Crosstalk between DNA Damage and Inflammation in the Multiple Steps of Carcinogenesis

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Received: 10 July 2017; Accepted: 10 August 2017; Published: 19 August 2017

Abstract: Inflammation can be induced by chronic infection, inflammatory diseases and physicochemical factors. Chronic inflammation is estimated to contribute to approximately 25% of human cancers. Under inflammatory conditions, inflammatory and epithelial cells release reactive oxygen (ROS) and nitrogen species (RNS), which are capable of causing DNA damage, including the formation of 8-oxo-7,8-dihydro-2′-deoxyguanosine and 8-nitroguanine. We reported that 8-nitroguanine was clearly formed at the sites of cancer induced by infectious agents including Helicobacter pylori, inflammatory diseases including Barrett’s esophagus, and physicochemical factors including asbestos. DNA damage can lead to mutations and genomic instability if not properly repaired. Moreover, DNA damage response can also induce high mobility group box 1-generating inflammatory microenvironment, which is characterized by hypoxia. Hypoxia induces hypoxia-inducible factor and inducible nitric oxide synthase (iNOS), which increases the levels of intracellular RNS and ROS, resulting DNA damage in progression with poor prognosis. Furthermore, tumor-producing inflammation can induce nuclear factor-κB, resulting in iNOS-dependent DNA damage. Therefore, crosstalk between DNA damage and inflammation may play important roles in cancer development. A proposed mechanism for the crosstalk may explain why aspirin decreases the long-term risk of cancer mortality.

Keywords: oxidative stress; inflammation; cancer

1. Introduction

Inflammation can be induced by a wide variety of factors, such as chronic infection, inflammatory diseases and physicochemical agents, and has been recognized to be causative and promotive of cancer [1]. Chronic inflammation is estimated to contribute to approximately 25% of human cancers [2]. Under inflammation, reactive oxygen species (ROS) and nitrogen species (RNS) are produced in inflammatory and epithelial cells, to damage a wide variety of biomolecules including nucleic acids, proteins and lipids [3,4]. ROS and RNS can damage DNA to form mutagenic lesions, such as 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) and 8-nitroguanine [5–7]. Especially, 8-nitroguanine formation may act as a key molecular event common to various types of inflammation-related carcinogenesis.

Under inflammatory conditions, nitric oxide (NO) is generated in inflammatory and epithelial cells, and this reaction is catalyzed by NO synthase (NOS), especially inducible nitric oxide synthase (iNOS). NO and NOS are known to play roles on both pro- and anti-carcinogenic effects [8]. Sustained induction of iNOS in chronic inflammation can produce ROS and RNS, causing DNA damage [9].
NO reacts with superoxide (O$_2^-$) to form peroxynitrite (ONOO$^-$), which causes guanine nitration to generate 8-nitroguanine [10,11]. 8-Nitroguanine is a mutagenic DNA damage. The glycosidic bond between 8-nitroguanine and deoxyribose in DNA strand is thermodynamically unstable. Therefore, 8-nitroguanine can be spontaneously released, leading to the formation of an apurinic site [12]. Adenine can be incorporated opposite the apurinic site during DNA synthesis according to the A-rule. Translesion DNA synthesis, which bypasses apurinic sites, is mediated by DNA polymerase ζ subunits, Rev1 and Rev3 [13]. 8-Nitroguanine can form a pair with adenine during DNA synthesis, and this process is catalyzed by polymerase η and a truncated form of polymerase κ [14]. These suggest that 8-nitroguanine formation leads to single base substitutions, particularly G:C to T:A transversions [15].

NO and O$_2^-$ are released from neutrophils or macrophages during inflammation. NO is long-lived enough to diffuse through the extracellular matrix, cross the plasma membrane and the cytoplasm of epithelial cells, and enter the nucleus, whereas O$_2^-$ is not sufficiently long-lived to react with DNA in the nucleus of epithelial cells [16]. Alternatively, inflammatory cells may release cytokines including tumor necrosis factor α (TNF-α) to stimulate O$_2^-$ accumulation in neighboring epithelial cells [17]. Relevantly, it was reported that interaction of TNF-α and TNF receptor 1 promotes gastric tumorigenesis via the induction of NAD(P)H oxidase (Nox) in tumor cells [18]. Nox generates O$_2^-$ in cancer cells. NO, which is generated by iNOS in tumor-associated macrophage (TAM), reacts with O$_2^-$ in cancer cells, forming ONOO$^-$. ONOO$^-$ causes DNA damage, mutation and genomic instability to proceed tumor malignancy (Figure 1).

**Figure 1.** Mechanism for DNA damage in epithelial cells by inflammation. NO and O$_2^-$ are produced during inflammation. Although NO is sufficiently long-lived to diffuse through the extracellular matrix, and enter the nucleus, O$_2^-$ released by neutrophils or macrophages during inflammation is not sufficiently long-lived. Alternatively, inflammatory cells may use cytokines such as TNF-α to stimulate O$_2^-$ formation via Nox in neighboring epithelial cells. NO, which is generated by especially iNOS, reacts with O$_2^-$ forming ONOO$^-$, which causes mutagenic DNA damage, such as 8-nitroguanine and 8-oxodG. NO and ROS can participate in inhibition of a number of DNA repair enzymes, which enhances mutations, leading to genomic instability.

Inflammation increases not only mutagenic DNA lesions, such as 8-nitroguanine and 8-oxodG, but also negatively impacts the DNA repair machinery by inhibiting a number of important DNA repair enzymes [19,20]. For example, O-6-methylguanine-DNA methyltransferase (MGMT), the specific DNA repair enzyme, is inhibited by S-nitrosation at the reactive and essential cysteine that performs...
the nucleophilic attack at alkylated nucleobases and confers dealkylation by alkyl transfer, thereby inactivating MGMT itself [19]. DNA damage can lead to mutations and genomic instability if not properly repaired. Genomic instability is defined as higher than normal rates of mutation, which arises from inactivation of DNA repair pathways and high levels of genotoxic ROS and RNS [21]. Therefore, inflammation and the related DNA damage should cause mutation and genomic instability, and finally lead to carcinogenesis. In the following sections, we will review DNA damage under inflammatory condition not only as causative of cancer but also as result of carcinogenesis.

2. Inflammation-Mediated DNA Damage

2.1. Inflammation-Mediated DNA Damage by Infectious Agents

The International Agency for Research on Cancer (IARC) has estimated that infectious diseases accounts for approximately 18% of cancer cases in the world [22]. We demonstrated that 8-nitroguanine and 8-oxodG were formed in clinical specimens and animal models related to a wide variety of inflammation-related carcinogenesis by immunohistochemical analysis. 8-Nitroguanine formation after iNOS expression was clearly observed in clinical specimens of patients infected with *Helicobacter pylori* (*H. pylori*), hepatitis B virus (HBV), hepatitis C virus (HCV), human papillomavirus (HPV), Epstein-Barr virus (EBV), *Schistosoma haematobium* (SH), and *Opisthorchis viverrini* (OV) [7] (Table 1). IARC has evaluated these infectious agents as group 1 carcinogens (carcinogenic to humans) [22,23]. Interestingly, nitrative and oxidative DNA damage occurred at the sites of carcinogenesis induced by infectious agents and various inflammatory conditions, as reviewed previously [23]. Immunohistochemistry showed that 8-nitroguanine was more clearly stained in the nuclei, when specimens were pre-treated with RNase before immunoreaction. Therefore, 8-nitroguanine was mainly formed in genomic DNA with potent mutagenicity, and might contribute to genomic instability.

Table 1. Causative factors and cancer sites, in which 8-nitroguanine, inflammation-related DNA damage, accumulated.

| Causative Factors   | H. pylori | Cancer Sites                           |
|---------------------|-----------|----------------------------------------|
| Bacteria            | HPV       | Cervix and other sites                 |
|                     | HBV       | Liver                                  |
|                     | HCV       | Lymph node, nasopharynx and other sites |
| Viruses             | EBV       |                                        |
| Parasites           | SH        | Bladder                                |
|                     | OV        | Bile duct                              |
| Inflammatory        | OLP       | Oral cavity                            |
|                     | BE        | Esophagus                              |
|                     | IBDs      | Colon                                  |
| Parasites           | MFH       | Soft tissue                            |
| Particulate matters | Asbestos  | Mesothelium, lung                      |

2.2. Inflammation-Mediated DNA Damage in Inflammatory Diseases

Inflammation-related carcinogenesis can be induced not only by infectious agents, but also by chronic inflammatory diseases (Table 1). Oral diseases such as oral lichen planus (OLP) and leukoplakia, Barrett’s esophagus (BE), and inflammatory bowel diseases (IBDs) are associated with oral squamous cell carcinoma (OSCC), Barrett’s esophageal adenocarcinoma (BEA), and colon cancer, respectively [24–30].

In oral tissues of leukoplakia patients, histological changes were observed such as epithelial dysplasia and infiltration of inflammatory cells. 8-Nitroguanine and 8-oxodG accumulated in oral epithelium in OLP and OSCC biopsy specimens, whereas staining was not significantly observed in
normal oral mucosa [31]. The accumulation of DNA damage was related to the expression of iNOS and the accumulation of 3-nitrotyrosine, an indicator of nitrative stress. An accumulation of mutated p53 was also observed in oral epithelium, more strongly in OSCC than in OLP, whereas p53 accumulation was not observed in normal oral mucosa. These suggest that iNOS-dependent DNA damage may lead to aberrant p53 accumulation and participates in oral carcinogenesis by OLP.

In mouse model for IBDs, we demonstrated that accumulations of 8-nitroguanine and 8-oxodG in colon epithelial cells [32]. This model showed severe inflammation in colon tissues and similar pathological findings to those of IBDs patients. The accumulation of DNA lesions was related to the expression of iNOS, proliferating cell nuclear antigen, and p53. These suggest that iNOS-dependent DNA damage is induced in colon epithelial cells of IBD model mice and may lead to cell proliferation and colon carcinogenesis.

In relation to BE patients, we observed that levels of 8-nitroguanine, 8-oxodG and iNOS were significantly higher in the order of BEA > BE > normal tissues [33,34]. In case of proton pump inhibitors (PPIs) treatment, which is expected to reduce BEA risk, DNA damage was significantly decreased in BE tissues. Moreover, the expression of Mn-SOD, an antioxidant enzyme, and the nuclear localization of Nrf2, the transcription factor of Mn-SOD, were significantly increased in BE tissues after PPIs treatment. These suggest that 8-nitroguanine and 8-oxodG play a role in BE-derived carcinogenesis, and that these DNA lesions may be suppressed by PPIs treatment not only by reduction of gastric acid, but also by activation of Nrf2 resulting in the expression of the antioxidant enzyme Mn-SOD.

2.3. Inflammation-Mediated DNA Damage by Particulate Matters

Chronic inflammation can be induced by many physical, chemical and immunological factors [35]. Inhalation of particulate matters, including diesel engine exhaust and nanomaterials, causes chronic inflammation in respiratory systems, that may lead to chronic obstructive pulmonary disease and cancer [36–40]. We reported that nitrative DNA damage was strongly formed at related cancer sites by particulate matters such as asbestos [41,42].

Asbestos is mineral fiber, which has been used as heat insulating material. It causes lung cancer and malignant mesothelioma in humans [43]. In asbestos-exposed mice, 8-nitroguanine was formed in the nucleus of bronchial epithelial cells, whereas 8-nitroguanine formation was not significantly observed in control mice [41]. In humans, 8-nitroguanine formation was associated with asbestos contents in lung tissues [42]. The precise mechanisms of asbestos-induced carcinogenesis have not well been understood, but appear to involve the following molecular events: (a) irritation of the tissues; (b) severing and/or piercing the mitotic spindle, resulting in disruption of mitosis and chromosomal damage including aneuploidy; (c) ROS generation catalyzed by iron to cause DNA damage [44].

Carbon nanotube (CNT) is an allotrope of carbon with a cylindrical shape, and expected to be used in the field of material science because of its unique physicochemical property [45,46]. However, intraperitoneal and intrascrotal administration of CNT caused mesothelioma in experimental animals, possibly involving chronic inflammation [47–50]. We have demonstrated that multi-walled CNT is taken up into cells through clathrin- and caveolae-mediated endocytosis, leading to inflammatory responses including iNOS expression and 8-nitroguanine formation, by using A549 human lung epithelial cells [51,52].

Carbon black (CB) is an extremely fluffy fine powder composed, which is widely used as a pigment in tires, inks, paints, coatings, and plastics [53]. Inhalation exposure of CB causes malignant lung tumors in experimental animals [40]. Our study revealed that CB induced 8-nitroguanine formation mainly in the nucleus of cells, after internalization into RAW 264.7 macrophage and A549 lung epithelial cells by clathrin-mediated endocytosis [54]. This finding raises a possibility that RNS released from CB-exposed inflammatory cells may also cause DNA damage in adjacent epithelial cells, contributing to carcinogenesis.
3. DNA Damage and Inflammation Interplay

3.1. Hypoxia-Related DNA Damage and Prognosis

Cancer is a disease potentiated by a great number of mutations in somatic cells. Using the integrated data sets, Kandoth et al. identified 127 significantly mutated genes in cancer [55,56]. Mutations are produced not only by DNA damage by environmental factors but also DNA damage mediated by inflammatory molecules of endogenous origin. Inflammatory microenvironment tends to hypoxia.

Intratumoral hypoxia induces a rapid increase in the expression of hypoxia-inducible factor (HIF)-1 protein, a heterodimer consisting of α and β subunits. Under hypoxic conditions, HIF-1α degradation is suppressed and this subunit dimerizes with HIF-1β to form the heterodimer in the nucleus, which promotes the expression of numerous target genes, including iNOS. We observed clear 8-nitroguanine formation in the tumor cells and inflammatory cells in patients with malignant fibrous histiocytoma (MFH), while HIF-1α expression was observed in the tumor cells [57]. The Kaplan-Meier method revealed that survival curves significantly differed between the groups of high and low 8-nitroguanine staining as well as HIF-1α [57].

MFH, which is one of the most common soft tissue sarcomas, is considered to be a lesion associated with inflammatory responses. We have examined nitrative DNA damage in tumor tissues of MFH patients by immunohistochemical analyses and the association with the prognosis [58]. Staining intensities of 8-nitroguanine and 8-oxodG were much greater in MFH tissues of deceased patients than in alive patients. Interestingly, survival curves analyzed by the Kaplan-Meier method showed that the staining intensity of 8-nitroguanine was significantly associated with poor prognosis. These results suggest that 8-nitroguanine participates in not only initiation but also progression and conversion of MFH, and could be a potential biomarker to evaluate the prognosis of cancer patients.

These results and the previous study [58] suggest that iNOS-dependent 8-nitroguanine formation by HIF-1α and nuclear factor-κB (NF-κB) plays a role in tumor progression and conversion [57].

Chronic infection with the liver fluke OV is closely associated with the pathogenesis of cholangiocarcinoma. We examined the relationship of DNA lesions and HIF-1α expression with tumor invasion in intrahepatic cholangiocarcinoma patients [59]. Immunohistochemical analysis showed that 8-nitroguanine and 8-oxodG were formed to a much greater extent in tumor tissues than in non-tumor tissues. HIF-1α expression was detected in tumor tissues in all patients, and correlated with iNOS expression and 8-oxodG formation. Double immunofluorescence technique revealed that iNOS and HIF-1α were co-localized in tumor tissues. Notably, 8-oxodG formation was significantly associated with lymphatic invasion. Moreover, 8-nitroguanine and 8-oxodG formation in non-tumor tissues were associated with neural invasion. These results raise a possibility that HIF-1α and iNOS activate each other to mediate persistent DNA damage, leading to accumulation of mutation, acquiring tumor invasiveness and poor prognosis.

3.2. Tumor Microenvironment-Induced Inflammation Followed by DNA Damage

Solid tumors often show signs of inflammation [60] and recruit innate immune cells, such as macrophages. TAM can constitutes up to 50% of the tumor mass [61,62]. TAMs accelerate progression by cytokines such as interleukin-6 (IL-6), which induces signal transducer and activator of transcription (STAT) 3 signaling, to promote growth, invasion and metastasis [63].

Nasopharyngeal carcinoma (NPC) is closely associated with EBV infection. We performed immunofluorescent staining to examine DNA damage in biopsy and surgical specimens of nasopharyngeal tissues from NPC patients in southern China [64]. Strong DNA damage occurred in cancer cells and inflammatory cells in the stroma of NPC patients. Intensive iNOS expression was observed in the cytoplasm of cancer cells positive for 8-nitroguanine. Staining of DNA lesions and iNOS was observed in epithelial cells of EBV-positive chronic nasopharyngitis patients as well, although their staining intensities were weaker than those in NPC patients. In EBV-negative subjects,
no or weak staining of DNA lesions and iNOS was observed. EGFR and phosphorylated STAT3 were clearly expressed in cancer cells of NPC patients, whereas no or weak NF-κB expression was induced. This result suggests that STAT3-dependent signaling pathway plays an important role in NPC carcinogenesis rather than NF-κB-mediated pathway. IL-6 was expressed mainly in macrophages present in nasopharyngeal tissues of patients with EBV infection. An in vitro experiment showed that IL-6 induced the expression of phosphorylated STAT3 and iNOS. These results suggest that EGFR accumulation in the nucleus and IL-6-mediated STAT3 activation participate in nitrative DNA damage, leading to EBV-mediated carcinogenesis.

Hypoxia is a characteristic feature of both tumors and inflammation [63]. Hypoxia promotes translocation of high mobility group box 1 (HMGB1) from the nucleus to the cytoplasm [65]. Extracellular HMGB1 promotes proliferation, inflammation, and angiogenesis and inhibits host antitumor immunity, which contributes to tumorigenesis [66]. In our study, CNT significantly increased nitrative DNA damage in A549 human lung epithelial cells through the release of HMGB1 and DNA into the extracellular space. HMGB1 and DNA form a complex, which binds to receptor for advanced glycation end products on neighboring cells, and CpG DNA is recognized by Toll-like receptor (TLR) 9 in lysosomes, leading to NO generation and 8-nitroguanine formation [51,52].

In cancer cells, immunogenic cell death, which is induced by ROS and RNS, can induce HMGB1 expression [67]. HMGB1 is passively released from damaged cells or necrotic cells [68]. Extracellular HMGB1 promotes NF-κB transportation to the nucleus and induces the expression of inflammatory molecules and tumor cell proliferation through TLR4-dependent pathway [69,70]. The mechanism of tumor progression is associated with local and chronic persistent inflammation. HMGB1 induces both recruited leukocytes and settled immune cells to release cytokines including TNF-α and IL-6, which amplify and extend the inflammatory response [71,72].

NF-κB is a key player in inflammation and regulates iNOS expression [73,74]. TNF-α and IL-6 activate each other to form the cytokine network in tumor tissues [75]. These cytokines are shown to induce iNOS expression, resulting in the formation of mutagenic DNA lesions and carcinogenesis under inflammatory microenvironment [73,74,76–78]. In this paper, the mechanism tends to focus only NF-κB and STAT3, although there are several papers suggesting the role of other signals on carcinogenesis. For example, mitogen-activated protein kinases are also important in the process of inflammation and cancer [79].

In response to ROS and DNA damage, autophagy is activated as well as low levels of cellular nutrients. Autophagy is required for several functional outcomes of DNA damage response (DDR) signaling, including repair of DNA lesions, and cell death. If not repaired, DNA damage may result in cell death and also be a major source of genomic instability. Recent studies have provided evidence showing that DDR and immune response networks functionally interact and that autophagy is involved in regulation of inflammatory pathways [80,81]. In summary, DNA damage events trigger the activation of DDR-driven pro-inflammatory signals, including NF-κB or various interleukins leading to chronic inflammation.

4. Expectation of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) as Chemical Cancer Prevention

NO can stimulate tumor growth and metastasis by promoting migration and invasion of tumor cells and angiogenesis, which can be triggered by cyclooxygenase-2 (COX-2) activation. Thus, selective inhibitors of NOS and/or COX may have a therapeutic potential against various cancers [9].

Several papers have revealed that daily aspirin, one of NSAIDs, reduces the long-term risk of cancer mortality [82–88]. Reduction in cancer mortality has been shown in colon cancer, probably in prostate cancer and possibly in breast cancer [87]. Rothwell et al. reported that aspirin of 5 years or longer reduced about 70% of risk of proximal colon cancer [88]. Meta-analyses have demonstrated that low-dose aspirin reduces the risk of metastasis of colon adenocarcinoma by 83% [89]. The present review has supported that NSAIDs such as aspirin show prevent effect on cancer. In inflammatory
pathways, the signaling cascade causes the translocation of NF-κB into the nucleus, where it induces pro-inflammatory genes including iNOS and COX-2. COX-2 catalyzes the conversion of arachidonic acid to prostaglandin H2 (PGH2), which is further converted into prostaglandin E2 (PGE2) by terminal prostaglandin Esynthase. PGE2 transduces signals via four different G-protein coupled receptors [90]. The prolonged release of PGE2 stimulates receptors on macrophages to induce iNOS through adenylyl cyclase/cyclic AMP/extracellular signal-regulated kinase signal [91]. Aspirin can inhibit COX-2, resulting in the decrease of PGE2 and iNOS, which should suppress the crosstalk between DNA damage and inflammation in cancer development (Figure 2). This is a possible mechanism by which aspirin reduces the long-term risk of cancer mortality.

**Figure 2.** Mechanism for crosstalk between DNA damage and inflammation in the multiple steps of carcinogenesis. In cancer cells, cell death, which is induced by ROS and RNS, can induce HMGB1 expression. HMGB1 is passively released into the extracellular space from damaged or necrotic cells. Hypoxia induces HIF-1 expression, which regulates iNOS expression, and promotes translocation of HMGB1 from the nucleus to the cytoplasm. Via TLR4, extracellular HMGB1 can promote NF-κB transportation to the nucleus and induce the expression of TNF-α and IL-6, which induce iNOS expression. NO, which is generated by iNOS in tumor-associated macrophage (TAM), is released to the extracellular space and interacts with $\text{O}_2^-$ generated via Nox in cancer cells to form ONOO$^-$. ONOO$^-$ causes DNA damage resulting in mutations and genomic instability as not properly repaired. NF-κB induces not only iNOS but also COX-2 expression. COX-2 participates in formation of PGE2, which induces iNOS. Aspirin can inhibit COX-2, resulting in the decrease of PGE2 and iNOS and suppression of the crosstalk between DNA damage and inflammation in cancer development. This is a possible mechanism by which aspirin reduces the long-term risk of death due to cancer.
5. Conclusions

Infectious agents such as \textit{H. pylori}, inflammatory diseases such as BE, and physicochemical factors, such as asbestos, cause DNA damage via chronic inflammation, leading to mutation and genomic instability. The initiated cell, which can escape from apoptosis, proliferates to form benign tumor. Inflammation is important causative of cancer and is promoted in cancer microenvironment including TAMs. In inflammatory microenvironment, DNA damage and mutation are accumulated, leading to carcinogenesis via genomic instability. Moreover, DNA damage response can also induce inflammation, again. Therefore, crosstalk between DNA damage and inflammation may play important roles in cancer development. DNA damage initiated from inflammation appears to be a key tool for the inflammation to transition to the cancer, and this helps understand the long-standing concept that inflammation is one of precancerous symptoms.

Abbreviations

\begin{itemize}
\item 8-oxodG 8-oxo-7,8-dihydro-2’-deoxyguanosine
\item BE Barrett’s esophagus
\item BEA Barrett’s esophageal adenocarcinoma
\item CB Carbon black
\item CNT Carbon nanotube
\item COX-2 Cyclooxygenase 2
\item DDR DNA damage response
\item EBV Epstein-Barr virus
\item \textit{H. pylori} Helicobacter pylori
\item HBV Hepatitis B virus
\item HCV Hepatitis C virus
\item HMGB1 High mobility group box 1
\item HPV Human papillomavirus
\item HIF Hypoxia-inducible factor
\item iNOS Inducible nitric oxide synthase
\item IBDs Inflammatory bowel diseases
\item IL-6 Interleukin-6
\item IARC International Agency for Research on Cancer
\item MFH Malignant fibrous histiocytoma
\item Nox NAD(P)H oxidase
\item NO Nitric oxide
\item NOS NO synthase
\item NSAIDs Non-steroidal anti-inflammatory drugs
\item NF-\kappa B Nuclear factor-\kappa B
\item OLP Oral lichen planus
\item OSCC Oral squamous cell carcinoma
\item OV \textit{Opisthorchis viverrini}
\item ONOO\textsuperscript{−} Peroxynitrite
\item RNS Reactive nitrogen species
\item PGH2 Prostaglandin H2
\item PGE2 Prostaglandin E2
\item PPIs Proton pump inhibitors
\item ROS Reactive oxygen species
\item SH \textit{Schistosoma haematobium}
\item STAT Signal transducer and activator of transcription
\item O\textsubscript{2}\textsuperscript{−} Superoxide
\item TNF-\alpha Tumor necrosis factor alpha
\item TAM Tumor-associated macrophage
\item TLR Toll-like receptor
\end{itemize}
Acknowledgments: This work was partly supported by a Grant-in-Aid from the Japan Society for the Promotion of Science (JSPS KAKENHI Grant Numbers 15K08787, 17K09168).

Author Contributions: Shosuke Kawanishi conceived of the design of the study. All authors participated to draft, read and approved the final manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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