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Author Manuscript

Int J Cancer. Author manuscript; available in PMC 2012 May 1.

Published in final edited form as:

Int J Cancer. 2011 May 1; 128(9): 1999–2009. doi:10.1002/ijc.25815.

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

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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

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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 ($1 \mu\text{M}$)^{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 ($\text{O}_2^{\bullet-}$) 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 $\text{O}_2^{\bullet-}$ and NO at diffusion-controlled rates leads to peroxyxynitrite (ONOO^-), which, in its protonated form, undergoes rapid ($t_{1/2} \sim 1$ s) homolysis to yield hydroxyl radical ($\bullet\text{OH}$) and the weak oxidant, nitrogen dioxide radical (NO_2^\bullet). Further reaction of ONOO^- with carbon dioxide leads to formation of nitrosoperoxycarbonate (ONOOCO_2^-), which also undergoes homolytic scission ($t_{1/2} \sim 50$ ms) to form carbonate radical anion ($\text{CO}_3^{\bullet-}$) 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 – $1 \mu\text{M}$ 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 peroxyxynitrite and nitrosoperoxyxynitrite

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-nitro-dG, 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-pentafuranosyl-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 spiroiminodihydroantoin (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 propanal 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-*e*-G to 2-oxo-1,*N*²-*e*-G and of the corresponding substituted adduct, heptanone-1,*N*²-*e*-G, to 2-oxoheptanone-1,*N*²-*e*-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.

Acknowledgments

The authors wish to acknowledge financial support from the National Institutes of Cancer and Environmental Health Science (grants CA116318, CA103146, CA026731, ES016450, ES002109, ES017010), the National Science Foundation (CHE-1019990), the MIT Westaway Fund and the Singapore-MIT Alliance for Research and Technology.

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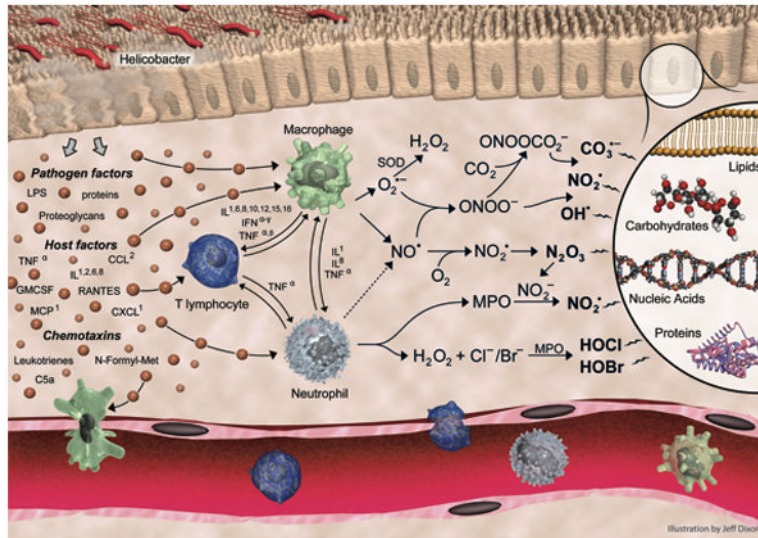


Figure 1. The chemical biology of chronic inflammation. Illustration by Jeff Dixon, copyright Peter Dedon.

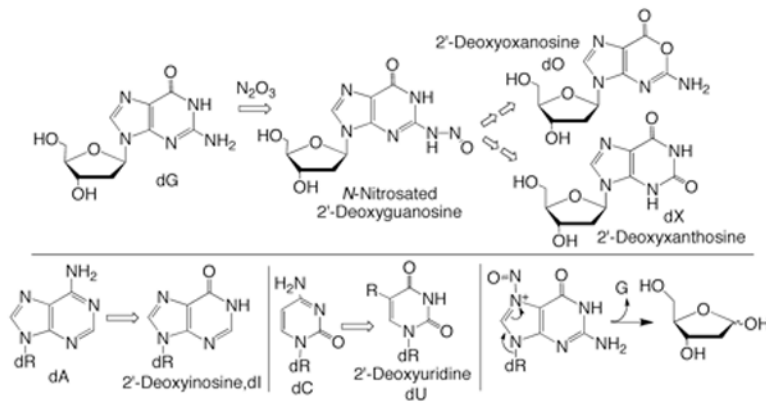


Figure 2. Spectrum of nitrosative DNA damage products thought to arise at sites of inflammation.

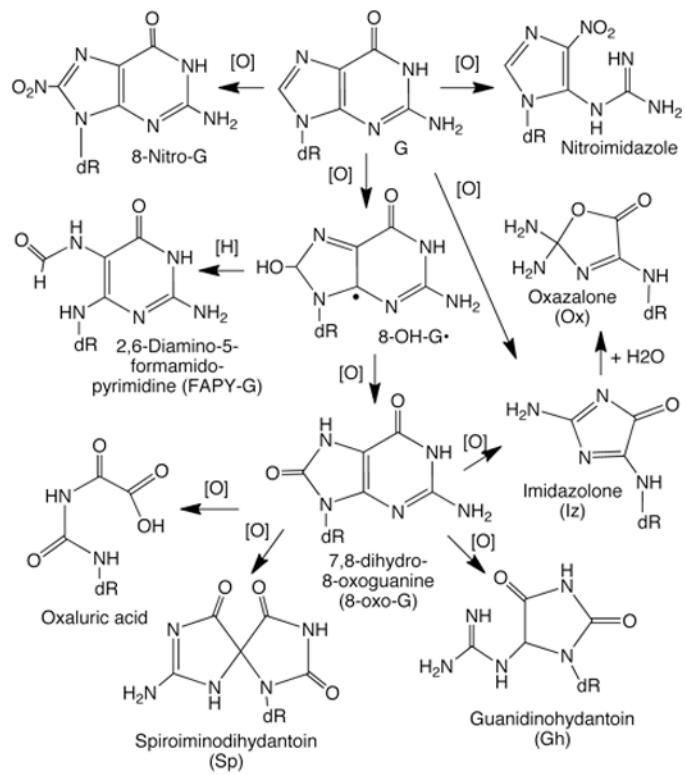


Figure 3. Spectrum of guanine oxidation products caused by reactive oxygen and nitrogen species.

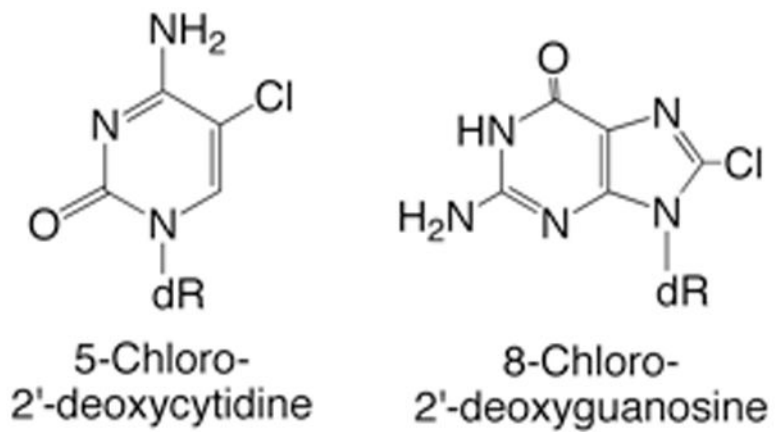


Figure 4.
DNA halogenation products arising from inflammation.

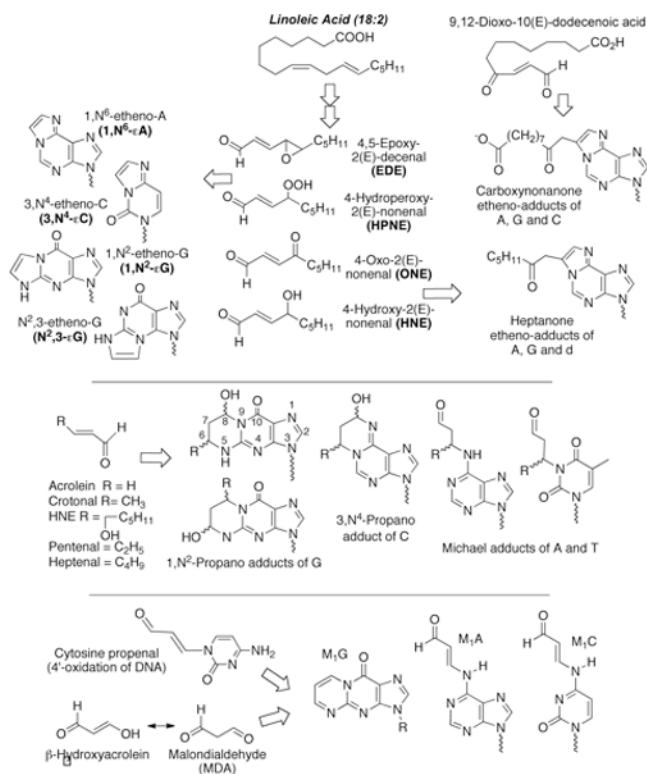


Figure 5. Examples of DNA adducts arising from reactive electrophiles generated from oxidation of lipids, DNA and carbohydrates.