Interplay between DNA repair and inflammation, and the link to cancer

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Abstract

DNA damage and repair are linked to cancer. DNA damage that is induced endogenously or from exogenous sources has the potential to result in mutations and genomic instability if not properly repaired, eventually leading to cancer. Inflammation is also linked to cancer. Reactive oxygen and nitrogen species (RONs) produced by inflammatory cells at sites of infection can induce DNA damage. RONs can also amplify inflammatory responses, leading to increased DNA damage. Here, we focus on the links between DNA damage, repair, and inflammation, as they relate to cancer. We examine the interplay between chronic inflammation, DNA damage and repair and review recent findings in this rapidly emerging field, including the links between DNA damage and the innate immune system, and the roles of inflammation in altering the microbiome, which subsequently leads to the induction of DNA damage in the colon. Mouse models of defective DNA repair and inflammatory control are extensively reviewed, including treatment of mouse models with pathogens, which leads to DNA damage. The roles of microRNAs in regulating inflammation and DNA repair are discussed. Importantly, DNA repair and inflammation are linked in many important ways, and in some cases balance each other to maintain homeostasis. The failure to repair DNA damage or to control inflammatory responses has the potential to lead to cancer.

Keywords

Colon cancer; DNA damage; infection; microbiota; pathogens; reactive oxygen; nitrogen species

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Introduction

In 1863, Rudolf Virchow hypothesized that the origin of cancer was at sites of chronic inflammation (Virchow, 1863), based on observations of the presence of a "lymphoreticular infiltrate" in human tumors. Inflammation is part of a complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells or irritants. In recent years, inflammation has taken its stage to be listed as the seventh hallmark of cancer (Hanahan & Weinberg, 2000). Epidemiological and clinical studies estimate that approximately 25% of all cancers are linked to chronic inflammation, inflammation induced by environmental exposures, or infection of pathogens (Balkwill & Mantovani, 2010, 2012; Saigo *et al.*, 2008). Many studies have characterized the roles that inflammation plays in the induction of a carcinogenic phenotype.

A mutator phenotype resulting from aberrant DNA repair and replication is also an important driver of cancer (Loeb, 2011). Aberrant mismatch repair (Fishel & Kolodner, 1995; Fishel *et al.*, 1993, 1994) deficient MutYH DNA glycosylase activity (for recent reviews, see Raetz *et al.*, 2012; Wallace *et al.*, 2012) and DNA polymerase misincorporation (Zhao *et al.*, 2013) are all examples of how aberrant functions of DNA repair and replication contribute to a mutator phenotype. A common link between inflammation and DNA repair is DNA damage. DNA damage is present during inflammation and accumulates during chronic inflammation. DNA repair plays an important role in counteracting this damage but is not always successful, often leading to cancer promotion. The focus of this review is on the interplay between inflammation and DNA repair and how an imbalance in these processes could lead to human cancer.

Endogenous RONs-induced DNA damage and repair

Reactive oxygen and nitrogen species (RONs) damage many cellular molecules including DNA (Nathan & Cunningham-Bussel, 2013; West & Marnett, 2006). Reactive oxygen species (ROS) arise endogenously as a result of mitochondrial respiration, cellular signaling and during the breakdown of fatty acids by the peroxisome. Endogenous reactive nitrogen species also arise from the production of nitric oxide from L-arginine and during cellular signaling processes. Redox homeostasis plays an important role in mitigating the effects of RONs through the actions of enzymes including superoxide dismutase, glutathione-S-transferase, and glutathione peroxidase. RONs that escape these defense systems damage DNA at a rate of at least 20 000 DNA base lesions per cell per day (Barnes & Lindahl, 2004). ROS can damage all four canonical bases in DNA along with the methylated form of deoxycytidine to generate a large number of oxidatively damaged bases (Svilar *et al.*, 2011). Chronic ROS can generate significant levels of lipid peroxidation products, which react with DNA to generate etheno-base DNA adducts. Nitric oxide (NO) can also generate etheno-base adducts (Nair *et al.*, 1998). In addition, peroxynitrite reacts with guanine to create 8-nitroguanine, which can spontaneously depurinate to generate abasic sites (Dedon & Tannenbaum, 2004; Mutamba *et al.*, 2011; Yermilov *et al.*, 1995). Peroxynitrite also induces single-strand breaks in DNA (Yermilov *et al.*, 1996).

DNA damage induced by RONs is generally repaired by the base excision repair (BER) pathway (for a review see Wallace *et al.*, 2012), which is a critically important pathway for the maintenance of genome integrity. Repair by BER involves removal of the damaged base and resulting abasic site by a DNA glycosylase with associated lyase activity or the combined actions of a glycosylase and AP endonuclease, followed by filling of the small DNA gap by a DNA polymerase, and concluding with ligation. Mutations in BER genes are associated with chronic inflammation. DNA damage induced by alkylating agents and reactive nitrogen species, including 1-methyladenine and 3-methylcytosine and 1,N6 – ethenoadenine (εA) and are removed by BER, but can also be eliminated by direct reversal. The ALKBH2 and ALKBH3 proteins catalyze direct reversal of the damage in the presence of α-ketoglutarate, oxygen and iron (Falnes *et al.*, 2002; Trewick *et al.*, 2002). Mismatch repair (MMR) is also affected by chronic inflammation. Replication errors, including base mismatches and small insertion/deletion loops (IDL), are repaired by the MMR system (Jiricny, 2006; Pena-Diaz & Jiricny, 2012). Following recognition of the mismatch or IDL on the newly synthesized DNA strand, a large fragment of DNA including the mismatch is excised. DNA synthesis then takes place to fill the large gap, followed by ligation of the nick. Overwhelming the system with RONs-induced DNA damage, or the presence of compromised DNA repair due to genetic abnormalities, can result in incomplete repair of DNA damage, leading to mutagenesis and/or chromosomal instability.

Inflammation-associated DNA damage and repair

Acute inflammation is a protective response against pathogens, but also important for the regeneration of damaged tissues after injury and infection (Ben-Neriah & Karin, 2011). RONs are generated by inflammatory cells that are recruited to the sites of infection and tissue regeneration.

Chronic inflammation results from persistent pathogen or viral infection, autoimmune reactions or persistent foreign bodies. One of the hallmarks of chronic inflammation is the infiltration of inflammatory cells including macrophages, neutrophils, and various types of lymphocytes. The presence of these cells leads to sustained production of pro-inflammatory mediators, such as cytokines, chemokines, interferon-γ and lipid mediators that coordinately constitute a cancer-prone microenvironment. Chronic inflammation often results in tissue damage, an increased mutation rate and genomic instability. If accumulated in excess the chronic inflammatory environment leads to the initiation of carcinogenesis (Coussens & Werb, 2002). Therefore, the balance between the pro and anti-inflammatory immune responses of the host cells during inflammation is critical to determine the fate of the cell. DNA repair is also the counter response of the host cells to chronic inflammation (Ferguson, 2010).

Interplay between chronic inflammation, DNA damage and repair

A growing body of evidence indicates that RONs can cause damage to cellular macromolecules. DNA is the most sensitive biological target for damage from oxidative stress (for a recent review see Federico *et al.*, 2007), as it is not well protected and has limited chemical stability (Lindahl, 1993; Taha *et al.*, 2010). Genomic damage that is either

left unrepaired or is repaired with errors may result in mutations of critical genes which ultimately leads to an elevated cancer risk (De Bont & van Larebeke, 2004; Trabulus *et al.*, 2012). Inflammation of the tissue surrounding a tumor can hasten the oncogenic process by directly promoting genetic instability and favoring or inducing gene mutations. RONs, which are abundant during inflammation, can induce DNA mutations, epigenetic alterations, and post-translational modifications of proteins that control the cell cycle or survival (Colotta *et al.*, 2009). In recent years new data suggest that the DNA damage response can initiate an immune response. The DNA damage response (DDR) directly activates a variety of transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and interferon regulatory factors (IRFs) (for a review see McCool & Miyamoto, 2012). These transcription factors induce the expression of various immune genes, including inflammatory cytokines and chemokines. In addition, the DDR and oxidative stress induce the expression of a number of ligands for activating immune receptors such as natural killer group 2, member D (NKG2D) and DNAX accessory molecule 1 (DNAM-1), which are mainly expressed by cytotoxic immune cells such as T cells and natural killer (NK) cells.

The presence of inflammatory cells at sites of chronic inflammation results in the local release of RONs, which results in DNA damage, as discussed earlier. Damage to DNA by RONs leads to mutations. Early studies, in which naked DNA was incubated with a variety of reactive oxygen generating systems followed by repair and replication in *E. coli*, demonstrated that oxidative DNA damage could induce mutations and produce mutagenic signatures (for a review see Feig *et al.*, 1994). Although repair pathways have evolved to process this DNA damage, they are imperfect leading to the induction of mutations and genomic instability. For example, exposure of mammalian cells to nitric oxide induces homologous recombination between direct repeat sequences (Kiziltepe *et al.*, 2005), much of which result from strand breaks and oxidized bases. A second example is that co-culture of mammalian cells with activated human promyelocytic cells or macrophages induces an increased frequency of mutations over background that were mediated by RONs (Kim *et al.*, 2003). Importantly, the increase in mutagenesis was reversed by incubation of the cells with oxygen radical scavengers.

Chronic inflammation and NF-κB

Nuclear factor of kappa light gene polypeptide gene enhancer in B cells (NF-κB) is a master regulator of the immune response by inducing transcription of proinflammatory genes (for a review see Tak & Firestein, 2001). NF-κB is also activated during chronic inflammation and during the cellular response to DNA damage. Ataxia telangiectasia mutated (ATM) and NF-κB essential modulator (NEMO) cooperate to activate NF-κB in response to DNA damage, which involves transport of NF-κB from the cytoplasm to the nucleus (for a review see McCool & Miyamoto, 2012). Once in the nucleus NF-κB is a transcription factor that upregulates the expression of both pro- and anti-apoptotic factors (Roos & Kaina, 2013), ultimately protecting the cell from apoptosis. Interestingly, DNA intercalators, which alter the structure of DNA, also induce activation of NF-κB, leading to a significant increase in DNA damage and ultimately, apoptosis (Karl *et al.*, 2009). Therefore the status of NF-κB

and its associated factors during chronic inflammation has great potential to influence the outcomes of inflammation, including accumulation of mutations, cell survival and cancer.

The DNA damage sensor PARP1 is a scaffold that coordinates assembly of inhibitor of kappa B kinase gamma (IKKγ), Ataxia Telangiectasia mutated (ATM) and the protein inhibitor of activated STAT gamma 1 (PIASγ1), small ubiquitin-like modifier (SUMO) ligase (Stilmann *et al.*, 2009). Sumoylation of IKKγ results in activation of NF-κB. Damage in the form of single-strand breaks (SSBs) and stalled replication forks is sensed by poly-ADP ribose polymerase 1 (PARP1) and can therefore result in activation of NF-κB. NF-κB itself stimulates DNA DSB repair (Volcic *et al.*, 2012). Specifically, inhibitor of kappa B alpha (IκBα) releases NF-κB dimers that associate with and stimulate the activity of the BRCA1-CtIP nuclease complex, resulting in end resection and initiation of homology dependent repair (HDR). This is followed by NF-κB-dependent upregulation of BRCA2 and ATM. The presence of the BRCA2 recombination mediator and stimulation of end-resection channel DSB repair into HDR. Therefore if bases damaged by ROS during inflammation lead to an accumulation of BER intermediates and eventual DSB formation, much of the repair will be channeled into HDR.

DNA damage and upregulation of IRFs

DNA damage induced in the chronic inflammatory environment has the capacity to upregulate interferon responsive factors (IRFs) including IRF1, 3 and 7. IRF1 is induced in response to DNA damage in an ATM dependent manner (Pamment *et al.*, 2002). Activation of IRF1 leads to expression of genes that function in cell cycle regulation, apoptosis and activation of T cells (Kirchhoff & Hauser, 1999; Matsuyama *et al.*, 1993; Stevens & Yu-Lee, 1992, 1994; Tamura *et al.*, 1995). Mouse cells deficient in IRF-1 are compromised in their abilities to repair damaged DNA (Prost *et al.*, 1998). DNA damage induces phosphorylation of IRF-3, resulting in its transport from the cytoplasm to the nucleus and activation of transcription (Kim *et al.*, 1999), leading to downregulation of proliferation. IRF-7 is also upregulated in response to DNA damage (Kim *et al.*, 2000).

DNA damaging agents and NKG2D

The natural killer group 2D (NKG2D) is an activating receptor in natural killer cells (NK) and in T cells. Binding of ligands to the NKG2D receptor induces lysis of cells expressing the receptor. Interestingly, NKG2D ligands (NKG2DL) are upregulated in response to oxidative stress, such as RONs (Yamamoto *et al.*, 2001). DNA damaging agents and replication inhibitors also upregulate the expression of NKG2D ligands in an ATM dependent manner (Gasser *et al.*, 2005). Thus, DNA damage sustained in a chronic inflammatory environment could result in the activation of the immune response, leading to the recruitment of natural killer cells which lyse severely damaged cells, resulting in cell death (Gasser & Raulet, 2006a,b).

DNA damage and the inflammasome

Following cellular damage the NOD-like receptor family pryin domain-containing 3 (NLRP3) protein forms a multi-protein complex called the inflammasome that culminates with the activation of caspase-1 and the maturation and secretion of proinflammatory

cytokines interleukin 1B (IL1B) and 18 (IL18) which can then drive inflammatory responses. Other activators of the inflammasome include bacteria and other pathogens and danger-associated molecular patterns (DAMPS) that work via a common downstream ligand, which is ROS. Recently it was shown that treatment of cells with MSU salt crystals or IR, both of which induce ROS and DNA damage activates the inflammasome (Licandro *et al.*, 2013). This stabilizes p53 and p21 and leads to cell death. Activation of the inflammasome also downregulates DSB repair and BER. Downregulation of DNA repair in conjunction with caspase 1 activation leads to cell death, which could be another mechanism used by the immune system to eliminate cells with severe DNA damage, such as that sustained under conditions of chronic inflammation.

DNA damage, repair and STING

One of the major oxidized bases found in DNA exposed to RONs is 8-hydroxyguanine (8-oxoG). Nucleic acids in the cytoplasm are sensed by the innate immune system through the presence of molecular recognition patterns. It has recently been shown that the presence of 8-oxoG in DNA from pathogens decreases its susceptibility to degradation by the TREX1 nuclease. This leads to the potentiation of cytosolic immune recognition through the endoplasmic reticulum-associated protein STING, and the release of type I interferon (Gehrke *et al.*, 2013). Thus, oxidized bases in DNA have the potential to activate immune signaling. In the case of chronic inflammation, RONs-induced DNA damage could potentiate immune responses, with the goal of leading to cell death. The meiotic recombination 11 homolog A (MRE11) and its associated protein, RAD50, function in DSB repair, and were recently shown to be necessary for activation of STING and release of interferon-β (IFN-β) through their ability to recognize and bind to double-stranded DNA, but not pathogens, in the cytoplasm (Kondo *et al.*, 2013). The origin of this DNA is not known at present. Because secretion of IFN-β could potentially be harmful, it is suggested that once MRE11-RAD50 binds to DNA and initiates signaling through STING, it processes this DNA using the nuclease activity of MRE11 to terminate the downstream signaling.

Chronic inflammation and SASP

Cellular senescence is a state of irreversible growth arrest induced by telomere shortening (replicative senescence), oncogene activation and persistent DNA damage (Collado *et al.*, 2007; Kuilman *et al.*, 2010). Cellular senescence significantly contributes as an anti-tumorigenic mechanism via induction of growth arrest (Kuilman *et al.*, 2010) and triggering of immune-mediated clearance of pre-malignant cells (Kang *et al.*, 2011). However, unlike apoptotic cells, senescent cells remain metabolically active and undergo widespread gene expression changes (Campisi & d'Adda di Fagagna, 2007). The signature of senescent cells is the acquisition of a senescent-associated secretory phenotype (SASP) (Coppe *et al.*, 2008). SASP proteins are generally induced at the level of mRNA (Coppe *et al.*, 2008) and include a wide range of growth factors, proteases, chemokines and cytokines. Proteins that are known to stimulate inflammation include interleukin 6, 8 and 1 (IL6, IL8, IL1), granulocyte macrophage colony stimulating factor (GM-CSF) and growth regulated oncogene (GRO) factors are secreted by senescent cells. Recent evidence suggests that monocyte chemotactic proteins 2 and 3 (MCP-2, MCP-3), matrixme-talloproteinase 1 and 3 (MMP-1, MMP-3) and many of the insulin-like growth factor (IGF)-binding proteins

(Kumar *et al.*, 1992) are among the most robustly induced and secreted of these factors. Although the immune system plays a major role in modulating the levels of pro- and anti-inflammatory factors, it is not the only source of these factors. However, SASP is also considered to be a mechanism responsible for chronic inflammation observed during aging (Coppe *et al.*, 2010; Freund *et al.*, 2010). On the other hand, SASP causes abundant secretion of various bioactive proteins from senescent cells and thereby activates neighboring non-senescent cancer cells, leading to promotion of tumor growth (Bavik *et al.*, 2006; Coppe *et al.*, 2008). Therefore, the SASP has the ability to induce and amplify local and chronic inflammation that can eventually lead to DNA damage in surrounding cells.

Mouse models of chronic inflammation: interaction with microbiota

It has been reported that 80% of immune cells reside and form a symbiotic relationship with commensal microbiota in the healthy gut. The colonic microbiota represents the largest microbe population in humans. Importantly, the commensal bacteria of patients with inflammatory bowel disease (IBD) and ulcerative colitis (UC) is altered compared to that of healthy individuals, suggesting that the microbiome represents a source of chronic inflammation (Frank *et al.*, 2011).

Due to the constant influx of foreign antigens and the presence of myriads of commensal bacteria, the control of inflammation in the intestinal tract has been extensively studied in very recent years. These studies suggest that microbe-induced chronic inflammation results in DNA damage in the gut. A possible scheme involves the emergence of certain members of the colonic microbial community as a result of proinflammatory immune responses leading to the remodeling of the microbiome. This results in the emergence of bacteria that can induce DNA damage and the DDR and promote colon cancer (Sears & Pardoll, 2011). For example, it has been suggested that various bacterial products such as polysaccharides have immunomodulatory effects (Hall *et al.*, 2008) (for a review see Chow *et al.*, 2010).

IL10 deficient mice and microbiota

IL10 suppresses macrophage activation and inhibits production of inflammatory cytokines. IL10-deficient mice develop anemia associated with chronic enterocolitis (Kuhn *et al.*, 1993). However, when the IL10-deficient mice are raised under specific pathogen-free (SPF) conditions, they develop only localized inflammation. This suggests that in the absence of IL10 there is little control over normal immune responses to enterobacteria, leading to overproduction of cytokines and resulting in chronic inflammation. The chronic inflammation associated with enterocolitis in the IL10-deficient mice was documented to involve uncontrolled cytokine production by activated macrophages (Berg *et al.*, 1996). It was subsequently shown that IL10-deficient mice raised in germ free conditions did not develop colitis, showing that resident enteric bacteria are necessary for the development of colitis in the IL10-deficient mouse model (Sellon *et al.*, 1998). Manipulation of the microbiota in the IL10-deficient mice influences the development of chronic inflammation and cancer in mice treated with azoxymethane (AOM) (Uronis *et al.*, 2009). Treatment of IL10-deficient mice with AOM leads to the development of colorectal tumors in most mice, whereas few tumors are observed in wild-type mice also treated with AOM. In these studies tumor multiplicity correlated with the presence of chronic inflammation. IL10-deficient

germ free and mice harboring mildly colitogenic bacterium and treated with AOM did not develop colitis or colon cancer. Importantly, enteric bacteria have the capacity to induce the DDR. For example, co-culture of eukaryotic cells with *E. coli* harboring the genomic island that encodes giant modular nonribosomal peptide and polyketide synthases (*pks*) induces DSBs and activation of the DDR (Nougayrede *et al.*, 2006). Recent sequencing shows that AOM-induced inflammation of the gut of IL10-deficient mice alters the composition of the microbiota including significantly increased abundance of Enterobacteriaceae (Arthur *et al.*, 2012), as shown in Figure 1. Specifically, the guts of IL10-deficient mice harbored a 100-fold increase in *E. coli*. Treatment of IL10-deficient mice with AOM either mono-associated with the human commensal *Enterococcus faecalis* or the adherent invasive *E. coli* NC101 resulted in severe colitis and similar induction of proinflammatory cytokines. However, only mice monoassociated with *E. coli* NC101 developed adenocarcinoma. Importantly, the NC101 *E. coli* harbor the polyketide synthetase (*pks*) island that was detected in 40% of patients with IBD, suggesting that it is related to disease pathology. Infection of non-transformed rat epithelial cells with *E. coli* harboring the *pks* island resulted increased levels of phosphorylated H2AX (γH2AX) but this was not observed in cells infected with *E. coli* deleted of the *pks* island. Interestingly, infection of the IL10-deficient mice with *E. coli* NC101 and with NC101 deleted of *pks* resulted in chronic inflammation, but a significantly greater tumor burden was observed in mice with bacteria harboring the *pks* island. The abundance of γH2AX foci in the crypts of mice infected with the *pks*-deleted *E. coli* was significantly less than that observed in mice infected with *pks*-proficient *E. coli*. These studies suggest that chronic inflammation alters the populations of microbiota in the gut, resulting in the expansion of microbes like *E. coli* NC101. These types of microbes induce DNA damage and activate the DDR, which likely leads to genotoxic damage and cancer, as shown in Figure 1. An elegant study demonstrated that the ablation of the TLR (Toll-like receptor)-mediated signaling pathway adaptor MyD88 impairs intestinal tumorigenesis (Rakoff-Nahoum *et al.*, 2006) in IL10 deficient mice.

In contrast, recent identification of commensal colonization factors (CCF) in microbial genomes and the identification of the toll-like receptor 2 (TLR2)-mediated pathway in the host demonstrated the important factors of bacterial colonization and stabilization for gut homeostasis (Lee *et al.*, 2013; Round & Mazmanian, 2009).

T-bet, chronic inflammation and DNA damage

Although several reports suggest that innate immunity via the TLR-MyD88 pathway is important, recent advances also indicate that there are MyD88-independent pathways that might be involved in colorectal cancer (CRC) development. T-bet is a T box transcription factor that is expressed only in immune cells, regulates host-commensal homeostasis, and chemokine and cytokine expression (Glimcher, 2007; Ma, 2007). T-bet plays an important role in the induction of inflammatory programs in both innate and adaptive immunity. Loss of T-bet in innate immune cells results in spontaneous colitis in the absence of adaptive immunity and influences the host microbiota to become coligenic, which could lead to induction of the DDR. Deletion of T-bet in Rag2-deficient mice results in the development of ulcerative colitis (TRUC mice) (Garrett *et al.*, 2007). A further study demonstrates that TRUC mice spontaneously develop colitis-associated adenocarcinoma (Garrett *et al.*, 2009).

The lack of T-bet in dendritic cells results in increased RONs production in colonic epithelial cells (CECs) from TRUC mice, which induced the formation of DNA adducts such as 8-oxoG. Importantly, such events were independent of the conventional TLR-MyD88 pathway while the presence of commensal bacteria was still critical. A follow-up study showed that metabolites such as short fatty chain acids from commensal bacteria may play a key role in colonic inflammation (Smith *et al.*, 2013).

Commensal bacteria protect tissue from inflammation

Commensal bacteria are also critical players in protection from inflammation in the gut. For example, dextran sodium sulfate (DSS) treatment induces inflammation in the colon, but oral administration of lactic acid bacteria (LAB) alleviated this inflammation (Kawashima *et al.*, 2013). Reduced levels of inflammatory cells including neutrophils, eosinophils and macrophages were observed in the lamina propria of mice fed LAB compared to controls. Interferon β (IFN-β), an important anti-inflammatory mediator, is secreted in response to the presence of LAB as a result of TLR3 acting as a sensor to the dsRNA of the commensal LAB. Expression of inflammatory mediators including IL6 and interleukin 17 (IL17) decreases in the inflamed colons of mice treated with LAB. Therefore, the microbiota exerts an influence over the inflammatory responses of the gut, which could ultimately control the levels of DNA damage and mutation.

Chronic inflammation, DNA repair and inflammatory bowel disease

Inflammation is an accepted factor contributing to colorectal carcinoma (CRC) progression (Feagins *et al.*, 2009; Thorsteinsdottir *et al.*, 2011; Ullman & Itzkowitz, 2011), and several inflammatory pre-neoplastic states result in an increased risk of cancer progression in affected patients (Colotta *et al.*, 2009; Grivennikov *et al.*, 2010; Mantovani *et al.*, 2008). In IBD patients, RONs generated during the inflammatory response result in oxidative damage within the colonic epithelium (Kruidenier *et al.*, 2003a; Singer *et al.*, 1996; Sohn *et al.*, 2012) and chronic inflammation results in an increased mutational load throughout the diseased colon (Hussain *et al.*, 2000; Risques *et al.*, 2011; Salk *et al.*, 2009; Willenbucher *et al.*, 1999). Consistent with increased mutagenesis, MMR gene expression is epigenetically down-regulated in mouse models of IBD (Edwards *et al.*, 2009), and oxidative stress can decrease expression of mut S homolog 6 (MSH6) and postmeiotic segregation 2 (PMS2) repair proteins by causing their denaturation (Chang *et al.*, 2002). In contrast, alkyladenine glycosylase (AAG) and AP endonuclease can be overexpressed within inflamed tissues of ulcerative colitis patients (Hofseth *et al.*, 2003). Aberrant expression of activation-induced cytidine deaminse (AID) is induced in ulcerative colitis and *H. pylori* inflamed patient epithelium (Gushima *et al.*, 2011). This AID expression is induced by TNF-α through the NK-κB signaling pathway and by interleukin 4 and 13 (IL4 and IL13) cytokines (Endo *et al.*, 2008). These studies suggest that chronic inflammation may promote mutagenesis by altering the expression of repair proteins in patient tissues, in addition to causing direct oxidative DNA damage.

Macrophages associated with IBD induce inflammation, cellular senescence and γH2AX foci, a marker of DNA damage (Sohn *et al.*, 2012). The induction of cellular senescence is associated with secretion of iNOS from macrophages both *in vivo* and *in vitro*. Thus, the

nitrosative stress induced by macrophages has a direct effect upon the induction of cellular senescence. Whether macrophage-induced senescent cells are part of the SASP remains to be determined.

Innate immunity and chronic inflammation

The TLR of the innate immune system was identified by Janeway (1989) and is considered as a receptor family that recognizes pathogen-associated molecular patterns (PAMPs). TLR signaling contributes to the growth of tumors in numerous organs and thus may represent an important component of tumorigenesis. PAMPs are present in all microorganisms regardless of their pathogenicity. Initial studies have shown that TLRs recognize microbial ligands as well as endogenous host-derived ligands. Stimulation of TLRs leads to the activation of NF-κB, c-jun, mitogen-activated protein kinase (MAPK) and IRF family-mediated gene transcription (for a review see Lee & Kim, 2007). Such a diverse set of signaling activation is also involved in tissue repair and regeneration. Initial studies regarding the role of TLRs in cancer has been focused on their functions as a receptor family to boost anti-tumor immunity upon testing of exogenous agonists of TLRs. Recent studies suggest that microbe-derived mutagens or microbe-induced chronic inflammation may be an oncogenic mechanism. Thus, it is reasonable to surmise that the protective role of TLRs in cancer may be associated with the prevention of pathogen-derived (e.g. EBV, HBV, *H. pylori*) cancers (for a review see Rakoff-Nahoum & Medzhitov, 2009). Recent studies also suggest that TLR signaling contributes to tumor growth in various organs as well. For example, MyD88 is an important stimulator of chemically induced tumors of both skin and connective tissue. MyD88-deficiency inhibited tumor formation upon administration of DMBA and TPA or 3′-methylcholanthrene (MCA), which led to the development of skin papillomas and sarcomas, respectively (Swann *et al.*, 2008). It has been demonstrated that chronic and unregulated TLR signaling leads to DNA damage and mutation as well as aberrant chromosomal translocation by inducing free radicals or activation-induced cytidine deaminase (AID) (Ferrero, 2005; Uno *et al.*, 2007; Xu *et al.*, 2007). A previous study demonstrated that the ablation of TLR-mediated signaling pathway adaptor MyD88 impairs intestinal tumorigenesis (Rakoff-Nahoum & Medzhitov, 2007). However, these results cannot be directly translated since the ablation of TLRs in the $Apc^{/Min+}$ mice model did not show a reduction of intestinal tumor formation. Thus, whether TLRs are involved in tumor initiation is yet to be determined. In contrast to the MyD88-deficient $Apc^{/Min+}$ mice, the IL10$^{-/-}$ mouse model of colitis-associated carcinoma shows that colitis is dependent upon TLR recognition of the intestinal microflora (Rakoff-Nahoum *et al.*, 2006). Therefore, the role of TLRs is yet to be determined in this context. This suggests that important yet unknown mechanisms may regulate TLRs and hence tumor immunity. One can envision several possible common pathways to govern the role of TLRs such as the Wnt and mTOR pathways that sense the metabolic status of bacteria and host cells.

MicroRNAs, inflammation and DNA repair

MicroRNAs and DNA repair

MicroRNAs (miRNAs) are small, non-coding RNA molecules that regulate post-transcriptional gene expression by targeting an mRNA transcript for translational repression

or degradation. miRNA regulation is becoming increasingly more important in understanding disease initiation and progression due to its nearly ubiquitous role in cellular pathway regulation and function. In fact, it has been estimated that miRNAs target at least 60% of the protein coding genome (Friedman *et al.*, 2009). Over the past decade, microRNAs have emerged as critical regulators of the DNA damage response, reviewed recently by Wang & Taniguchi (2013). Here, we discuss a few select microRNAs that have been shown to be involved in both DNA repair and inflammation, namely miR-155, miR-210 and miR-21, all of which are frequently overexpressed in cancer.

miR-155 is a widely studied microRNA that targets several genes essential for the DNA damage response. Overexpression of miR-155 has been observed in a variety of solid tumors and hematologic malignancies (Eis *et al.*, 2005; Iorio *et al.*, 2005; Shibuya *et al.*, 2010) and has been correlated with poor prognosis in lung and pancreatic cancer (Papaconstantinou *et al.*, 2013; Yanaihara *et al.*, 2006). Overexpression of miR-155 has been demonstrated via multiple pathways. Most relevant, miR-155 expression is driven by inflammation, leading to an increase in mutation as a result of WEE1 repression, a miR-155 target (Tili *et al.*, 2011). It has also been shown that miR-155 overexpression can be a consequence of hypoxia, driven by the transcription factor, HIF-1α (Babar *et al.*, 2011; Bruning *et al.*, 2011). Furthermore, it was shown that the induction of miR-155 in hypoxia promotes radiation resistance in hypoxic lung cancer cells, potentially through the repression of FOXO3a, a pro-apoptotic factor (Babar *et al.*, 2011). Additional transcriptional regulation of miR-155 exists, including the recent finding that BRCA1 epigenetically regulates miR-155 expression (Chang *et al.*, 2002). Importantly, BRCA1, a key player in the DNA damage response, is often repressed in cancer, which could result in the overexpression of miR-155. It has also been demonstrated that miR-155 targets mismatch repair proteins, MLH1, MSH2 and MSH6 promoting microsatellite instability (Valeri *et al.*, 2010). Taken together, these data suggest that miR-155 overexpression in cancer might lead to mismatch repair inhibition and increased mutagenesis as well as therapeutic radiation resistance, driving tumor progression.

Another microRNA of interest, miR-210, is also involved in both the DNA damage response and inflammation. Similar to miR-155, miR-210 overexpression has been observed in several types of cancer (Camps *et al.*, 2008; Foekens *et al.*, 2008; Huang *et al.*, 2009; Malzkorn *et al.*, 2010; Papaconstantinou *et al.*, 2013). miR-210 expression is also induced by hypoxia, again driven by HIF-1α (Crosby *et al.*, 2009) and has been shown to promote radiation resistance in hypoxic lung cancer cells (Grosso *et al.*, 2013). Interestingly, miR-210 was recently shown to stabilize HIF-1α under normal oxygen conditions and promote a hypoxic-like environment, rendering normoxic cells more resistant to radiation (Grosso *et al.*, 2013). Although targets of miR-210 have been difficult to identify, a few DNA damage response members have emerged as confirmed targets. miR-210 has been shown to target RAD52, a key player in the homology dependent repair (HDR) pathway (Crosby *et al.*, 2009). Inhibition of RAD52 by miR-210 overexpression could lead to a decrease in HDR and promote mutagenesis. In addition to DNA repair targets, miR-210 has been shown to target SHIP1, an important negative regulator of cell proliferation involved in inflammation response (Lee *et al.*, 2013). Interestingly, miR-155 has also been shown to target SHIP1 (O'Connell *et al.*, 2009), suggesting a role for hypoxia-driven miRNAs in

regulating the inflammation response. It is important to note that although the mechanism behind miR-210 pathogenesis remains largely unclear, it is well-established that miR-210 and its inhibition could become an important prognostic and therapeutic tool in cancer treatment (reviewed recently Hong *et al.*, 2013).

Finally, another miRNA involved in both DNA repair and inflammation is miR-21. Similar to both miR-155 and miR-210, miR-21 is induced by hypoxia and deregulated in a number of different cancer types leading to a poorer prognosis in patients with miR-21 overexpressing tumors (de Oliveira *et al.*, 2009; Nair *et al.*, 2012). Overexpression of miR-21 could significantly impair the DNA damage response due to the involvement of multiple miR-21 targets in DNA damage recognition and repair. One of the first targets identified for miR-21 was phosphatase and tensin homolog (PTEN), a key regulator of the PI3K/AKT signaling pathway (Meng *et al.*, 2006). In the presence of DNA damage, the PI3K/AKT pathway is activated, inhibiting apoptosis and enabling DNA repair. PTEN, a negative regulator of AKT, inhibits the PI3K/AKT pathway and promotes apoptosis. Overexpression of miR-21 in cancer likely results in PTEN inhibition and activation of the PI3K/AKT pathway and DNA repair, resulting in tumor cell survival. Another target of miR-21 is CDC25A, which is also involved in the DNA damage response during cell cycle checkpoint activation. Overexpression of miR-21 has been demonstrated to inhibit CDC25A, which halts the cell cycle, and facilitates DNA repair (Anastasov *et al.*, 2012). The targeting of both PTEN and CDC25A by miR-21 overexpression results in radiation resistance, suggesting a mechanism by which miR-21 functions in tumor progression (Anastasov *et al.*, 2012; Liu *et al.*, 2013).

MicroRNAs and inflammation

It is commonly accepted that a proinflammatory tumor microenvironment may hamper anti-tumor immunity and favor cancer initiation and progression. The discovery of small non-coding regulatory RNAs, namely microRNAs (miRNAs) shed a new light on regulatory mechanisms linking inflammation and cancer. miRNA expression changes are observed in autoimmune diseases and cancers.

miR-21 is frequently up-regulated in human cancers such as breast cancer and glioma (Krichevsky & Gabriely, 2009). Functional roles for miR-21 have been reported in B cells, T (Th) cells, dendritic cells (DCs) and in various types of autoimmune diseases (Garchow *et al.*, 2011; Lu *et al.*, 2009, 2011). Dysregulation of miR-21 has been also found in some autoimmune conditions and mouse models of cancer (Fenoglio *et al.*, 2011; Kiyohara & Hirohata, 1994; Ruan *et al.*, 2011). DNA methylation is regulated by miRNAs that target the DNA methylation machinery. Pan *et al.* showed that miR-21 was overexpressed in CD4+ T cells from SLE patients and MRL/lpr mice, where miR-21 promoted cell hypomethylation by inhibiting DNA methyltransferase 1 (DNMT1) expression (Pan *et al.*, 2010). Detailed analysis indicated that miR-21 indirectly targeted RASGRP1 and down-regulated DNMT1 expression. This process is mediated by the Ras-MAPK pathway upstream of DNMT1. In contrast, repressing miR-21 expression in CD4+ T cells from SLE patients up-regulated DNMT1 expression and attenuated DNA hypomethylation.

miR-155 plays a role in innate immunity in macrophages. Lipopolysaccharide (LPS)-mediated activation of TLR signaling induces miR-155 in human macrophages. miR-155 is involved in the activation of tumor necrosis factor-α (TNF-α) and interleukin 6 (IL6), suggesting its critical role in tumor microenvironment formation. miR-155-deficient dendritic cells showed impaired antigen presentation and are subsequently unable to activate T cells to promote inflammation (Rodriguez *et al.*, 2007).

Macrophage inflammatory responses to infection involve the upregulation of several miRNAs including miR-21 (Bazzoni *et al.*, 2009; Liu *et al.*, 2009; Sheedy *et al.*, 2010). Regulation of the tumor suppressor protein programmed cell death 4 (PDCD4) is critical for the control of inflammation induced by LPS. LPS induces activation of TLR 4, which leads to upregulation of PDCD4, and proinflammatory mediators NF-κB and IL6. miR-21 is also induced in response to LPS in many cell types, and this is dependent on MyD88 and NF-κB. Once induced, miR-21 inhibits expression of PDCD4, thus promoting expression of IL10, an anti-inflammatory cytokine. LPS also induces the expression of miR-155, which results in a decrease in SHIP1 expression and promotion of the inflammatory response. However, in the presence of IL10, miR-155 expression is inhibited, which switches off the pro-inflammatory response (McCoy *et al.*, 2010).

In adaptive immunity, the role of miRNAs in distinct effector T helper cell subsets has been recently reported. An important role of miR-155 is implicated in regulatory T (Treg) cell formation and function. Forkhead box P3 (FOXP3), a lineage specific transcription factor for Treg cells, may directly regulate the expression of miR-155 (Zheng & Rudensky, 2007). Likewise, miRNA-155-deficient mice are immunodeficient, indicating that miR-155 is critical for homeostasis and the immune system. The fact that miR-21 and miR-155 overexpression impair Treg suppressor activity suggests additional inflammatory effects of these two miRNAs (Rodriguez *et al.*, 2007). Often miRNAs increase the buffering force of gene regulatory networks by targeting factors implicated in the same proinflammatory pathways. For example, miR-155 targets different DNA repair enzymes or DNA damage-induced checkpoints.

miR-210 is a typical hypoxia-induced miRNA, thus its expression is increased by low oxygen in a HIF-dependent manner (Biswas *et al.*, 2010). Like miR-21, miR-210 expression was upregulated in mouse peritoneal macrophages treated with LPS, suggesting a regulatory role of miR-210 in LPS/TLR4 signaling (Qi *et al.*, 2012). Likewise, over-expression of miR-210 inhibits TLR4-induced secretion of IL6 and tumor necrosis factor (TNF) via its targeting of NF-κB1 (p105) transcripts. This suggests that miR-210 is a negative feedback regulator in LPS/TLR4 signaling (Qi *et al.*, 2012). miR-210 may represent a miRNA that links inflammatory signals in the hypoxic microenvironment. It is notable that the expression of miR-21, miR-155 or miR-210 is controlled by the same immune/inflammatory and oncogenic signals. The regulatory mechanism of the expression of these miRNAs may explain converging points between immune and tumorigenic signaling pathways. miR-21 and miR-210 are important for transformation, tumorigenicity, DNA repair and chemotactic cell invasion and are under the control of signal transducer and activator of transcription (STAT3)-mediated transcription (Iliopoulos *et al.*, 2009). Since STAT3 is a target of IL6 signaling, the ability of these two miRNAs to transform cells places them in a positive

regulatory circuit with NF-κB, IL6 and STAT3. Interestingly, a similar feedback loop was found in other cancer cell lines and in patient cancer tissues (Iliopoulos *et al.*, 2009).

It has been suggested that the expansion of Tregs occurs in an inflammatory hypoxic environment. It has been shown that hypoxia is an intrinsic molecular cue that promotes FoxP3 expression, resulting in immunosuppressive mechanisms to prevent possible tissue damage in conditions of reduced oxygen availability (Clambey *et al.*, 2012). It has been also suggested that Treg cells provide a complementary immunological mechanism to protect tissue injury that is driven by low oxygen tension (i.e. hypoxia) in inflamed or cancerous tissues mainly via the cAMP-elevating A2A and A2B adenosine receptors (Sitkovsky, 2009). Collectively, this suggests that the dysregulation of miRNA can both promote tumor microenvironment formation and cellular transformation.

miRNAs clearly play an important role in regulating both the DNA damage response and inflammation pathways. Although only a select few miRNAs were covered here, many other members of the DNA damage response are also subject to miRNA regulation. The three miRNAs discussed here were chosen for both their overlap with inflammation as well as their similarity in expression, such that overexpression is observed for each of these miRNAs in multiple cancer types and that this induction of expression can be driven, at least in part, by hypoxia. Further investigation will be necessary to determine the importance of the multifaceted role of these and other oncogenic miRNAs. Enhancing our understanding of aberrantly expressed miRNAs and their function in different oncogenic pathways will likely improve current cancer therapy.

Interplay between infection-induced inflammation and DNA repair

Introduction

Since the discovery that *Helicobacter pylori* infection leads to gastric cancer (Warren, 1983), other chronic bacterial infections have been shown to cause cancer (Houghton & Wang, 2005). *Streptococcus bovis* (*S. bovis*)/*infantarius* was traditionally considered a lower grade pathogen frequently involved in bacteremia and endocarditis (Biarc *et al.*, 2004). This bacterium became important in human health as it was shown that 25–80% of patients who presented with *S. bovis* bacteremia also had a colorectal tumor (Biarc *et al.*, 2004). It has been estimated that over 25% of human malignancies are attributable to chronic inflammatory status, which arises as a consequence of infection and immunologic abnormality (Bouvard *et al.*, 2009). In developing countries, up to 23% of malignancies are caused by infectious agents, including hepatitis B and C viruses (liver cancer), human papilloma-viruses (cervical cancers) and *H. pylori* (stomach cancer) (de Martel *et al.*, 2012). In contrast, in developed countries, cancers caused by chronic infections are estimated to amount to approximately 8% of all malignancies (de Martel *et al.*, 2012). There are pathogenic factors or conditions that facilitate chronic inflammation subsequently increase the risk of cancer development. In many cases, one can observe a direct connection between inflammation caused by infectious pathogens and cancer (Darveau, 1999). The inflammatory response triggered by infection precedes tumor development and is a part of the normal host defense, the goal of which is pathogen elimination (Coussens & Werb, 2002). Some pathogens can directly induce cell transformation but most, if not all, also

induce a state of chronic inflammation that favors initiation, promotion and progression of tumors (Balkwill & Coussens, 2004; Fitzpatrick, 2001). Many bacteria that cause persistent infections produce toxins that specifically disrupt cellular signaling to perturb the regulation of cell growth (Wei *et al.*, 2012) or to induce inflammation. Other bacterial toxins directly damage DNA (Cortes-Bratti *et al.*, 2001; Frisan *et al.*, 2002). Such toxins mimic carcinogens and tumor promoters, like TNF-α, and might represent a paradigm for bacterially induced carcinogenesis (Rogers & Fox, 2004). In this part of the review, we will cover infection-associated inflammation that is mediated via infiltration of phagocytes and generation of ROS that induces genomic instability that leads to cell dysfunction, mutation and cancer.

Pathogens impair DNA repair function

Helicobacter pylori infection results in the development of gastric cancer in 5% of infected people (Suerbaum & Michetti, 2002; Uemura *et al.*, 2001; Wroblewski *et al.*, 2010). The presence of *Helicobacter* in the stomach results in a host immune response aiming to swiftly eradicate the invading organisms by phagocytosis or secreted anti-microbial substances (Karin & Greten, 2005). In response to *H. pylori* infection, mucosal leukocytes up-regulate enzymes such as iNOS, myeloperoxidases, NADPH oxidases and peroxidases which generate a great amount of reactive oxygen and nitrogen species (RONs). To inhibit the bactericidal effects of nitric oxide (NO), *H. pylori* itself produces a great amount of superoxide anions (Nagata *et al.*, 1998) and releases anti-oxidant enzymes (e.g. catalase, superoxide dismutase) to escape the host immune response. A growing body of evidence indicates that RONs produced by neutrophils and macrophages can directly induce DNA base oxidation, single strand breaks, generate excessive base excision repair intermediates and deamination, and can indirectly lead to base alkylation (Coussens & Werb, 2002; Kumagai *et al.*, 2003; Reuter *et al.*, 2010) as discussed above. In the case of infection, tissues are injured resulting in the local release of cytokines and other chemotactic factors that lead to infiltration and activation of macrophages and neutrophils to produce large quantities of proinflammatory mediators as well as reactive chemical species that cause mutagenic and cytotoxic damage (Dale *et al.*, 2008; Terzic *et al.*, 2010). For example, RONs-induced DNA damage contributes to tumor development in the Aag glycosylase deficient mouse model suggesting that DNA repair is an important suppressor of colon cancer in response to chronic inflammation, thus providing robust evidence that repair of RONs-associated DNA lesions is important for the suppression of inflammation-induced tumorigenesis (Meira *et al.*, 2008). The mechanism of how *H. pylori* infection leads to a disequilibrium in genomic integrity of the host cells is likely a multifaceted one. It is possible to identify three mechanisms by which *H. pylori* infection leads to loss of genomic integrity and promotes carcinogenesis.

Increased levels of oxidized base lesions such as 7,8-dihydro-8-oxoguanine (8oxoG) are found in the inflamed gastric mucosa of *H. pylori*-infected people (Baik *et al.*, 1996; Tardieu *et al.*, 2000) along with reduced DNA damage repair (MMR, BER and DSBR) (Colotta *et al.*, 2009; Kim *et al.*, 2002; Maddocks *et al.*, 2009; Mangerich *et al.*, 2012; Mirzaee *et al.*, 2008). Defects in human DNA MMR result in microsatellite instability (MSI) and predisposition to several types of epithelial cancer (Ou *et al.*, 2007; Seruca *et al.*, 1995).

In addition, lack of MMR enhances the mutation frequency in tumor suppressor genes such as p53 resulting in disregulation of the cell cycle (Wei *et al.*, 2012). The resulting increased mutation frequency likely correlates with the increase of aberrant expression of activation-induced cytidine deaminase (AID) in inflamed epithelial cells infected with *H. pylori* (Endo *et al.*, 2008). A second alternative pathway for the promotion of genomic instability by *H. pylori* is increased mutations in mitochondrial DNA that alter the normal respiratory functions including the oxidative phosphorylation pathway (Carew & Huang, 2002; Machado *et al.*, 2010). Even though the random mutation frequency of tumor mtDNA is significantly lower than surrounding normal tissue (Ericson *et al.*, 2012; Kidane & Sweasy, 2012), mutation frequencies in both the mitochondrial D-loop region and in several genes encoding respiratory subunits increase in human cells infected with *H. pylori* (Touati, 2010).

The third mechanism stems from pathogen-mediated epigenetic changes in DNA repair genes (Ando *et al.*, 2009; Bierne *et al.*, 2012). Diverse cellular functions including the expression of inflammatory genes, DNA repair and cell proliferation are regulated by infection-mediated epigenetic changes (Adcock *et al.*, 2007). There is considerable evidence suggesting that epigenetic mechanisms may mediate development of chronic inflammation by modulating the expression of pro-inflammatory cytokines such as TNF-α, IL1B, tumor suppressor genes, oncogenes and activation of transcription factors such as NF-κB (Gou *et al.*, 2012; Gupta *et al.*, 2010; Pikarsky *et al.*, 2004; Taylor & Cummins, 2009). Epigenetic inactivation of DNA repair genes in cancer has been reported for several DNA repair pathways including BER, NER, MMR and several other DNA damage processing mechanisms (Benachenhou *et al.*, 1998; Dobrovic & Simpfendorfer, 1997; Guan *et al.*, 2008; Lawes *et al.*, 2005). Aberrant DNA methylation is one of the major inactivating mechanisms of tumor suppressor genes and is deeply associated with *H. pylori* infection (Ding *et al.*, 2010; Gupta *et al.*, 2010; Niwa *et al.*, 2010). *H. pylori* infection frequently methylates the CpG island in the promoter region of the E-cadherin gene (Chan *et al.*, 2003). It has been reported that IL1 can modulate CpG island methylation through activation of DNA methyltransferase (Hmadcha *et al.*, 1999). Interleukin 1B (IL1B) modulates methylation-dependent gene silencing via nitric oxide (NO) production (Hmadcha *et al.*, 1999), DNA hypermethylation of tumor suppressor genes, extensive genomic DNA hypomethylation and alteration of histone modification patterns (Lopez-Serra & Esteller, 2012). This suggests that IL1B is an inducing factor in gastric inflammation and carcinogenesis (El-Omar *et al.*, 2000; El-Omar, 2001). Epigenetic chromatin marks are unstable and they rapidly change in response to any external stimulus including infection (Berger, 2007). Permanent changes to the DNA methylation can lead to development of cancer.

Chronic inflammation is deeply involved in the induction of aberrant DNA methylation (Niwa *et al.*, 2010). It was suggested that severity of inflammation characterized by expression of specific types of inflammatory related genes such as IL1B and iNOS are necessary for the initiation and maintenance of methylation induction (Hur *et al.*, 2011). The less severe gastric inflammatory response induced by *H. pylori* infection in interleukin 1 receptor, type 1 (IL1R1) deficient mice with less promoter methylation of E-cadherin (Huang *et al.*, 2013) suggested that epigenetic changes on chromatin structure likely play a

crucial role in *H. pylori*-induced gastric inflammation (Huang *et al.*, 2013). The crosstalk between DNA repair and pro-inflammatory cytokines during chronic inflammation exacerbates the methylation of CpG islands of tumor suppressor genes including in mismatch and base excision repair genes (Kane *et al.*, 1997; Kuniyasu *et al.*, 2004). In addition, IL6 has been reported to control DNA methylation (Isomoto *et al.*, 2007) and modulated iNOS expression during cancer development (Ma *et al.*, 2008). In contrast, deletion of DNA repair genes such as OGG1 (Mabley *et al.*, 2005) or expression of a mutated variant of BRCA1 (Zielinski *et al.*, 2003) resulted in low or defective pro-inflammatory cytokines (TNF-α, interleukin 12A (IL12A) and IL1B).

Inflammatory immune response and infection

The immune response is characterized by mucosal infiltration of various cells of the innate immune system leading to an acute gastric inflammation. If the bacteria can be eliminated successfully, acute inflammation is readily resolved and the normal tissue architecture is restored. However, incomplete bacterial eradication leads to a persistent inflammatory process resulting in chronic inflammation for longer time (Han & Ulevitch, 2005). The majority of infected individuals develop a continuous and progressive chronic inflammatory process initiated by non-atrophic gastritis and followed by multifocal atrophic gastritis, intestinal metaplasia, and dysplasia, symptoms considered to be hallmarks of the truly precancerous stage of the disease cascade (Zabaleta *et al.*, 2006, Zabaleta, 2012). The predisposing inflammation is most often caused by colonization of the gastric epithelium by *H. pylori*, and chronically infected individuals have an increased risk of developing gastric cancer (El-Omar, 2001). Cells of the innate immune system recognize the bacteria through receptors of so called PAMPs. PAMPs include microbial components such as LPS, peptidoglycan, flagellin and double-stranded RNA that are recognized by TLRs (Takeda & Akira, 2003). The initial response is characterized by neutrophil and macrophage infiltration (Peek, 2001) and the release of high levels of pro-inflammatory cytokines including interleukin 8 (IL8), IL1B, TNF-α, IL6 and iNOS (Bogdan, 2001; Crabtree *et al.*, 1991; Rad *et al.*, 2004) and chemokines such as RANTES and MIP-1α and β (Gasperini *et al.*, 1999). For example, IL8 is a neutrophil- and lymphocyte-activating chemotactic cytokine and its secretion by gastrointestinal epithelial cells is enhanced by *H. pylori* colonization (Crabtree *et al.*, 1995; Peek *et al.*, 1995). In contrast, if *H. pylori* infection induces infiltration of T lymphocytes and expression of the CCR6 ligand, CCL20 chemokine, this potentially triggers inflammation to augment apoptosis in inflamed gastric tissues. While it is clear that inflammatory cytokines contribute to inflammation-associated cancer susceptibility, the possible, and likely, contribution of the DNA damage that accompanies chronic inflammation has not been fully tested during *H. pylori* infection. Furthermore, DNA repair gene polymorphisms could influence the degree of inflammation in response to *H. pylori* infection that eventually impact the outcome of the tumor latency after infection. However, the connection between genetic polymorphisms in DNA repair genes in relation to infection will shed light in the future on the mechanisms of how DNA repair gene polymorphisms shape the outcome of the infection-induced inflammatory response. In addition, the infection mediated DNA damage response can also propagate inflammatory signaling and lead to more DNA damage to release more pro-inflammatory cytokines. Therefore, it may be possible to use DNA repair inhibitors to not only treat familial cancers, but also to treat and

even prevent cancers related to infections, particularly cancers associated with chronic inflammation as discussed below.

Minimizing inflammatory response by DNA repair inhibitors

From the standpoint of infection, the functional plasticity of inflammatory and pro-inflammatory cytokines and innate immune cells, macrophages in particular, may potentially offer new targets for the therapeutic use if they are connected with the role and function of DNA repair genes. Several studies with genetically modified mice, along with the analysis of human tumors, have highlighted that altered expression of selected pro-inflammatory (e.g. TNF-α, IL1B, IL6) and/or anti-inflammatory cytokines (e.g. IL10, TGF-β) have a crucial role in the promotion of different types of tumors, including gastric, colorectal, liver, breast and skin tumors (Lin & Karin, 2007). The molecular pathways underlying pathogen-induced inflammation are expected to provide novel anticancer strategies to develop drug targets that reverse inflammation-mediated genomic instability. Even though PARP-1 inhibitors have emerged as promising and effective therapeutics for breast, ovarian, melanoma and lymphoid cancers, the use of PARP-1 inhibitors for the treatment of pathogen-associated (e.g. *H. pylori*) cancers remains to be evaluated clinically. Few studies have demonstrated suppression of the inflammatory response by PARP inhibitors in mice infected with *H. pylori* (Nossa *et al.*, 2009) and prevention of the formation of *Helicobacter*-induced precancerous conditions in mice deficient of anti-inflammatory cytokine. PARP-1 sits at the center of the game not only to assist in repair of RONS-induced DNA lesions, but it also can contribute to further damage by promoting inflammation. Together, this points to PARP inhibition as an attractive target to suppress the DNA damage response that may block excessive inflammation acting potentially as a preventative agent for genomic instability and carcinogenesis.

Mouse models of inflammation, DNA repair and cancer

Several mouse models of inflammation and DNA repair are discussed below. The findings are summarized in Table 1.

AAG DNA glycosylase

Alkyladenine DNA glycosylase (AAG) functions in BER and has a broad substrate specificity. AAG recognizes a variety of base damage that is induced by RONs including 3-methyladenine, 7-methylguanine, hypoxanthine, ethenoadenine and ethenoguanine. Treatment of AAG-deficient mice with dextran sulfate sodium (DSS) or DSS plus azoxymethane (AOM), which mimics the episodic inflammation in individuals with chronic inflammatory disease of the colon, induces significant inflammation compared to treatment of wild-type control mice (Meira *et al.*, 2008). These treatments also result in an increase in etheno-base lesions and in 8-oxoG in the DNA. Importantly, AAG deficient mice exhibit significantly elevated colon tumor multiplicity, suggesting a link between chronic inflammation, DNA damage, and cancer. These results also suggest that AAG protects against inflammation and cancer.

ALKBH2 and ALKBH3 proteins

The *E. coli* AlkB protein repairs etheno-bases and also repairs 1-methyladenine and 3-methylcytosine by direct reversal that depends on iron, oxygen and α-ketoglutarate. The human homologs of *E. coli* AlkB include the ALKBH2 and ALKBH3 proteins, which are known to repair etheno bases (Mishina *et al.*, 2005; Ringvoll *et al.*, 2008). Treatment of wild-type, *ALKBH2*-deficient, *ALKBH3*-deficient, and *ALKBH2/3*-deficient mice with AOM plus DSS resulted in colon tumorigenesis (Calvo *et al.*, 2012). *ALKBH2*-deficient mice exhibited greater tumor multiplicities than wild-type mice. *ALKBH3*-deficient mice did not develop significantly more tumors than wild-type mice, but *ALKBH2/3*-deficient mice exhibited elevated tumorigenesis compared to *ALKBH2*-deficient mice alone. Under these conditions *ALKBH3*-deficient mice displayed significantly higher levels of inflammation than either *ALKBH2*-or *ALKBH2/3*-deficient mice. Similar levels of tumor development were observed in $AAG^{-/-} ALKBH2^{-/-}$ and A$AG^{-/-}ALKBH3^{-/-}$ mice. However, a single cycle of AOM/DSS or DSS alone resulted in lethality in the $AAG^{-/-}ALKBH2^{-/-}ALKBH3^{-/-}$ mice. This was accompanied by increased levels of etheno-bases but less colonic inflammation. $AAG^{-/-}ALKBH2^{-/-}ALKBH3^{-/-}$ mice recover from inflammation induced by cerulein but not by LPS. Importantly, DSS and LPS induce inflammation that is mediated by TLR signaling, whereas this is not the case with cerulean (Kim, 2008; Poltorak *et al.*, 1998). This suggests that DNA repair by AAG, ALKBH2 and ALKBH3 is necessary for survival of inflammation that is mediated by TLR-signaling.

OGG1 and MUTYH DNA glycosylases

One of the most common mutagenic adducts that results from oxidative DNA damage is 7,8-dihyro-8-oxoguanine (8-oxoG) (Barnes & Lindahl, 2004). Adenine pairs with 8-oxoG during DNA synthesis, ultimately resulting in G to T transversions. The OGG1 DNA glycosylase, a member of the BER pathway, excises both 8-oxoG and 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyG) (Bjoras *et al.*, 1997; Girard *et al.*, 1997; Ohtsubo *et al.*, 2000; Thomas *et al.*, 1997). The presence of 8-oxoG in DNA is considered to be a signature of DNA damage induced by ROS. The *MUTYH* DNA glycosylase, which also functions in BER, removes adenine opposite 8-oxoG and 2-hydroxyadenine opposite guanine, and a deficiency in this process leads to increased levels of mutagenesis. Importantly, biallelic mutations in *MUTYH* are associated with an inherited colorectal cancer syndrome resembling adenomatous polyposis (Al-Tassan *et al.*, 2002; Jones *et al.*, 2002; Sampson *et al.*, 2003; Sieber *et al.*, 2003).

Mice deleted of *OGG1* exhibit increased levels of 8-oxoG in their tissues, but show only moderate increases in tumorigenesis (Klungland *et al.*, 1999; Minowa *et al.*, 2000). *MUTYH* deficient mice develop greater numbers of intestinal tumors than wild-type mice, and these adenomas harbor G:C to T:A mutations in the *APC* gene (Sakamoto *et al.*, 2007). Mice doubly deleted of *OGG1* and the *MUTYH* DNA glycosylase are predisposed to development of lung and ovarian tumors tumors (Russo *et al.*, 2004). Treatment of these mice with $KBrO_3$, an agent that induces oxidative base damage, significantly increases tumorigenesis. The lung tumors of *MUTYH*-deficient mice have G:C to T:A transversions in the *K-RAS* oncogene. Therefore, tumorigenesis results from the accumulation of G to T mutations as a result of increased levels of 8-oxoG and deficiency in the removal of adenine opposite 8-

oxoG by the *MUTYH* DNA glycosylase, but the roles of inflammation in tumorigenesis were not characterized in these studies.

A recent report shows that *OGG1*-deficient mice are resistant to systemic inflammation induced by endotoxin (Mabley *et al.*, 2005), as assessed by decreased levels of chemokines and cytokines in serum, compared to *OGG1*-proficient mice. The use of an airway inflammation model (Bacsi *et al.*, 2013) yielded similar results in that down-regulation of OGG1 in the airways of mice challenged with ragweed pollen grain extract resulted in significantly less inflammation than in mice with normal levels of OGG1 in their airways. Lower levels of inflammation correlated with fewer strand breaks resulting from incision of the DNA by OGG1, suggesting that strand breaks augment the inflammatory process. Use of the *OGG1*-deleted mouse yielded similar results upon challenge with OVA or house dust mites (Li *et al.*, 2012). The *OGG1*-deficient animals exhibited less interleukin 4, 6,10, 17 (IL4, 6, 10, 17) in challenged lung tissues and decreased expression of STAT6 and NF-κB. Interestingly, it has recently been shown that OGG1 glycosylase binds to the excised 8-oxoG base, and interacts with *RAS* family of GTPases to serve as a nucleotide exchange factor (Boldogh *et al.*, 2012). Whether this novel activity of OGG1 is related to inflammation awaits further study. Treatment of *MUTYH*-deficient mice with dextran sulfate sodium (DSS) resulted in increased levels of 8-oxoG but significantly lower levels of inflammation compared to what was observed in wild-type mice (Casorelli *et al.*, 2010). There was little change in the expression of pro- and anti-inflammatory cytokines in these mice, which correlated with the observed low levels of inflammation.

NTH1 and NEIL DNA glycosylases

Human NTH1, like all the EcoNth orthologs, possesses DNA-glycosylase/lyase activity on oxidized pyrimidines, formami-dopyrimidines, 5-formyluracil and incises AP sites (Asagoshi *et al.*, 2000a,b; Eide *et al.*, 2001; Ikeda et al, 1998; Jiang *et al.*, 1997b; Marenstein *et al.*, 2001, 2003; Melamede *et al.*, 1994; Miyabe *et al.*, 2002; Purmal *et al.*, 1998; Sarker *et al.*, 1998). In *E.coli* a backup activity to EcoNth for oxidized pyrimidines, EcoNei, was identified and characterized (Dizdaroglu *et al.*, 2001; Jiang *et al.*, 1997a; Melamede *et al.*, 1994; Purmal *et al.*, 1998; Zhang *et al.*, 2000) and its first eukaryotic homologs were found in humans and designated NEIL1, NEIL2 and NEIL 3 (NEI-like). Like hNTH1, NEIL1 recognizes oxidized pyrimidines, formado-pyrimidines and thymine residues oxidized in the methyl group (Bandaru *et al.*, 2002; Hazra *et al.*, 2002; Hu *et al.*, 2005; Wallace *et al.*, 2003; Zhang *et al.*, 2005). Unlike hNTH1, NEIL1 recognizes both stereoisomers of thymine glycol (McTigue *et al.*, 2004, Miller *et al.*, 2004). Thus far, the best substrates for hNEIL1 appear to be the hydantoin lesions, guanidinohydantoin (Gh) and spiroiminodihydantoin (Sp) (Krishnamurthy *et al.*, 2008). NEIL1 is also capable of removing lesions from single-stranded DNA as well as from bubble and forked DNA structures (Dou *et al.*, 2003, 2008). NEIL2 also prefers oxidized pyrimidines but shows a greater preference than NEIL1 for lesions in single-stranded and bubble structures (Dou *et al.*, 2008). Because the expression of NEIL1 is cell-cycle dependent (Hazra *et al.*, 2002), it acts on forked DNA structures (Hegde *et al.*, 2008), and it interacts with PCNA (Dou *et al.*, 2008) and FEN-1 (Hegde *et al.*, 2008), it has been proposed that NEIL1 functions in replication associated repair. Although mice deleted of the NTH1 DNA glycosylase have no

reported phenotype (Ocampo *et al.*, 2002) and NEIL1 DNA glycosylase deletion in mice develop metabolic syndrome (Vartanian *et al.*, 2006), mice deleted of both NEIL1 and NTH1 exhibit an increase in both pulmonary and hepatic carcinogenesis (Chan *et al.*, 2009). The lung tumors contained GC to AT transitions at codon 12 of the *KRAS* gene, suggesting they arose as a result of oxidative damage at guanine residues in the DNA. Interestingly, 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyG) was enriched in the tissues of the *NTH1 NEIL1*-deficient mice, and 8-oxo-G was not. This suggests that oxidative damage to guanine occurred in the mice, leading to the induction of transition mutations that arose from deficient repair of FapyG due to lack of initiation of BER and perhaps bypass of the oxidative lesion. The oxidative DNA damage could have arisen from either endogenous ROS or ROS as a result of inflammation, but no information regarding lyphocytic infiltration of tissues or tumors was reported.

FANC C-deficient mice and inflammation

The FANC C protein is a member of the Fanconi anemia pathway, which is responsible for the repair of crosslinks and also functions in homology-directed repair (for a review see Kim & D'Andrea, 2012). Bone marrow failure is a leading cause of death in patients with Fanconi anemia. *FANC C*-deficient mice are hypersensitive to LPS-induced inflammation and septic shock that is intrinsic to the hematopoietic system and results in its suppression, which suggests that bone marrow failure may result in part from an inflammatory process (Sejas *et al.*, 2007; Du *et al.*, 2014). The hematopoietic suppression observed in the *FANC C* deficient mice appears to be dependent upon increased expression of tumor necrosis factor alpha (TNF-α) and ROS. Interestingly, inactivation of *FANC C* results in increased activation of toll like receptor 8 (TLR 8) (Vanderwerf *et al.*, 2009) leading to an increase in the expression of TNF-α. Although specific mutants of *FANC C* were able to rescue the crosslink repair defects of *FANC C* deficient cells, they were not able to suppress TNF-α overexpression, suggesting a role for *FANC C* in suppression of TLR 8 that is independent of its role in crosslink repair.

SMAD 4 deletion, inflammation and cancer

SMAD 4 is a central regulator of TGF-β signaling and is found to be downregulated in human head and neck squamous cell carcinoma (HNSCC) and adjacent buccal mucosa (Bornstein *et al.*, 2009). Loss of *SMAD4* leads to increased expression of TGF-β. Homozygous deletion of *SMAD 4* in mice results in spontaneous HNSCC, downregulation of BRCA1, FANC A and FANC D2, which are members of the Fanconi anemia pathway. *SMAD 4* deficient mice also exhibit increased levels of inflammation in head and neck epithelia, similar to what is observed in human tumors, and this is correlated with increased expression of TGF-β. Increased levels of genomic instability were observed in *SMAD 4* deficient mice, likely as a result of downregulation of BRCA1 and genes of the Fanconi anemia pathway. These results suggest that SMAD4 is a "guardian gene", at least within the context of HNSCC.

Colon cancer in Rag2$^{-/-}$ mice infected with *Helicobacter hepaticus*

Rag2$^{-/-}$ mice have no B or T lymphocytes to fight infection, but do have cells of monocyte origin including macrophages and neutrophils. Infection of these mice with *H. hepaticus* results in the development of severe colitis by 10 weeks and colon carcinoma by 20 weeks post infection (Mangerich *et al.*, 2012). Elevated levels of infiltration of neutrophils and macrophages accompanying the colitis are observed in *H. hepaticus*-infected Rag2$^{-/-}$ mice compared to controls, suggesting the presence of an inflammatory response. Importantly, significant DNA damage, including high levels of halogenated bases were identified in these mice. Transcriptional profiling demonstrated that many of the genes encoding proteins involved with the generation of reactive chemical species were upregulated in infected mice, whereas DNA repair genes were downregulated in colon tissue (Mangerich *et al.*, 2012). Therefore, the lack of regulatory T cells disturbs the balance of immune cells in the lamina propria, leading to high levels of inflammation and cancer. Use of a iNOS inhibitor was shown to block NO production and a reduction in colitis-associated pathology (Erdman *et al.*, 2009) as was depletion of GR-1 cells. Given that much of the damage observed was in the form of halogenated lesions, it is likely the neutrophils, which are the source of hypochlorous acid via activation of myeloperoxidase (MPO), induce the colitis-associated DNA damage. This correlates with the observation that MPO and neutrophils are associated with the intestinal lesions of IBD patients (Knutson *et al.*, 2013; Kruidenier *et al.*, 2003a,b; Robinson *et al.*, 1997).

APC (Adenomatous polyposis coli)

APC has been characterized in multiple studies, but its main role as a tumor suppressor was recognized in colorectal cancer. Approximately 81% of hypermutated tumors and 53% of non-hypermutated tumors in the colon harbor mutations in the *APC* gene. The function(s) of the Apc protein are diverse and include cellular proliferation, differentiation, apoptosis, migration, and cytoskeletal regulation (Zeineldin & Neufeld, 2013). APC has been known as a tumor suppressor particularly in human colorectal cancer while acting as an inhibitor for hyperactivation of canonical Wnt signaling (Fearon, 2011). However, the critical role of APC is not limited to only colon cancer but includes other types of cancer with the importance of the Wnt signaling pathway in cell proliferation and differentiation in general (Karim *et al.*, 2004). Germline mutations in the *APC* gene predispose individuals to an inherited form of colon cancer termed familial adenomatous polyposis (FAP) (Groden *et al.*, 1991; Joslyn *et al.*, 1991; Kinzler *et al.*, 1991). Colorectal carcinogenesis results from one inherited germline mutation in the *APC* gene, followed by loss of heterozygosity (LOH) in the second copy of the *APC* gene, resulting in lack of functional APC protein in the cells.

Karin et al. demonstrated that chronic epithelial NF-κB activation that occurs in intestinal epithelia cells (IEC) constitutively active for Iκκ-β expression accelerates the loss of APC through iNOS (inducible nitric oxide synthase) upregulation (Shaked *et al.*, 2012). Here the constitutive expression of active Iκκ-β induced chronic activation of the NF-κB pathway and did not interfere with the Wnt pathway-mediated β-catenin accumulation, suggesting that the decoupling of the Wnt pathway and chronic inflammation does occur with the loss APC protein in intestinal epithelial cells (IECs). Also such activation induced iNOS, and resulted in excessive DNA damage, particularly elevated amounts of 8,5′-cyclo-2′-

deoxyadenosine (cdA) and 8,5′-cyclo-2′-deoxyguanosine (cdG), which are oxidatively induced DNA lesions in Iκκ-β in the IEC of mice. Of note, cdA and cdG are two of many endogenous reactive oxygen species (ROS)-induced DNA lesions. This study also elegantly demonstrated that IECs are undergoing constant DNA damage and repair. Consistent with this, very recent study (Pribluda *et al.*, 2013), which suggested that inhibition of the chronic NF-κB pathway by NSAIDs is beneficial in preventing DNA damage in IECs. Inhibition of NOS by pharmacological treatment of *APC*$^{min/+}$ mice with guanidinoethyldisulfide (GED) reduced the intestinal tumor load and oxidative stress in these mice as does gene knockout of iNOS (Ahn & Ohshima, 2001; Mabley *et al.*, 2004).

IL17 and the linkage between DNA repair and inflammation

In recent years, interleukin 17 (IL17) has been mostly described as a proinflammatory cytokine for tumorigenesis and autoimmune diseases. IL17 was initially identified as an important CD4 T cell-derived proinflammatory cytokine in autoimmune diseases models such as EAE (Baeten *et al.*, 2013). It has been suggested that IL6 and TGF-β1 are two critical cytokines that influence the development of Th17 cells, while other proinflammatory cytokines including IL1β and IL23 further develop pathogenic Th17 cells' pathogenicity. IL17 has six family members (IL17A-F). Two isoforms, IL17A and IL17F, have similar structures whereas the others are distant family members (Iwakura *et al.*, 2011). The differential role of IL17A and IL17F has been documented previously (Ishigame *et al.*, 2009). Of note, the particular presence of IL17 in the intestinal lamina propria raised questions regarding its role in gut inflammation. Several groups have reported IL17 as a critical stimulator of intestinal tumorigenesis in spontaneous and a bacterial toxin-mediated pathway (Blatner *et al.*, 2012; Chae & Bothwell, 2011; Chae *et al.*, 2010; Wu *et al.*, 2009). The molecular mechanism of IL17-mediated tumorigenesis is still unclear. However, there are several studies that indicate the importance of a constant level of IL17 and its recognition of commensal microbiota in intestinal tumorigenesis. It has been reported that IL17 is constantly expressed by CD4 T cells and this was maintained by commensal microbiota (Atarashi *et al.*, 2008). Also the recognition of microbiota by the adaptor protein MyD88 has been found to be important to develop intestinal tumorigenesis (Rakoff-Nahoum & Medzhitov, 2007). Hence, it is very likely that the recognition of commensal bacteria and subsequent maintenance of a basal level of inflammation by IL17 is protective under normal circumstances. However, when a critical component of a tumor suppressor/DNA repair related component such as APC is affected, this protective process could turn into a "feeding" role for transformed cells. For example, a very recent study suggested that Tpl2 (tumor progression locus 2) activity is modulated by IL17 via AP-1 to induce neoplastic transformation in epidermal cells and human breast cancer cells MCF7 (Kim *et al.*, 2013).

In a broader sense the involvement of IL17 in different types of cancers, previous and recent studies reported that polymorphisms in IL17 gene are associated with various types of cancer such as gastric, cervical, colorectal and breast cancer (Wu *et al.*, 2010). It is known that IL17 can markedly activate the NF-κB pathway (Chang *et al.*, 2011).

Although very much speculative in its current stage, it could be possible that IL17 may lead to hyperactivation of the NF-κB pathway to induce *APC* loss. Such an LOH event driven by

a constantly activated NF-κB pathway has been suggested previously (Shaked *et al.*, 2012). Loss of APC protein eventually leads to the accumulation of mutations, which may in part result from its ability to interfere with BER. Future studies need to address whether IL17 is directly or indirectly regulating DNA damage control in the above cancer types.

Seminal studies showed that Th17 cells are an important cell subset to induce both spontaneous and Enterotoxigenic Bacteroides fragilis (EBTF)-driven intestinal tumorigenesis (Chae *et al.*, 2010; Wu *et al.*, 2009). Notably the maintenance of such Th17 cell populations was dependent on the bacterial ATP production in the gut (Atarashi *et al.*, 2008).

Tumor microenvironment, inflammation and DNA repair

Introduction

Chronic inflammation has been considered as the "fuel" for tumorigenesis is to promote the generation of a tumor microenvironment that enables angiogenesis and recruitment of inflammatory mediators and cell types. The complex interaction between intrinsic mutations and tumor microenvironment eventually leads to cancer. Thus, the formation of a permissive tumor environment could be considered as a sum of collective counter responses as well as manipulation of host immune system by tumors that accumulated mutations to evade intrinsic and extrinsic checkpoints in the host.

Eradication of cancerous cells by immune system

Over the past 20 years, the availability of mouse genetic models facilitated study of the challenging question of how immunity can protect the host from cancer. One hypothesis is that the immune system plays three distinct roles in cancer prevention. First, the immune system protects the host from viral/bacterial infection that can induce tumors by eliminating such pathogens. Second, it abolishes the establishment of a proinflammatory microenvironment that facilitates tumorigenesis by eliminating pathogens and by prompt resolution of inflammation, so that it does not enter the chronic inflammation stage. Third, the immune system eliminates tumor cells in certain tissues by recognizing ligands for activating receptors on innate immune cells and tumor antigens that are co-expressed in nascent transformed cells. Such events lead to the activation of the adaptive immune system and eventually result in tumor clearance (for a review see Schreiber *et al.*, 2011). A more sophisticated view of the control of tumor "quantity" as well as "quality" was established a decade ago (Dunn *et al.*, 2002; Schreiber *et al.*, 2011; Shankaran *et al.*, 2001). These findings led to investigation of three stages of immune surveillance or so called cancer immunoediting – *Elimination Equilibrium* and *Escape* (Schreiber *et al.*, 2011).

The concept of the *Elimination* phase is the step at which the innate and adaptive immune systems detect the presence of a developing tumor and destroy it. Several alerting mechanisms for the immune system are likely to include Type I IFNs, endogenous danger signal ligands from tumor cells such as HMGB1 or hyaluronan fragments, and expression of stress ligands such as RAE-1 and H60 (mouse) or MICA/B (human) (Steinle *et al.*, 2001) (for reviews see Matzinger, 1994; Sims *et al.*, 2010). Such mechanisms alert the innate

immune cells to release proinflammatory and immunomodulatory cytokines to facilitate the development of tumor-specific adaptive immunity.

After undergoing the rigorous and robust *Elimination* step, only a few tumor cell variants may survive. At this point the *Equilibrium* stage is initiated. At this stage, the adaptive immune system prevents tumor cell outgrowth and also edits the antigenicity of the tumor cells. This can be considered as a functional state of dormancy. The evidence for the existence of an equilibrium phase came from a study showing that immunocompetent mice treated with low-dose carcinogen 3′-methylcholanthrene (MCA) harbored occult cancer cells for an extended time period, and then the depletion of IFN-γ and T cells resulted in rapid reappearance of the tumor at the original MCA injection site in half of the mice (Sims *et al.*, 2010). Once tumor cells acquire the ability to outmaneuver immune recognition and/or destruction, they can emerge as visible tumors. By modulating their own response against the host immune system progressive growth of tumors is possible.

Tumor cell *Escape* can occur through several mechanisms (for a review see Dunn *et al.*, 2004).At the tumor cell level, loss of antigens would abrogate immune recognition for the cytotoxic effects of immunity and subsequently promote tumor outgrowth. Such loss can be achieved by emergence of tumor cells that lack strong rejection antigens (DuPage *et al.*, 2012; Monjazeb *et al.*, 2013). Alternatively, loss of the major histocompatibility complex (MHC) class I proteins that load tumor antigenic peptide or loss of antigen processing functions within the tumor cell that are needed to produce the antigenic peptide epitope can achieve escape from immune surveillance (Siddle *et al.*, 2013). Interestingly, these alterations are probably driven by a combination of genetic instability, inherent in tumor cells, and the process of immunoselection during the elimination and equilibrium stages (Khong & Restifo, 2002). The establishment of the tumor microenvironment is also an important mechanism of escape. Tumor cells can promote the development of an immunosuppressive microenvironment by producing immunosuppressive cytokines (VEGF, TGF-β) and recruitment of immunosuppressive lymphocytes (e.g. Tregs). The accumulation of Tregs in the tumor microenvironment often leads to a poor prognosis (Darrasse-Jèze & Podsypanina, 2013).

Control of DNA repair, inflammation and cancer by the immunosuppressive cytokine IL10

In addition to the proinflammatory role of IL17 in the intestine, recent studies identify regulatory T cells (Tregs) as an important player in colon cancer as well as other types of cancer such as ovarian cancer and renal cell carcinoma (Adeegbe & Nishikawa, 2013; Menetrier-Caux *et al.*, 2012). Regulatory T cells are generated from both the thymus and periphery, and the transcription factor Foxp3 is a lineage specification marker (Josefowicz *et al.*, 2012). Their main role is to suppress hyperactivation of the immune system, thus preventing autoimmunity and allergic reactions as well as excessive inflammation by infectious pathogens. Tregs are equipped with multiple mechanisms to perform negative regulatory functions by highly expressing negative co-stimulatory molecules for T cell activation such as programmed cell death 1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4), and also secretion of immunosuppressive cytokines (IL10 and TGF-β). Growing evidence suggests that the accumulation of such immunosuppressive Tregs in the tumor

microenvironment often results in a poor outcome for cancer patients. The important role of Tregs in the tumor microenvironment is often to inhibit effective anti-tumor immunity. Thus, targeting Tregs in the tumor microenvironment has been considered an effective approach to circumvent immunosuppression of multiple types of cancers such as non-small lung cancer (e.g. NSLCC and melanoma). Some of these approaches have now reached clinical trials in cancer patients (Hamid *et al.*, 2013; Holmgaard *et al.*, 2013). While targeting of immunosuppressive Tregs in the tumor microenvironment is beneficial, this systematic depletion of Tregs may have a possibility of causing autoimmunity. As cancer develops it may have accumulated myriads of mutations, which escape the host immune system, so it may be worth considering targeting of the immune system where inflammation and DNA repair are interacting at an early stage.

Interestingly, the inflammation event at an early stage would have more of a "feeding" role for tumorigenesis, and therefore the immunosuppressive nature of Treg cells could be beneficial. Such a hypothesis was supported by Erdman *et al.* demonstrating that the adoptive transfer of regulatory T cells could regress tumors within 1–3 weeks in the $APC^{/Min+}$ mouse model (Erdman *et al.*, 2005). They also elegantly showed that the transfer of IL-10 deficient regulatory T cells could not regress tumors, further suggesting that the immunosuppressive cytokine IL10 is critical to inhibit intestinal tumorigenesis (Erdman *et al.*, 2003). In addition, other groups have shown that IL10 from regulatory T cells and CD4 T cells is a critical source of suppression for tumorigenesis (Dennis *et al.*, 2013; Gounaris *et al.*, 2009). Since IL10 is highly expressed in CD4+ T cells in the colonic lamina propria (Maynard & Weaver, 2008), it would be reasonable to think that IL10 may regulate intestinal tumorigenesis fed by IL17-mediated inflammation.

We have recently shown that the endogenous Tregs in $APC^{/Min+}$ mice are not capable of regressing tumors while the depletion of endogenous Tregs regresses tumorigenesis (unpublished data). Further, we showed that the heterozygous mutation of *APC* in Tregs from otherwise wild-type mice restored their tumor regression capacity (unpublished data). These results demonstrate the effect of the tumor microenvironment on the development of Tregs function. They also suggest that IL10 from Tregs is critical at an early stage of intestinal tumorigenesis, and hereditary FAP colon cancer patients such as FAP patients may have further complications in their immune systems as a consequence of the germline mutation in the *APC* gene.

The contribution of the immunosuppressive cytokine IL10 to the DNA damage response needs to be addressed in future studies. A previous study showed that DNA damage triggers IL10 production after UV irradiation in mouse keratinocytes (Nishigori *et al.*, 1996). This suggests that unrepaired DNA damage could induce systemic induction of the immunosuppressive cytokine. Additional evidence suggests that IL10 single nucleotide polymorphism (SNP) variants are associated with basal cell carcinoma alongside with DNA repair gene variants and also with genes such as iNOS that is associated with prostate cancer recurrence (Dluzniewski *et al.*, 2012; Festa *et al.*, 2005). Since the relationship between IL10 and the DNA damage response is unclear, future studies will require molecular and biochemical characterization of this pathway.

Antigenicity and tumor mutagenesis

Microsatellite DNA sequences comprise short tandem repeat (STR) motifs of one to six base pairs, and are ubiquitous in eukaryotic genomes, making up ~3% of total DNA in the human genome (Consortium, 2004). Microsatellites often display allele length alterations in tumor tissues, relative to normal tissue, or microsatellite instability (MSI) (Hile *et al.*, 2013). Mismatch repair-deficient tumors display an MSI-High (MSI-H) phenotype due to widespread genome instability at microsatellites and other sequences. Loss of MMR protein expression and MSI-H is observed in Lynch syndrome tumors, and to varying degrees in sporadic colorectal cancer (CRC) and colitis-associated cancerous lesions (de la Chapelle & Hampel, 2010; Fleisher *et al.*, 2000; Svrcek *et al.*, 2007; Tahara *et al.*, 2005). Tumor-specific loss of MMR destabilizes STRs genome-wide, including those present within protein-coding sequences. Consequently, translation of the resulting frameshift mutations generates truncated peptides. In another familial CRC predisposition syndrome, *MUTYH*-associated polyposis (MAP), loss of the base excision repair MUTYH glycosylase protein also results in a mutator phenotype, but one restricted to elevated transversion base substitution mutations (Al-Tassan *et al.*, 2002; Nielsen *et al.*, 2009).

Both MSI-H and MAP tumors carry a high mutational load due to loss of DNA repair, and are characterized by a strong immune response, relative to repair competent CRCs (de Miranda *et al.*, 2012; Kloor *et al.*, 2010). MSI-H tumors contain higher numbers of infiltrating, activated cytotoxic lymphocytes than do repair-proficient CRCs (Dolcetti *et al.*, 1999; Guidoboni *et al.*, 2001; Phillips *et al.*, 2004). One hypothesis to explain these observations is that the high mutation rate within repair-deficient tumors produces aberrant tumor-specific antigens, thus triggering a strong, anti-tumor immune response (Linnebacher *et al.*, 2001). Indeed, tumor infiltrating lymphocytes and peripheral blood lymphocytes from patients with MSI-H tumors can be reactive against epitopes representing tumor-specific frameshift antigens, and display cytotoxic activity towards MSI-H tumor cells (Ishikawa *et al.*, 2003; Saeterdal *et al.*, 2001). MSI-H tumors have a significantly better clinical prognosis than do repair-proficient CRCs (Popat *et al.*, 2005), and the high density of infiltrating T cells in MSI-H tumors is correlated with favorable prognosis (Buckowitz *et al.*, 2005; Guidoboni *et al.*, 2001).

Paradoxically, the same increased mutation rate that enhances the immunogenicity of tumors also contributes to immune escape during tumor progression. One mechanism involved in immune escape is mutational inactivation of genes involved in antigen processing and recognition within repair-deficient tumors (de Miranda *et al.*, 2012; Kloor *et al.*, 2010). Defective HLA Class I expression is observed in both MMR-and BER repair-deficient tumors, and can be caused by somatic mutations at STRs within the β2-microglobin, TAP1 and TAP2 genes (Bicknell *et al.*, 1996; de Miranda *et al.*, 2009; Kloor *et al.*, 2005). Despite their strong immunogenicity, 28% of MSI-H tumors do not express HLA Class II antigens (Lovig *et al.*, 2002). Recently, somatic STR mutations within the cIITA and RFX5 genes have been reported in MSI-H CRCs, consistent with defective HLA Class II antigen presentation (Michel *et al.*, 2010).

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The potential relevance of STR targets within genes to tumorigenesis and cancer progression was recognized in early studies describing MSI-H tumors (Duval & Hamelin, 2002). Approximately 17% of human genes contain microsatellites within coding regions (Gemayel *et al.*, 2010), and one report estimates that STRs are present in the exons of 92% of human genes (Madsen *et al.*, 2008). Furthermore, STRs are over-represented in genes related to cancer and immune system diseases (Madsen *et al.*, 2008). The current selective targets database (www.seltarbase.org) documents gene associated STRs that are mutated in cancers, and the large number of entries emphasizes the impact of this class of mutation to tumor development and immunological responses (Woerner *et al.*, 2010). Intriguingly, intragenic microsatellite variation of *S. cerevisiae* genes can generate functional diversity of cell surface antigens (Verstrepen *et al.*, 2005), and microsatellite length mutations underlie some forms of phase variation in bacterial species (Gemayel *et al.*, 2010). Thus, mutations within repeated sequences also may be a process by which pathogens can elude the host immune system.

Summary

We have focused this review on links between DNA repair and inflammation as they relate to cancer. Although at this point in time, much remains to be elucidated, there are many links between DNA repair and inflammation. NF-κB, a master regulator of the immune response, and IRFs are upregulated in an ATM-dependent manner as part of the DNA damage response, as shown in Figure 3. DNA damage also upregulates NKG2D ligands, which can lead to death of severely damaged cells that reside in a chronic inflammatory environment. Activation of the inflammasome by DNA damage leads to downregulation of DNA repair and cell death, which could also be a protective mechanism in a chronic inflammatory environment. In some cases, as with the *OGG1*-deficient mouse model, the lack of DNA repair of 8-oxo-G results in tissues that are actually resistant to inflammation. Oxidized bases themselves have the capacity to potentiate immune responses. Specific miRNAs are upregulated under conditions of hypoxia and inflammation and some of these miRNAs downregulate DNA repair. Tumors with MSI and a high mutational load, as a result of deficient DNA repair, produce aberrant tumor-specific antigens and as a result are heavily infiltrated with lymphocytes, leading to a better prognosis.

Activation of the immune inflammatory response to pathogens or microbiota and induction of the SASP in senescent cells leads to chronic inflammation, as depicted in Figure 2. It is known that inflammatory cells release RONs that result in DNA damage (Figure 1). An inability to regulate the inflammatory response or to repair the DNA, as a result of mutations in DNA repair or immune genes leads to cancer development. Overwhelming the cells with DNA damage, which might occur under conditions of chronic inflammation and deficient repair, as during infection with pathogens, can also lead to carcinogenesis. Thus, DNA repair and inflammation act together to maintain homeostasis.

Acknowledgments

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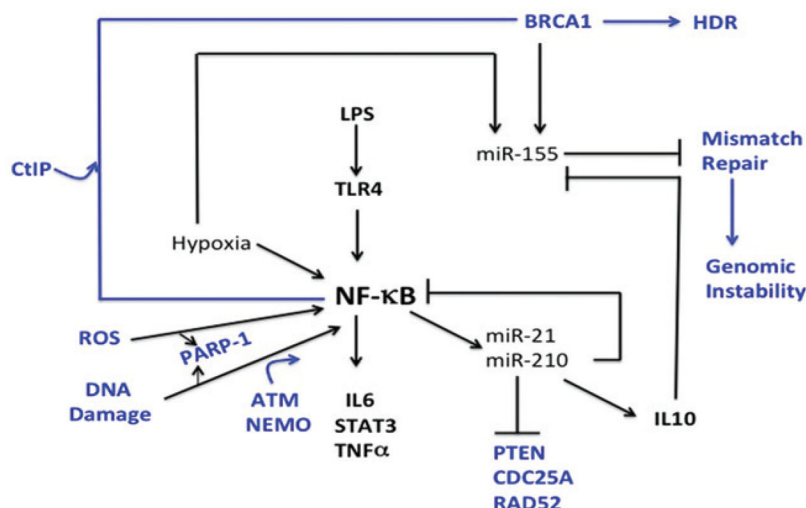
Figure 1.
NF-κB and the interplay between DNA repair and inflammation. NF-κB is a master regulator of the inflammatory response. After activation through TLR4, several proinflammatory genes are activated, including IL6, STAT3 and TNFα, which has the potential to lead to a cytokine storm. NF-κB is also induced by DNA damage, ROS and hypoxia, leading to the expression of proinflammtory genes. Induction of NF-κB by DNA damage is regulated by ATM, a master regulation of the DNA damage response, and this occurs with assistance from NEMO. Induction of NF-κB also leads to the induction of miR-21 and miR-210, resulting in induction of IL10, and anti-inflammatory cytokine, but also downregulation of PTEN, CDC25A and RAD52, proteins that are involved in the DNA damage response. Not only does hypoxia induce activation NF-κB, but it also induces expression of miR-155, which downregulates mismatch repair, with the potential to lead to genomic instability. However, IL10, which is indirectly induced by NF-κB, has the capacity to downregulate miR-155. Of special interest for this review is the finding that NF-κB stimulates the CtIP-BRCA1 complex, thereby promoting homology-directed repair (HDR). (see colour version of this figure at www.informahealthcare.com/bmg).
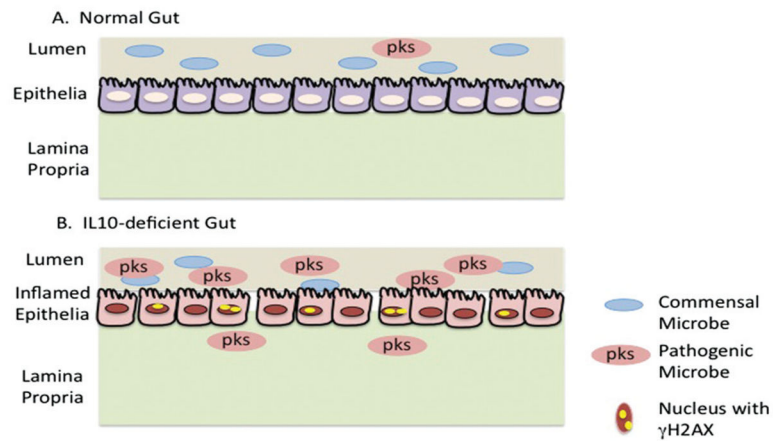
Figure 2.
Interplay between microbiota, chronic inflammation and DNA damage in the gut. A. Healthy epithelia. Commensal microorganisms reside in the lumen, with very few pathogenic bacteria harboring the polyketide synthase (*pks*) pathogenicity island. B. Gut epithelia of an IL10-deficient mouse. The chronic inflammatory environment in the IL10-deficient mouse encourages enrichment of pathogenic *E. coli* that harbor the *pks* pathogenicity island. These pathogenic *E. coli* induce DNA damage in nearby epithelial cells that has the capacity to result in genomic instability and tumorigenesis. (see colour version of this figure at www.informahealthcare.com/bmg).
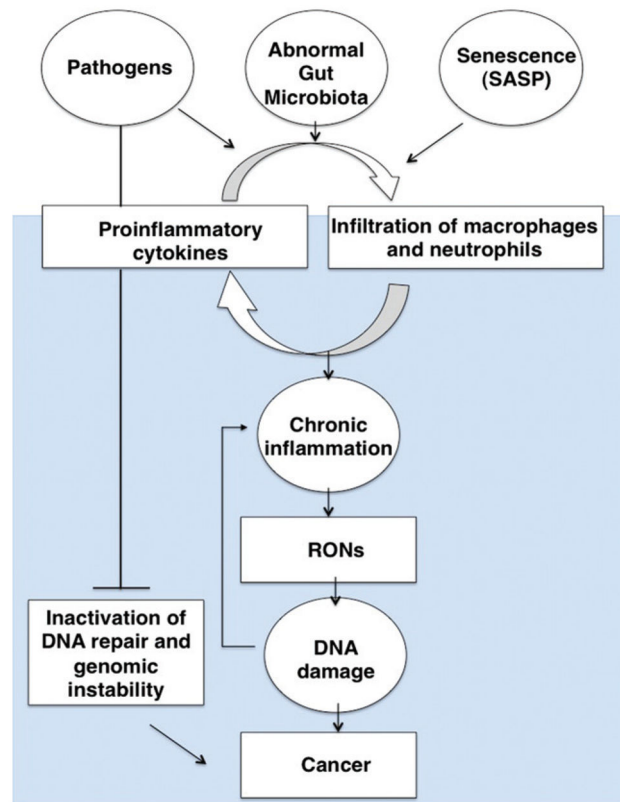
Figure 3.
A model of the links between DNA damage and inflammation. Activation of the immune response occurs as a result of infection with pathogens, exposure to the microbiota of the gut and the secretory associated senescence phenotype (SASP). Acute inflammation can lead to chronic inflammation as described in this review, resulting in the generation of RONs and leading to DNA damage. Pathogens, genetic mutations in DNA repair genes and environment-associated expression of miRNAs can inactivate DNA repair, which results in a mutator phenotype, genomic instability and cancer. (see colour version of this figure at www.informahealthcare.com/bmg).

Table 1

Phenotypes of mouse models of DNA repair and inflammation.

Gene	Role of gene product	Phenotype of mouse deletion	References
AAG/MPH	Alkyladenine DNA glycosylase	Inflammation and colon cancer upon treatment with DSS/AOM	Meira *et al.*, 2008
ALKBH2 ALKBH3	Direct reversal of alkyation; repair of ethenobases	Inflammation and colon cancer upon treatment with AOM plus DSS; lethal in combination with AAG-deletion in the presence of AOM plus DSS	Calvo *et al.*, 2012
OGG1	DNA glycosylase that removes 8-oxoG and Fapy G	Inflammation resistant; moderate tumorigenesis	Klungland *et al.*, 1999; Minowa *et al.*, 2000; Mabley *et al.*, 2005; Bacsi *et al.*, 2013
MUTYH	DNA glycosylase that removes adenine opposite 8-oxoG	Intestinal adenomas with G:C to T:A mutations in the *APC* gene; mice doubly deficient in *OGG1* and *MUTYH* are predisposed to lung and ovarian tumors	Sakamoto *et al.*, 2007; Russo *et al.*, 2004
NEIL1 NTH1	DNA glycosylases that removed oxidized bases	Mice doubly deleted of these glycosylases develop lung and liver tumors	Chan *et al.*, 2009
FANC C	Member of Fanconi Anemia crosslink repair pathway	Hypersensitive to LPS-induced inflammation intrinsic to hematopoietic system.	Sejas *et al.*, 2007; Du *et al.*, 2014
SMAD4	Regulator of TGF-β signaling	Inflammation and spontaneous head and neck cancer	Bornstein *et al.*, 2009
RAG2	Adaptive immune response; V(D)J recombination	Infection with *Helicobacter hepaticus* leads to inflammation and colon cancer	Mangerich *et al.*, 2012
IL 10	Suppressor of macrophage induction; inhibitor of proinflammatory cytokines	Spontaneous chronic inflammation and colon cancer that depends on commensal bacteria	Kuhn *et al.*, 1993
T-bet	T box transcription factor	Spontaneous colitis	Garrett *et al.*, 2007