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Reactive species and DNA damage in chronic inflammation: Reconciling chemical mechanisms and biological fates

Pallavi Lonkar and Peter C. Dedon*

Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139

Abstract

Chronic inflammation has long been recognized as a risk factor for many human cancers. One mechanistic link between inflammation and cancer involves the generation of nitric oxide, superoxide and other reactive oxygen and nitrogen species by macrophages and neutrophils that infiltrate sites of inflammation. While pathologically high levels of these reactive species cause damage to biological molecules, including DNA, nitric oxide at lower levels plays important physiological roles in cell signaling and apoptosis. This raises the question of inflammation-induced imbalances in physiological and pathological pathways mediated by chemical mediators of inflammation. At pathological levels, the damage sustained by nucleic acids represents the full spectrum of chemistries and likely plays an important role in carcinogenesis. This suggests that DNA damage products could serve as biomarkers of inflammation and oxidative stress in clinically accessible compartments such as blood and urine. However, recent studies of the biotransformation of DNA damage products prior to excretion point to a weakness in our understanding of the biological fates of the DNA lesions and thus to a limitation in the use of DNA lesions as biomarkers. This review will address these and other issues surrounding inflammation-mediated DNA damage on the road to cancer.

More than an association between chronic inflammation and cancer

Stemming from the original observations by Virchow,¹ the link between chronic inflammation and cancer is now recognized as essentially a cause-and-effect relationship.^{2–7} Epidemiological evidence suggests that more than 20% of all cancers are caused by chronic infection or other types of chronic inflammation,⁸ with multiple lines of evidence from laboratory and population-based studies pointing to a persistent local inflammatory state in organ-specific carcinogenesis^{9–15} even for tumors not epidemiologically linked to infection or inflammation. There are extremely strong correlations between chronic exposure to asbestos and mesothelioma,^{16,17} and chronic infections and cancer for liver flukes (*O. viverrini*) and cholangiocarcinoma,^{18,19} *Helicobacter pylori* and gastric cancer,^{20–22} viral hepatitis and liver cancer,²³ and *Schistosoma haematobium* and bladder cancer.^{24,25}

While the epidemiological evidence is well established, the mechanisms underlying the link between chronic inflammation and cancer are not. These mechanisms can be arbitrarily divided into biological and chemical as illustrated in Figure 1 for infection-induced inflammation. The initial infection leads to cell death and changes in cell phenotype, with the release of cytokines and chemotactic factors that cause infiltration of macrophages, neutrophils, lymphocytes and other immune cells. The biological side of chronic

* Author to whom correspondence should be addressed: Peter C. Dedon, Department of Biological Engineering, NE47-277, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139; tel +1-617-251-8017; fax +1-617-324-7554; pcdedon@mit.edu.

inflammation entails the effects of cytokines and chemokines on host cell cycle and apoptosis, while the chemical side involves generation of a variety of reactive oxygen and nitrogen species by activated phagocytes with the goal of eradicating the infection.^{2,4,22,26–30} This review will focus on our current understanding of the chemical side of inflammation as illustrated by our current understanding of the chemical mediators of inflammation, the damage they produce in DNA and the biological fates of the damage products.

The spectrum of reactive oxygen and nitrogen species in chronic inflammation: balancing physiology and pathology

As illustrated in Figure 1, activated phagocytes generate a battery of reactive oxygen and nitrogen species that can directly damage all types of cellular biomolecules and also alter cell physiology by non-destructive means. These chemical mediators of inflammation span a wide range of reactions, including nitrosation, nitration, oxidation and halogenation. Activated macrophages generate nitric oxide (NO),^{29,31,32} which at low concentrations (nM) under non-inflammation conditions is an important signaling molecule and regulator of the cardiovascular, nervous, and immune systems.^{33–39} The high concentrations of NO (1 μ M)^{40–42} produced by macrophages at sites of inflammation is considered to be pathological due to interference with NO signaling pathways or by reactions with oxygen and superoxide ($O_2^{\bullet-}$) to generate a variety of highly reactive nitrogen species.^{27,29,43,44} Autooxidation of NO generates the nitrosating agent, nitrous anhydride (N_2O_3 ; Figure 1), while the reaction of $O_2^{\bullet-}$ and NO at diffusion-controlled rates leads to peroxynitrite ($ONOO^-$), which, in its protonated form, undergoes rapid ($t_{1/2} \sim 1$ s) homolysis to yield hydroxyl radical ($\bullet OH$) and the weak oxidant, nitrogen dioxide radical (NO_2^\bullet). Further reaction of $ONOO^-$ with carbon dioxide leads to formation of nitrosoperoxycarbonate ($ONOO-CO_2^-$), which also undergoes homolytic scission ($t_{1/2} \sim 50$ ms) to form carbonate radical anion ($CO_3^{\bullet-}$) and NO_2^\bullet . Neutrophils contribute to inflammation with myeloperoxidase-mediated generation of hypochlorous acid (HOCl), a potent oxidizing and halogenating agent, and conversion of nitrite to NO_2^\bullet .^{45–48}

While these highly reactive oxygen and nitrogen species molecules cause damage to all types of cellular biomolecules, including lipids, proteins, nucleic acids, carbohydrates and small metabolites, there is an emerging appreciation for the problem of reconciling the pathological effects of high levels of NO and the physiological role of NO in signaling pathways related to apoptosis, cell cycle and other facets of cell function. This is further complicated by the recently recognized activity of nitroxyl (HNO) in signaling pathways and pathophysiology.⁴⁹ NO-mediated signaling appears to occur by either activation of soluble guanylate cyclase⁵⁰ or by S-nitrosylation of proteins⁵¹ possibly mediated by thioredoxin.⁵² Through these and other pathways, NO displays often contradictory effects on cell growth and cytotoxicity, variably promoting and inhibiting apoptosis in normal and tumor cells.^{39,53–55} Wink and coworkers have dissected these apparently contradictory observations and they have proposed a set of five graduated dose-response relationships for the biological activity of NO, with low levels of NO generally promoting cell survival and proliferation and high concentrations leading to cell cycle arrest and apoptosis.³⁹ This series ranges from processes involving guanylate cyclase/cGMP at NO concentrations less than 30 nM, to Akt phosphorylation at ~ 30 –100 nM, stabilization of HIF-1 α at ~ 100 –300 nM, p53 phosphorylation > 400 nM and overt toxicity at 0.5–1 μ M NO.³⁹ This model is consistent with much of the otherwise contradictory data and points to the need to specify dose, dose-rate and cell types when comparing NO effect *in vitro* and *in vivo*. The following review addresses toxic levels of NO generated by activated macrophages at sites of inflammation in humans, along with the other reactive oxygen, nitrogen and halogen species produced during inflammation.

The chemistry of DNA damage occurring in chronic inflammation

The DNA damage predicted to arise during chronic inflammation may be viewed as a paradigm for other pathological chemical reactions caused by the chemical mediators of inflammation. The reactive chemical mediators of inflammation are capable of damaging nucleic acids by two routes. One involves direct reaction with DNA and RNA, such as nitrosative deamination, oxidation and halogenation. Alternatively, the reactive chemicals can cause nucleic acid damage indirectly by formation of DNA adducts with electrophiles generated from other reactions with polyunsaturated fatty acids (PUFA), proteins, carbohydrates, small molecule metabolites, and even nucleic acids themselves. This portion of the review addresses the variety of DNA damage chemistries arising at sites of chronic inflammation.

Nitrosative deamination of nucleobases in DNA and RNA

Deamination of DNA and RNA can occur by a variety of mechanisms, including simple hydrolysis, enzymatic activities and nitrosative processes.^{56–65} While nitrosative deamination of nucleobases in DNA and RNA can occur in acidified solutions of nitrite (NO_2^-),^{66–68} inflammation-induced deamination of DNA and RNA bases *in vivo* is thought to be mediated primarily by the nitrosative chemistry of N_2O_3 .²⁹ As shown in Figure 2, products of nitrosative deamination for canonical nucleobases are hypoxanthine (2-deoxyinosine/dI and inosine/rI as nucleosides) derived from adenine; uracil (2-deoxyuridine/dU, uridine/rU) from cytosine; xanthine (2-deoxyxanthosine/dX, xanthosine/rX) and oxanine (2-deoxyoxanosine/dO, oxanosine/rO) derived from guanine. Nitrosation of DNA also leads to formation of inter- and intra-strand G-G/G-A cross links and abasic sites arising from N^7 -nitrosation of purines.²⁹ Oxanine presents a unique problem as one of the two deamination products arising from G. It has been observed to form in purified DNA exposed to nitrite under acidic conditions,^{69,70} but it has not been detected by LC-MS or LC-MS/MS under biologically relevant conditions in purified DNA and cells exposed to NO and O_2 *in vitro*^{71,72} or in tissues from a mouse model of NO-overproduction.⁷³ To explain this discrepancy, Glaser and coworkers have proposed a model which accounts for most, if not all, of the observed deamination products under different conditions and predicts that significant levels of O should be found in nucleosides, nucleotides and single-stranded DNA under conditions of nitrosative stress.⁷⁴ With respect to the other base deamination products (X, I and U), the cellular environment provides an approximately four-fold protective effect against nitrosative deamination, with significant elevations of X, I and U only when cells are exposed to toxic concentrations of NO and associated N_2O_3 .^{71,72} Similar results were obtained in animal model of inflammation.^{73,75} It is possible that the modest increases in the steady-state levels of DNA deamination products results from limited exposure of nuclear DNA to nitrosating species or from a balance between the rates of formation and repair of nucleobase deamination lesions in DNA.

Guanine oxidation by peroxynitrite and nitrosoperoxycarbonate

Guanine is the most easily oxidized structure in DNA ($E^0 = 1.29 \text{ V vs. NHE}^{76}$) and is thus the major target for oxidation by reactive nitrogen, oxygen and halogen species arising at sites of inflammation. As shown in Figure 3, the oxidation of G in DNA by ONOO^- and ONOOCO_2^- , which is mediated by the $\cdot\text{OH}$ ($2.3 \text{ V vs. NHE}^{77}$) and $\text{CO}_3^{\cdot-}$ ($1.7 \text{ V vs. NHE}^{78}$) intermediates arising from these species, respectively, produces several products including 8-nitrodG, the instability of which leads to depurination; 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxo-dG); 5-guanidino-4-nitroimidazole (nitroimidazole); and 2,2-diamino-4-(2-deoxy-beta-D-erythro-penta-furanosyl-amino)-5 (2H)-oxazolone (oxazolone). This spectrum of products is complicated by the fact that 8-oxo-G ($E^0 = 0.74 \text{ V vs. NHE}^{79}$) is ~1000-fold more reactive than the parent G toward further oxidation⁸⁰ and its oxidation

gives rise to a variety of more stable secondary products (Figure 3). Of these products, only the diastereomeric spiroiminodihydantoin (Sp) lesions have been detected in cells.⁸¹ The spectrum of G oxidation products arising from reactive nitrogen species differs from the three major G oxidation products arising from γ -irradiation of DNA: *N*-(2,6-diamino-4-hydroxy-5-formamidopyrimidine (Fapy-G), 8-oxo-G and Ox.^{82,83}

Halogenation

Another class of oxidatively induced nucleobase lesions, the halogenation products, appears to be unique to myeloperoxidase-generated hypohalous acids. The reaction of DNA and RNA with HOCl produced by neutrophils and HOBr produced by eosinophils leads to the formation of the respective 5-halo-dC and 8-halo-dG and -dA lesions^{32,84–88} (chlorination products shown in Figure 4). Additionally, HOCl and HOBr can oxidize proteins, carbohydrates and polyunsaturated fatty acids to generate adduct forming electrophiles. Given the apparent strong association between chloro-tyrosine levels and cardiovascular disease,⁸⁹ it is possible that similar granulocyte-mediated chemistry with DNA and RNA will yield useful biomarkers of inflammation.

Indirect reactions to form DNA adducts

Recent work has highlighted the importance of reactions of DNA with electrophilic products derived from oxidation of other cellular components, such as PUFA, proteins and carbohydrates. For example, peroxidation of linoleic acid, the most abundant mammalian PUFA in cell membranes, gives rise to several α,β -unsaturated aldehydes, such as *trans*-4-hydroxy-2-nonenal, acrolein and 4-oxo-2-nonenal, which can react with A, G and C to form substituted and unsubstituted etheno adducts (Figure 5).^{90–92} Elevated levels of these lesions have been found under conditions of oxidative stress in human and mouse tissues.^{91,93–97}

Lipid peroxidation also produces a host of enal-containing compounds, such as heptenal, pentenal, crotonaldehyde and acrolein, which react with DNA to form simpler Michael adducts including the propano adducts shown in Figure 5.^{98–110} Again, these adducts have been detected in a variety of rodent and human tissues.^{91,101,111–115}

One well-studied DNA adduct,^{91,116–122} the pyrimidopurinone adduct of dG, M₁dG (Figure 5), illustrates the challenge of defining chemical mechanisms in the complex pathobiology of inflammation. While the adduct was originally observed *in vitro* in reactions of the lipid peroxidation product, malondialdehyde, with dG and DNA, it also arises in reactions of DNA with the base propenal products of 4'-oxidation of DNA.^{123–126} In light of the potential mobility of M₁dG in the genome^{127–132} and the potential for transfer of the oxopropenyl group to and from DNA *via* N^e-oxopropenyllysine adducts in histone proteins,¹³³ it will be difficult to precisely define the source of M₁dG adducts *in vivo*.

Nucleic acid damage products as biomarkers of chronic inflammation:

Attention to the biological and metabolic fates of DNA damage products

With the recent definition of the spectrum of possible DNA damage products arising at sites of inflammation, there has been a significant effort to develop the damage products as biomarkers. The development of a biomarker can be viewed as a three-step process¹³⁴ starting with the identification of a candidate molecule, one that is specific to the disease or pathology. In the case of linking inflammation to cancer, there is a strong argument for direct involvement of DNA damage in the carcinogenic process, such that DNA damage products immediately arise as biomarker candidates. The second step has also been accomplished with the development of analytical methods to quantify the DNA damage

products. However, we are only partly underway with the third step in biomarker development, which involves demonstrating that the level of the molecule correlates with inflammation and cancer risk. As noted earlier in this review, there have been many studies correlating the level of one or more DNA damage products with an inflammatory condition or induced state of oxidative stress. What is missing is the added association of cancer risk.

Nonetheless, there are several problems facing the development of DNA damage products as biomarkers, the most important of which is the difficulty of obtaining tissue samples in large epidemiological or clinical studies. One approach to this problem is to assume that DNA damage products eventually appear in blood and are excreted in urine, the two most clinically accessible sampling compartments. To this end, there have been numerous studies quantifying DNA damage products in urine.^{95–97,135–141} Excretion rates range from 0.4–20 nmol of 8-oxo-dG per nmol of creatinine,¹⁴² 0.01–14 fmol of etheno-dA and etheno-dC per μ mol of creatinine,^{95,97,137} and 10–20 fmol of M₁dG per kg per 24 hr,¹⁴¹ with orders-of-magnitude increases often associated with disease states.^{95,97,137,142} A major problem in the development of urinary biomarkers is the lack of standardization in reporting values, with many reports lacking reference to creatinine excretion rates or 24-hour collection periods to control for the high variation in urine concentration, and the tremendous variation in the accuracy of different analytical methods and different practitioners.¹⁴² It is very difficult to compare data from different studies and the reported values must be viewed with great skepticism. The development of urinary DNA damage products as biomarkers is further complicated by a lack of understanding of the fate of DNA damage products following their release from a cell. Among the issues that arise are (1) the chemical form of a damage product released from the site of formation; (2) the mechanism by which the released damage product reaches the systemic circulation; (3) the potential for the damage product to be chemically modified between release and excretion; (4) the mechanism of excretion; and (5) the potential for further chemical modification in the excretory compartment.

These issues surrounding the fate of DNA damage products are perhaps best illustrated with the well-studied 7,8-dihydro-8-oxoguanine (8-oxo-G; Fig. 1), with recent reviews providing a comprehensive consideration of factors surrounding its use as a urinary biomarker.^{135,136} This relatively unstable DNA damage product, which is prone to artifacts of both formation and destruction,¹⁴³ has nonetheless been touted as a biomarker of oxidative stress, as illustrated in a sampling of the literature.^{135,136,144,145} There are four fates of 8-oxo-dG in cellular DNA and the nucleotides pool: further oxidation to more stable products, removal from DNA by repair mechanisms, removal from the nucleotide pool by nucleotide di- and tri-phosphatases, and eventual release from DNA following cell death. While 8-oxo-dG in DNA is removed by the base excision repair pathway,^{146–149} with release of free 8-oxo-G nucleobase, the dephosphorylation of 8-oxo-dGTP and -dGDP in the nucleotide pool ultimately releases 8-oxo-dGMP and 8-oxodG, which are also the likely forms of 8-oxo-G released from DNA following cell death. We are thus faced with the choice of quantifying either 8-oxo-G, 8-oxo-dG or 8-oxo-dGMP in sampling compartments such as blood and urine. The most abundant of these species appears to be 8-oxo-dG, which is amenable to quantification by liquid chromatography-coupled mass spectrometry. While the excretion of 8-oxo-dG may correlate well with conditions of oxidative stress and inflammation,¹³⁶ the source of this 8-oxodG has yet to be established. Further, the fact that 8-oxoG is readily oxidized to more stable forms (Figure 3) and may be subject to hepatic metabolism prior to reaching the urine suggests that any 8-oxo-dG in the urine may underestimate the true level formed at sites of inflammation.

Another confounding factor is illustrated with the metabolism of etheno adducts and M₁dG. Both adducts have been studied as urinary biomarkers^{95–97,137–141} in their 2-deoxynucleoside forms. However, as recently observed by Marnett and coworkers, M₁dG

and substituted and unsubstituted etheno adducts are subject to metabolism, presumably in the liver.^{150–153} With regard to etheno adducts, 2-deoxynucleoside forms of G-derived etheno adducts are subject to deglycosylation followed by oxidation of 1,*N*²-ε-G to 2-oxo-1,*N*²-ε-G and of the corresponding substituted adduct, heptanone-1,*N*²-ε-G, to 2-oxoheptanone-1,*N*²-ε-G.¹⁵³ With M₁dG, metabolic and pharmacokinetic studies in rats revealed a biphasic elimination from plasma with M₁dG found in the urine for more than 24 hr after dosing.¹⁵⁰ Analysis of urine revealed a metabolite of M₁dG, 6-oxo-M₁dG, likely derived from hepatic xanthine oxidase activity,¹⁵⁰ with evidence for further oxidation of 6-oxo-M₁dG on the imidazole ring to give 2,6-dioxo-M₁G.¹⁵¹ Both of these studies raise the possibility that urinary biomarker studies may be underestimating the true level of adducts as a result of loss of the parent forms.

Summary

While much remains to be learned, we are beginning to understand the mechanistic connections between inflammation and cancer. The damage produced by pathologically high levels of phagocyte-generated reactive oxygen, nitrogen and halogen species can cause cell death and mutation, while high concentrations of nitric oxide can interfere with normal cell signaling and apoptosis pathways. At pathological levels, the damage sustained by nucleic acids represents the full spectrum of chemistries possible with the reactive species generated by phagocytes and it likely plays a substantial role in the carcinogenic process. The final step of establishing an association between DNA damage and cancer risk is hampered by a limited appreciation for the biotransformation of DNA damage products prior to their appearance in clinically accessible compartments such as blood and urine. These challenges represent the new opportunities for future research in defining the mechanistic link between chronic inflammation, DNA damage and cancer.

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References

1. Virchow, R. Vorlesungen gehalten während des Wintersemesters. Berlin: Hirschwald; 1863. Die krankhaften Geschwulste: 30; p. 1862–63.
2. Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002; 420:860–7. [PubMed: 12490959]
3. Balkwill F, Charles KA, Mantovani A. Smoldering and polarized inflammation in the initiation and promotion of malignant disease. *Cancer Cell*. 2005; 7:211–7. [PubMed: 15766659]
4. Hussain SP, Harris CC. Inflammation and cancer: an ancient link with novel potentials. *Int J Cancer*. 2007; 121:2373–80. [PubMed: 17893866]
5. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: How are they linked? *Free Radic Biol Med*. 2010 epub 2010/9/6.
6. Schottenfeld D, Beebe-Dimmer J. Chronic inflammation: a common and important factor in the pathogenesis of neoplasia. *CA Cancer J Clin*. 2006; 56:69–83. [PubMed: 16514135]
7. Thun MJ, Henley SJ, Gansler T. Inflammation and cancer: an epidemiological perspective. *Novartis Found Symp*. 2004; 256:6–21. [PubMed: 15027481]
8. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Coglianò V. A review of human carcinogens--Part B: biological agents. *Lancet Oncol*. 2009; 10:321–2. [PubMed: 19350698]

9. Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. *Am J Physiol Gastrointest Liver Physiol.* 2004; 287:G7–17. [PubMed: 15194558]
10. Nelson WG, De Marzo AM, DeWeese TL, Isaacs WB. The role of inflammation in the pathogenesis of prostate cancer. *J Urol.* 2004; 172:S6–11. [PubMed: 15535435]
11. Whitcomb DC. Inflammation and Cancer V. Chronic pancreatitis and pancreatic cancer. *Am J Physiol Gastrointest Liver Physiol.* 2004; 287:G315–9. [PubMed: 15246966]
12. Olliver JR, Hardie LJ, Gong Y, Dexter S, Chalmers D, Harris KM, Wild CP. Risk factors, DNA damage, and disease progression in Barrett's esophagus. *Cancer Epidemiol Biomarkers Prev.* 2005; 14:620–5. [PubMed: 15767340]
13. Farrell RJ, Peppercorn MA. Ulcerative colitis. *Lancet.* 2002; 359:331–40. [PubMed: 11830216]
14. Herszenyi L, Miheller P, Tulassay Z. Carcinogenesis in inflammatory bowel disease. *Dig Dis.* 2007; 25:267–9. [PubMed: 17827953]
15. Seril DN, Liao J, Yang GY, Yang CS. Oxidative stress and ulcerative colitis-associated carcinogenesis: studies in humans and animal models. *Carcinogenesis.* 2003; 24:353–62. [PubMed: 12663492]
16. Mossman BT, Bignon J, Corn M, Seaton A, Gee JB. Asbestos: scientific developments and implications for public policy. *Science.* 1990; 247:294–301. [PubMed: 2153315]
17. Mossman BT, Gee JB. Asbestos-related diseases. *N Engl J Med.* 1989; 320:1721–30. [PubMed: 2659987]
18. Schistosomes, liver flukes and *Helicobacter pylori*. IARC Monogr Eval Carcinog Risks Hum; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans; Lyon. 7–14 June 1994; 1994. p. 1-241.
19. Sripa B, Kaewkes S, Sithithaworn P, Mairiang E, Laha T, Smout M, Pairojkul C, Bhudhisawasdi V, Tesana S, Thinkamrop B, Bethony JM, Loukas A, et al. Liver fluke induces cholangiocarcinoma. *PLoS Med.* 2007; 4:e201. [PubMed: 17622191]
20. Asaka M, Takeda H, Sugiyama T, Kato M. What role does *Helicobacter pylori* play in gastric cancer? *Gastroenterology.* 1997; 113:S56–60. [PubMed: 9394761]
21. Ebert MP, Yu J, Sung JJ, Malfertheiner P. Molecular alterations in gastric cancer: the role of *Helicobacter pylori*. *Eur J Gastroenterol Hepatol.* 2000; 12:795–8. [PubMed: 10929908]
22. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis.* 2009; 30:1073–81. [PubMed: 19468060]
23. Groopman JD, Kensler TW. Role of metabolism and viruses in aflatoxin-induced liver cancer. *Toxicol Appl Pharmacol.* 2005; 206:131–7. [PubMed: 15967201]
24. Mostafa MH, Sheweita SA, O'Connor PJ. Relationship between schistosomiasis and bladder cancer. *Clin Microbiol Rev.* 1999; 12:97–111. [PubMed: 9880476]
25. Badawi AF, Mostafa MH, Probert A, O'Connor PJ. Role of schistosomiasis in human bladder cancer: evidence of association, aetiological factors, and basic mechanisms of carcinogenesis. *Eur J Cancer Prev.* 1995; 4:45–59. [PubMed: 7728097]
26. Nathan C. Points of control in inflammation. *Nature.* 2002; 420:846–52. [PubMed: 12490957]
27. Sawa T, Ohshima H. Nitrate DNA damage in inflammation and its possible role in carcinogenesis. *Nitric Oxide.* 2006; 14:91–100. [PubMed: 16099698]
28. Tan TT, Coussens LM. Humoral immunity, inflammation and cancer. *Curr Opin Immunol.* 2007; 19:209–16. [PubMed: 17276050]
29. Dedon PC, Tannenbaum SR. Reactive nitrogen species in the chemical biology of inflammation. *Arch Biochem Biophys.* 2004; 423:12–22. [PubMed: 14989259]
30. Visconti R, Grieco D. New insights on oxidative stress in cancer. *Curr Opin Drug Discov Devel.* 2009; 12:240–5.
31. Ohshima H. Genetic and epigenetic damage induced by reactive nitrogen species: implications in carcinogenesis. *Toxicol Lett.* 2003; 140–141:99–104.
32. Ohshima H, Tatemichi M, Sawa T. Chemical basis of inflammation-induced carcinogenesis. *Arch Biochem Biophys.* 2003; 417:3–11. [PubMed: 12921773]

33. Bredt D, Snyder S. Nitric oxide: A physiologic messenger molecule. *Neuron*. 1994; 63:175–95.
34. Gross S, Wolin M. Nitric oxide: Pathophysiological mechanisms. *Ann Rev Physiol*. 1995; 57:737–69. [PubMed: 7539995]
35. Lancaster J. Nitric oxide in cells. *Amer Sci*. 1992; 80:248–59.
36. MacMicking J, Xie Q, Nathan C. Nitric oxide and macrophage function. *Ann Rev Immunol*. 1997; 15:323–50. [PubMed: 9143691]
37. Moncada S, Palmer RM, Higgs EA. Nitric oxide: physiology, pathophysiology, and pharmacology. *Pharmacol Rev*. 1991; 43:109–42. [PubMed: 1852778]
38. Nathan C. Nitric oxide as a secretory product of mammalian cells. *FASEB J*. 1992; 6:3051–64. [PubMed: 1381691]
39. Thomas DD, Ridnour LA, Isenberg JS, Flores-Santana W, Switzer CH, Donzelli S, Hussain P, Vecoli C, Paolocci N, Ambs S, Colton CA, Harris CC, et al. The chemical biology of nitric oxide: implications in cellular signaling. *Free Radic Biol Med*. 2008; 45:18–31. [PubMed: 18439435]
40. Miwa M, Stuehr DJ, Marletta MA, Wishnok JS, Tannenbaum SR. Nitrosation of amines by stimulated macrophages. *Carcinogenesis*. 1987; 8:955–8. [PubMed: 2439225]
41. Stuehr DJ, Marletta MA. Synthesis of nitrite and nitrate in murine macrophage cell lines. *Cancer Res*. 1987; 47:5590–4. [PubMed: 3117354]
42. Lewis RS, Tamir S, Tannenbaum SR, Deen WM. Kinetic analysis of the fate of nitric oxide synthesized by macrophages in vitro. *J Biol Chem*. 1995; 270:29350–55. [PubMed: 7493969]
43. Mancardi D, Ridnour LA, Thomas DD, Katori T, Tocchetti CG, Espey MG, Miranda KM, Paolocci N, Wink DA. The chemical dynamics of NO and reactive nitrogen oxides: a practical guide. *Curr Mol Med*. 2004; 4:723–40. [PubMed: 15579020]
44. Hughes MN. Chemistry of nitric oxide and related species. *Meth Enzymol*. 2008; 436:3–19. [PubMed: 18237624]
45. van der Vliet A, Eiserich JP, Halliwell B, Cross CE. Formation of reactive nitrogen species during peroxidase-catalyzed oxidation of nitrite. A potential additional mechanism of nitric oxide-dependent toxicity. *J Biol Chem*. 1997; 272:7617–25. [PubMed: 9065416]
46. Hazen SL, Zhang R, Shen Z, Wu W, Podrez EA, MacPherson JC, Schmitt D, Mitra SN, Mukhopadhyay C, Chen Y, Cohen PA, Hoff HF, et al. Formation of nitric oxide-derived oxidants by myeloperoxidase in monocytes: pathways for monocyte-mediated protein nitration and lipid peroxidation in vivo. *Circ Res*. 1999; 85:950–8. [PubMed: 10559142]
47. Wu W, Chen Y, Hazen SL. Eosinophil peroxidase nitrates protein tyrosyl residues. Implications for oxidative damage by nitrating intermediates in eosinophilic inflammatory disorders. *J Biol Chem*. 1999; 274:25933–44. [PubMed: 10464338]
48. Eiserich JP, Hristova M, Cross CE, Jones AD, Freeman BA, Halliwell B, van der Vliet A. Formation of nitric oxide-derived inflammatory oxidants by myeloperoxidase in neutrophils. *Nature*. 1998; 391:393–7. [PubMed: 9450756]
49. Flores-Santana W, Switzer C, Ridnour LA, Basudhar D, Mancardi D, Donzelli S, Thomas DD, Miranda KM, Fukuto JM, Wink DA. Comparing the chemical biology of NO and HNO. *Arch Pharm Res*. 2009; 32:1139–53. [PubMed: 19727606]
50. Cary SP, Winger JA, Derbyshire ER, Marletta MA. Nitric oxide signaling: no longer simply on or off. *Trends Biochem Sci*. 2006; 31:231–9. [PubMed: 16530415]
51. Lima B, Forrester MT, Hess DT, Stamler JS. S-nitrosylation in cardiovascular signaling. *Circ Res*. 2010; 106:633–46. [PubMed: 20203313]
52. Holmgren A, Lu J. Thioredoxin and thioredoxin reductase: current research with special reference to human disease. *Biochem Biophys Res Commun*. 2010; 396:120–4. [PubMed: 20494123]
53. Hirst DG, Robson T. Nitrosative stress as a mediator of apoptosis: implications for cancer therapy. *Curr Pharm Des*. 2010; 16:45–55. [PubMed: 20214617]
54. Wink DA, Mitchell JB. Nitric oxide and cancer: an introduction. *Free Radic Biol Med*. 2003; 34:951–4. [PubMed: 12684080]
55. Wink DA, Ridnour LA, Hussain SP, Harris CC. The reemergence of nitric oxide and cancer. *Nitric Oxide*. 2008; 19:65–7. [PubMed: 18638716]

56. Barnes DE, Lindahl T. Repair and genetic consequences of endogenous DNA base damage in mammalian cells. *Ann Rev Genetics*. 2004; 38:445–76. [PubMed: 15568983]
57. Reynaud CA, Aoufouchi S, Faili A, Weill JC. What role for AID: mutator, or assembler of the immunoglobulin mutasome? *Nat Immunol*. 2003; 4:631–8. [PubMed: 12830138]
58. Visnes T, Doseth B, Pettersen HS, Hagen L, Sousa MM, Akbari M, Otterlei M, Kavli B, Slupphaug G, Krokan HE. Review. Uracil in DNA and its processing by different DNA glycosylases. *Phil Trans Royal Soc London B Biol Sci*. 2009; 364:563–8.
59. Harris RS, Sheehy AM, Craig HM, Malim MH, Neuberger MS. DNA deamination: not just a trigger for antibody diversification but also a mechanism for defense against retroviruses. *Nat Immunol*. 2003; 4:641–3. [PubMed: 12830140]
60. Anant S, Davidson NO. Hydrolytic nucleoside and nucleotide deamination, and genetic instability: a possible link between RNA-editing enzymes and cancer? *Trends Mol Med*. 2003; 9:147–52. [PubMed: 12727140]
61. Chaudhuri J, Alt FW. Class-switch recombination: interplay of transcription, DNA deamination and DNA repair. *Nat Rev Immunol*. 2004; 4:541–52. [PubMed: 15229473]
62. Pham P, Bransteitter R, Goodman MF. Reward versus risk: DNA cytidine deaminases triggering immunity and disease. *Biochemistry*. 2005; 44:2703–15. [PubMed: 15723516]
63. Keegan LP, Leroy A, Sproul D, O'Connell MA. Adenosine deaminases acting on RNA (ADARs): RNA-editing enzymes. *Genome Biol*. 2004; 5:209. [PubMed: 14759252]
64. Hoopengardner B, Bhalla T, Staber C, Reenan R. Nervous system targets of RNA editing identified by comparative genomics. *Science*. 2003; 301:832–6. [PubMed: 12907802]
65. Yonekura SINN, Yonei S, Zhang-Akiyama QM. Generation, biological consequences and repair mechanisms of cytosine deamination in DNA. *J Radiat Res (Tokyo)*. 2009; 50:19–26. [PubMed: 18987436]
66. Turney TA, Wright GA. Nitrous acid and nitrosation. *Chem Rev*. 1959; 59:497–513.
67. Shapiro R, Pohl SH. The reaction of ribonucleosides with nitrous acid. Side products and kinetics. *Biochemistry*. 1968; 7:448–55. [PubMed: 5758560]
68. Shapiro R, Yamaguchi H. Nucleic acid reactivity and conformation. I. Deamination of cytosine by nitrous acid. *Biochim Biophys Acta*. 1972; 281:501–6. [PubMed: 4653128]
69. Suzuki T, Yamaoka R, Nishi M, Ide H, Makino K. Isolation and characterization of a novel product, 2'-deoxyxanosine, from 2'-deoxyguanosine, oligodeoxynucleotide, and calf thymus DNA treated with nitrous acid and nitric oxide. *J Am Chem Soc*. 1996; 118:2515–16.
70. Suzuki T, Kanaori K, Tajima K, Makino K. Mechanism and intermediate for formation of 2'-deoxyxanosine. *Nucleic Acids Symp Ser*. 1997:313–14. [PubMed: 9586125]
71. Dong M, Dedon PC. Relatively small increases in the steady-state levels of nucleobase deamination products in DNA from human TK6 cells exposed to toxic levels of nitric oxide. *Chem Res Toxicol*. 2006; 19:50–57. [PubMed: 16411656]
72. Dong M, Wang C, Deen WM, Dedon PC. Absence of 2'-deoxyxanosine and presence of abasic sites in DNA exposed to nitric oxide at controlled physiological concentrations. *Chem Res Toxicol*. 2003; 16:1044–55. [PubMed: 12971791]
73. Pang B, Zhou X, Yu H, Dong M, Taghizadeh K, Wishnok JS, Tannenbaum SR, Dedon PC. Lipid peroxidation dominates the chemistry of DNA adduct formation in a mouse model of inflammation. *Carcinogenesis*. 2007; 28:1807–13. [PubMed: 17347141]
74. Glaser R, Wu H, Lewis M. Cytosine catalysis of nitrosative guanine deamination and interstrand cross-link formation. *J Am Chem Soc*. 2005; 127:7346–58. [PubMed: 15898783]
75. Lim KS, Huang SH, Jenner A, Wang H, Tang SY, Halliwell B. Potential artifacts in the measurement of DNA deamination. *Free Radic Biol Med*. 2006; 40:1939–48. [PubMed: 16716895]
76. Steenken S, Jovanovic SV. How easily oxidizable is DNA? One-electron reduction potentials of adenosine and guanosine radicals in aqueous solution. *J Am Chem Soc*. 1997; 119:617–18.
77. Buettner GR. The pecking order of free radicals and antioxidants: lipid peroxidation, alpha-tocopherol, and ascorbate. *Arch Biochem Biophys*. 1993; 300:535–43. [PubMed: 8434935]

78. Shafirovich V, Dourandin A, Huang W, Geacintov NE. The carbonate radical is a site-selective oxidizing agent of guanine in double-stranded oligonucleotides. *J Biol Chem*. 2001; 276:24621–26. [PubMed: 11320091]
79. Yanagawa H, Ogawa Y, Ueno M. Redox ribonucleosides. Isolation and characterization of 5-hydroxyuridine, 8-hydroxyguanosine, and 8-hydroxyadenosine from *Torula* yeast RNA. *J Biol Chem*. 1992; 267:13320–6. [PubMed: 1618833]
80. Uppu RM, Cueto R, Squadrito GL, Salgo MG, Pryor WA. Competitive reactions of peroxynitrite with 2'-deoxyguanosine and 7,8-dihydro-8-oxo-2'-deoxyguanosine (8-oxodG): Relevance to the formation of 8-oxodG in DNA exposed to peroxynitrite. *Free Rad Biol Med*. 1996; 21:407–11. [PubMed: 8855454]
81. Hailer MK, Slade PG, Martin BD, Sugden KD. Nei deficient *Escherichia coli* are sensitive to chromate and accumulate the oxidized guanine lesion spiroiminodihydantoin. *Chem Res Toxicol*. 2005; 18:1378–83. [PubMed: 16167829]
82. Pouget JP, Frelon S, Ravanat JL, Testard I, Odin F, Cadet J. Formation of modified DNA bases in cells exposed either to gamma radiation or to high-LET particles. *Radiat Res*. 2002; 157:589–95. [PubMed: 11966325]
83. Douki T, Riviere J, Cadet J. DNA tandem lesions containing 8-oxo-7,8-dihydroguanine and formamido residues arise from intramolecular addition of thymine peroxy radical to guanine. *Chem Res Toxicol*. 2002; 15:445–54. [PubMed: 11896694]
84. Asahi T, Kondo H, Masuda M, Nishino H, Aratani Y, Naito Y, Yoshikawa T, Hisaka S, Kato Y, Osawa T. Chemical and immunochemical detection of 8-halogenated deoxyguanosines at early stage inflammation. *J Biol Chem*. 2010; 285:9282–91. [PubMed: 20081197]
85. Badouard C, Masuda M, Nishino H, Cadet J, Favier A, Ravanat JL. Detection of chlorinated DNA and RNA nucleosides by HPLC coupled to tandem mass spectrometry as potential biomarkers of inflammation. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2005; 827:26–31.
86. Masuda M, Suzuki T, Friesen MD, Ravanat JL, Cadet J, Pignatelli B, Nishino H, Ohshima H. Chlorination of guanosine and other nucleosides by hypochlorous acid and myeloperoxidase of activated human neutrophils. Catalysis by nicotine and trimethylamine. *J Biol Chem*. 2001; 276:40486–96. [PubMed: 11533049]
87. Shen Z, Wu W, Hazen SL. Activated leukocytes oxidatively damage DNA, RNA, and the nucleotide pool through halide-dependent formation of hydroxyl radical. *Biochemistry*. 2000; 39:5474–82. [PubMed: 10820020]
88. Henderson JP, Byun J, Williams MV, McCormick ML, Parks WC, Ridnour LA, Heinecke JW. Bromination of deoxycytidine by eosinophil peroxidase: a mechanism for mutagenesis by oxidative damage of nucleotide precursors. *Proc Natl Acad Sci U S A*. 2001; 98:1631–6. [PubMed: 11172002]
89. Hazen SL, Heinecke JW. 3-Chlorotyrosine, a specific marker of myeloperoxidase-catalyzed oxidation, is markedly elevated in low density lipoprotein isolated from human atherosclerotic intima. *J Clin Invest*. 1997; 99:2075–81. [PubMed: 9151778]
90. Bartsch H, Nair J. Oxidative stress and lipid peroxidation-derived DNA-lesions in inflammation driven carcinogenesis. *Cancer Detect Prev*. 2004; 28:385–91. [PubMed: 15582261]
91. Nair U, Bartsch H, Nair J. Lipid peroxidation-induced DNA damage in cancer-prone inflammatory diseases: a review of published adduct types and levels in humans. *Free Radic Biol Med*. 2007; 43:1109–20. [PubMed: 17854706]
92. Blair IA. DNA adducts with lipid peroxidation products. *J Biol Chem*. 2008; 283:15545–9. [PubMed: 18285329]
93. Godschalk RW, Albrecht C, Curfs DM, Schins RP, Bartsch H, van Schooten FJ, Nair J. Decreased levels of lipid peroxidation-induced DNA damage in the onset of atherogenesis in apolipoprotein E deficient mice. *Mutat Res*. 2007; 621:87–94. [PubMed: 17418875]
94. Nair J, De Flora S, Izzotti A, Bartsch H. Lipid peroxidation-derived etheno-DNA adducts in human atherosclerotic lesions. *Mutat Res*. 2007; 621:95–105. [PubMed: 17412369]
95. Meerang M, Nair J, Sirrankapracha P, Thephinlap C, Srichairatanakool S, Fucharoen S, Bartsch H. Increased urinary 1,N⁶-ethenodeoxyadenosine and 3,N⁴-ethenodeoxycytidine excretion in

- thalassemia patients: markers for lipid peroxidation-induced DNA damage. *Free Radic Biol Med*. 2008; 44:1863–8. [PubMed: 18342016]
96. Dechakhamphu S, Pinlaor S, Sitthithaworn P, Nair J, Bartsch H, Yongvanit P. Lipid peroxidation and etheno DNA adducts in white blood cells of liver fluke-infected patients: protection by plasma alpha-tocopherol and praziquantel. *Cancer Epidemiol Biomarkers Prev*. 2010; 19:310–8. [PubMed: 20056652]
97. Nair J, Srivatanakul P, Haas C, Jedpiyawongse A, Khuhaprema T, Seitz HK, Bartsch H. High urinary excretion of lipid peroxidation-derived DNA damage in patients with cancer-prone liver diseases. *Mutat Res*. 2010; 683:23–8. [PubMed: 19822158]
98. Winter CK, Segall HJ, Haddon WF. Formation of cyclic adducts of deoxyguanosine with the aldehydes trans-4-hydroxy-2-hexenal and trans-4-hydroxy-2-nonenal in vitro. *Cancer Res*. 1986; 46:5682–6. [PubMed: 3756915]
99. Douki T, Odin F, Caillat S, Favier A, Cadet J. Predominance of the 1,N²-propano 2'-deoxyguanosine adduct among 4-hydroxy-2-nonenal-induced DNA lesions. *Free Radic Biol Med*. 2004; 37:62–70. [PubMed: 15183195]
100. Pan J, Chung FL. Formation of cyclic deoxyguanosine adducts from omega-3 and omega-6 polyunsaturated fatty acids under oxidative conditions. *Chem Res Toxicol*. 2002; 15:367–72. [PubMed: 11896684]
101. Zhang S, Villalta PW, Wang M, Hecht SS. Detection and quantitation of acrolein-derived 1,N²-propanodeoxyguanosine adducts in human lung by liquid chromatography-electrospray ionization-tandem mass spectrometry. *Chem Res Toxicol*. 2007; 20:565–71. [PubMed: 17385896]
102. Chung FL, Young R, Hecht SS. Formation of cyclic 1,N²-propanodeoxyguanosine adducts in DNA upon reaction with acrolein or crotonaldehyde. *Cancer Res*. 1984; 44:990–5. [PubMed: 6318992]
103. Pawlowicz AJ, Kronberg L. Characterization of adducts formed in reactions of acrolein with thymidine and calf thymus DNA. *Chem Biodiversity*. 2008; 5:177–88.
104. Cho YJ, Kozekov ID, Harris TM, Rizzo CJ, Stone MP. Stereochemistry modulates the stability of reduced interstrand cross-links arising from R- and S-alpha-CH₃-gamma-OH-1,N²-propano-2'-deoxyguanosine in the 5'-CpG-3' DNA sequence. *Biochemistry*. 2007; 46:2608–21. [PubMed: 17305317]
105. Cho YJ, Wang H, Kozekov ID, Kozekova A, Kurtz AJ, Jacob J, Voehler M, Smith J, Harris TM, Rizzo CJ, Lloyd RS, Stone MP. Orientation of the crotonaldehyde-derived N²-[3-Oxo-1(S)-methyl-propyl]-dG DNA adduct hinders interstrand cross-link formation in the 5'-CpG-3' sequence. *Chem Res Toxicol*. 2006; 19:1019–29. [PubMed: 16918240]
106. Huang H, Wang H, Qi N, Lloyd RS, Rizzo CJ, Stone MP. The stereochemistry of trans-4-hydroxynonenal-derived exocyclic 1,N²-2'-deoxyguanosine adducts modulates formation of interstrand cross-links in the 5'-CpG-3' sequence. *Biochemistry*. 2008; 47:11457–72. [PubMed: 18847226]
107. Kozekov ID, Nechev LV, Moseley MS, Harris CM, Rizzo CJ, Stone MP, Harris TM. DNA interchain cross-links formed by acrolein and crotonaldehyde. *J Am Chem Soc*. 2003; 125:50–61. [PubMed: 12515506]
108. Stone MP, Cho YJ, Huang H, Kim HY, Kozekov ID, Kozekova A, Wang H, Minko IG, Lloyd RS, Harris TM, Rizzo CJ. Interstrand DNA cross-links induced by alpha,beta-unsaturated aldehydes derived from lipid peroxidation and environmental sources. *Acc Chem Res*. 2008; 41:793–804. [PubMed: 18500830]
109. Minko IG, Kozekov ID, Kozekova A, Harris TM, Rizzo CJ, Lloyd RS. Mutagenic potential of DNA-peptide crosslinks mediated by acrolein-derived DNA adducts. *Mutat Res*. 2008; 637:161–72. [PubMed: 17868748]
110. Sanchez AM, Kozekov ID, Harris TM, Lloyd RS. Formation of inter- and intrastrand imine type DNA-DNA cross-links through secondary reactions of aldehydic adducts. *Chem Res Toxicol*. 2005; 18:1683–90. [PubMed: 16300377]

111. Budiawan, Eder E. Detection of 1,N(2)-propanodeoxyguanosine adducts in DNA of Fischer 344 rats by an adapted (32)P-post-labeling technique after per os application of crotonaldehyde. *Carcinogenesis*. 2000; 21:1191–6. [PubMed: 10837009]
112. Chung FL, Nath RG, Nagao M, Nishikawa A, Zhou GD, Randerath K. Endogenous formation and significance of 1,N²-propanodeoxyguanosine adducts. *Mutat Res*. 1999; 424:71–81. [PubMed: 10064851]
113. Chung FL, Pan J, Choudhury S, Roy R, Hu W, Tang MS. Formation of trans-4-hydroxy-2-nonenal- and other enal-derived cyclic DNA adducts from omega-3 and omega-6 polyunsaturated fatty acids and their roles in DNA repair and human p53 gene mutation. *Mutat Res*. 2003; 531:25–36. [PubMed: 14637245]
114. Chung, FL.; Zhang, L.; Ocando, JE.; Nath, RG. Role of 1,N²-propanodeoxyguanosine adducts as endogenous DNA lesions in rodents and humans. *IARC Sci Publ*; 1999. p. 45-54.
115. Zhang S, Villalta PW, Wang M, Hecht SS. Analysis of crotonaldehyde- and acetaldehyde-derived 1,N(2)-propanodeoxyguanosine adducts in DNA from human tissues using liquid chromatography electrospray ionization tandem mass spectrometry. *Chem Res Toxicol*. 2006; 19:1386–92. [PubMed: 17040109]
116. Blair IA. Lipid hydroperoxide-mediated DNA damage. *Exp Gerontol*. 2001; 36:1473–81. [PubMed: 11525870]
117. Lee SH, Blair IA. Oxidative DNA damage and cardiovascular disease. *Trends Cardiovasc Med*. 2001; 11:148–55. [PubMed: 11686005]
118. Marnett LJ. Oxy radicals, lipid peroxidation and DNA damage. *Toxicology*. 2002; 181–182:219–22.
119. Marnett LJ. DNA adducts of alpha,beta-unsaturated aldehydes and dicarbonyl compounds. *IARC Sci Publ*. 1994; 125:151–63. [PubMed: 7806310]
120. Marnett LJ. Oxyradicals and DNA damage. *Carcinogenesis*. 2000; 21:361–70. [PubMed: 10688856]
121. Marnett LJ, Burcham PC. Endogenous DNA adducts: Potential and paradox. *Chem Res Toxicol*. 1993; 6:771–85. [PubMed: 8117915]
122. Dedon PC. The chemical toxicology of 2-deoxyribose oxidation in DNA. *Chem Res Toxicol*. 2008; 21:206–19. [PubMed: 18052112]
123. Jeong YC, Swenberg JA. Formation of M₁G-dR from endogenous and exogenous ROS-inducing chemicals. *Free Radic Biol Med*. 2005; 39:1021–9. [PubMed: 16198229]
124. Zhou X, Taghizadeh K, Dedon PC. Chemical and biological evidence for base propenals as the major source of the endogenous M₁dG adduct in cellular DNA. *J Biol Chem*. 2005; 280:25377–82. [PubMed: 15878883]
125. Dedon PC, Plastaras JP, Rouzer CA, Marnett LJ. Indirect mutagenesis by oxidative DNA damage: formation of the pyrimidopurine adduct of deoxyguanosine by base propenal. *Proc Natl Acad Sci U S A*. 1998; 95:11113–6. [PubMed: 9736698]
126. Plastaras JP, Dedon PC, Marnett LJ. Effects of DNA structure on oxopropenylation by the endogenous mutagens malondialdehyde and base propenal. *Biochemistry*. 2002; 41:5033–42. [PubMed: 11939800]
127. Mao H, Schnetz-Boutaud NC, Weisenseel JP, Marnett LJ, Stone MP. Duplex DNA catalyzes the chemical rearrangement of a malondialdehyde deoxyguanosine adduct. *Proc Natl Acad Sci U S A*. 1999; 96:6615–20. [PubMed: 10359760]
128. Schnetz-Boutaud N, Daniels JS, Hashim MF, Scholl P, Burrus T, Marnett LJ. Pyrimido[1,2-alpha]purin-10(3H)-one: a reactive electrophile in the genome. *Chem Res Toxicol*. 2000; 13:967–70. [PubMed: 11080044]
129. Schnetz-Boutaud NC, Saleh S, Marnett LJ, Stone MP. Structure of the malondialdehyde deoxyguanosine adduct M₁G when placed opposite a two-base deletion in the (CpG)₃ frameshift hotspot of the *Salmonella typhimurium* hisD3052 gene. *Adv Exper Med Biol*. 2001; 500:513–6. [PubMed: 11764989]
130. Wang Y, Schnetz-Boutaud NC, Saleh S, Marnett LJ, Stone MP. Bulge migration of the malondialdehyde OPdG DNA adduct when placed opposite a two-base deletion in the (CpG)₃

frameshift hotspot of the *Salmonella typhimurium* hisD3052 gene. *Chem Res Toxicol.* 2007; 20:1200–10. [PubMed: 17645303]

131. Riggins JN, Pratt DA, Voehler M, Daniels JS, Marnett LJ. Kinetics and mechanism of the general-acid-catalyzed ring-closure of the malondialdehyde-DNA adduct, N²-(3-oxo-1-propenyl)deoxyguanosine (N²OPdG-), to 3-(2'-Deoxy-beta-D-erythro-pentofuranosyl)pyrimido[1,2-alpha]purin-10(3H)-one (M₁dG). *J Am Chem Soc.* 2004; 126:10571–81. [PubMed: 15327313]
132. Riggins JN, Daniels JS, Rouzer CA, Marnett LJ. Kinetic and thermodynamic analysis of the hydrolytic ring-opening of the malondialdehyde-deoxyguanosine adduct, 3-(2'-deoxy-beta-D-erythro-pentofuranosyl)-pyrimido[1,2-alpha]purin-10(3H)-one. *J Am Chem Soc.* 2004; 126:8237–43. [PubMed: 15225065]
133. Plastaras JP, Riggins JN, Otteneider M, Marnett LJ. Reactivity and mutagenicity of endogenous DNA oxopropenylating agents: base propenals, malondialdehyde, and N(epsilon)-oxopropenyllysine. *Chem Res Toxicol.* 2000; 13:1235–42. [PubMed: 11123964]
134. Halliwell B. Effect of diet on cancer development: is oxidative DNA damage a biomarker? *Free Radic Biol Med.* 2002; 32:968–74. [PubMed: 12008112]
135. Cooke MS, Henderson PT, Evans MD. Sources of extracellular, oxidatively-modified DNA lesions: implications for their measurement in urine. *J Clin Biochem Nutr.* 2009; 45:255–70. [PubMed: 19902015]
136. Evans MD, Olinski R, Loft S, Cooke MS. Toward consensus in the analysis of urinary 8-oxo-7,8-dihydro-2'-deoxyguanosine as a noninvasive biomarker of oxidative stress. *FASEB J.* 2010; 24:1249–60. [PubMed: 19966135]
137. Dechakhamphu S, Yongvanit P, Nair J, Pinlaor S, Sitthithaworn P, Bartsch H. High excretion of etheno adducts in liver fluke-infected patients: protection by praziquantel against DNA damage. *Cancer Epidemiol Biomarkers Prev.* 2008; 17:1658–64. [PubMed: 18628417]
138. Chen HJ, Kao CF. Effect of gender and cigarette smoking on urinary excretion of etheno DNA adducts in humans measured by isotope dilution gas chromatography/mass spectrometry. *Toxicol Lett.* 2007; 169:72–81. [PubMed: 17241756]
139. Hillestrom PR, Covas MI, Poulsen HE. Effect of dietary virgin olive oil on urinary excretion of etheno-DNA adducts. *Free Radic Biol Med.* 2006; 41:1133–8. [PubMed: 16962938]
140. Chen HJ, Lin GJ, Lin WP. Simultaneous quantification of three lipid peroxidation-derived etheno adducts in human DNA by stable isotope dilution nanoflow liquid chromatography nanospray ionization tandem mass spectrometry. *Anal Chem.* 2010; 82:4486–93. [PubMed: 20429514]
141. Hoberg AM, Otteneider M, Marnett LJ, Poulsen HE. Measurement of the malondialdehyde-2'-deoxyguanosine adduct in human urine by immuno-extraction and liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry. *J Mass Spectrom.* 2004; 39:38–42. [PubMed: 14760611]
142. Cooke MS, Olinski R, Loft S. Measurement and meaning of oxidatively modified DNA lesions in urine. *Cancer Epidemiol Biomarkers Prev.* 2008; 17:3–14. [PubMed: 18199707]
143. EESCoOD. Comparative analysis of baseline 8-oxo-7,8-dihydroguanine in mammalian cell DNA, by different methods in different laboratories: an approach to consensus. *Carcinogenesis.* 2002; 23:2129–33. [PubMed: 12507938]
144. Shigenaga MK, Aboujaoude EN, Chen Q, Ames BN. Assays of oxidative DNA damage biomarkers 8-oxo-2'-deoxyguanosine and 8-oxoguanine in nuclear DNA and biological fluids by high-performance liquid chromatography with electrochemical detection. *Meth Enzymol.* 1994; 234:16–33. [PubMed: 7808289]
145. Broedbaek K, Poulsen HE, Weimann A, Kom GD, Schwedhelm E, Nielsen P, Boger RH. Urinary excretion of biomarkers of oxidatively damaged DNA and RNA in hereditary hemochromatosis. *Free Radic Biol Med.* 2009; 47:1230–3. [PubMed: 19686840]
146. Paz-Elizur T, Sevilya Z, Leitner-Dagan Y, Elinger D, Roisman LC, Livneh Z. DNA repair of oxidative DNA damage in human carcinogenesis: potential application for cancer risk assessment and prevention. *Cancer Lett.* 2008; 266:60–72. [PubMed: 18374480]

147. Maynard S, Schurman SH, Harboe C, de Souza-Pinto NC, Bohr VA. Base excision repair of oxidative DNA damage and association with cancer and aging. *Carcinogenesis*. 2009; 30:2–10. [PubMed: 18978338]
148. Friedman JI, Stivers JT. Detection of damaged DNA bases by DNA glycosylase enzymes. *Biochemistry*. 2010; 49:4957–67. [PubMed: 20469926]
149. David SS, O'Shea VL, Kundu S. Base-excision repair of oxidative DNA damage. *Nature*. 2007; 447:941–50. [PubMed: 17581577]
150. Otteneder MB, Knutson CG, Daniels JS, Hashim M, Crews BC, Rummel RP, Wang H, Rizzo C, Marnett LJ. In vivo oxidative metabolism of a major peroxidation-derived DNA adduct, M₁dG. *Proc Natl Acad Sci U S A*. 2006; 103:6665–9. [PubMed: 16614064]
151. Knutson CG, Akingbade D, Crews BC, Voehler M, Stec DF, Marnett LJ. Metabolism in vitro and in vivo of the DNA base adduct, M(1)G. *Chem Res Toxicol*. 2007; 20:550–57. [PubMed: 17311424]
152. Knutson CG, Skipper PL, Liberman RG, Tannenbaum SR, Marnett LJ. Monitoring in vivo metabolism and elimination of the endogenous DNA adduct, M₁dG {3-(2-deoxy-beta-D-erythro-pentofuranosyl)pyrimido[1,2-alpha]purin-10(3H)-one}, by accelerator mass spectrometry. *Chem Res Toxicol*. 2008; 21:1290–4. [PubMed: 18461974]
153. Knutson CG, Robinson EH, Akingbade D, Anderson CS, Stec DF, Petrova KV, Kozekov ID, Guengerich FP, Rizzo CJ, Marnett LJ. Oxidation and glycolytic cleavage of etheno and propano DNA base adducts. *Biochemistry*. 2009; 48:800–9. [PubMed: 19132922]

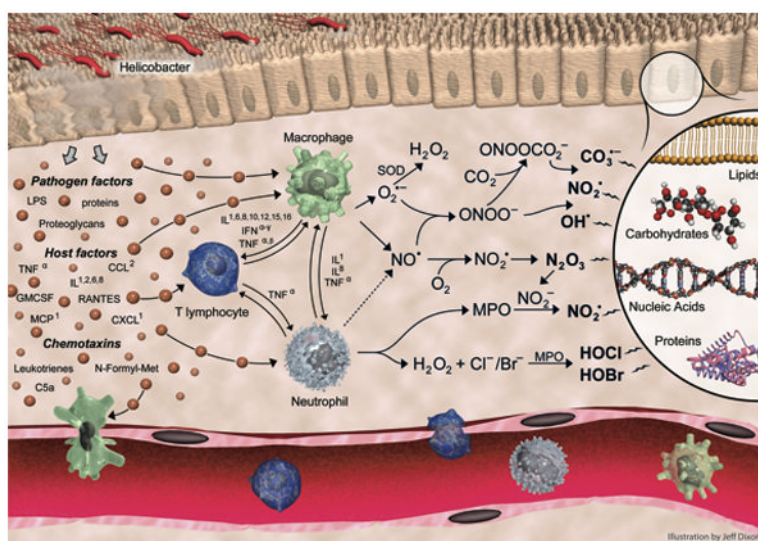


Figure 1.
The chemical biology of chronic inflammation. Illustration by Jeff Dixon, copyright Peter Dedon.

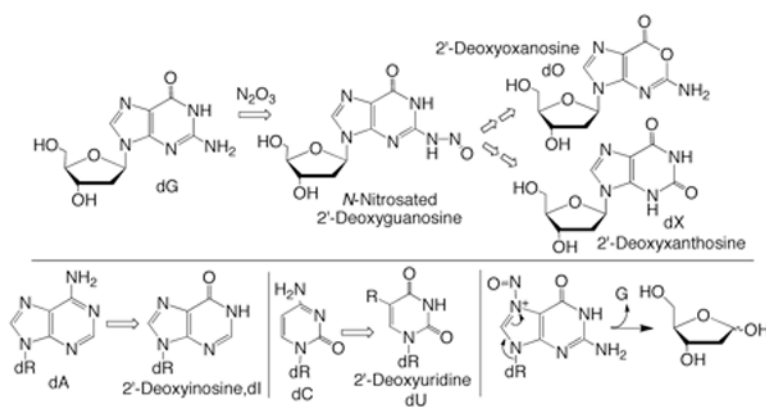


Figure 2. Spectrum of nitrosative DNA damage products thought to arise at sites of inflammation.

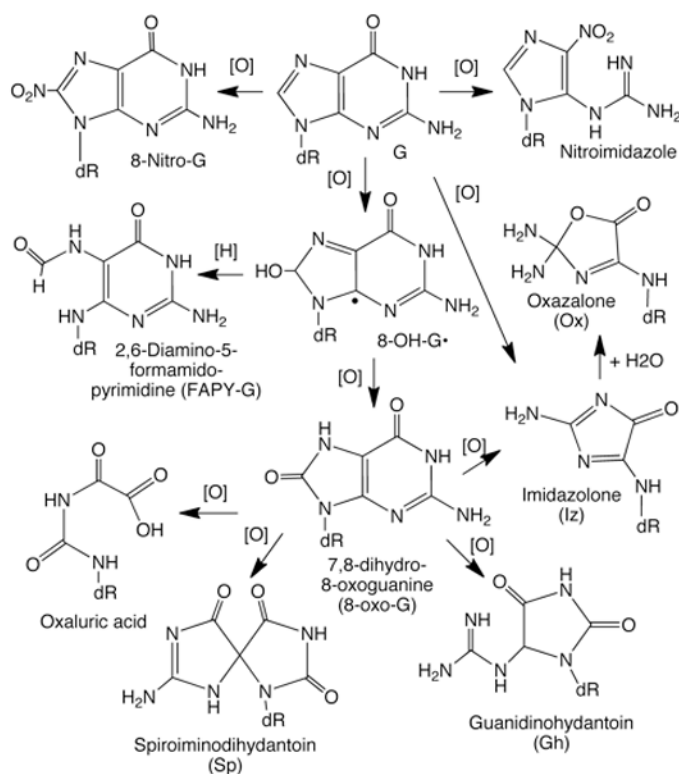


Figure 3.
Spectrum of guanine oxidation products caused by reactive oxygen and nitrogen species.

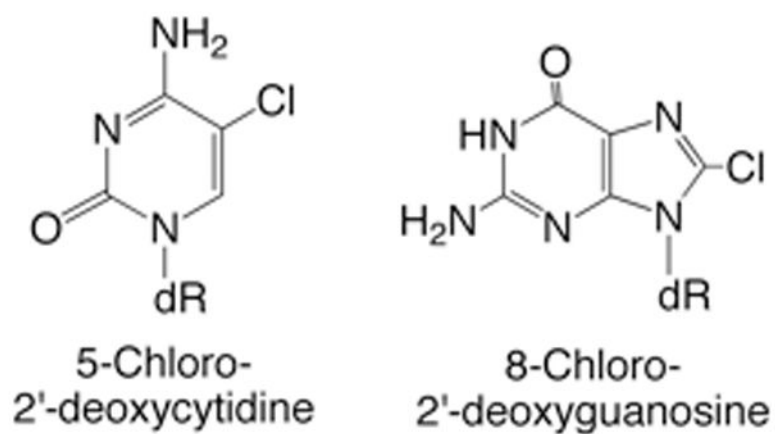


Figure 4.
DNA halogenation products arising from inflammation.

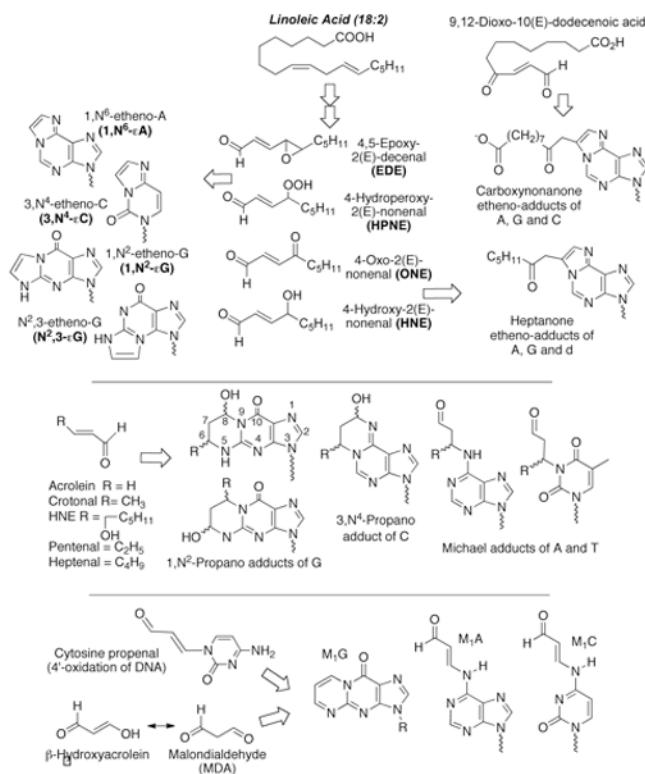


Figure 5.
Examples of DNA adducts arising from reactive electrophiles generated from oxidation of lipids, DNA and carbohydrates.