## DNA damage

## <<https://en.wikipedia.org/wiki/DNA_repair>>

<<<https://www.khanacademy.org/science/high-school-biology/hs-molecular-genetics/hs-discovery-and-structure-of-dna/a/dna-proofreading-and-repair>>>

DNA damage, due to environmental factors and normal [metabolic](https://en.wikipedia.org/wiki/Metabolism) processes inside the cell, occurs at a rate of 10,000 to 1,000,000 molecular lesions per cell per day.[[2]](https://en.wikipedia.org/wiki/DNA_repair#cite_note-lodish-2) While this constitutes only 0.000165% of the human genome's approximately 6 billion bases (3 billion base pairs), unrepaired lesions in critical genes (such as [tumor suppressor genes](https://en.wikipedia.org/wiki/Tumor_suppressor_gene)) can impede a cell's ability to carry out its function and appreciably increase the likelihood of [tumor](https://en.wikipedia.org/wiki/Tumor) formation and contribute to [tumour heterogeneity](https://en.wikipedia.org/wiki/Tumour_heterogeneity).

The vast majority of DNA damage affects the [primary structure](https://en.wikipedia.org/wiki/Primary_structure) of the double helix; that is, the bases themselves are chemically modified. These modifications can in turn disrupt the molecules' regular helical structure by introducing non-native chemical bonds or bulky adducts that do not fit in the standard double helix. Unlike [proteins](https://en.wikipedia.org/wiki/Protein) and [RNA](https://en.wikipedia.org/wiki/RNA), DNA usually lacks [tertiary structure](https://en.wikipedia.org/wiki/Tertiary_structure) and therefore damage or disturbance does not occur at that level. DNA is, however, [supercoiled](https://en.wikipedia.org/wiki/Supercoil) and wound around "packaging" proteins called [histones](https://en.wikipedia.org/wiki/Histone) (in eukaryotes), and both superstructures are vulnerable to the effects of DNA damage.

#### Sources

DNA damage can be subdivided into two main types:

1. [endogenous](https://en.wikipedia.org/wiki/Endogenous) damage such as attack by [reactive oxygen species](https://en.wikipedia.org/wiki/Reactive_oxygen_species) produced from normal metabolic byproducts (spontaneous mutation), especially the process of [oxidative deamination](https://en.wikipedia.org/wiki/Oxidative_deamination)
   1. also includes [replication errors](https://en.wikipedia.org/wiki/DNA_error)
2. exogenous damage caused by external agents such as
   1. ultraviolet [UV 200–400 [nm](https://en.wikipedia.org/wiki/Nanometre)] [radiation](https://en.wikipedia.org/wiki/Radiation) from the sun
   2. other radiation frequencies, including [x-rays](https://en.wikipedia.org/wiki/X-ray) and [gamma rays](https://en.wikipedia.org/wiki/Gamma_ray)
   3. [hydrolysis](https://en.wikipedia.org/wiki/Hydrolysis) or thermal disruption
   4. certain [plant](https://en.wikipedia.org/wiki/Plant) [toxins](https://en.wikipedia.org/wiki/Toxin)
   5. human-made [mutagenic chemicals](https://en.wikipedia.org/wiki/Mutagen), especially [aromatic](https://en.wikipedia.org/wiki/Aromatic) compounds that act as DNA [intercalating agents](https://en.wikipedia.org/wiki/Intercalation_(biochemistry))
   6. [viruses](https://en.wikipedia.org/wiki/Virus)[[8]](https://en.wikipedia.org/wiki/DNA_repair#cite_note-pmid10547702-8)

The replication of damaged DNA before cell division can lead to the incorporation of wrong bases opposite damaged ones. Daughter cells that inherit these wrong bases carry mutations from which the original DNA sequence is unrecoverable (except in the rare case of a [back mutation](https://en.wikipedia.org/wiki/Mutation#By_effect_on_function), for example, through [gene conversion](https://en.wikipedia.org/wiki/Gene_conversion)).

### Types[[edit](https://en.wikipedia.org/w/index.php?title=DNA_repair&action=edit&section=3)]

There are several types of damage to DNA due to endogenous cellular processes:

1. [*oxidation*](https://en.wikipedia.org/wiki/DNA_oxidation) of bases [e.g. 8-oxo-7,8-dihydroguanine (8-oxoG)] and generation of DNA strand interruptions from reactive oxygen species,
2. [*alkylation*](https://en.wikipedia.org/wiki/Alkylation) of bases (usually [methylation](https://en.wikipedia.org/wiki/Methylation)), such as formation of [7-methylguanosine](https://en.wikipedia.org/wiki/7-methylguanosine), 1-methyladenine, [6-O-Methylguanine](https://en.wikipedia.org/wiki/6-O-Methylguanine)
3. [*hydrolysis*](https://en.wikipedia.org/wiki/Hydrolysis) of bases, such as [deamination](https://en.wikipedia.org/wiki/Deamination), [depurination](https://en.wikipedia.org/wiki/Depurination), and depyrimidination.
4. ["bulky adduct formation"](https://en.wikipedia.org/wiki/DNA_adduct) (e.g., benzo[a]pyrene diol epoxide-dG adduct, aristolactam I-dA adduct)
5. *mismatch* of bases, due to errors in [DNA replication](https://en.wikipedia.org/wiki/DNA_replication), in which the wrong DNA base is stitched into place in a newly forming DNA strand, or a DNA base is skipped over or mistakenly inserted.
6. Monoadduct damage cause by change in single nitrogenous base of DNA
7. Diadduct damage

Damage caused by exogenous agents comes in many forms. Some examples are:

1. [*UV-B light*](https://en.wikipedia.org/wiki/UV_light) causes crosslinking between adjacent cytosine and thymine bases creating [*pyrimidine dimers*](https://en.wikipedia.org/wiki/Pyrimidine_dimers). This is called [direct DNA damage](https://en.wikipedia.org/wiki/Direct_DNA_damage).
2. [*UV-A light*](https://en.wikipedia.org/wiki/UV_light) creates mostly free radicals. The damage caused by free radicals is called [indirect DNA damage](https://en.wikipedia.org/wiki/Indirect_DNA_damage).
3. [*Ionizing radiation*](https://en.wikipedia.org/wiki/Ionizing_radiation) such as that created by radioactive decay or in [*cosmic rays*](https://en.wikipedia.org/wiki/Cosmic_rays) causes breaks in DNA strands. Intermediate-level ionizing radiation may induce irreparable DNA damage (leading to replicational and transcriptional errors needed for neoplasia or may trigger viral interactions) leading to pre-mature aging and cancer.
4. *Thermal disruption* at elevated temperature increases the rate of [depurination](https://en.wikipedia.org/wiki/Depurination) (loss of [purine](https://en.wikipedia.org/wiki/Purine) bases from the DNA backbone) and single-strand breaks. For example, hydrolytic depurination is seen in the [thermophilic bacteria](https://en.wikipedia.org/wiki/Thermophilic_bacteria), which grow in [hot springs](https://en.wikipedia.org/wiki/Hot_springs) at 40–80 °C.[[9]](https://en.wikipedia.org/wiki/DNA_repair#cite_note-9)[[10]](https://en.wikipedia.org/wiki/DNA_repair#cite_note-Toshihiro-10) The rate of depurination (300 [purine](https://en.wikipedia.org/wiki/Purine) residues per genome per generation) is too high in these species to be repaired by normal repair machinery, hence a possibility of an [adaptive](https://en.wikipedia.org/wiki/Adaptive) response cannot be ruled out.
5. *Industrial chemicals* such as [vinyl chloride](https://en.wikipedia.org/wiki/Vinyl_chloride) and [hydrogen peroxide](https://en.wikipedia.org/wiki/Hydrogen_peroxide), and environmental chemicals such as [polycyclic aromatic hydrocarbons](https://en.wikipedia.org/wiki/Polycyclic_aromatic_hydrocarbon) found in smoke, soot and tar create a huge diversity of DNA adducts- ethenobases, oxidized bases, alkylated phosphotriesters and [crosslinking of DNA](https://en.wikipedia.org/wiki/Crosslinking_of_DNA), just to name a few.

UV damage, alkylation/methylation, X-ray damage and oxidative damage are examples of induced damage. Spontaneous damage can include the loss of a base, deamination, sugar [ring puckering](https://en.wikipedia.org/wiki/Ring_pucker) and tautomeric shift. Constitutive (spontaneous) DNA damage caused by endogenous oxidants can be detected as a low level of histone H2AX phosphorylation in untreated cells.[[11]](https://en.wikipedia.org/wiki/DNA_repair#cite_note-11)

### Nuclear versus mitochondrial[[edit](https://en.wikipedia.org/w/index.php?title=DNA_repair&action=edit&section=4)]

In human cells, and [eukaryotic](https://en.wikipedia.org/wiki/Eukaryotic) cells in general, DNA is found in two cellular locations – inside the [nucleus](https://en.wikipedia.org/wiki/Cell_nucleus) and inside the [mitochondria](https://en.wikipedia.org/wiki/Mitochondria). Nuclear DNA (nDNA) exists as [chromatin](https://en.wikipedia.org/wiki/Chromatin) during non-replicative stages of the [cell cycle](https://en.wikipedia.org/wiki/Cell_cycle) and is condensed into aggregate structures known as [chromosomes](https://en.wikipedia.org/wiki/Chromosomes) during [cell division](https://en.wikipedia.org/wiki/Cell_division). In either state the DNA is highly compacted and wound up around bead-like proteins called [histones](https://en.wikipedia.org/wiki/Histones). Whenever a cell needs to express the genetic information encoded in its nDNA the required chromosomal region is unravelled, genes located therein are expressed, and then the region is condensed back to its resting conformation. Mitochondrial DNA (mtDNA) is located inside mitochondria [organelles](https://en.wikipedia.org/wiki/Organelles), exists in multiple copies, and is also tightly associated with a number of proteins to form a complex known as the nucleoid. Inside mitochondria, [reactive oxygen species](https://en.wikipedia.org/wiki/Reactive_oxygen_species) (ROS), or [free radicals](https://en.wikipedia.org/wiki/Radical_(chemistry)), byproducts of the constant production of [adenosine triphosphate](https://en.wikipedia.org/wiki/Adenosine_triphosphate) (ATP) via [oxidative phosphorylation](https://en.wikipedia.org/wiki/Oxidative_phosphorylation), create a highly oxidative environment that is known to damage mtDNA. A critical enzyme in counteracting the toxicity of these species is [superoxide dismutase](https://en.wikipedia.org/wiki/Superoxide_dismutase), which is present in both the mitochondria and [cytoplasm](https://en.wikipedia.org/wiki/Cytoplasm) of eukaryotic cells.

### Senescence and apoptosis[[edit](https://en.wikipedia.org/w/index.php?title=DNA_repair&action=edit&section=5)]

Senescence, an irreversible process in which the cell no longer [divides](https://en.wikipedia.org/wiki/Mitosis), is a protective response to the shortening of the [chromosome ends](https://en.wikipedia.org/wiki/Telomeres). The telomeres are long regions of repetitive [noncoding DNA](https://en.wikipedia.org/wiki/Noncoding_DNA) that cap chromosomes and undergo partial degradation each time a cell undergoes division (see [Hayflick limit](https://en.wikipedia.org/wiki/Hayflick_limit)).[[12]](https://en.wikipedia.org/wiki/DNA_repair#cite_note-braig-12) In contrast, [quiescence](https://en.wikipedia.org/wiki/G0_phase) is a reversible state of cellular dormancy that is unrelated to genome damage (see [cell cycle](https://en.wikipedia.org/wiki/Cell_cycle)). Senescence in cells may serve as a functional alternative to apoptosis in cases where the physical presence of a cell for spatial reasons is required by the organism,[[13]](https://en.wikipedia.org/wiki/DNA_repair#cite_note-Lynch-13) which serves as a "last resort" mechanism to prevent a cell with damaged DNA from replicating inappropriately in the absence of pro-growth [cellular signaling](https://en.wikipedia.org/wiki/Cellular_signaling). Unregulated cell division can lead to the formation of a tumor (see [cancer](https://en.wikipedia.org/wiki/Cancer)), which is potentially lethal to an organism. Therefore, the induction of senescence and apoptosis is considered to be part of a strategy of protection against cancer.[[14]](https://en.wikipedia.org/wiki/DNA_repair#cite_note-pmid17667954-14)

### Mutation[[edit](https://en.wikipedia.org/w/index.php?title=DNA_repair&action=edit&section=6)]

It is important to distinguish between DNA damage and mutation, the two major types of error in DNA. DNA damage and mutation are fundamentally different. Damage results in physical abnormalities in the DNA, such as single- and double-strand breaks, [8-hydroxydeoxyguanosine](https://en.wikipedia.org/wiki/8-hydroxydeoxyguanosine) residues, and polycyclic aromatic hydrocarbon adducts. DNA damage can be recognized by enzymes, and thus can be correctly repaired if redundant information, such as the undamaged sequence in the complementary DNA strand or in a homologous chromosome, is available for copying. If a cell retains DNA damage, transcription of a gene can be prevented, and thus translation into a protein will also be blocked. Replication may also be blocked or the cell may die.

In contrast to DNA damage, a mutation is a change in the base sequence of the DNA. A mutation cannot be recognized by enzymes once the base change is present in both DNA strands, and thus a mutation cannot be repaired. At the cellular level, mutations can cause alterations in protein function and regulation. Mutations are replicated when the cell replicates. In a population of cells, mutant cells will increase or decrease in frequency according to the effects of the mutation on the ability of the cell to survive and reproduce.

Although distinctly different from each other, DNA damage and mutation are related because DNA damage often causes errors of DNA synthesis during replication or repair; these errors are a major source of mutation.

Given these properties of DNA damage and mutation, it can be seen that DNA damage is a special problem in non-dividing or slowly-dividing cells, where unrepaired damage will tend to accumulate over time. On the other hand, in rapidly-dividing cells, unrepaired DNA damage that does not kill the cell by blocking replication will tend to cause replication errors and thus mutation. The great majority of mutations that are not neutral in their effect are deleterious to a cell's survival. Thus, in a population of cells composing a tissue with replicating cells, mutant cells will tend to be lost. However, infrequent mutations that provide a survival advantage will tend to clonally expand at the expense of neighboring cells in the tissue. This advantage to the cell is disadvantageous to the whole organism, because such mutant cells can give rise to cancer. Thus, DNA damage in frequently dividing cells, because it gives rise to mutations, is a prominent cause of cancer. In contrast, DNA damage in infrequently-dividing cells is likely a prominent cause of aging.[[15]](https://en.wikipedia.org/wiki/DNA_repair#cite_note-nDNA-15)

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**DNA Repair :**

DNA repair is a collection of processes by which a [cell](https://en.wikipedia.org/wiki/Cell_(biology)) identifies and corrects damage to the [DNA](https://en.wikipedia.org/wiki/DNA) molecules that encode its [genome](https://en.wikipedia.org/wiki/Genome).[[1]](https://en.wikipedia.org/wiki/DNA_repair#cite_note-Jackson-Bartek-2009-1) In human cells, both normal [metabolic](https://en.wikipedia.org/wiki/Metabolism) activities and environmental factors such as [radiation](https://en.wikipedia.org/wiki/Radiation) can cause DNA damage, resulting in as many as 1 [million](https://en.wikipedia.org/wiki/Million) individual [molecular lesions](https://en.wikipedia.org/wiki/Molecular_lesion) per cell per day.[[2]](https://en.wikipedia.org/wiki/DNA_repair#cite_note-lodish-2) Many of these lesions cause structural damage to the DNA molecule and can alter or eliminate the cell's ability to [transcribe](https://en.wikipedia.org/wiki/Transcription_(biology)) the [gene](https://en.wikipedia.org/wiki/Gene) that the affected DNA encodes. Other lesions induce potentially harmful [mutations](https://en.wikipedia.org/wiki/Mutation) in the cell's genome, which affect the survival of its daughter cells after it undergoes [mitosis](https://en.wikipedia.org/wiki/Mitosis). As a consequence, the DNA repair process is constantly active as it responds to damage in the DNA structure. When normal repair processes fail, and when cellular [apoptosis](https://en.wikipedia.org/wiki/Apoptosis) does not occur, irreparable DNA damage may occur, including double-strand breaks and [DNA crosslinkages](https://en.wikipedia.org/wiki/Crosslinking_of_DNA) (interstrand crosslinks or ICLs).[[3]](https://en.wikipedia.org/wiki/DNA_repair#cite_note-acharya-3)[[4]](https://en.wikipedia.org/wiki/DNA_repair#cite_note-Bjorksten-4) This can eventually lead to malignant tumors, or [cancer](https://en.wikipedia.org/wiki/Cancer) as per the [two hit hypothesis](https://en.wikipedia.org/wiki/Knudson_hypothesis).

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Repair processes that help fix damaged DNA include:-

* Direct reversal: Some DNA-damaging chemical reactions can be directly "undone" by enzymes in the cell.
* Excision repair: Damage to one or a few bases of DNA is often fixed by removal (excision) and replacement of the damaged region. In base excision repair, just the damaged base is removed. In nucleotide excision repair, as in the mismatch repair we saw above, a patch of nucleotides is removed.
* Double-stranded break repair: Two major pathways, non-homologous end joining and homologous recombination, are used to repair double-stranded breaks in DNA (that is, when an entire chromosome splits into two pieces).