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Inflammation and cancer: An ancient link with novel potentials

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Infection and chronic inflammation contribute to about 1 in 4 of all cancer cases. Mediators of the inflammatory response, *e.g.*, cytokines, free radicals, prostaglandins and growth factors, can induce genetic and epigenetic changes including point mutations in tumor suppressor genes, DNA methylation and post-translational modifications, causing alterations in critical pathways responsible for maintaining the normal cellular homeostasis and leading to the development and progression of cancer. Recent discovery of an interaction between microRNAs and innate immunity during inflammation has further strengthened the association between inflammation and cancer.

Key words: inflammation; microRNA; nitric oxide; cancer

Recent evidence has strengthened and reignited the interest of cancer researchers in the exciting and promising concept of an association of inflammation and cancer.[1–4] More than a century ago, Virchow hypothesized a link between inflammation and cancer, based on the presence of leukocytes in neoplastic tissue. Immune cells can regulate almost every stage of cancer development.[5] Because of the fact that chronic infection and inflammation contribute to about 25% of all cancer cases worldwide, and patients with chronic inflammatory and oxyradical overload diseases are at a much higher risk of developing cancer, exploration of the possible mechanisms offers the potential for improved diagnosis, prevention and therapy (Table I). Inflammation involves a well-coordinated response of an innate and adaptive immune system following infection or injury by exogenous or endogenous means. Any disturbance in tissue homeostasis activates the innate immune cells that are a first line of defense. The innate immune cells, *e.g.*, macrophages, mast cells, dendritic cells (DC) and natural killer (NK), cells can initiate the inflammatory response by releasing cytokines, chemokines, matrix-remodeling proteases, and reactive oxygen and nitrogen species, leading to the elimination of pathogens and repair of tissue damage. Furthermore, DC and NK cells can also activate the adaptive immune response that requires antigen specificity.[5] However, any failure in the precise control of immune components can lead to chronic inflammation, generating a pathologically conducive microenvironment that may favor the initiation and progression of cancer (Fig. 1). A sustained inflammatory microenvironment provides a constant supply of a variety of reactive nitrogen and oxygen species, reactive aldehydes, cytokines, chemokines and growth factors, which can alter crucial biological processes responsible for maintaining normal cellular homeostasis, leading to genomic instability and the risk of cancer development. The interplay of both the extrinsic (microenvironment surrounding the preneoplastic cells) and intrinsic pathways (within the preneoplastic cells) is required for inflammation-associated tumorigenesis.[6] Recent studies have shown that RalB GTPase can both promote cell survival and activate the production of inflammatory mediators through the innate immune system.[7,8] A human ortholog of immunity-related p47 guanosine triphosphatases (IRGM) plays a role in autophagy and reduces intracellular bacteria.[9] Single nucleotide polymorphism 313T>C in *IRGM*, an autophagy inducing gene, is associated with Crohn disease, indicating an association between the defect in early immune response and Crohn disease.[10] Cytokines, chemokines, nuclear factor (NF)-κB, nitric oxide synthase-2 (NOS2), cyclooxygenase-2 (COX2), hypoxia inducible factor-1α (HIF1-α), signal transducers and activators of transcription 3 (STAT3), nuclear factor erythroid 2-related factor 2 (Nrf2) and nuclear factor of activated T cells (NFAT) have been reported as key molecular players linking inflammation to cancer.[11] This review focuses primarily on some key molecular components and pathways that may be responsible for inflammation-associated cancer. Excellent reviews describing the role of individual immune cells of an innate and adaptive immune system in inflammation can be found elsewhere.[2,5] *In vitro* and *in vivo* evidence implicate inflammation in altering multiple pathways related to cancer development (Fig. 2). The identification of specific alterations in critical cellular components and their interactive pathways due to unresolved inflammation can provide molecular targets for early detection, prevention and therapy of inflammation-associated cancer.

Role of reactive oxygen and nitrogen species in inflammation-associated carcinogenesis

A sustained generation of reactive oxygen and nitrogen species, *e.g.*, $OH^{\bullet}$, $NO^{\bullet}$, $O2^{\bullet}$, $OONO^{-}$, contributes to the pathological consequences of chronic inflammation (Fig. 3). Earlier studies suggested that a pro-oxidant state promotes neoplastic growth.[12] Reactive oxygen or nitrogen species produced by activated inflammatory cells inflict a variety of damages ranging from mutations in tumor suppressor genes to the post-translational modification of proteins involved in essential cellular processes including apoptosis, DNA repair and cell cycle checkpoint. A variety of DNA alterations are produced by reactive species that involve both oxidation and nitration reactions causing strand break or specific mutations in DNA bases. However, the type of free radicals, their half-life and accessibility to the target determines the degree and specificity of damage.

Reactive nitrogen species (RNS) can further generate other reactive species, *e.g.*, reactive aldehydes-malondialdehydes (MDA) and 4-hydroxynonenal (4-HNE), by inducing excessive lipid peroxidation. Both MDA and 4-HNE induce point mutations in tumor suppressor genes and are associated with increased cancer risk in chronic inflammatory diseases.[13,14] Furthermore, RNS are mediators of signal transduction pathways including the MAPK signaling cascade, leading to the induction of protooncogenes, including *c-Fos* and *c-Jun*, and AP-1-dependent gene expression involved in proliferation, differentiation, cell death and transformation.[15,16]

Post-translational modifications of proteins can alter cellular homeostasis. Key post-translational modifications and their functional consequences due to free radical exposure have been earlier described (reviewed in Ref. 3). We and others have earlier reported that exposure to nitric oxide ($NO^{\bullet}$) leads to the post-translational modification of *p53* and *Rb* tumor suppressor genes at residues that are crucial to its function.[17,18] Furthermore, exposure to $NO^{\bullet}$ activates DNA repair and signal transduction molecules, such as DNA protein kinases.[19,20] Therefore, sustained generation and the accumulation of free radicals, can inflict oxidative and nitrosative damage on critical genes and proteins leading to a protumorigenic microenvironment.

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TABLE I – CHRONIC INFLAMMATION AND INFECTION CAN INCREASE CANCER RISK

Disease	Tumor site	Risk
Inherited		
Hemochromatosis	Liver	219
Crohn's disease	Colon	3
Ulcerative colitis	Colon	6
Acquired		
Viral		
Hepatitis B	Liver	88
Hepatitis C	Liver	30
Bacterial		
Helicobacter pylori	Gastric	11
PID	Ovary	3
Parasitic		
S. hematobium	Urinary bladder	2–14
S. japonicum	Colon	2–6
Liver Fluke	Liver	14
Chemical/physical/metabolic		
Acid reflux	Esophagus	50–100
Asbestos	Lung pleural	>10
Obesity	Multiple sites	1.3–6.5

"18% of human cancers, *i.e*, 1.6 million per year, are related to infection." - B. Stewart and P. Kleihues, World Cancer, Report, IARC Press, Lyon 2003, p. 57.

- Rheumatoid arthritis is an example of a chronic inflammatory disease without an increased cancer risk, *e.g*., joint sarcoma.
- Oncogenic human papilloma viruses are examples of cancer-prone chronic infections without inflammation.

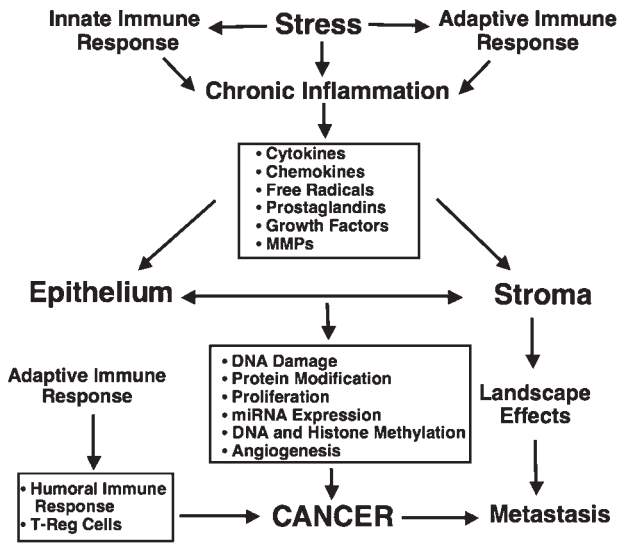

FIGURE 1 – Schematic presentation of a procarcinogenic scenario during chronic inflammation. Generation and accumulation of cytokines, growth factors, free radicals, matrix proteinases and prostaglandins induces several protumorigenic alterations including DNA damage, protein modifications, changes in gene expression profiles and the expression of specific miRNA. Combined with the stromal–epithelial interaction and immune suppressive effect of adaptive immune response, these changes can support tumor development and invasion.

Inflammation, NO• and p53

NO• is a key signaling molecule and a critical component of inflammatory responses. It participates in crucial physiological processes including vasodilation, neurotransmission and host defense. However, it also can be deleterious at higher concentration by causing alterations in DNA and essential cellular proteins by post-translational modifications. NO• holds a unique status in the field of cancer biology because of its proneoplastic and antineoplastic functions.[3,21] These antagonistic functions of NO• are

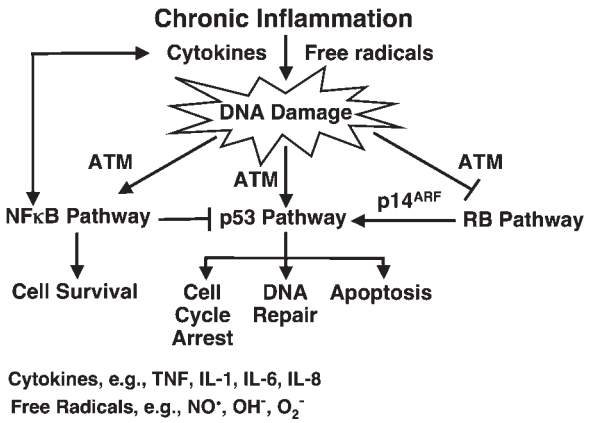

FIGURE 2 – Chronic inflammation affects several crucial pathways involved in the maintenance of cellular homeostasis. Free radicals generated during inflammation cause DNA damage leading to the activation of a p53 stress response pathway and the inactivation of the pRb tumor suppressive pathway through their post-translational modifications. However, the oncogenic pathway, *e.g*., the activation of NF-κB, also occurs along with the inactivation or oncogenic transformation of p53 gene due to missense mutations affecting DNA repair, cell cycle arrest and apoptosis.

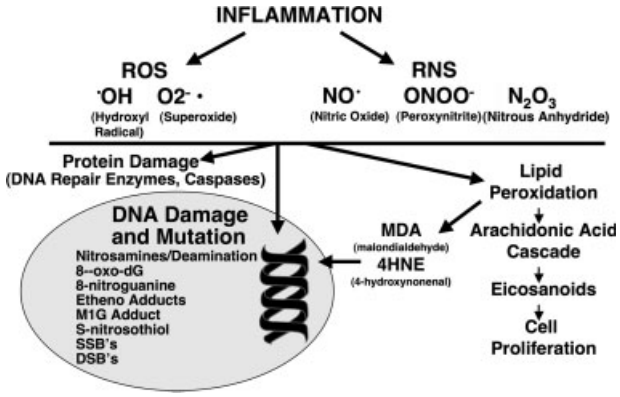

FIGURE 3 – Several reactive oxygen (ROS) and reactive nitrogen species (RNS) are generated during chronic inflammation. The reactive species can induce DNA damage, including point mutations in cancer-related genes, and modifications in essential cellular proteins that are involved in DNA repair, apoptosis and cell cycle, either directly or indirectly through the activation of lipid peroxidation and generation of reactive aldehydes, *e.g*., malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE).

primarily governed by the quantity of NO•, cell type, redox status and the inflammatory microenvironment.[3,22–24]

NO• is produced by a family of enzymes called nitric oxide synthase (NOS), which catalyzes the conversion of L-arginine to citruline and uses molecular oxygen and NADPH as cofactors.[25,26] Three major isoforms of NOS have been described. NOS1 (neuronal NOS) and NOS3 (endothelial NOS) are primarily constitutive and Ca^{2+}-dependent isoforms, whereas NOS2 (inducible NOS) is primarily inducible and Ca^{2+}-independent isoform. However, few exceptions have been reported in the mode of expression of these isoforms, where NOS1 and NOS3 have been shown to be inducible and NOS2 as constitutively expressed (reviewed in Ref. 27). The quantity of NO• produced by these isoforms is remarkably different and can produce dissimilar outcomes. NOS1 and NOS3 produce a low level of NO• ranging from picomolar to nanomolar concentrations, whereas NOS2 produces a much higher level of NO• in the micromolar range for a prolonged period of time.[22,28] NOS2 is induced by a variety of different stimuli including

hypoxia, Wnt-pathway, inflammatory cytokines and NF-κB. We have recently reported that *NOS2* is a target of Wnt/β-catenin signaling.[29]

$NO^{\bullet}$ exerts its effect through either cGMP-dependent or -independent pathways. A lower level of $NO^{\bullet}$ usually acts through cGMP-dependent pathways leading to the activation of soluble guanylate cyclase (sGC) and formation of cGMP, which can have multiple effects including the regulation of cGMP-dependent protein kinases, cyclic nucleotide phosphodiesterases and the cation channel.[30] In contrast, a higher level of $NO^{\bullet}$ acts through cGMP-independent mechanisms, either by direct interaction with biological macromolecules or through the formation of different RNS, *e.g.*, peroxynitrite ($ONOO^-$), nitrosoperoxycarbonate ($ONOOCO_2^-$) and nitrogen dioxide (NO_2).[27] RNS can induce a variety of different mutations in cancer-related genes.[31–34]

p53 acts as a key molecular node in the inflammatory stress response pathway regulating the expression of a specific set of genes to a particular inflammatory stimulus.[35] An interesting interaction between p53 and $NO^{\bullet}$ was reported: the existence of a negative feedback loop in which $NO^{\bullet}$ causes the stabilization and accumulation of p53, which in turn, transrepresses *NOS2*.[36,37] During chronic inflammation, $NO^{\bullet}$ induces p53 post-translational modification through the activation of ATM and ATR kinases.[19] $NO^{\bullet}$-mediated p53 accumulation and post-translational modification inhibits cellular growth and induces apoptosis, which can lead to the selective clonal expansion of mutated p53 cells.[18,38] Several studies have shown antineoplastic function of $NO^{\bullet}$. Genetic deletion of NOS2 in p53-deficient C57BL6 mouse model of Li-Fraumeni syndrome accelerates the development of lymphoma and sarcomas.[21,39] The deletion of NOS2 in p53-deficient mice showed lower apoptotic and higher proliferation indices.[21] These results are consistent with the hypothesis that p53 and $NO^{\bullet}$ cooperatively regulate tumorigenesis. Interestingly, a higher level of $NO^{\bullet}$ in an inflammatory condition can accelerate spontaneous development of lymphoma and sarcomas in p53-deficient mice (Hussain *et al*., unpublished data). An association between NOS2 expression and *p53* mutation has been reported in cancer and cancer-prone inflammatory diseases.[40,41] Inflamed lesions in the colon of patients with ulcerative colitis showed an increase in p53 mutation frequency at codons 247 and 248 and an increased NOS2 expression.[41] Likewise, G:C to T:A transversions at p53 codon 249 along with increased NOS2 expression are found in the liver tissue from patients with hemochromatosis.[13] Therefore, $NO^{\bullet}$ can both activate the p53 tumor suppressive pathway and induce oncogenic mutations in the *p53* gene (Fig. 4).

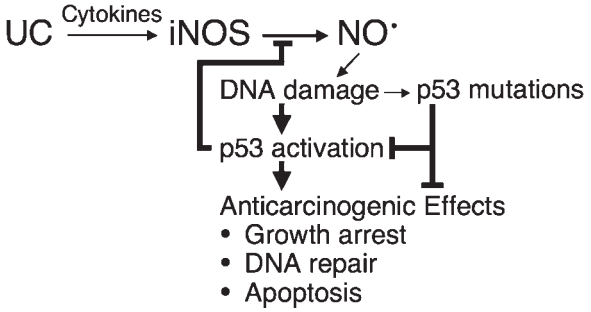

FIGURE 4 – $NO^{\bullet}$ possesses both protumorigenic and antitumorigenic properties. It can activate the protective p53 stress response pathway and cause oncogenic p53 mutations.

Cytokines

Cytokines are key regulators of inflammation with pro- and anti-inflammatory functions, and therefore, can either stimulate or inhibit tumor growth and progression.[42–44] Specific polymorphisms in cytokine genes are associated with an increased risk of cancer.[45] Cytokines are produced as a host response to cellular stress caused by either exogenous or endogenous agents to control and minimize cellular damage. However, an uncontrolled and sustained generation of cytokines can lead to altered cell growth, differentiation and apoptosis. Proinflammatory cytokines implicated in carcinogenesis include IL-1, IL-6, IL-15, colony stimulating factors (CSF), TNF-α and the macrophage migration inhibitory factor (MIF).[43,44] A unique immune response signature, consisting predominantly of humoral cytokines, promotes metastasis in hepatocellular carcinoma.[46] Likewise, a signature consisting of 11 cytokine genes in the lung environment predicted lymph node metastasis and prognosis of lung adenocarcinoma with *IL-8* and *TNF*α as the top 2 genes for predicting prognosis.[47] *IL-8* was originally described as a monocyte-derived neutrophil chemotactic factor (MNDCF) that specifically attracted neutrophils and was renamed due to its multiple function (reviewed in Ref. 48). *IL-8* can have angiogenic activities in several cancers including non-small cell lung cancer (NSCLC) and can function as a positive autocrine growth factor.[49–53] In the same study, increased IL-1 expression is reported in more than 50% of gastric cancer cases and is associated with liver metastasis.[54] Chemically induced skin carcinogenesis in mice enhances IL-1 expression in keratinocytes.[55,56] Both *TNF*-α and *IL-6* contributed to the chemically induced skin tumors and lymphomas in mice.[57–59] *IL-6* can mediate the pRb hyperphosphorylation and can induce antiapoptotic genes *Bcl2* and *Bcl-XL*.[60,61] Furthermore, genetic-deficiency in TNF receptor-I (TNFRI) inhibited tumor formation in a mouse model of liver cancer.[62] An increase in CSF-1 and its receptor is associated with an increase in ovarian endometrial and breast cancer.[63]

MIF plays a central role in the innate immune response.[64] The MIF polymorphism is associated with the severity of chronic inflammatory diseases.[65] MIF possesses unique biological activities, which include its role in the regulation of the p53 tumor suppressor gene, angiogenesis, cell cycle and senescence, and is a strong candidate linking inflammation and cancer. MIF initiates a cascade of events including the phosphorylation of ERK1/ERK2 pathways leading to the increase in COX2 and NOS2, inhibition of p53-dependent and -independent apoptosis, and growth arrest and the activation of NF-κB. In contrast to the tumor supportive cytokines, there are many examples of cytokines that inhibit tumorigenesis. IFN-γ is an excellent example. Mice lacking IFN-γ are sensitive to chemical carcinogens and show an increased tumor frequency and shorter tumor latency.[66–68] Mice deficient in both IFN-γ and p53 showed a reduced tumor latency and a broader tumor spectrum.[67] Mice deficient in GM-CSF and IFN-γ develop a high frequency of hematologic and solid neoplasms within a background of infection and inflammation.[69] Therefore, the interplay of these cytokines during inflammation may require an optimal balance and any disturbance in the fine tuning of their regulation may favor tumor progression.

NF-κB

NF-κB is a transcription factor and a key molecular link between inflammation and cancer.[70,71] Following its discovery almost 20 years ago, accumulated evidence has confirmed its role in mediating a variety of protumorigenic processes. NF-κB regulates several genes whose products inhibit apoptosis and enhance cell cycle progression, angiogenesis and metastasis.[70,72,73] Furthermore, a considerable number of NF-κB target genes encode mediators of the innate immune response and inflammation, which include cytokines, chemokines, proteases, NOS2 and COX2.[71] Under normal conditions, NF-κB is bound to IκB and remains inactive. Following stimulation by proinflammatory cytokines and microbial infection, IκB is phophorylated and undergoes proteasomal-degradation by the IKK complex. The IKK complex is composed of two catalytic subunits, IKK-α (IKK-1) and IKK-β (IKK-2) and a regulatory protein IKK-γ, also known as NEMO. The degradation of IκB frees NF-κB, which then moves to the

nucleus to mediate the transcription of target genes. NF-κB, which is activated as a response to inflammation, also maintains and regulates the inflammatory microenvironment. IKK-γ- or NEMO-deficient mice showed severe deregulation of immune homoeostasis in the gastro-intestinal tract and an inflammatory bowel disease-like phenotype.[74] The inhibition of IKK-β-dependent activation of NF-κB leads to the decrease in tumor incidence in inflammation-associated murine models of liver and colon cancer.[75,76] Mutations in the *NOD2* gene are implicated in the development of cancer-prone Crohn disease.[77,78] These mutations enhance NF-κB activity and increased the production of IL-1β.[79] Although the majority of evidence supports a role of NF-κB in tumor progression, its antitumorigenic function has also been reported in certain cell types (reviewed in Ref. 71).

Inflammation and microRNA

MicroRNA (miRNA) is a small (~22 nucleotide) gene-silencing RNA that binds to its target mRNA, leading to its cleavage and degradation.[80–82] Precursor miRNAs that are produced in the nucleus undergo several rounds of processing in the nucleus and cytoplasm involving specific proteins, *e.g.*, Drosha, DGCR8/Pasha and Dicer, before they are loaded onto the RNA-induced silencing complex (RISC) to modify the target mRNAs. Recent analyses have reported the presence of many miRNAs, which constitute about 3% of the human genome,[83–85] indicating that thousands of human genes can be the target of miRNA-mediated regulation.[86]

Substantial evidence supports the role of miRNA in the initiation and progression of human cancer (reviewed in Refs. 87–89). In the recent past, we reported unique miRNA profiles associated with the diagnosis and prognosis in lung cancer in which high mir-155 and low mir-let7a-2 expression correlated with poor survival.[90] The complexity of the immune system requires layers of well-coordinated mechanism to control its initiation and termination. miRNA has the potential to mediate the complex regulation of gene-expression associated with an immune response. In relation to the association of inflammation and miRNA, two obvious questions arise. Does inflammation cause the expression of specific miRNAs and do the inflammation-associated miRNAs regulate the expression of genes that are expressed during an inflammatory response? The answers to these questions can identify novel links between inflammation and cancer. Results from studies testing these hypotheses have started to emerge and provide evidence that answers these questions in the affirmative. miRNAs are important regulators of innate immune responses (reviewed in Ref. 91) (Fig. 5). A unique pattern of miRNA expression is found in different hematopoietic cell lineages and plays a role in their proliferation and differentiation[92] (reviewed in Ref. 91). Altered expression of miRNA in hematopoietic cells is associated with cancer of the immune system (reviewed in Ref. 87). Mir-17p, 20a and 106a inhibit the differentiation and maturation of monocytes by binding and inhibiting acute myeloid leukemia-1 (AML1, also known as RUNX1) expression and the subsequent downregulation of macrophage colony stimulating factor receptor (M-CSFR).[93] The same study also showed that AML1 binds the mir-17-5p-92 and 106a-92 cluster promoters and transcriptionally inhibits mir-175p, -20a and -106a expression, thus indicating the existence of a negative feedback loop. Inflammatory activation of monocytes leads to the NF-κB-dependent induction of miR-146, which, in turn, inhibits TNF receptor-associated factor 6 (*TRAF6*) and IL-1 receptor associated kinase 1 (*IRAK1*) genes, the two key molecules downstream to the Toll-like receptor and cytokine signaling.[94] Mir-155 is reported to be substantially upregulated in murine macrophages activated with polyriboinosinic:polyribocytidylic acid [poly (I:C)] or IFN-β.[95] Interestingly, this induction involved TNF-α and JNK pathways, and can be regarded as a common and critical target of inflammatory mediators. mir-155-deficient mice are immunodeficient and have a defective germinal center response.[96,97] IL-6 induces mir-let-7a and contributes to its survival effect by increasing signal transducers and activators of transcription-3 (STAT3) phosphorylation by a mechanism involving neurofibromatosis 2 (NF2) gene in human cholangiocytes.[98] These studies provide evidence of a nexus among inflammation, miRNA and cancer. The elucidation of the exact mechanisms of inflammation-associated regulation of miRNA expression and miRNA-mediated regulation of the immune response will provide markers for diagnosis and targets for therapy of cancer.

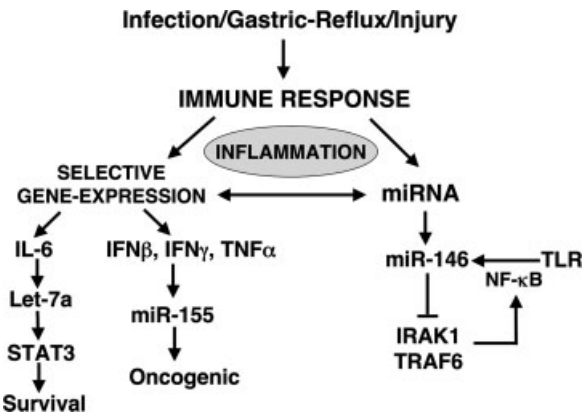

FIGURE 5 – Examples of cytokine–miRNA interactions in inflammation.

Inflammation and DNA methylation

Epigenetic modifications cause genetic disturbance and changes in gene-expression profile. One of the common epigenetic changes is DNA methylation, which results in the addition of a methyl (CH_3) group at the carbon 5 position of the cytosine ring resulting in 5-methyl cytosine. Alteration in DNA methylation patterns, predominantly hypermethylation, is common in a variety of human cancers (reviewed in Refs. 99–101). However, global hypomethylation is also associated with cancer.[102–104] Hypermethylation of promoters leads to the transcriptional silencing of several tumor suppressor genes including *APC*, *p16*, *BRCA1*, *Rb* and *MDM2*, and is associated with cancer development (reviewed in Ref. 100). Methylated CpG sites are also prone to the deamination, leading to missense mutations in cancer-related genes.[105] Evidence supports an association between chronic inflammation and hypermethylation both in the presence and absence of microbial infection.[101] *H. pylori*-infected patients with and without cancer show a several-fold higher methylation pattern in 8 regions of the 7 CpG islands.[106] Furthermore, hypermethylation of the *E-cadherin* gene is associated with *H. pylori* infection and gastric cancer.[107] Patients with cancer-prone chronic inflammatory diseases, *e.g.*, ulcerative colitis and Barretts esophagus, show hypermethylation in several different genes including *p16*, *RUNX3*, *HPP1* and *MLH1*.[108,109] In the recent past, it was shown that inflammation-mediated cytosine damage can alter the methylation pattern and critical gene regulation.[110] IL-6, a pro-inflammatory cytokine, enhances and maintains hypermethylation of the *p53* tumor suppressor gene and *hHR23B* gene, a key component of the nucleotide excision repair, promoter in multiple myeloma cell line KAS-6/1.[111] Furthermore, IL-6 decreases promoter methylation of epidermal growth factor receptor (EGFR), leading to the enhanced expression and growth of cholangiocarcinoma cells.[112] These results suggest that DNA methylation is a mechanism that could contribute to inflammation-associated tumorigenesis.

COX2

COX catalyzes a key step in arachidonic acid metabolism and production of prostaglandins. The two COX isoforms, COX1 and COX2, differ in their expression patterns. COX1 is constitutively

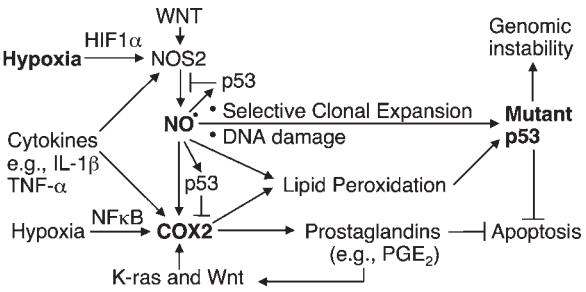

FIGURE 6 – Both NOS2 and COX2 cooperate in colon carcinogenesis. The inflammation and Wnt-signaling can induce NOS2 and COX2 leading to the generation of a high level of $NO^{\bullet}$ and PGE2, respectively. $NO^{\bullet}$ and reactive aldehydes cause DNA alterations including p53 mutations causing a selective growth advantage of the p53 mutant cells. PGE2, in addition to inhibiting apoptosis, can further enhance COX2 production through the activation of the Wnt-pathway. However, $NO^{\bullet}$-induced post-translational modification of p53 can activate p53, which can inhibit NOS2 and inhibit or activate COX2. Furthermore, $NO^{\bullet}$ can induce and activate COX2. The ultimate effect of these interactions can lead to genomic instability and cancer.

expressed and is present in most of the tissues, whereas COX2 is usually undetectable and is induced by several stimuli including inflammation, hypoxia and Wnt-signaling.[113,114] Furthermore, depending on the extent of activation, p53 can either inhibit or activate COX2.[115,116] Recently, K-ras has been shown to stabilize COX2 expression, and β-catenin-TCF4 in the Wnt-pathway can increase transcription of the COX2 gene.[114,117] Prostaglandins display diverse physiological roles, which include immunity, reproduction, maintenance of vascular tone and nerve growth.[118] Prostaglandins, in particular PGE2, can enhance tumorigenesis (reviewed in Ref. 119) and activate the Wnt pathway.[120] An elevated expression of COX2 is frequently reported in a variety of different human cancer and has been localized in both tumor epithelial cells and stroma supporting autonomous as well as landscaping effects in tumor development (reviewed in Ref. 113). COX2 overexpression and enzymatic activation can enhance the level of antiapoptotic protein BCL2 and members of the matrix metalloproteinase (MMP) family.[121,122] Genetic deletion of COX2 in $Apc^{\Delta 716}$ knockout mice led to the suppression of intestinal polyposis.[123] Interestingly, genetic deletion of COX1 also inhibited intestinal tumorigenesis that was comparable with COX2.[124] Genetic deletion of COX1 in heterozygous p53 mice delayed the development of lymphoma and sarcomas (Hussain *et al*., unpublished data). However, the mechanism leading to the inhibition of intestinal tumorigenesis in COX1-deficient mice is not clearly understood. Antiapoptotic and proangiogenic -proliferative and -inflammatory functions of COX2 support its role in tumorigenesis.[125,126] Epidemiological, animal and human clinical studies have shown that nonsteroidal anti inflammmatory drugs (NSAIDs) are chemopreventive for colon adenoma and cancer.[113] NOS2 can enhance the activation of COX2.[127,128] One of the mechanisms of COX2 activation is through S-nitrosylation by NOS2.[128] Therefore, it is plausible that increased NOS2 and COX2 during inflammation cooperatively contribute to human colon cancer (Fig. 6).

Conclusion

Deregulation in a complex and well-coordinated response to inflammation can lead to unresolved inflammation and a protumorigenic microenvironment. Mediators of inflammation can inflict genetic alteration including point mutations in tumor suppressor genes, change gene-expression profile and induce post-translational modifications leading to genetic and physiological instability and cancer. These alterations have been described in cancer-prone chronic inflammatory diseases before the development of cancer. However, some of these mediators can have both protumorigenic and antitumorigenic functions, one example of which is $NO^{\bullet}$, confirming the complex nature of their role in human biology. The elucidation of the mechanisms of inflammatory processes, and their possible association with cancer, has identified several targets for diagnosis and therapy. Discovery of miRNA and its involvement in cancer and inflammation offers unlimited opportunities to develop therapeutic regimens for inflammation-associated cancers.

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