HHS Public Access

Author manuscript

*DNA Repair (Amst)*. Author manuscript; available in PMC 2020 November 01.

Published in final edited form as:

*DNA Repair (Amst)*. 2019 November ; 83: 102673. doi:10.1016/j.dnarep.2019.102673.

# Inflammation-Induced DNA Damage, Mutations and Cancer

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## Abstract

The relationships between inflammation and cancer are varied and complex. An important connection linking inflammation to cancer development is DNA damage. During inflammation reactive oxygen and nitrogen species (RONS) are created to combat pathogens and to stimulate tissue repair and regeneration, but these chemicals can also damage DNA, which in turn can promote mutations that initiate and promote cancer. DNA repair pathways are essential for preventing DNA damage from causing mutations and cytotoxicity, but RONS can interfere with repair mechanisms, reducing their efficacy. Further, cellular responses to DNA damage, such as damage signaling and cytotoxicity, can promote inflammation, creating a positive feedback loop. Despite coordination of DNA repair and oxidative stress responses, there are nevertheless examples whereby inflammation has been shown to promote mutagenesis, tissue damage, and ultimately carcinogenesis. Here, we discuss the DNA damage-mediated associations between inflammation, mutagenesis and cancer.

## 1. Introduction

As early as 1863, Rudolf Virchow recognized the inextricable connections between the immune system and cancer development. Virchow's prediction that cancer arises at sites of "lymphoreticular infiltrate" has been confirmed many times over, as pancreatitis, hepatitis, colitis, and other chronic inflammatory diseases are now known to be major risk factors for cancer in those tissues (1-6). In fact, chronic inflammation is often necessary for tumor development (1, 7-9). The inflammatory environment promotes cellular proliferation (10-12) and survival (13), degradation and remodeling of the extracellular matrix (13-15), and weakening of vascular barriers to facilitate immune cell migration (16), all of which enable cancer progression (17, 18). In addition, collateral damage from inflammation can result in apoptosis (19), necrosis (20, 21), and mutations (12, 22-24), driving the tissue further away from homeostasis and accelerating transformation. Inflammation is so pro-tumorigenic that

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The authors declare no conflicts of interest.

tumors can even generate their own inflammatory microenvironment to facilitate growth (7, 25, 26). Accordingly, mitigating inflammation is often an effective strategy for slowing or even preventing neoplasia (3, 27, 28). There are many excellent reviews on a wide range of connections between inflammation and cancer (7, 17,18, 26, 29). Here, we will focus on how inflammation and DNA damage contribute to each other, as well as to the development of cancer.

The many departures from normal behavior that cancer cells exhibit, such as unchecked proliferation and aberrant migration, can be traced to alterations in DNA that accumulate over time. Mutations generally arise from damaged DNA, and inflammation can cause high levels of mutagenic DNA damage. A key feature of inflammation is the production of reactive chemicals designed to destroy pathogens, and while these chemicals are essential for protecting the body from infection, they can damage host biomolecules as well, including DNA. Efficient repair of DNA damage is crucial to prevent mutations in the genetic code. As such, several DNA repair mechanisms have evolved to address the many types of DNA damage. However, DNA repair can be fallible or unable to handle excessive damage, allowing mutations to occur. Since cancer develops from accumulated mutations, it logically follows that unrepaired DNA damage from inflammation contributes to cancer development by increasing mutagenesis.

It is broadly appreciated that genomic instability is a hallmark of cancer, and that inflammation contributes to genomic instability (30-33). The human haploid genome contains $3.2\times10^{9}$ base pairs, and the spontaneous rate of mutation in normal human cells is estimated to be on the order of $1\times10^{-10}$ nucleotides/cell/division (34, 35). Several driver mutations are required within the same cell lineage for it to become malignant, and although the number of necessary mutations has not been defined and likely depends on the type of cancer, the minimum number is around three (36, 37). There are approximately $3\times10^{13}$ cells in the human body, and the average human lifespan comprises $10^{16}$ cell divisions (BNIDs 100379, 108562). According to Loeb, the probability of any one cell acquiring three mutations is approximated by (1×10−10 spontaneous mutations/cell/division)$^{3}$($10^{16}$ cell divisions/lifetime) = $10^{-14}$ potential cancer cells/lifetime (35). In other words, the prevalence of cancer in the population should be orders of magnitude less frequent than the observed probability of developing cancer, which is greater than 30% (38). In order to accumulate multiple mutations within a cell lineage, additional factors such as genetics, environmental exposures, and physiology (including inflammatory conditions) must increase mutation frequency beyond the normal rate, a quality known as a mutator phenotype (35). Thus, while only a few mutations are needed to promote cancer, the increased mutation rate not only leads to the required cancer driving mutations, but also dozens if not hundreds of associated mutations. A continually growing body of evidence indicates that inflammation is one such factor that contributes to accelerated mutagenesis and genomic instability.

Inflammation and genomic instability have a complex relationship (a simplified model is shown in Figure 1). Inflammation contributes to mutagenesis through production of RONS that can damage DNA, and DNA damage can also exacerbate inflammation. This positive feedback loop is carefully regulated by a network of DNA repair pathways, transcription

factors, and cellular signals. Due to the intricate relationships linking inflammation, DNA damage, and DNA repair, these processes can easily become dysregulated, leading to cancer.

## 2. Inflammation Leads to DNA Damage and Mutations

Most inflammation-induced DNA damage is caused by RONS, which are evolved by immune cells to destroy pathogens, but which can also damage nearby human cells. Importantly, the damage that RONS inflict upon DNA can be potently mutagenic. One pleiotropic RONS chemical is nitric oxide (NO), which is an essential signaling molecule (39, 40) at concentrations below 400 nM (41). During inflammation, however, innate immune cells produce NO at high levels (approaching μM levels (42, 43)). In addition, neutrophils and macrophages produce superoxide ($O^{\bullet}2^{-}$) and numerous enzymes contribute to a cascade of chemical reactions that produce a range of RONS (Figure 2), including radicals (e.g., superoxide, hydroxyl radical $^{\bullet}OH$, and nitrogen dioxide $NO^{\bullet}_2$), anions (e.g., peroxynitrite $ONOO^{-}$, and nitrosoperoxycarbonate $ONOOCO_2^{-}$), anhydrides (e.g., nitrous anhydride $N_2O_3$), hypohalous acids (e.g., hypochlorous acid HOCl and hypobromous acid HOBr) and hydrogen peroxide ($H_2O_2$) (44-46). In addition to the RONS produced by immune cells, pro-inflammatory cytokines can stimulate intracellular RONS production (47-49). For excellent reviews on RONS and their chemistry, please see (50, 51).

To understand the associations between inflammation and mutagenesis, one must first recognize the chemical modifications to DNA and the mechanisms for repair of those lesions. We begin with a discussion of the DNA damage produced from RONS, including nucleobase oxidation, deamination, halogenation, and alkylation, as well as strand breaks of the phosphodiester backbone. Subsequent sections will review the major repair pathways for these types of damage, the mechanisms that balance DNA damage, DNA repair, and inflammation, and the implications for carcinogenesis.

### 2.1 Oxidation

Many RONS are potent oxidizing agents and can produce a variety of DNA lesions. While there are many potential products of DNA oxidation (52), guanine is the most easily oxidized DNA base (51, 53) and is therefore the primary target for reaction with nucleophilic RONS and the focus of this section. Primary oxidation of guanine by RONS produces 8-oxo-guanine (8oxoG, which is mutagenic) and 8-nitro-guanine (which is unstable and quickly becomes an abasic site) (Figure 3A). 8oxoG in the normal anti conformation pairs with cytosine, but rotation of the glycosidic bond to the syn position allows human polymerases to pair it with A (Figure 3B) thus, 8oxoG can lead to G→T transversions (54-57). The potential for 8oxoG to cause this mutation depends on the polymerase that encounters it, as will be described in later sections (56-58). 8oxoG is ~1000 times more prone to oxidation than its parent guanine, leading to production of several more stable and mutagenic secondary products (Figure 3A) (59). These include spiroiminodihydantoin (Sp), guanidinohydantoin (Gh), oxazolone (Oz), oxaluric acid (Oa), and cyanuric acid (Ca) (see Figure 3 for examples). Oz, Oa and Ca have been shown to produce G→T transversions with much higher potency than the parent 8oxoG in *E. coli* (60). Gh primarily leads to G→C mutations, and Sp causes both →T and G→C mutations,

both with frequencies at least an order of magnitude higher than that of 8oxoG in *E. coli* (61). While Gh is relatively easily bypassed (albeit mutagenically), Sp blocks replication (61) and leads to strand slippage, producing broken replication forks and single base pair deletions in addition to transversions *in vitro* (61-65).

In addition to secondary oxidation, 8oxoG can be reduced, opening the imidazole ring to form a 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyG). FapyG produces G→T transversions in mammalian cells (66), and some studies suggest it may be more mutagenic than the parent 8oxoG (67).

## 2.2 Deamination

In addition to oxidation, nitrosative RONS can deaminate DNA bases. Deamination products are particularly mutagenic because the chemistry occurs on the functional groups that determine hydrogen bonding, altering the pattern of H-bond donors and acceptors and leading to base mispairing. The chemical primarily responsible for base deamination is thought to be nitrous anhydride (50), generating the products from canonical bases shown in Figure 4 (note that hypoxanthine (Hx) is called deoxyinosine (dI) in DNA). Many *in vitro* studies have shown that NO chemistry causes high levels of U, Hx and X in DNA (68, 69), and Hx and X are also elevated in inflamed tissues (70).

Deamination of cytosine or its methylated form 5meC changes the base into uracil or thymine, respectively, causing C→T transitions. The mutational signature corresponding to spontaneous deamination of 5meC has been found in all cancers, and the abundance of these mutations correlates with age of cancer diagnosis, supporting the hypothesis that cancer-associated inflammation causes deamination and accumulation of mutations (71). Recently it has been shown in human cells that deamination of adenine to produce Hx can cause either A→G transitions or deletions, depending on the cell type and whether the lesion is on the leading or lagging strand (72). Finally, guanine deamination to X is generally not mutagenic, as X preferentially pairs with C, but polymerases sometimes incorrectly pair X with T to cause G→A transitions *in vitro* (73, 74), possibly by tautomerization of X to an enol form (see Figure 4). Nitrosative deamination of G or A at the $N^7$ position can also cause depurination to form an abasic site (75).

## 2.3 Halogenation

In addition to reactive oxygen and nitrogen species, inflammatory cells can also generate hypohalous acids. Neutrophils secrete the enzyme myeloperoxidase to produce hypochlorous acid (HOCl) (76-78), and eosinophils secrete eosinophil peroxidase to produce hypobromous acid (HOBr) (79, 80) (Figure 2). These hypohalous acids readily react with DNA during inflammation to form the adducts shown in Figure 5 (81). Interestingly, the most abundant halogenated nucleobase, 5-chlorocytosine (5ClC) (81, 82), accumulates to a greater degree than oxidative, deamination or lipid peroxidation (LPO, described below) DNA lesions in mouse models (70, 83). Due to its significant and persistent accumulation, perhaps a result of inefficient repair, 5ClC has been designated a biomarker for chronic inflammation (70, 83, 84).

The mutagenicity of halogenated DNA has only recently been demonstrated. Halogenation had previously been shown to impact epigenetic modifications (85), but now 5ClC has been shown to cause C→T transitions when encountered by any class of DNA polymerase (84). These mutations are frequently observed in tissues under inflammatory stress as well as in inflammation-associated cancers (83, 84, 86), further supporting the designation of 5ClC as a pertinent biomarker for inflammation.

### 2.4 Lipid Peroxidation-Derived Adducts

Oxidative chemicals can inflict damage on DNA bases themselves, as described above, but they can also cause indirect damage by creating reactive species from other biomolecules. Specifically, when RONS encounter polyunsaturated fatty acids, they cause lipid peroxidation to generate electrophilic, DNA-reactive aldehyde species. The best-studied of these aldehyde species are 4-hydroxy-2-nonenal (HNE), malondialdehyde (MDA), acrolein, and crotonaldehyde (87), of which HNE and MDA have been directly implicated in carcinogenesis (88, 89). The resulting LPO-induced DNA adducts are exocyclic additions of two (ε, etheno-) or three (P, propano-) carbons onto a base (87, 89, 90). Examples of etheno adducts are shown in Figure 6. Many studies have demonstrated significant accumulation of etheno adducts as a result of inflammation in mammals, and this is often associated with increased incidence of cancers (23, 70, 89, 91, 92).

The most abundant etheno adduct found in DNA is $N^2$,3-εG (92-94). $N^2$,3-εG is a potent inducer of G→A transitions, and its isomer 1,$N^2$-εG causes G→T and G→C transversions with *E. coli* and mammalian polymerases (93, 95-97). In mammalian cells, 1,$N^6$-εA causes primarily A→G and A→T mutations (98, 99), and 3,$N^4$-εC potently induces C→A and C→T mutations (90, 100). All etheno lesions can block replication to some extent (93, 96, 100), which can lead to larger-scale mutations (discussed below).

### 2.5 Single Strand Breaks (SSBs)

While lesions on nucleobases are an important source of mutations, breakage of the DNA backbone is a far greater threat to genomic integrity. Strand breaks potentiate large scale sequence rearrangement mutations, such as deletions, insertions, and translocations, and they can also cause stress signaling, cell cycle arrest, and cytotoxicity if not efficiently repaired (101-105). During inflammation, SSBs can arise from direct reaction with RONS: for example, radicals can hydrolyze the phosphodiester backbone, and peroxynitrite produces single strand breaks and abasic sites (106). SSBs also occur naturally as intermediates of some DNA repair pathways, including pathways involved with repair of inflammation-associated damage (described below).

### 2.6 Double Strand Breaks (DSBs)

Double strand breaks (DSBs) also arise from a variety of sources (see (107) for a review). Some enzymes, such as endonucleases and topoisomerases, cut the backbone to produce DSBs (108, 109). SSBs can also potentiate DSBs (110, 111): for example, two opposed SSBs less than 7 base pairs apart reduce the structural integrity of the DNA duplex, causing breakage into two DSB ends (112) (Figure 7A). Additionally, if a polymerase encounters a SSB during replication, the replication machinery cannot synthesize past the gap, and the

replication fork collapses, leaving a one-ended DSB (Figure 7B) (113). Similarly, replication-blocking lesions (such as εA and εC) can cause DSBs (114-116), possibly because the stress of a replication fork encountering a lesion that cannot be bypassed causes breakage of the backbone, though the exact mechanism(s) for this breakage remains unclear (117, 118). Both DSBs and SSBs have been observed in cells co-cultured with activated macrophages, confirming that phagocyte-associated RONS can cause these lesions (119). While both DSBs and SSBs can be mutagenic, DSBs are one of the most deleterious types of DNA damage (102, 120). Strand breaks potentiate large-scale mutations, including insertions, deletions, translocations, and sequence rearrangements (102, 116, 121-125).

## 3. Tolerance and Repair of Inflammation-Induced DNA Lesions

In order to minimize mutations, multiple mechanisms have evolved to address different types of DNA damage. The simplest way to prevent mutations is through accurate replication of DNA. Polymerases read the template strand and select the correct nucleotide, based on the template base's shape and hydrogen bonding pattern, to extend the strand being synthesized. When the hydrogen bonding of a base is altered (e.g., by deamination) or blocked (e.g., by etheno adducts), the cell first attempts to synthesize past the lesion (translesion synthesis, or TLS), often using a low-fidelity polymerase, which is only sometimes accurate (67, 116, 126). Since persistent signals of DNA damage can lead to cytotoxicity, mutagenic TLS can be favorable to enable cell survival. However, some lesions cannot be efficiently bypassed by TLS, causing the replication fork to stall (127). Several mechanisms are capable of protecting (128) and restoring stalled replication forks (please see (129-131) for reviews), some of which leave the lesion in place (117), but inefficient fork restoration can cause strand breakage as described above. For reviews of TLS in eukaryotes, please see (132) and (133).

In addition to polymerase selectivity and proofreading, several DNA repair pathways have evolved to correct lesions before and during replication. The rate of incorrect base incorporation (point mutation) for replicative polymerases is on the order of $10^{-6}$ to $10^{-8}$ nucleotides (134, 135), and with $3.2\times10^{9}$ bases in the genome, at least ten point mutations would occur with every cell division. DNA repair processes reduce point mutation frequency to $10^{-10}$ (34, 35) and also protect against large-scale mutations such as insertions, deletions and rearrangements (116, 123-125). DNA repair is of particular importance during inflammation because of (i) the large amount of reactive chemicals produced (91) and (ii) the stimulation of cellular proliferation to regenerate damaged tissue (12).

Most DNA damage from inflammation is addressed by the Direct Reversal (DR), Base Excision Repair (BER), and Homologous Recombination (HR) pathways. Here we will briefly describe each pathway and discuss their interactions for robust repair of inflammation-derived damage.

### 3.1 Direct Reversal (DR)

Some DNA alkyl adducts can be directly removed from the base in a process called Direct Reversal, leaving the original base intact. For example, the $O^6$-methylguanine DNA methyltransferase (MGMT) protein repairs $O^6$-methylguanine by transferring the methyl

group to a cysteine residue in its active site (136, 137). The other mammalian DR enzymes belong to the ALKBH family, which utilize oxygen, $Fe^{2+}$ and α-ketoglutarate as co-factors for oxidative dealkylation, releasing the alkyl lesion as an aldehyde and restoring the original base (138, 139). Importantly, ALKBH enzymes can repair etheno adducts, and therefore supplement BER during inflammation (91, 140, 141).

### 3.2 Base Excision Repair (BER)

In general, Base Excision Repair deals with single-base lesions that do not significantly distort the DNA helix; since this encompasses most inflammation-derived lesions, BER is the primary pathway responsible for DNA repair during inflammation. Indeed, BER activity has been shown to be key in removing DNA lesions and protecting against mutations in animal models of inflammation (23, 91).

An overview of the BER pathway is shown on the left side of Figure 8 and reviewed in (142) and (143). BER enzymes scan DNA for base lesions through processive searching (144). Upon recognition of a substrate, the first step of BER is removal of the damaged base by one of several DNA glycosylases. Monofunctional glycosylases remove only the DNA base, leaving an abasic site (as shown in Figure 8), whereas bifunctional glycosylases also nick the DNA backbone. In the case of monofunctional glycosylases, the second step is to nick the backbone by AP endonuclease-1 (APE1). The two ends of the single strand break must then be processed to produce a 3'OH (with APE1, Polβ, or PNKP) capable of extension and a $5'PO_4$ (with Polβ or PNKP) capable of ligation. The gap is filled in with a polymerase (Polβ for single nucleotides, and Polδ or Polε for larger gaps (145)), and ligase seals the nick to complete the process. The elements of BER downstream of the glycosylase can also contribute to repair of SSBs.

Each glycosylase has its own repertoire of substrates, and there is some redundancy in substrate recognition to ensure a robust response. Some of the most important DNA glycosylases for repairing damage from inflammation are 8-oxo-guanine glycosylase (OGG1), which removes 8oxoG and FapyG (146), and alkyladenine glycosylase (AAG, also known as MPG or ANPG), which removes εA, $1,N^2$ -εG, Hx, and 8oxoG, among others (91, 147, 148). AAG also recognizes and binds to εC, but it cannot excise the base, instead blocking replication and contributing to its increased genotoxicity (100). Damaged pyrimidines may be excised by pyrimidine-specific glycosylases such as MBD4, UNG, TDG, and SMUG1 (147). The enzyme MYH also uniquely protects against 8oxoG mutagenesis, because it specifically recognizes and excises A misincorporated across from 8oxoG during replication (149-151). Other BER glycosylases, such as NTHL1, NEIL1, and NEIL2, can recognize a broad range of substrates, including FapyG, hydantoin lesions, 8oxoG, and oxidized pyrimidines (63, 147, 152-154), providing robust repair of single-base lesions.

Importantly, every intermediate of the BER pathway contains a potentially toxic lesion: either an abasic site or some kind of strand break. Normally, the cell is able to complete BER without toxicity, but this is not always the case. If there is a large amount of damage, the cell may be unable to efficiently or adequately repair the DNA, leading to an accumulation of cytotoxic lesions and subsequent apoptosis (111, 155). Alternatively, if a

replication fork encounters a BER intermediate, the fork may break down, creating a DSB (110, 156). Thus, while BER is essential for repairing DNA damage during inflammation, accelerated BER can sometimes have negative effects on mutagenesis and survival due to the production of toxic intermediates (157-159).

### 3.3 Double Strand Break Repair

Although DSBs generally arise as secondary lesions in inflammation (e.g., from replication fork breakdown or nearby opposing SSBs) these lesions are one of the most toxic types of DNA damage (102, 120-122, 160). Here, we will briefly describe the two major pathways responsible for DSB repair: Non-Homologous End Joining (NHEJ) and Homologous Recombination (HR). A review on the significance of DSBs and DSB repair in mutagenesis and carcinogenesis can be found here (120).

NHEJ, the dominant repair mechanism in G1 phase (161), functions by joining two DSB ends with the Ku70/80 and DNA-PK complexes, and ligating the strands together (162). This process occurs quickly but is very prone to error. For example, if the two DSB ends are from different chromosomes, translocations occur. However, since DSBs are generally rare in G1, NHEJ sufficiently preserves genomic integrity during this cell cycle phase.

Homologous Recombination repairs DSBs much more accurately than NHEJ, but it acts more slowly and functions mainly during the S and G2 phases of the cell cycle (163, 164). Since the risk for mutations is highest during replication, and since HR can rescue replication stress, this pathway is of greater importance for inflammation-induced DNA damage. Induction of HR during inflammation has been shown in mice (12).

HR comprises multiple subpathways with distinct mechanisms, so here we will provide a basic overview of the major steps (Figure 8, right side). HR begins by ATM-assisted recognition of the DSB by CtIP and the MRN complex (consisting of MRE11, NBS1 and RAD50). The 5’ end of the DNA is resected by EXO1 to leave a 3’ overhang of single stranded DNA, which is stabilized by the protein RPA. BRCA2 displaces the RPA, replacing it with RAD51, and this 3’ nucleoprotein filament searches nearby DNA for a homologous sequence. Usually, the cell identifies the correct homologous sequence on the nearby sister chromatid, which it invades and utilizes as a template to resume extension. There are several sub-pathways of HR, but the most common is synthesis-dependent strand annealing (SDSA) (for more detailed descriptions and digital animations of HR mechanisms, please see (165)). In SDSA, once enough DNA has been synthesized from the template, the overhang will re-hybridize with its original strand, any remaining gaps will be filled, and DNA ligation completes repair of the DSB.

Since HR utilizes a homologous region of DNA as a template, this process is mostly error-free as long as the cell identifies the correct sequence in the sister chromatid. However, identification of homology in the homologous chromosome rather than the sister chromatid can lead to loss of heterozygosity, a significant source of tumor suppressor inactivation (125, 166, 167). Furthermore, a significant portion of the genome has been identified as repetitive or repeat-derived: nearly 10% of the genome consists of Alu repeats (168, 169), and a recent analysis estimates 2/3 of the genome consists of repetitive elements (170). Thus, there are

many opportunities for HR to identify a homologous sequence in the wrong location. Aberrant HR can lead to sequence rearrangement mutations, such as translocations, deletions, insertions (171-176). Some of the mechanisms for HR-derived mutations are illustrated in Figure 9. In addition to these large-scale mutations, HR can also produce point mutations, because the polymerases that participate in HR are often error-prone (127, 177-179).

As mentioned earlier, an important source of DSBs during inflammation is broken replication forks, which generate only one DSB end (see Figure 7), and thus cannot be accurately repaired by NHEJ. Therefore, lesions that cause replication fork breakdown (including replication blocking lesions and SSBs) necessitate HR to restore the replication fork (114, 115, 180). Notably, many of the intermediates of the BER pathway are SSBs, so if replication forks encounter these breaks before BER is completed, HR may be initiated as well (Figure 8) (111, 181).

For more information on HR mechanisms and the role of HR in cancer, please see (182, 183), and for a review of HR-related signaling, repair, and cell fate, refer to (184).

## 4. Coordination of DNA Repair During Inflammation

During inflammation, DNA repair must be coordinated and balanced to ensure that mutagenic lesions are corrected efficiently and accurately. In this section, we will illustrate the relationships and balance between different DNA repair pathways and discuss mechanisms by which inflammatory processes help coordinate DNA repair processes.

### 4.1 Fate of the Lesion

To illustrate the relationships among the DNA repair mechanisms described here, we consider the mammalian response to εA (Figure 10), an LPO lesion that accumulates during inflammation. Efficient repair of εA can be accomplished with either DR, which removes the etheno lesion and leaves the undamaged base intact, or BER, which excises the entire base and re-synthesizes the DNA properly (91, 141, 148, 185). However, if εA is encountered during replication, mutagenic consequences can arise. Translesion synthesis by an error-prone polymerase allows the putative development of a point mutation (116); if the εA lesion is repaired following inaccurate TLS, the mutation will become fixed. εA may also block some polymerases (100, 116), causing the replication fork to stall. Stalled replication forks can be restarted by several mechanisms (117), some of which leave the lesion intact (131), but they may also break down to produce a one-ended DSB. Accurate restoration of the replication fork by HR prevents mutagenesis, but aberrant HR or NHEJ causes large-scale mutations, such as translocations, insertions and deletions (some examples are shown in Figure 9) (121, 173, 174, 180). DSBs are also highly cytotoxic, so persistence or abundance of DSBs in the cell can signal for it to undergo apoptosis (101, 120, 186, 187). Thus, a single εA lesion creates the opportunity for many types of mutations through multiple repair pathways.

### 4.2 Intra-Pathway Balance

The importance of balance within a repair pathway has been illustrated with studies of modulated expression of BER proteins. Mice that contain a transgene for increased expression of Aag are more sensitive to alkylation damage, whereas *Aag*$^{-/-}$ mice are more resistant (157). This varied sensitivity stems from the fact that BER intermediates (abasic sites and SSBs) are often more toxic than the original lesion itself (188). If the downstream repair proteins do not keep up with glycosylase activity, intermediates accumulate and increase mutagenesis (189, 190) or signal cell death (111). Accordingly, elevated AAG expression in humans has been associated with lung cancer risk (191, 192) and poor glioma prognosis (193).

### 4.3 Inter-Pathway Redundancy and Crosstalk

To account for potential imbalances or perturbations within repair pathways, there must also be inter-pathway crosstalk, regulation and redundancy. The coordination of multiple DNA repair pathways allows the network to address lesions quickly and compensate with other repair mechanisms if the pathway is not resolved efficiently.

There is often redundancy within and between pathways so that multiple mechanisms can correct the same lesion with equivalent efficacy. For example, supplementary to BER, direct reversal enzymes ALKBH2 and ALKBH3 can repair etheno lesions (91, 194), and nucleotide excision repair (NER) can contribute to repair of the hydantoin lesions Sp and Gh (195, 196). Redundancy between pathways is so important that mice lacking AAG, ALKBH2 and ALKBH3 are unable to survive even one episode of colonic inflammation (91).

In other cases, potentially redundant repair pathways are coordinated by cell cycle and crosstalk between repair machinery. For example, NHEJ is the dominant mechanism to repair DSBs during G0 and G1 phases of the cell cycle, when non-specific ligation is sufficiently accurate and there is no sister chromatid present for homology-directed repair (161). During replication, however, there are likely to be more DSBs and therefore a much greater risk that non-specific ligation will produce a mutation, and so the slower but more accurate mechanism HR is preferred (163, 164). Thus, NHEJ and HR activities are regulated in part by cell cycle, and many of the proteins that recognize and bind DSBs contribute to the choice of which pathway will complete repair (197-201).

Finally, repair processes may compensate for each other if the pathway that initiated repair is not resolved efficiently. A particularly relevant example is that BER intermediates can cause replication forks to break down, inducing HR for repair (Figure 8) (111, 181, 202). Kiraly *et al.* showed that wild type levels of the BER protein AAG caused a greater accumulation of HR-driven mutations compared to Aag−/− mice (181), indicating that even normal BER glycosylase activity may result in aberrant DSB repair. Further, HR-driven mutations increased synergistically when alkylation damage occurred during proliferation (12, 181). When Aag activity exceeds the capacity of downstream enzymes, as described above, accumulated BER intermediates can cause stress signaling and apoptosis (157), or they can elicit responses from other pathways, providing the opportunity for different types of

mutations than the initial lesion might have created (189, 190, 203). Of course, there are many ways in which intermediates of some pathways may be substrates for other pathways, but for the scope of this review we confine this example to BER and HR (203).

### 4.4 ROS promote DNA repair through ATM activation

A key mechanism for stimulating DNA repair during inflammation is through oxidation of ATM. When the inactive ATM dimer is activated at DNA DSBs, ATM is monomerized (204) and promotes DNA repair via HR (205), p53 (206), and checkpoint activation (207-209). However, oxidation of the ATM dimer (e.g., by ROS) allows it to promote DNA repair and/or apoptosis via p53 and CHK2 pathways, independent of the presence DNA DSBs (210, 211). Oxidized ATM can also be exported from the nucleus to activate NFκB signaling (212), which is a major transcriptional regulator of inflammation, and which enhances some DNA repair pathways (described below). The dual roles of ATM in DNA damage and redox sensing are highlighted by the fact that different amino acid residues are involved in activation by DSB detection vs oxidation (210). Thus, stimulation of cells with oxidative chemicals such as ROS during inflammation elicits a modified DNA damage response by activating ATM, regardless of DNA DSB induction (213).

### 4.5 Transcriptional regulation of DNA repair during inflammation

To cope with the barrage of DNA damage, inflammatory signaling includes upregulation of DNA repair. Indeed, increasing severity of inflammation and precancerous lesions correlates positively with DNA damage response indicators (203, 214, 215). Elements of BER and HR are promoted in inflammatory environments (214-219), and they have been shown to protect against inflammation-driven mutations (23, 220-222). Here we will describe a few major examples of transcription factors that moderate inflammation and their roles in promoting DNA repair.

One of the most important responses to oxidative stress is mediated by NRF2, a transcription factor that regulates the expression of antioxidants and other cytoprotective elements. Briefly, NRF2 is sequestered by KEAP1 in the cytoplasm until stimulation by oxidative stress (223, 224), whereupon NRF2 translocates to the nucleus (225) to bind antioxidant response elements (AREs) in target gene promoters (226-228). Target genes of NRF2 include glutathione *S*-transferase (GST) (229, 230), NADPH quinone oxidoreductase 1 (NQO1) (231, 232) and superoxide dismutase (SOD) (233, 234), known collectively as the adaptive response to oxidative and electrophilic damage (227, 235). Neutralizing RONS to less reactive species protects DNA from much of the deleterious reactions described earlier. Interestingly, increases in the pro-inflammatory cytokine IL6 has been shown to reduce DNA damage after radiation, in part through upregulation of the NRF2 pathway to reduce oxidative stress (236), and possibly through promoting DNA DSB repair (237, 238).

In addition to antioxidant and metabolic enzymes, AREs have also recently been identified in promoters of several DNA repair genes, including components of HR (216), NHEJ (239), and BER (240). Indeed, disruption of NRF2 activity has been shown to result in decreased DNA repair activity (216) and increased levels of DNA adducts (241-243). Thus, when

present, NRF2 helps to manage the self-damage from inflammation by increasing expression of genes that neutralize oxidative stressors and promote DNA repair.

Several other transcriptional regulators of inflammation may also play roles in promoting DNA repair. NFκB is a key transcription factor with roles in induction, propagation, and eventual downregulation of inflammation, and DNA damage is one of many signals that can activate it (244-246). There is also evidence that NFκB enhances HR by stabilizing the CtIP-BRCA1 complex (218). Similarly, several members of the interferon regulatory factor (IRF) transcription factor family promote DNA repair (247, 248). For example, recognition of DSBs can induce IRF1 signaling (247), and some of its target genes include elements of HR and BER (217).

Overall, because inflammation produces a great deal of DNA damage, and the pathogenic insults that cause inflammation also can cause DNA damage, transcriptional regulation of inflammation includes increased DNA repair. Indeed, the only way an organism could evolve to have a self-damaging physiological response like inflammation is to also be capable of efficiently repairing the damage it causes.

## 5. DNA Damage Promotes Inflammation in a Positive Feedback Loop

Many pathogens can cause DNA damage (219, 249-253), which may be why DNA damage can promote inflammation. Regardless of the reason for this evolved mechanism, the proteins that detect and respond to DNA damage can trigger cell cycle arrest, apoptosis, senescence, and necrosis, of which the latter two can promote inflammatory signaling (254-261). Further, proteins involved in DNA repair can serve to promote NFκB transcription of pro-inflammatory genes (246, 262-264). Unfortunately, DNA damage and inflammation can therefore create a positive feedback loop, which can be difficult to regulate. Additionally, response to DNA damage in one cell can induce damage in nearby cells through extracellular signals and epigenetic modifications (265-268). The propagation of genomic instability to such “bystander” cells, along with systemic inflammatory signals, may contribute to genotoxicity in off-target tissues during inflammation (269-272).

### 5.1 DNA Damage Signals for Inflammation

There are many elements of the DNA damage response that promote inflammation. For example, PARP1 (poly(ADP-ribose) polymerase 1) detects and binds SSBs to recruit BER machinery (273-277), and it has been closely linked to inflammation promotion. PARP1 builds branched polymers of ADP-ribose moieties out of $NAD^+$ (called PARylation) at strand breaks to help recruit BER proteins and initiate repair. PARP1 is also capable of post-translational PARylation of proteins to modify their activity, notably including the key inflammatory regulator NFκB (244-246, 278). Indeed, several components of the NFκB complex display increased activity following PARylation (244, 246).

Inhibition of PARP1 has repeatedly been demonstrated to decrease the severity of inflammation in the intestines (279), pancreas (280), heart (281), brain (282), liver (283), and many other tissues and model systems (284-288). In particular, studies have shown that inhibition of PARP1 results in decreased inflammatory cytokine expression (244, 280, 289,

290) decreased adhesion molecule production (280, 285, 289), decreased inflammation-associated enzyme activity, including iNOS, COX2 and NADPH oxidase (285, 291-294), and decreased immune cell infiltration (280, 290, 295). These molecular and cellular alterations all support a model wherein PARP1 activity contributes to increased inflammatory signaling, and its inhibition protects the organism from inflammation-associated damage.

PARP inhibitors have shown significant clinical success as adjuvants in cancer therapy. PARP inhibition is particularly effective in HR-deficient cancers due to synthetic lethality (296), and many other DNA damage-related chemotherapeutics show increased efficacy in combination with PARP inhibitors (297-299). PARP inhibitors can also enhance anticancer activity of PD-1/PD-L1 or CTLA-4 inhibition (300, 301), demonstrating that in addition to DNA damage and repair impacts, the immunogenic effects of PARP can also be exploited for cancer therapy (302, 303). For reviews on PARP inhibitor cancer therapies, please refer to (304, 305).

The BER glycosylase OGG1 can also augment inflammation through NFκB. OGG1 bound to 8oxoG facilitates NFκB binding (306, 307) and increases expression of its pro-inflammatory target genes (262). Similar to inhibition of PARP1, downregulation, knockout, or inhibition of OGG1 can also reduce expression of pro-inflammatory genes and inflammation severity (263, 308, 309) through prevention of NFκB transcription (263, 264, 306). Interestingly, the free OGG1-8oxoG complex also acts as a guanine exchange factor and activates Ras family GTPases, further promoting inflammation through the MEK/ERK pathway (310). Together, the profound effects of BER proteins OGG1 and PARP1 in the transcription of pro-inflammatory genes demonstrate the importance of BER in regulation of inflammatory responses.

Proteins involved in double strand break repair have also been implicated in pro-inflammatory signaling. DSBs can be recognized and bound by ATM, and RPA-coated single stranded DNA (an early intermediate of HR) is recognized by ATR. Multiple studies have shown that ATM (218, 255, 256, 311) and ATR (311) can both promote NFκB signaling independent of downstream DNA damage responses. Accordingly, ATM/ATR activity results in increased cytokine production (255-257, 312), and knockdown of ATM or ATR inhibits the production of the immune cell-activating ligand NKG2D (311).

Inflammation can also be promoted by generalized DNA damage, independent of BER or HR initiation. For instance, the growth arrest and DNA damage-inducible protein 34 (GADD34) is upregulated in response to multiple types of cellular stress, including DNA damage and ER-stress (259). In two models of DNA damage-induced cancer, mice knocked out for GADD34 display significantly decreased levels of pro-inflammatory cytokines, immune cell infiltration and malignant lesions (313) (314). Genomic instability often involves the generation of micronuclei, composed of tiny fragments of DNA encased by nuclear envelopes separate from the nucleus, which can promote inflammation as well. Breakdown of micronuclear envelopes release DNA into the cytosol (315), which can trigger activation of the pro-inflammatory cytokines IL-1β (316) and IFNγ (317-319). Cytosolic

DNA also activates the cGAS-STING pathway, activating of IRF3 and inducing IFNβ expression (320, 321).

### 5.2 DNA Damage Promotes Inflammation by Cell Death and Senescence

In addition to the direct upregulation of inflammation by the DNA damage response, DNA damage also indirectly promotes inflammation through cytotoxicity (322). Too much DNA damage, especially during a proliferative phase, cannot be processed sufficiently by DNA repair pathways, so the cell is eventually forced to undergo apoptosis, necroptosis, necrosis, or senescence.

DNA damage-induced apoptosis is generally not considered pro-inflammatory, and indeed most forms of apoptotic cell death are not inflammatory. However, there are exceptions. For example, the Fas ligand acts as a DNA damage sensor, activating the Fas-mediated apoptosis pathway (323), and studies have shown that FasL-mediated apoptosis promotes inflammation (324, 325).

Necroptosis is another form of programmed cell death that closely resembles necrosis and is far more pro-inflammatory than apoptosis. One type of necroptosis, known as parthanatos, is triggered by excessive PARP1 activation at DNA single strand breaks. It has widely been hypothesized that persistent or extensive PARP1 activation can cause cellular $NAD^+$ and ATP depletion and bioenergetic collapse, leading to necrosis (20, 326, 327). However, more recent studies show that PARP1 is a mediator of parthanatos, in which excessive PARP1 activation leads to PAR accumulation in the cytosol, translocation of AIF from mitochondria to the nucleus (328) and activation of RIP1/RIP3-mediated necroptosis (329-332). Necroptosis resembles necrosis in that both involve swelling and plasma membrane rupture, releasing intracellular contents and promoting inflammation. Molecules that would not normally be found outside the cell are known as damage-associated molecular patterns (DAMPs). Extracellular DAMPs, such as IL1-family cytokines, uric acid, ATP, or HMGB1, trigger activation of immune cells, including macrophages, mast cells, neutrophils, and B-cells (261). Thus, PARP-mediated necroptosis is a significant source of pro-inflammatory signals.

In addition to cell death, DNA damage can lead to senescence (reviewed here (333) and here (334)), wherein the cell permanently arrests growth and secretes inflammatory cytokines (255). DNA double strand breaks activate p53, persistent activation of which can lead to either apoptosis or senescence *in vivo* (335). Senescent cells develop a senescence-associated secretory phenotype (SASP), which includes release of many inflammatory cytokines (255, 336). Over time, senescence is maintained by SASP signaling as well as persistent DNA damage-related foci, such as activated ATM, γH2AX, 53BP1, and CHK2 (336). In fact, ATM has been found to be required for maintenance of senescent-associated production of cytokine IL-6 (255). Depending on biological context, SASP components reinforce growth arrest (337) or promote cancer cell growth and invasion (338-340). For a more detailed discussion of the complex and varied consequences of senescence in inflammation and tumor development, see (341).

The positive feedback relationship between DNA repair and inflammation is somewhat unexpected, because repair of inflammation-derived lesions can promote inflammation further. This mechanism may have evolved to ensure that inflammation persists long enough to thoroughly remove the perceived insult before down-regulation to baseline levels. However, the processes by which this positive feedback loop is suppressed have yet to be revealed.

## 6. Inflammation Impairs Some DNA Repair Processes

In addition to direct damage by RONS, pro-inflammatory cytokines have also been shown to contribute to DNA damage. This signal-induced damage is due in part to the cytokine-stimulated increase of intracellular RONS (47-49) and in part to impairment of some DNA repair components (342-350). Since RONS readily react with cysteine residues on proteins, many cellular functions are susceptible to disruption from RONS (351). Indeed, Jaiswal *et al.* demonstrated that inflammatory cytokines were capable of both inducing DNA damage (as measured by the comet assay) and impairing DNA repair activity (as measured by radiolabel incorporation) via a NO-dependent mechanism (342).

More targeted studies have defined particular components of DNA repair that are disrupted by inflammation. Reaction of NO with glutathione (GSH) produces S-nitrosoglutathione (GSNO), which acts as an NO reservoir as well as a vehicle for cysteine nitrosylation on other proteins. S-nitrosylation can have a variety of consequences for protein function, such as altering activity or localization (352), and notable targets include DNA repair enzymes. One of the most thoroughly studied targets of S-nitrosylation is the Direct Reversal protein MGMT, which removes methyl lesions from nucleotides by directly transferring the alkyl group onto a cysteine residue (136, 353). Nitrosylation of MGMT's active cysteine disables the enzyme (354), causing an accumulation of the genotoxic lesion $O^6$-methylguanine (347). While DNA methylation is not a major type of inflammation-derived damage, all DNA repair pathways are essential for genomic maintenance, so inhibition of MGMT can increase stress on other repair pathways to compensate. It is noteworthy that inflammation can increase sensitivity to types of DNA damage that are not produced by inflammation.

Ironically, while BER is responsible for repairing many of the inflammation-induced DNA lesions, it is also especially susceptible to disruption by inflammation. For instance, S-nitrosylation of OGG1 decreases its activity (348, 349, 355), and S-nitrosylation of APE1 causes it to be exported from the nucleus (344, 349, 356). Thus, two key steps in repairing oxidative damage can be impeded by excess NO. Additionally, a common genetic variant of OGG1 in humans (Ser326Cys), associated with increased lung cancer risk (357), is susceptible to inactivation by intracellular RONS following pro-inflammatory stimulation (343). The relationship between OGG1 and inflammation is thus quite complex: OGG1 repairs the most common type of oxidative DNA damage, and it promotes transcription of pro-inflammatory genes, but it is also prone to inactivation by inflammation. These seemingly contradictory functions may help serve to regulate the positive feedback loop between inflammation and DNA damage.

Interestingly, and underscoring the complexity of the equilibrium between inflammation and DNA repair, S-nitrosylation of AAG slightly increases its activity (349, 356). However, rather than accelerating BER, increased AAG activity can produce more BER intermediates than the downstream enzymes can efficiently process, leading to increased tissue damage and mutations (181, 188). Indeed, excess AAG has been shown to contribute to microsatellite instability in the inflamed colon (203), highlighting the importance of balance among DNA repair components in maintaining genomic integrity.

Finally, rejoining broken DNA strands via ligase is the final step of nearly all DNA repair pathways, and evidence suggests that S-nitrosylation reduces ligase activity (350, 355), causing accumulation of unresolved strand breaks that can be cytotoxic or mutagenic.

## 7. Inflammation ⟷ DNA Damage → Mutations → Cancer

The studies described here all support to the paradigm that inflammation and DNA damage contribute to each other and to the development of mutations and cancer, but few have explicitly demonstrated their direct connections. First, we integrate the collective importance inflammation and DNA damage to mutagenesis. This is perhaps exemplified by the fact that DNA damage during periods of increased cell division, such as inflammation-associated proliferation, has been shown to greatly increase mutation frequency (12). Frequency of cellular transformation in livers treated with the DNA alkylating agent N-methyl-N-nitrosourea (MNU) was shown to correlate directly with the number of proliferating cells in the tissue at the time of dosing (358). Further, two closely related studies showed that DNA damage occurring during a period of increased proliferation synergistically increases the frequency of mutant cell populations within the pancreas (12, 181). The first of these studies showed that MNU-induced DNA damage and hormone-induced proliferation both increase the frequency of mutant populations in the tissue, but when MNU was given during proliferation, the frequency of mutant clusters increased synergistically (181). A follow-up study then demonstrated that overlapping bouts of inflammation, wherein the DNA damage of one bout of inflammation coincides with the regenerative proliferation of an earlier bout, also synergistically increased the frequency of mutant populations compared to non-overlapping bouts of inflammation (12). These studies show that proliferation coinciding with DNA damage, whether induced exogenously or from inflammation, vastly increases the frequency of mutant cells in a tissue.

Second, studies from the Samson laboratory have demonstrated that DNA damage from inflammation drives mutations as well as cancer development (23, 359). In one such study, mice lacking the BER glycosylase Aag were treated with a common colitis model of DSS in drinking water. The $Aag^{-/-}$ animals developed far more severe tissue damage and neoplasia than wild type, which correlated with a dramatic increase in DNA damage. Oxidation, deamination, and LPO-derived base lesions accumulated, particularly εA, and some genetic deletions were observed, suggesting aberrant repair of broken replication forks. Sequencing tumors revealed point mutations in oncogenes that correspond with the mutational signatures associated with inflammation (23). Similar results were obtained in stomach tissue when $Aag^{-/-}$ and wild type animals were treated with *H. pylori*, a prevalent source of gastric inflammation and cancer (23, 360). Another study demonstrated the importance of BER on

deamination products during inflammation, observing more severe pathology in DSS-treated *Mbd4*$^{-/-}$ mice compared to wild type (359). Further research revealed that DNA repair is essential to tolerating inflammation, as mice lacking multiple repair enzymes could not tolerate even a single bout of DSS-induced colitis (91). With these targeted studies, the Samson lab has uniquely contributed to this field by directly demonstrating the importance of DNA damage and its repair for tolerating inflammation Further such research revealing the presence of DNA strand breaks and oxidation, deamination, lipid peroxidation and halogenation base lesions, combined with analyses of DNA repair pathway activity and mutagenic consequences, will provide a more thorough understanding of the specific DNA transactions that occur during inflammation.

## 8. Conclusions

The relationships between inflammation and DNA damage are mediated by many factors, including a complex network of chemical reactions, DNA repair and tolerance pathways, cell cycle arrest mechanisms, and intra- and extracellular signaling pathways (Figure 11). Inflammation causes DNA damage primarily via RONS, which can produce DNA base and backbone lesions both by direct reaction or via reactive LPO intermediates. The detection and response to DNA damage by BER (e.g., PARP, OGG1), HR (e.g., ATM/ATR), or generalized damage recognition can signal for increased inflammation, creating a positive feedback loop. Inflammatory transcription factors such as NRF2 can mitigate the damage to DNA by neutralizing reactive chemicals with antioxidants and upregulating DNA repair pathways. However, nitric oxide can impair some repair enzymes, complicating the network and increasing the potential for dysregulation. Failure to repair DNA damage can lead to the mutations that initiate cancer, and additional physiological processes involved in inflammation (e.g., proliferation, migration) also promote cancer development. Given the number of mechanisms by which DNA damage and inflammation stimulate each other, it is no wonder that autoimmune and inflammatory diseases are so prevalent, difficult to control, and carcinogenic.

## Acknowledgements

This work was supported in part by Superfund Research Program grant P42ES027707, NIEHS Training Grant T32-ES007020, and NCI Program Project Grant P01-CA026731.

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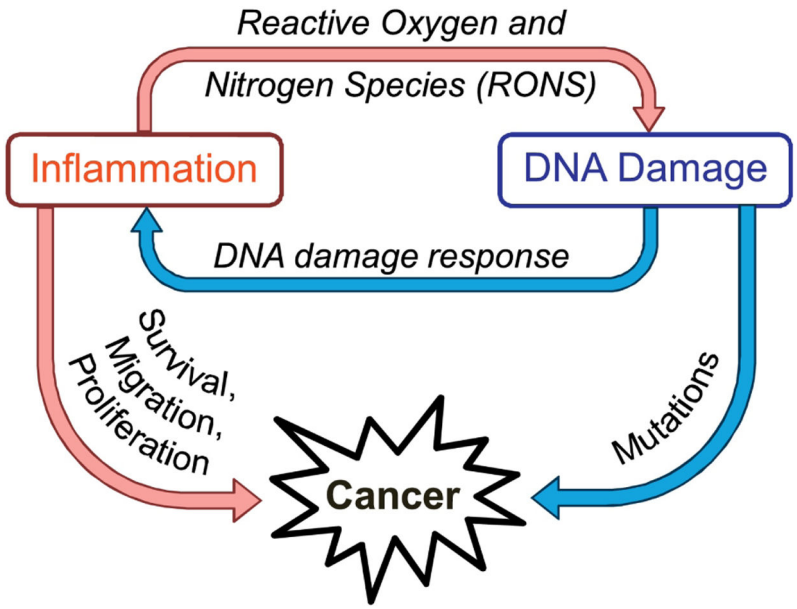


**Figure 1.**
Diagram describing the relationship between inflammation and DNA damage and how they contribute to cancer.

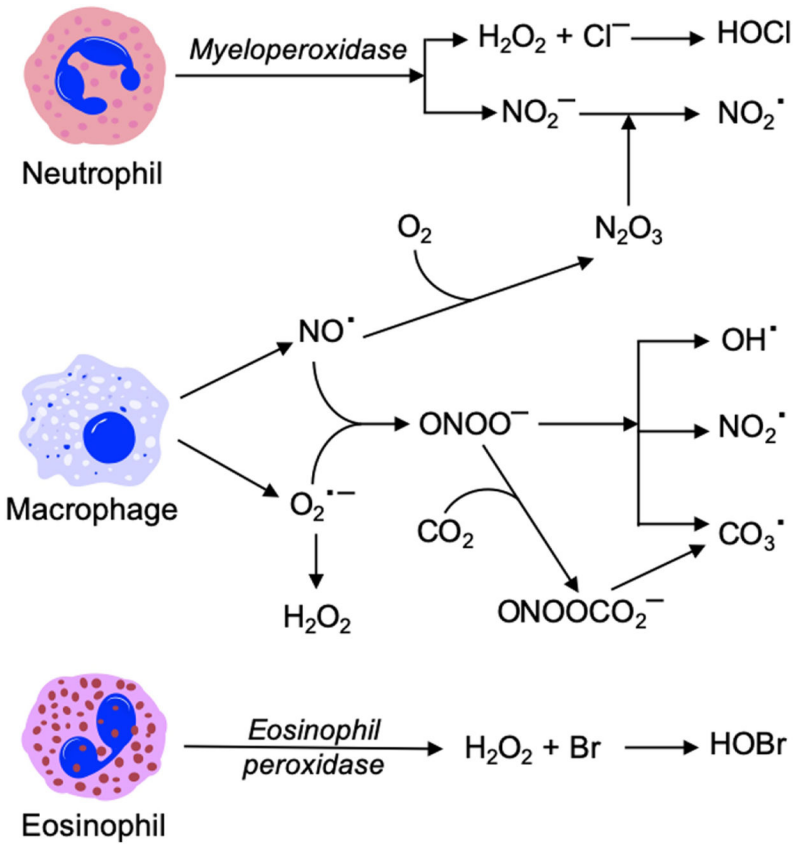


**Figure 2.**

Many reactive oxygen and nitrogen species are produced or derived from innate immune cells.

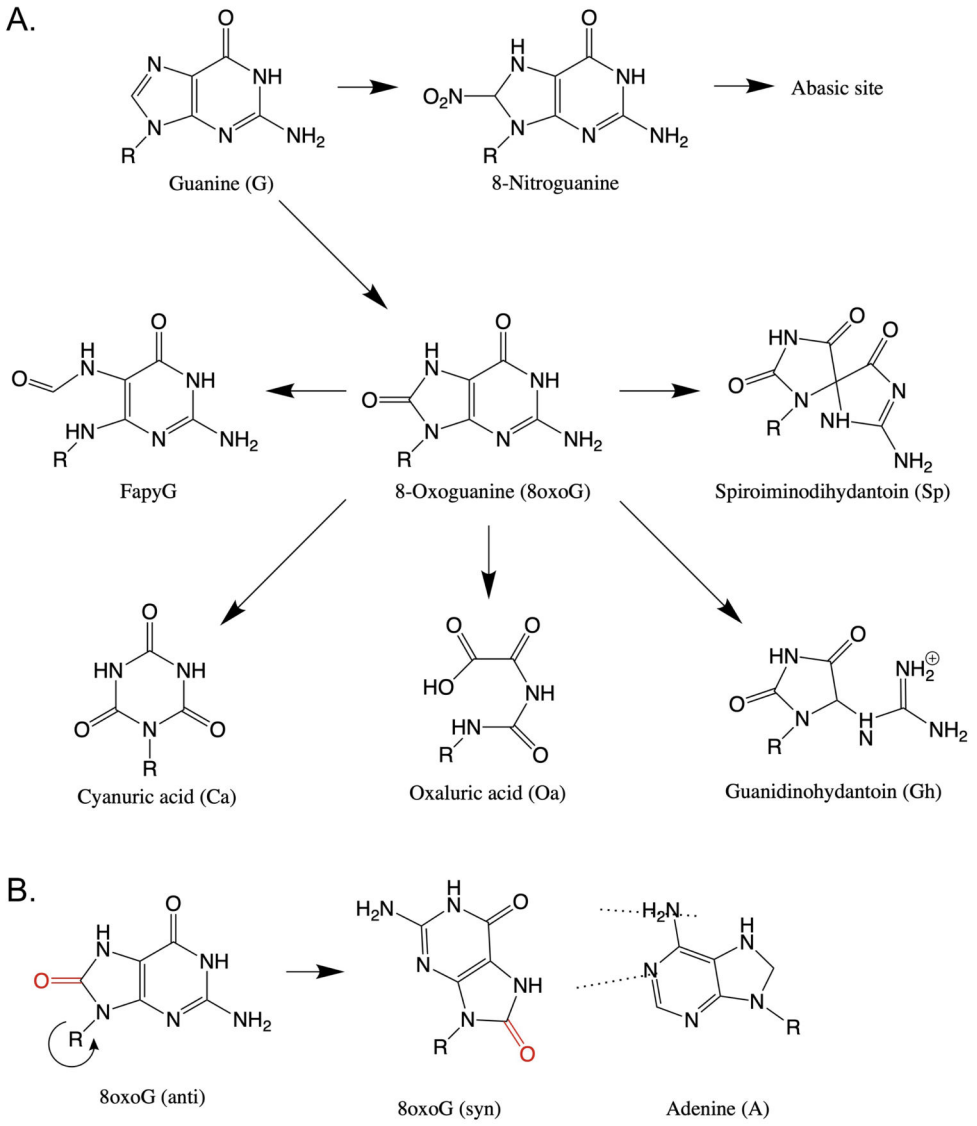


**Figure 3.**

Products of guanine oxidation. A. Primary nitrosation of guanine leads to an abasic site. Primary oxidation of guanine produces 8oxoG, and oxidation of 8oxoG leads to a variety of secondary oxidation products. B. Rotation of the glycosidic bond allows 8oxoG to mispair with A.

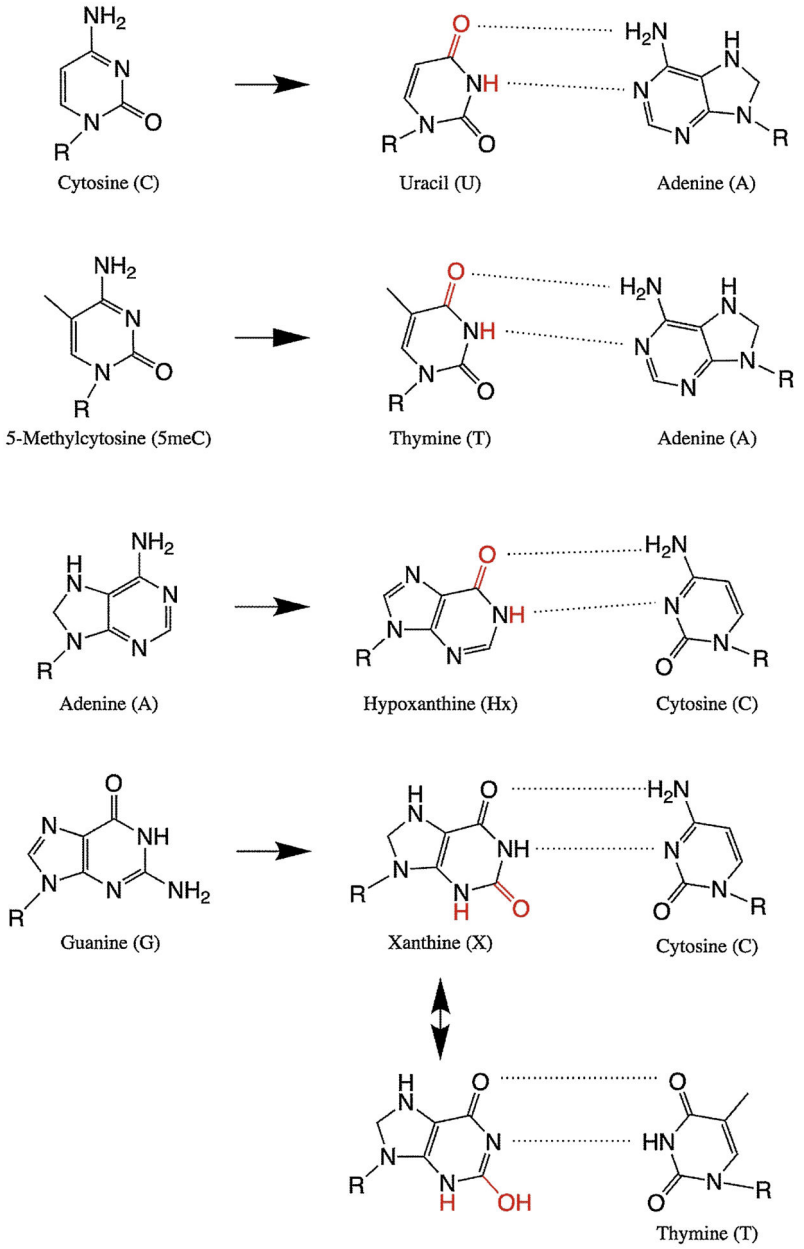


**Figure 4.**
Products of DNA deamination and subsequent base mispairing.

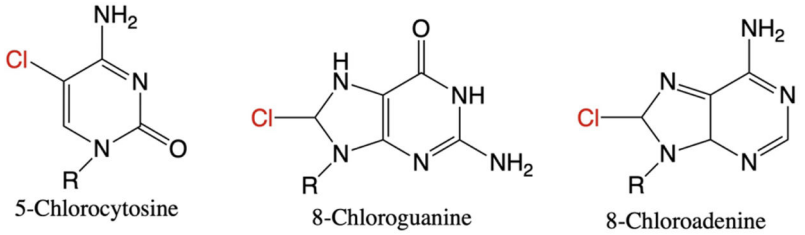


**Figure 5.**
Products of DNA halogenation

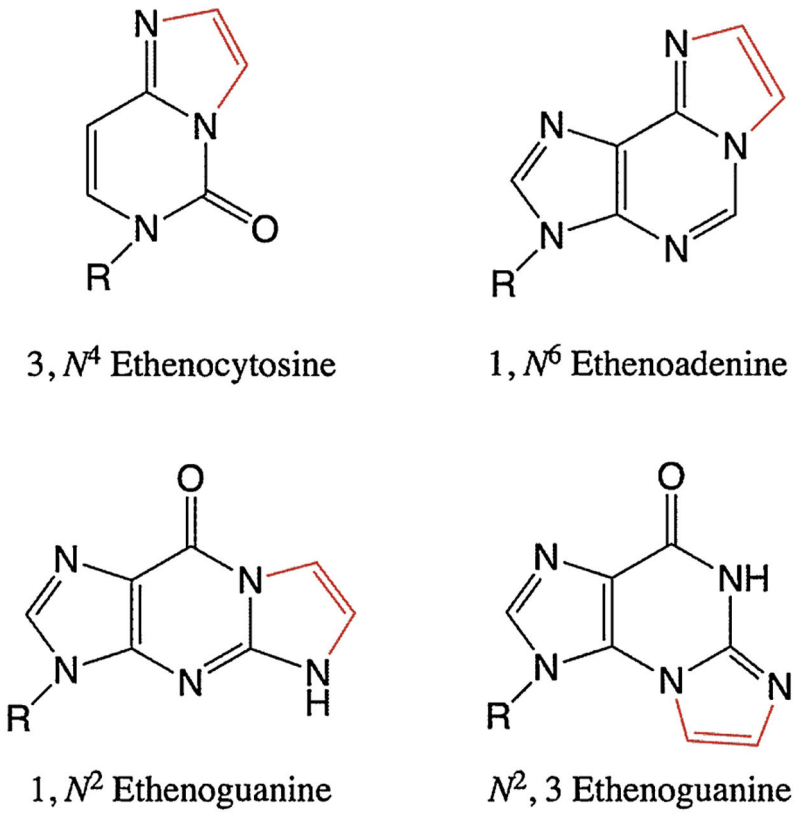


**Figure 6.**
Products of DNA alkylation following electrophilic attack by lipid peroxidation products

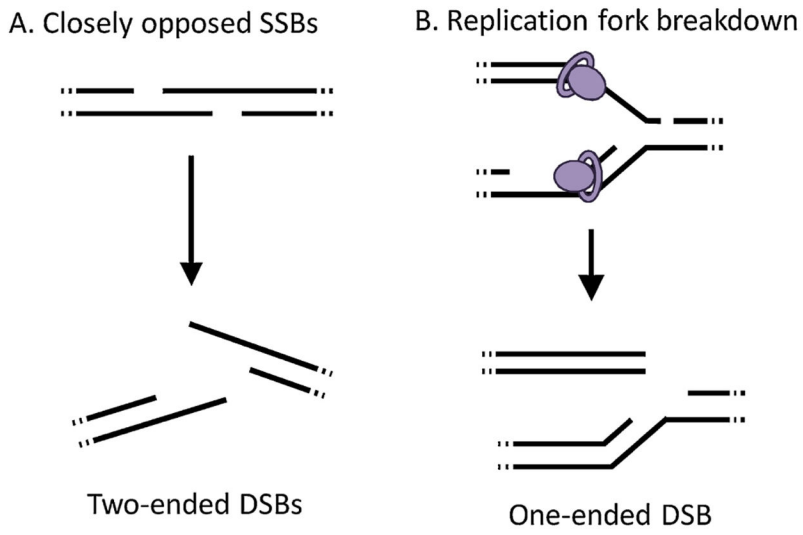


**Figure 7.**
Modes by which single strand breaks may lead to double strand breaks.

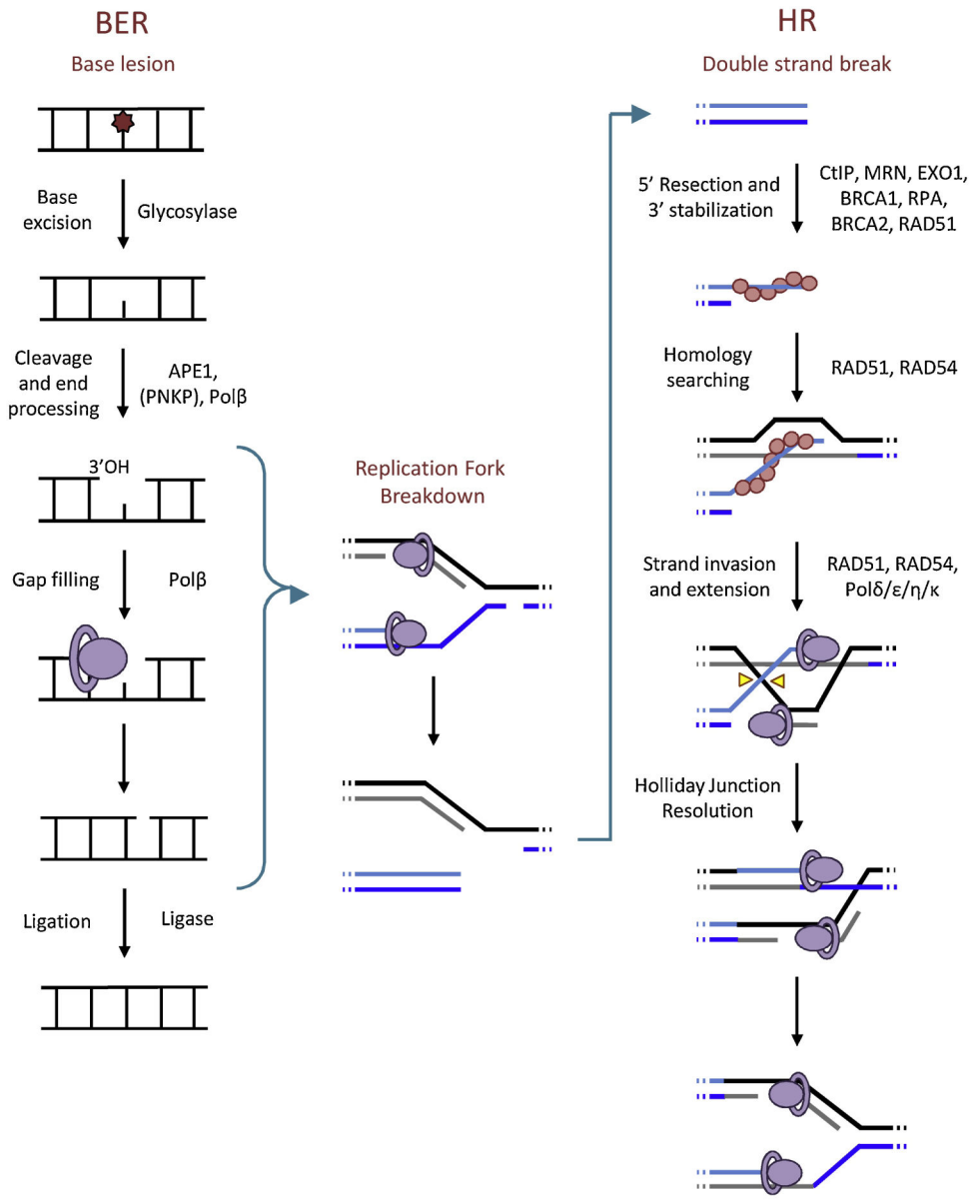


**Figure 8.**

Base excision repair pathway, homologous recombination pathway, and how BER intermediates may lead to HR

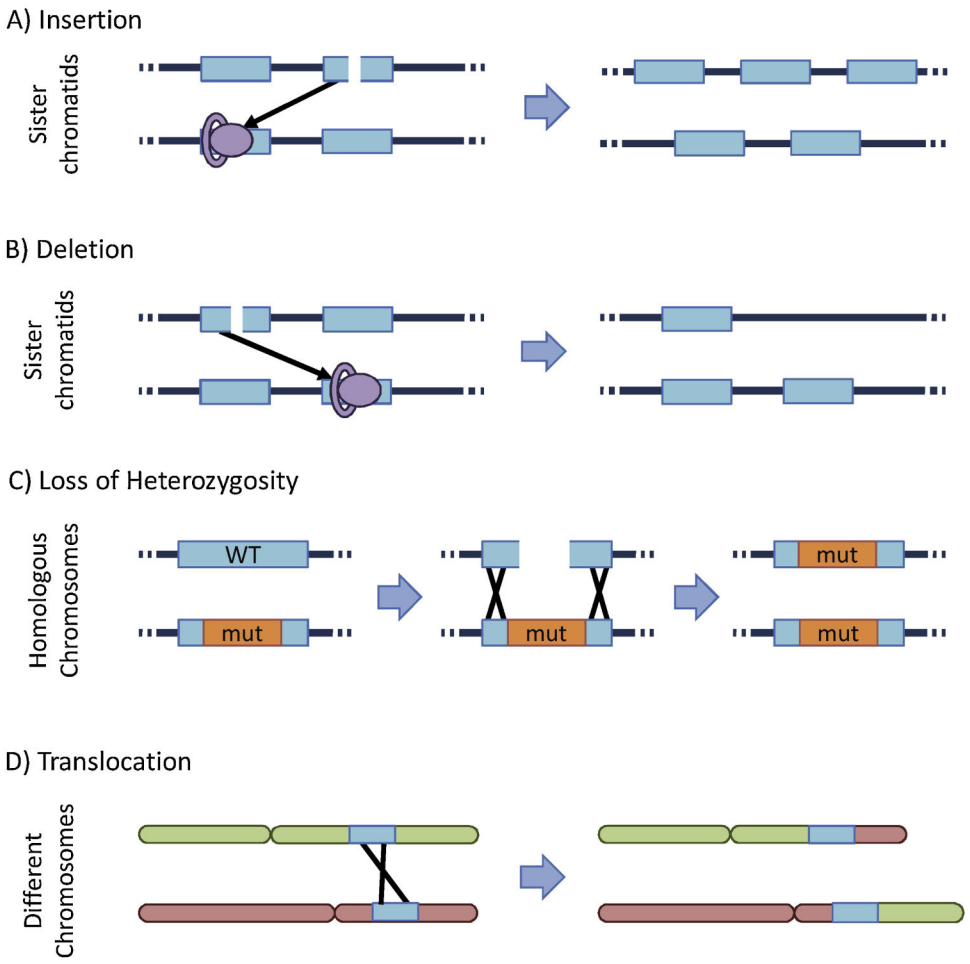


**Figure 9.**
Several mechanisms for HR-derived mutations.

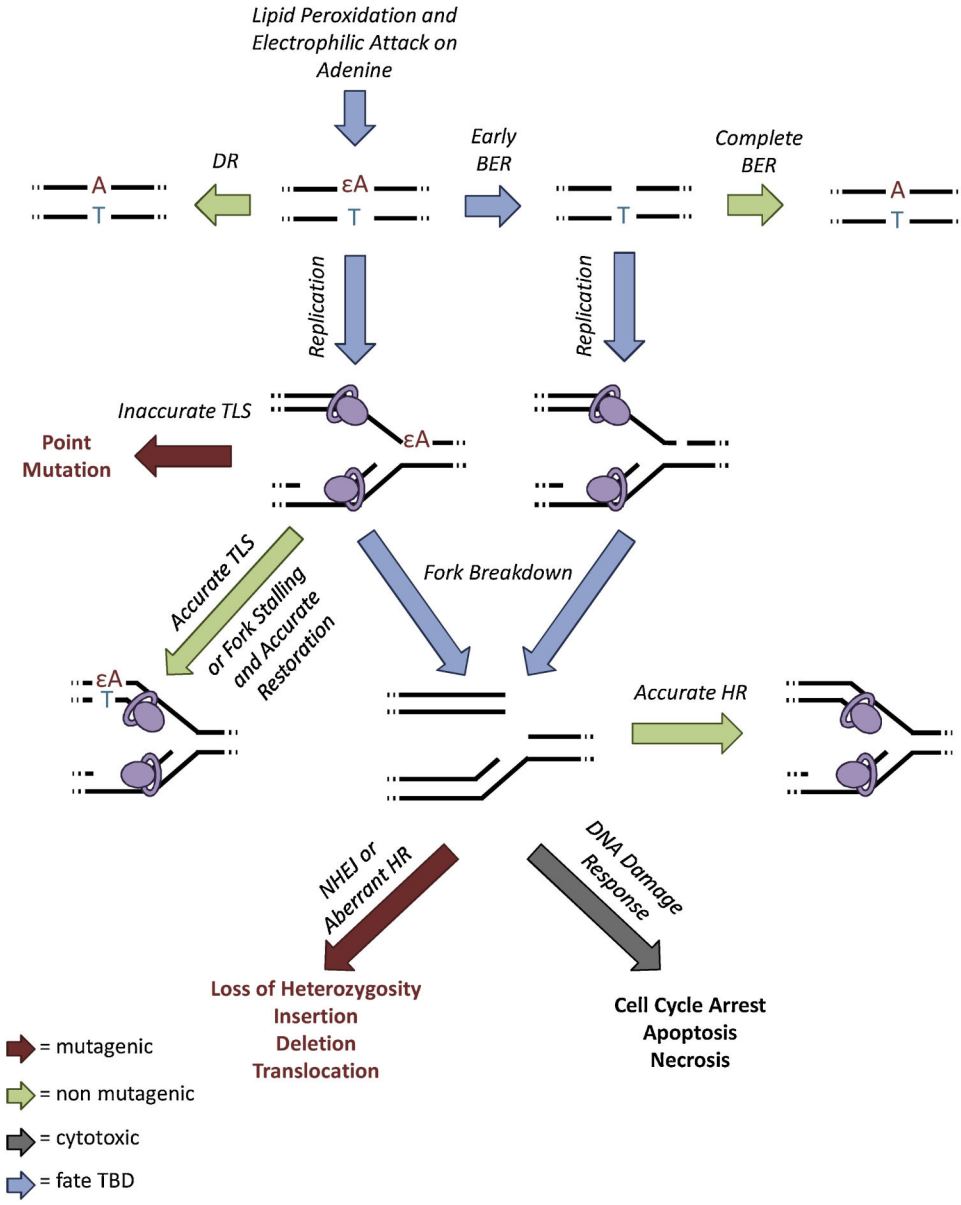


**Figure 10.**
Pathways leading from a single εA lesion to multiple types of mutations.

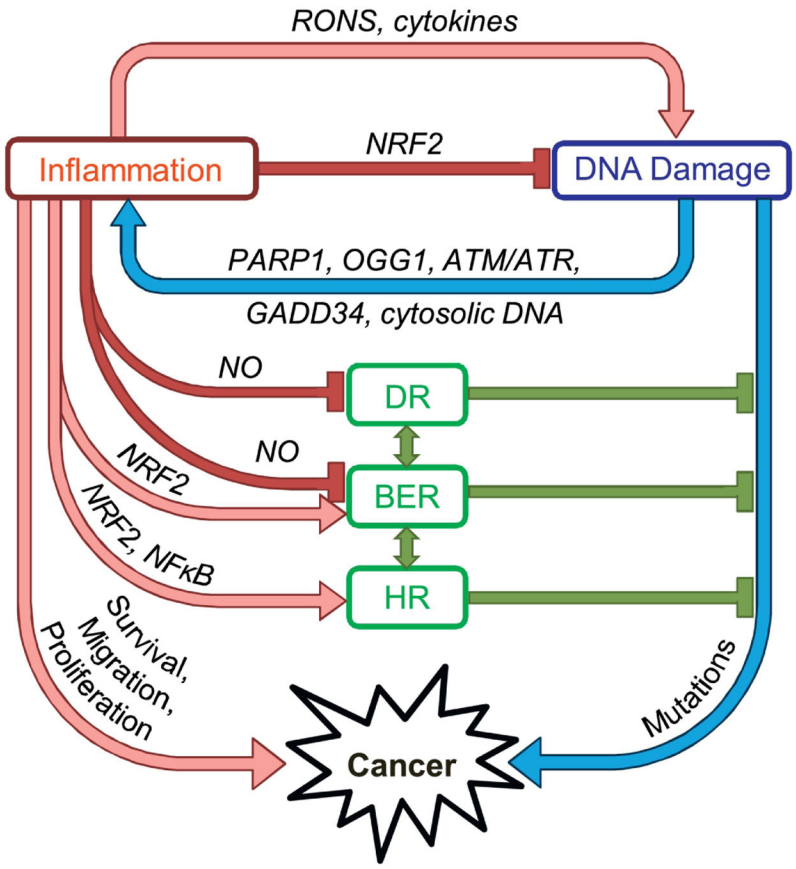


**Figure 11.**

Expanded paradigm describing relationships between inflammation, DNA damage and cancer