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.

Recent evidence has strengthened and rekindled the interest of cancer researchers in the exciting and promising concept of an association of inflammation and cancer. 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. 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. However, any failure in the precise control of immune components can lead to chronic inflammation, generating a pathologically conducive microenvironment that may favor the immortalization 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. Recent studies have shown that Rb GTase can both promote cell survival and activate the production of inflammatory mediators in the innate immune system. A human ortholog of immunity-related p47 guanosine triphosphatases (IRGM), an autophagy inducing gene, is associated with Crohn disease, indicating an association between the defect in early immune response and Crohn disease. 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. 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. 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., NO*, O2*, ONOO−, contributes to the pathological consequences of chronic inflammation (Fig. 3). Earlier studies suggested that a pro-oxidant state promotes neoplastic growth. 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. 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.

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*) leads to the post-translational modification of p53 and Rb tumor suppressor genes at residues that are crucial to its function. Furthermore, exposure to NO* activates DNA repair and signal transduction molecules, such as DNA protein kinase. 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.
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 can also be deleterious at higher concentrations 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 anti-neoplastic functions.3,21 These antagonistic functions of NO are primarily governed by the quantity of NO, cell type, redox status and the inflammatory microenvironment.3,22–24

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**TABLE 1 – CHRONIC INFLAMMATION AND INFECTION CAN INCREASE CANcer RISK**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Tumor site</th>
<th>Risk</th>
</tr>
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<tbody>
<tr>
<td>Inherited</td>
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<tr>
<td>Hemochromatosis</td>
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<td>219</td>
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<td>Crohn’s disease</td>
<td>Colon</td>
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<tr>
<td>Ulcerative colitis</td>
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<tr>
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<td>Ovary</td>
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<td>Urinary bladder</td>
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<td>S. japonicum</td>
<td>Colon</td>
<td>2–6</td>
</tr>
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<td>Liver</td>
<td>14</td>
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<tr>
<td>Chemical/physical/metabolic</td>
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<td>Esophagus</td>
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<td>Asbestos</td>
<td>Lung pleural</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Obesity</td>
<td>Multiple sites</td>
<td>1.3–6.5</td>
</tr>
</tbody>
</table>

*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.

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**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.

**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-kB, 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).
hypoxia, Wnt-pathway, inflammatory cytokines and NF-κB. We have recently reported that NOS2 is a target of Wnt/β-catenin signaling.\textsuperscript{29} NO\textsuperscript{*} exerts its effect through either cGMP-dependent or -independent pathways. A lower level of NO\textsuperscript{*} 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 calcium channel.\textsuperscript{30} In contrast, a higher level of NO\textsuperscript{*} acts through cGMP-independent mechanisms, either by direct interaction with biological macromolecules or through the formation of different RNS, e.g., peroxynitrite (ONOO\textsuperscript{-}), nitrosoepoxypropane (ONOOCO\textsubscript{2} \textsuperscript{-}) and nitrogen dioxide (NO\textsubscript{2}).\textsuperscript{27} RNS can induce a variety of different mutations in cancer-related genes.\textsuperscript{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.\textsuperscript{35} An interesting interaction between p53 and NO\textsuperscript{*} was reported: the existence of a negative feedback loop in which NO\textsuperscript{*} causes the stabilization and accumulation of p53, which in turn, transrepresses NOS2.\textsuperscript{36,37} During chronic inflammation, NO\textsuperscript{*} induces p53 post-translational modification through the activation of ATM and ATR kinases.\textsuperscript{38} NO\textsuperscript{*}-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.\textsuperscript{18,38} Several studies have shown antineoplastic function of NO\textsuperscript{*}. Genetic deletion of NOS2 in p53-deficient C57BL6 mouse model of Li-Fraumeni syndrome accelerates the development of lymphoma and sarcomas.\textsuperscript{39,40} The deletion of NOS2 in p53-deficient mice showed lower apoptotic and higher proliferation indices.\textsuperscript{41} These results are consistent with the hypothesis that p53 and NO\textsuperscript{*} cooperatively regulate tumorigenesis. Interestingly, a higher level of NO\textsuperscript{*} in an inflammatory condition can accelerate spontaneous development of lymphoma and sarcomas in p53-deficient mice (Husain et al., unpublished data). An association between NOS2 expression and p53 mutation has been reported in cancer and cancer-prone inflammatory diseases.\textsuperscript{42,43} Inflamed lesions in the colon of patients with ulcerative colitis showed an increased in p53 mutation frequency at codons 247 and 248 and an increased NOS2 expression.\textsuperscript{44} Likewise, G-C to T-A transversions at p53 codon 175 have recently been reported in the liver tissue from patients with hemochromatosis.\textsuperscript{13} Therefore, NO\textsuperscript{*} can both activate the p53 tumor suppressive pathway and induce oncogenic mutations in the p53 gene (Fig. 4).

**Cytokines**

Cytokines are key regulators of inflammation with pro- and anti-inflammatory functions, and therefore, can either stimulate or inhibit tumor growth and progression.\textsuperscript{42–44} Specific polymorphisms in cytokine genes are associated with an increased risk of cancer.\textsuperscript{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).\textsuperscript{46,47} A unique immune response signature, consisting predominantly of humoral cytokines, promotes metastasis in hepatocellular carcinoma.\textsuperscript{48} 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 TNFα as the top 2 genes for predicting prognosis.\textsuperscript{49} 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 nonsmall cell lung cancer (NSCLC) and can function as a positive autocrine growth factor.\textsuperscript{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.\textsuperscript{54} Chemically induced skin carcinogenesis in mice enhances IL-1 expression in keratinocytes.\textsuperscript{55–57} Both TNF-α and IL-6 contributed to the chemically induced skin tumors and lymphomas in mice.\textsuperscript{58,59} IL-6 can mediate the p5b hyperphosphorylation and can induce antipoptotic genes Bel2 and Bel-1l.\textsuperscript{60,61} Furthermore, genetic-deficiency in TNF receptor-I (TNFR1) inhibited tumor formation in a mouse model of liver cancer.\textsuperscript{62} An increase in CSF-1 and its receptor is associated with an increase in ovarian endometrial and breast cancer.\textsuperscript{63}

MIF plays a central role in the innate immune response.\textsuperscript{64} The MIF polymorphism is associated with the severity of chronic inflammatory diseases.\textsuperscript{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 tumor growth. 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.\textsuperscript{66–68} Mice deficient in GM-CSF and IFN-γ develop a high frequency of hematologic and solid neoplasms within a background of infection and inflammation.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{71} Under normal conditions, NF-κB is bound to IκB and remains inactive. Following stimulation by proinflammatory cytokines and microbial infection, IκB is phosphorylated 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 IκK-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 homeostasis in the gastro-intestinal tract and an inflammatory bowel disease-like phenotype.93 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, DGCRI8/Pasha and Dicer, before they are loaded onto the RNA-induced silencing complex (RISC) to modify the target mRNAs. Recent analyses 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 a complex (RISC) to modify the target mRNAs. Recent analyses have reported the presence of many miRNAs, which constitute a complex (RISC) to modify the target mRNAs. Recent analyses have reported the presence of many miRNAs, which constitute a complex (RISC) to modify the target mRNAs. Recent analyses have reported the presence of many miRNAs, which constitute a complex (RISC) to modify the target mRNAs.

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.218 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 differentiation92 (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-kB-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-a 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-let7a 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.

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 (CH3) 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). Methylation 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.106 H. pylori-infected patients with and without cancer show a several-fold higher methylation pattern in 8 regions of the 7 CpG islands.107 Furthermore, hypermethylation of the E-cadherin gene is associated with H. pylori infection and gastric cancer.108 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 cytosome 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.

**Figure 5** – Examples of cytokine-miRNA interactions in inflammation.

**COX2**

COX catalyzes a key step in arachidonic acid metabolism and production of prostaglandins. The two COX isofoms, COX1 and COX2, differ in their expression patterns. COX1 is constitutively
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. Furthermore, depending on the extent of activation, p53 can either inhibit or activate COX2. 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. Prostaglandins display diverse physiological roles, which include immunity, reproduction, maintenance of vascular tone and nerve growth. Prostaglandins, in particular PGE2, can enhance tumorigenesis (reviewed in Ref. 119) and activate the Wnt-pathway. 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 landscape in tumour 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. Genetic deletion of COX2 in ApoE-/- mice led to the suppression of intestinal polyposis. Interestingly, genetic deletion of COX1 also inhibited intestinal tumorigenesis that was comparable with COX2. 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.

**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-promoting inflammatory diseases before the development of cancer. However, some of these mediators can have both protumorigenic and antimutagenic functions, one example of which is NO, 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 miRNome and its involvement in cancer and inflammation offers unlimited opportunities to develop therapeutic regimens for inflammation-associated cancers.

**Acknowledgements**

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**References**