of blood donors will help to reduce blood transfusion-associated transmission of HBV (Schreiber et al. 1996). For the multitude of chronically HBV-infected persons, HBV vaccinations would not be effective in preventing HCC. Here, control of HBV viremia is the major therapeutic goal to reduce hepatic inflammation and disease progression to cirrhosis and HCC. If liver histologic diagnosis in chronic HBV carriers indicates the requirement of a therapeutic intervention, interferon-α and/or nucleoside analoga are applied to control the viral burden, a management that additionally has the beneficial effect to avoid HCC development. However, resistance development to nucleoside analoga remains a problem (Colombo and Donato 2005).

Unfortunately, no functional vaccines against HCV are available to prevent HCV-associated HCC. Only a few vaccine candidates have proceeded to clinical phase I/II trials but it is not yet clear whether these will reach clinical applicability (Torresi et al. 2011). Whereas effective vaccination strategies are still under investigation, significant advances have been made in the treatment of both acute and chronic HCV infection. With current medical therapy, based on pegylated IFN-α and ribavirin, approximately 50 % of patients can be cured. However, the recently developed 'directly acting viral agents' (DAAs) such as inhibitors of the NS3/4A protease or cyclophilin B inhibitors, promise further improvements to achieve sustained virologic responses in treatment of HCV infection (Patel and Heathcote 2011; Kronenberger and Zeuzem 2012; McHutchison et al. 2009).

In case of HPV, the availability of an effective vaccine represents a milestone for prevention of cervical cancer worldwide. Bivalent and quadrivalent vaccines prepared from empty virus shells (virus-like-particles) effectively prevent infection by high-risk HPV genotypes 16 and 18 that account for 70 % of cervical cancer (Garland et al. 2007; Paavonen et al. 2007). Some protection against other genotypes related to 16/18 has been reported (Joura et al. 2007).

4.2 Antifibrotic Therapy

Transient fibrogenesis and later reversal of fibrotic scar tissue is a hallmark of wound healing. Though not fully understood, the mechanisms of perpetuating fibrogenesis in case of chronic tissue damage and their fatal consequences have been intensively studied in the liver. Liver cirrhosis, the end stage of fibrotic reorganization of liver tissue, is a frequent complication of chronic HBV or HCV

infections. Liver cirrhosis is associated with portal hypertension, reduced liver functions, and with an increased risk at developing HCC. A heterogenous cell population of profibrogenic myofibroblasts (MFB), originating from hepatic stellate cells (HSC) is known to orchestrate liver fibrogenesis (Lee and Friedman 2011). Upon liver injury and inflammation, a key event in the onset of fibrosis is the activation of quiescent HSCs, that can be triggered by several factors including reactive oxygen species, TLR4 ligands, uptake of apoptotic bodies and paracrine stimulation by adjacent hepatocytes, Kupffer cells and liver sinusoidal endothelial cells (LSEC). The perpetuation of the fibrogenic phenotype of MFB mainly results from a microenvironment wherein profibrogenic cytokines and growth factors such as TGF-β and PDGF are dominating. Activated cholangiocytes have been identified as an important source of these profibrogenic mediators. Phenotypic markers of activated MFBs are expression of α-smooth muscle actin (SMA), excessive collagen production, enhanced proliferation and reduced lipid content contributing to tissue stiffness. With regard to specific gene regulation, it has been shown that angiotensin 2 activates the transcription factor NF-κB thus rendering MFBs less sensitive against induction of apoptosis and promoting cell survival (Oakley et al. 2009). Recent data demonstrated that activation of the NF-κB pathway in hepatocytes induces liver fibrosis in mice (Sunami et al. 2012). Accumulation of extracellular matrix (ECM) is a further characteristic of fibrogenesis which contributes to tissue stiffening. Major regulators of ECM are matrix metalloproteinases (MMP), enzymes that are responsible for matrix degradation and removal of scar tissue. Net production of ECM results from a dysbalance of MMP expression, and secretion of their specific inhibitors (tissue inhibitors of metalloproteinases or TIMPs) by MFBs. During physiological regeneration and repair of liver damage, mechanisms exist that can mediate regression of fibrotic scar tissue once the initial cause of tissue damage has been resolved. In this process, MFBs finally disappear from the hepatic scar by phenotypic reversion, senescence, and deletion by natural killer cells. Thereby, fibrotic tissue is removed by enhanced MMP activity and reduced TIMP levels. Hepatic macrophages have been demonstrated to be involved in this regulation and scar tissue remodeling.

The ideal anti-fibrotic therapy consists of the withdrawal of the underlying disease trigger. Virus elimination in chronic HBV or HCV infection can lead to regression of fibrosis and improved liver function even in cirrhotic patients. For patients that do not sufficiently respond to antiviral treatments, specific antifibrotic therapies are urgently needed to slow down the progress of fibrosis and to reduce the risk of late stage complications and HCC development. Patients with increased risk at developing fibrosis should be determined by targeted screenings. As example, a 'seven gene signature' with specific polymorphisms in genes with relevance to fibrosis risk such as e.g. TGF-β, TNF-α, or IL-10, has a significant predictive value (cirrhosis risk score) for fibrosis progression in patients with chronic HCV (Huang et al. 2007). Consequent monitoring of those patients to determine progression of fibrosis should be performed. Non-invasive methods like Fibroscan, a sonographic evaluation of liver stiffness, could be valuable alternatives to liver biopsy in the future. Combined with serologic markers like

α-fetoprotein this allows for detecting HCC at an early, potentially curable stage (Mok et al. 2005). For antifibrotic therapies, all molecular factors or mechanisms that contribute to progression or regression of fibrosis can be considered suitable targets (Fallowfield 2011). Liver damage due to inflammation and oxidative stress can be addressed by so-called hepatoprotectants. The hepatoprotective activity of some of these substances can be attributed to their ability to suppress the inflammatory activation of NFκB. A number of natural substances that can be long-term consumed in significant amounts have been investigated for their antioxidant and hepatoprotective effect such as resveratrol (from red wine), silymarin (from milk thistle), coffee and vitamin E.

Hepatocyte growth factor (HGF) has been identified to stimulate hepatocyte generation and demonstrated promising results in inhibition of experimental fibrosis in animal models (Xia et al. 2006). However, since HGF is a potent mitogen for hepatocytes, concerns about potential oncogenesis remain. A further potential target is the reduction of apoptotic cell turnover during liver inflammation. Apoptosis of hepatocytes activates HSC directly or via Kupffer cells. Consequently, the pan-caspase inhibitor VX-166 demonstrated antifibrotic activity in animal models (Witek et al. 2009). In contrast, pro-apoptotic strategies could also be an alternative if cell death can be selectively induced in activated HSC. To this end, the proapoptotic IkB inhibitor gliotoxin has been coupled to a single-chain antibody against synaptophysin which is selectively expressed on these cells. This approach reduced fibrosis in a rat model of CCl_4 intoxication (Douglass et al. 2008). As an alternative strategy to induce apoptosis of activated HSC, interference with cannabinoid receptor signaling has led to promising results in fibrotic animal models (Teixeira-Clerc et al. 2006), but showed psychomimetic side effects in clinical trials. Further strategies to prevent HSC activation like ligands ("glitazones") for the peroxisome proliferator-activator receptor-γ (PPAR-γ), Farnesoid-X-receptor-agonists, or HMG-CoA reductase inhibitors ("statins") have shown antifibrotic activity in experimental models that awaits confirmation in clinical trials. Angiotensin system inhibitors are on the cusp to clinical application. Both angiotensin-converting enzyme inhibitors and angiotensin-1 receptor antagonists ("sartans") can inhibit fibrosis in animals. Importantly, the AT1R antagonist losartan slowed down progression of fibrosis in patients with chronic HCV. Further future strategies could be targeting of the TGF-β pathway. Neutralizing antibodies, decoy receptors and siRNA have been studied but are not yet ready for clinical application. Pirfenidone, an inhibitor of TGF-β production has shown promising results in a non-controlled pilot study (Armendariz-Borunda et al. 2006). αvβ6 integrin activates matrix-bound, latent TGF-β in the local microenvironment. The specific inhibition of this integrin could therefore be an intriguing approach to avoid side effects of systemic TGF-β inhibition. Neutralizing antibodies against αvβ6 integrin inhibited cholangiocyte activation and collagen deposition in biliary and non-biliary fibrosis models (Popov et al. 2008). Agents, that stimulate the collagenolytic activity of MMP, such as the oral alkaloid Halofuginone, showed promise in animal models but still needs investigations in patients. Notably, the clinical success achieved so far does not correlate with the antifibrotic effects in

experimental animal models suggesting that the available animal fibrosis models may not fully reflect the influence of ECM maturation by crosslinking and the potential existence of a "point of no return" in fibrosis (Rockey 2008). Nevertheless, functional antifibrotic therapies are urgently needed, and first progress towards clinical application becomes visible.

4.3 Anti-Inflammatory Treatment

Since chronic inflammation contributes to carcinogenesis and dissemination, antiphlogistic drugs appear to be a promising preventive regimen for infected patients upon diagnosis of virus-mediated tissue damage. Several factors that fuel cancer-associated inflammatory processes have been identified and are therefore reasonable molecular targets to prevent cancer in risk-associated patients. Several antiphlogistic drugs have been shown to reduce the incidence of cancer when used as prophylactics or to slow down tumor growth and improve survival when given as therapeutics, e.g. in colon cancer (Gupta and DuBois 2001). At first, preventive use of classical non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin could be a method of choice (Cuzick et al. 2009; Langley et al. 2011). NSAIDs are cheap, off-patent, well established and long-term clinical experience exists for low-dose usage as anti-thrombotic prophylaxis. It has been demonstrated that preventive Aspirin treatment can significantly reduce the long-term risk to develop colorectal cancer (Flossmann and Rothwell 2007; Rothwell et al. 2010). A large meta analysis showed a reduced cancer risk in several solid, mainly gastrointestinal tumors, such as gastric, oesophageal, colorectal and pancreatic cancer, but also in lung cancer (Rothwell et al. 2011). Benefit correlated with duration of aspirin uptake and with increasing age of the individual. Notably, no benefit was seen in hematological malignancies consistent with the hypothesis that the anti-inflammatory treatment is mainly directed against the chronic inflammatory microinvironment of a solid tumor. Regarding the risk and benefit balance, the Rothwell study suggests that the additional risk of aspirin-associated gastrointestinal bleedings (including fatal bleedings) is outweighed by a gain of 10 % reduction in all-cause mortality after 5–10 years daily aspirin consumption. It has to be pointed out, that the patients in these studies were not stratified whether they actually had any inflammatory burden or not. It has been shown that aspirin reduces the risk of prostate cancers, but only in individuals carrying a particular polymorphic allele of the lymphotoxin α gene which leads to increased lymphotoxin expression (Liu et al. 2006). This observation illustrates the need to early identify those patients with elevated cancer risk by genetic screenings and/or by monitoring inflammatory parameters, which would likely profit most from anti-inflammatory treatment. To reduce gastrointestinal complications in long-term treatments, selective COX-2 inhibitors could be an alternative as preventive cancer treatment (Kawamori et al. 1998; Reddy et al. 2000). In studies of several preclinical models of inherited or carcinogen-induced cancers of colon, intestine, skin and bladder it could be observed that celecoxib

could significantly reduce cancer incidence (Fischer et al. 2011). Also in studies in human patients, celecoxib showed promise in prevention of spontaneous colorectal adenomas and reduced the number of polyps in familial adenomatous polyposis (Bertagnolli et al. 2006; Arber et al. 2006; Steinbach et al. 2000). However, it has to be considered that celecoxib has been associated with adverse cardiovascular events (Mukherjee et al. 2001).

Drugs that address specific molecular targets in cytokine or chemokine signaling involved in inflammatory processes also represent promising alternatives. However, most of these agents are already in use for the treatment of chronic inflammatory diseases such as rheumatoid arthritis, psoriasis, or inflammatory bowel diseases (IBD) or are in clinical development for cancer therapy. It is yet unclear whether these agents are suitable for long-term treatments. The structural analogue of thalidomide, lenalidomide, is known to suppress the production of several inflammation-associated cytokines and has shown to be active against melanoma in combination with dexamethasone (Weber et al. 2007).

As already mentioned, NFκB and STAT3 pathways play a critical role in both carcinogenesis and resistance to therapy suggesting that targeted inhibitors could have significant preventive or therapeutic potential. However, pharmacologic long-term inhibition of NFκB can lead to severe immunodeficiency, neutrophilia and enhanced acute inflammation due to increased IL-1β levels (Greten et al. 2007). Alternatively, it appears to be more promising to address defined upstream targets of NFκB since multiple extrinsic and intrinsic pathways converge to activate this central transcription factor. Inhibitors for STAT3 and JAK2, which is upstream of STAT3, have been developed and showed oncostatic activity in solid tumors in mouse xenograft models (Hedvat et al. 2009). Furthermore, receptor antagonists and blocking antibodies addressing IL-6, IL-6 receptor, CCR2, CCR4, and CXCR4 are in clinical development for the treatment of several tumor entities. TNFα-antibodies such as infliximab has been a breakthrough for the treatment of IBD and, importantly, long term application appears to be safe (Fidder et al. 2009). First clinical studies of TNFα antagonists in patients with advanced cancer have resulted in stable disease or partial responses (Brown et al. 2008; Harrison et al. 2007). It is further known that infliximab also reduced colitis-associated cancer in mice (Kim et al. 2010) suggesting a cancer preventive benefit in patients. On the other hand, TNFα has been implicated in the clearance of virus infections (Trevejo et al. 2001) and has been shown to be critical for induction of antitumoral T cell responses in animals (Calzascia et al. 2007). Due to this complex and sometimes contradictory biology of TNFα it is currently difficult to estimate whether TNFα antagonists could be promising as preventive mean for cancer that is caused by virus-mediated inflammation. From the clinical point of view, metastases are the much more challenging manifestation of a malignant disease compared to the primary nodule. Since inflammation is a central driving force of dissemination, application of anti-inflammatory drugs could be an effective intervention to prevent the development of metastases. Recently, the antagonistic RANKL antibody denosumab, initially developed for the treatment of osteoporosis, delayed the development of bone metastases in advanced clinical studies in prostate and breast

cancer (Stopeck et al. 2010; Smith et al. 2012). For prevention of metastases, inhibition of TNFα could also be promising, since mouse experiments have shown that blocking TNFα can convert inflammation-promoted metastatic tumor growth to TRAIL-mediated tumor regression (Luo et al. 2004). Altogether, these examples show that molecular mechanisms and signaling pathways involved in tumor- and metastases-associated inflammation are promising targets for preventive and therapeutic interventions.

5 Outlook: Perspectives in Cancer Immunotherapy

Not only for prevention but also in therapy of cancer, antitumoral immune responses are coming more and more into focus. Antitumoral immune responses can even be triggered by conventional chemotherapeutic treatments and may significantly contribute to the therapeutic outcome (Casares et al. 2005; Apetoh et al. 2008). Our current knowledge about tumor-immune responses basically suggests two different strategies for tumor immunotherapy. One strategy is to support or reactivate innate or preexisting adaptive immune responses, the other is *de novo* induction of adaptive responses by therapeutic interventions. Both are about equally challenging, since tumors have developed numerous ways to escape immune attacks. Even if we are able to elucidate the underlying mechanisms and have many therapies at hand, we still cannot be sure, whether a certain therapy could be undermined by the tumor's mechanisms of immune suppression in the individual case. Therefore, the ideal immunotherapeutic strategy aims at the achilles heel of the tumor and would be additionally applicable for all solid tumor entities.

Recent findings on the importance of the chronic inflammatory tumor-environment for tumor-maintainance and –progression have lead to the idea to use anti-inflammatory drugs for cancer therapy. The fundamental advantage of this approach is, that immune cells are not prone to develop drug resistance. However, it is likely, that anti-inflammatory therapy does not exhibit sufficient cytotoxic effects on cancer cells and thus must be combined with additional therapies to manifest effective therapeutic effects. As already mentioned above, some phase I/II clinical trials investigate efficacy of anti-IL6 and anti-TNF-α drugs in various cancers (Balkwill 2009).

Among adaptive immune responses, cytotoxic T cells, which are able to mediate direct lysis of transformed cells, are commonly regarded as the most promising cell type for cancer immunotherapy. However, effective tumor-specific CD8 T cell responses are difficult to induce in tumor-bearing hosts. Paracrine mediators, like adenosine, prostaglandin E2, VEGF-A, and TGF-ß mediate direct and indirect immunosuppressive activities and act on different levels of the immune system. It has been shown that immunosuppressive activities lead to blunted spontaneous adaptive responses by T cell exhaustion (Fourcade et al. 2010; Sakuishi et al. 2010; Baitsch et al. 2011) or take effect on dendritic cells, inducing defective maturation by inhibiting costimulatory signals, which in turn fails to prime a tumor-directed CD8

T cell response (Sharma et al. 2010). Therefore, a careful design of a vaccine to elicit an effective tumor-directed CD8 T cell response must encompass a strategy to block the tumors counteractions as well. In a melanoma mouse model inhibition of IDO (indoleamine 2,3-dioxygenase)-mediated immune suppression by use of 1-methyl-tryptophan allowed for induction of potent cytotoxic responses with a CD8 T cell-vaccine by protecting DCs in TDLN from malfunction (Sharma et al. 2010). Another approach to circumvent tumor-mediated immunosuppression is an infection mediated by a lytic virus in a tumor nodule. The infection disrupts tumor architecture and leads to an inflammation, which is accompanied by leukocytic infiltration and abundant tumor-cell death. When a tumor-directed DC-vaccine is applied at this time point of virus-mediated inflammation, it triggers a strong cytotoxic CD8 T cell response, whereas other timepoints of vaccination in combination with virotherapy does not exhibit a significant therapeutic effect. Interestingly, compared to a true virus infection, inflammations mediated by toll-like receptor ligands failed to support effective induction of CD8 T cell response by DC-vaccination, most likely due to lacking cross-presentation of tumor-associated antigens by dendritic cells within the infected tumor (Woller et al. 2011).

The clinical translation of immunotherapeutic strategies in the recent years raises hope to establish a new field in the treatment of cancer, a field, which might be also combined with conventional therapies. A GM-CSF-armed, tk-deficient poxvirus showed promising results in clinical studies, where significant responses were observed in hepatocellular carcinoma (Breitbach et al. 2011; Park et al. 2008). In a clinical study phase I/II patients with advanced solid tumors of different origin received anti-PD-1 antibodies to reverse exhausted T cells. Some observable responses were durable for more then one year. However, treatment with a blocking PD-1 antibody only showed objective responses in patients with a positive staining of PD-L1 in tumor-tissue (Topalian et al. 2012).

These studies, among many others, elucidate novel interventions and possibilities for immunotherapy of cancer. They are based on accumulating knowledge about the immune system, cancer biology, and interactions between both. Induction of specific immune reactions redirected to the tumor appears to open up an exiting new field in the treatment of malignant diseases. On the other hand, many lessons have to be learned and it is still a long way to go from the more or less experimental approach of immunotherapy towards well-established therapies.

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