= DNA repair =

DNA repair is a collection of processes by which a cell identifies and corrects damage to the DNA molecules that encode its genome . In human cells , both normal metabolic activities and environmental factors such as radiation can cause DNA damage , resulting in as many as 1 million individual molecular lesions per cell per day . Many of these lesions cause structural damage to the DNA molecule and can alter or eliminate the cell 's ability to transcribe the gene that the affected DNA encodes . Other lesions induce potentially harmful mutations in the cell 's genome , which affect the survival of its daughter cells after it undergoes 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 does not occur , irreparable DNA damage may occur , including double @-@ strand breaks and DNA crosslinkages (interstrand crosslinks or ICLs) . This can eventually lead to malignant tumors , or cancer as per the two hit hypothesis .

The rate of DNA repair is dependent on many factors , including the cell type , the age of the cell , and the extracellular environment . A cell that has accumulated a large amount of DNA damage , or one that no longer effectively repairs damage incurred to its DNA , can enter one of three possible states :

an irreversible state of dormancy , known as senescence

cell suicide , also known as apoptosis or programmed cell death

unregulated cell division , which can lead to the formation of a tumor that is cancerous

The DNA repair ability of a cell is vital to the integrity of its genome and thus to the normal functionality of that organism . Many genes that were initially shown to influence life span have turned out to be involved in DNA damage repair and protection .

The 2015 Nobel Prize in Chemistry was awarded to Tomas Lindahl , Paul Modrich , and Aziz Sancar for their work on the molecular mechanisms of DNA repair processes .

= = DNA damage = =

DNA damage , due to environmental factors and normal metabolic processes inside the cell , occurs at a rate of 10 @,@ 000 to 1 @,@ 000 @,@ 000 molecular lesions per cell per day . 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) can impede a cell 's ability to carry out its function and appreciably increase the likelihood of tumor formation and contribute to tumour heterogeneity .

The vast majority of DNA damage affects the 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 and RNA , DNA usually lacks tertiary structure and therefore damage or disturbance does not occur at that level . DNA is , however , supercoiled and wound around " packaging " proteins called histones (in eukaryotes) , and both superstructures are vulnerable to the effects of DNA damage .

= = = Types of damage = = =

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

oxidation of bases [e.g. 8 @-@ oxo @-@ 7 @,@ 8 @-@ dihydroguanine (8 @-@ oxoG)] and generation of DNA strand interruptions from reactive oxygen species ,

alkylation of bases (usually methylation) , such as formation of 7 @-@ methylguanosine , 1 @-@ methyladenine , 6 @-@ O @-@ Methylguanine

hydrolysis of bases , such as deamination , depurination , and depyrimidination .

" bulky adduct formation " (i.e. , benzo [a] pyrene diol epoxide @-@ dG adduct , aristolactam I @-@ dA adduct)

mismatch of bases , due to errors in 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 .
Monoadduct damage cause by change in single nitrogenous base of DNA
Diadduct damage
Damage caused by exogenous agents comes in many forms . Some examples are :
UV @-@ B light causes crosslinking between adjacent cytosine and thymine bases creating pyrimidine dimers . This is called direct DNA damage .
UV @-@ A light creates mostly free radicals . The damage caused by free radicals is called indirect DNA damage .
Ionizing radiation such as that created by radioactive decay or in 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 .
Thermal disruption at elevated temperature increases the rate of depurination (loss of purine bases from the DNA backbone) and single @-@ strand breaks . For example , hydrolytic depurination is seen in the thermophilic bacteria , which grow in hot springs at 40 @-@ 80 ° C. The rate of depurination (300 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 response cannot be ruled out .
Industrial chemicals such as vinyl chloride and hydrogen peroxide , and environmental chemicals such as polycyclic aromatic hydrocarbons found in smoke , soot and tar create a huge diversity of DNA adducts- ethenobases , oxidized bases , alkylated phosphotriesters and 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 and tautomeric shift .

= = = Nuclear versus mitochondrial DNA damage = = =

In human cells , and eukaryotic cells in general , DNA is found in two cellular locations ? inside the nucleus and inside the mitochondria . Nuclear DNA (nDNA) exists as chromatin during non @-@ replicative stages of the cell cycle and is condensed into aggregate structures known as chromosomes during cell division . In either state the DNA is highly compacted and wound up around bead @-@ like proteins called 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 , 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 (ROS) , or free radicals , byproducts of the constant production of adenosine triphosphate (ATP) via 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 , which is present in both the mitochondria and cytoplasm of eukaryotic cells .

= = = Senescence and apoptosis = = =

Senescence , an irreversible process in which the cell no longer divides , is a protective response to the shortening of the chromosome ends . The telomeres are long regions of repetitive noncoding DNA that cap chromosomes and undergo partial degradation each time a cell undergoes division (see Hayflick limit) . In contrast , quiescence is a reversible state of cellular dormancy that is unrelated to genome damage (see 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 , 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 . Unregulated

cell division can lead to the formation of a tumor (see 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 .

= = = DNA damage and mutation = = =

It is important to distinguish between DNA damage and mutation , the two major types of error in DNA . DNA damages and mutation are fundamentally different . Damages are physical abnormalities in the DNA , such as single- and double @-@ strand breaks , 8 @-@ hydroxydeoxyguanosine residues , and polycyclic aromatic hydrocarbon adducts . DNA damages can be recognized by enzymes , and , thus , they 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 damages and mutations are related because DNA damages often cause 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 damages are a special problem in non @-@ dividing or slowly dividing cells , where unrepaired damages will tend to accumulate over time . On the other hand , in rapidly dividing cells , unrepaired DNA damages that do 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 damages in frequently dividing cells , because they give rise to mutations , are a prominent cause of cancer . In contrast , DNA damages in infrequently dividing cells are likely a prominent cause of aging .

= = DNA repair mechanisms = =

Cells cannot function if DNA damage corrupts the integrity and accessibility of essential information in the genome (but cells remain superficially functional when non @-@ essential genes are missing or damaged) . Depending on the type of damage inflicted on the DNA 's double helical structure , a variety of repair strategies have evolved to restore lost information . If possible , cells use the unmodified complementary strand of the DNA or the sister chromatid as a template to recover the original information . Without access to a template , cells use an error @-@ prone recovery mechanism known as translesion synthesis as a last resort .

Damage to DNA alters the spatial configuration of the helix , and such alterations can be detected by the cell . Once damage is localized , specific DNA repair molecules bind at or near the site of damage , inducing other molecules to bind and form a complex that enables the actual repair to take place .

= = = Direct reversal = = =

Cells are known to eliminate three types of damage to their DNA by chemically reversing it . These mechanisms do not require a template , since the types of damage they counteract can occur in

only one of the four bases . Such direct reversal mechanisms are specific to the type of damage incurred and do not involve breakage of the phosphodiester backbone . The formation of pyrimidine dimers upon irradiation with UV light results in an abnormal covalent bond between adjacent pyrimidine bases . The photoreactivation process directly reverses this damage by the action of the enzyme photolyase , whose activation is obligately dependent on energy absorbed from blue / UV light (300 ? 500 nm wavelength) to promote catalysis . Photolyase , an old enzyme present in bacteria , fungi , and most animals no longer functions in humans , who instead use nucleotide excision repair to repair damage from UV irradiation . Another type of damage , methylation of guanine bases , is directly reversed by the protein methyl guanine methyl transferase (MGMT) , the bacterial equivalent of which is called ogt . This is an expensive process because each MGMT molecule can be used only once ; that is , the reaction is stoichiometric rather than catalytic . A generalized response to methylating agents in bacteria is known as the adaptive response and confers a level of resistance to alkylating agents upon sustained exposure by upregulation of alkylation repair enzymes . The third type of DNA damage reversed by cells is certain methylation of the bases cytosine and adenine .

= = = Single @-@ strand damage = = =

When only one of the two strands of a double helix has a defect , the other strand can be used as a template to guide the correction of the damaged strand . In order to repair damage to one of the two paired molecules of DNA , there exist a number of excision repair mechanisms that remove the damaged nucleotide and replace it with an undamaged nucleotide complementary to that found in the undamaged DNA strand .

Base excision repair (BER) repairs damage to a single nitrogenous base by deploying enzymes called glycosylases . These enzymes remove a single nitrogenous base to create an apurinic or apyrimidinic site (AP site) . Enzymes called AP endonucleases nick the damaged DNA backbone at the AP site . DNA polymerase then removes the damaged region using its 5 ? to 3 ? exonuclease activity and correctly synthesizes the new strand using the complementary strand as a template .

Nucleotide excision repair (NER) repairs damaged DNA which commonly consists of bulky , helix @-@ distorting damage , such as pyrimidine dimerization caused by UV light . Damaged regions are removed in 12 @-@ 24 nucleotide @-@ long strands in a three @-@ step process which consists of recognition of damage , excision of damaged DNA both upstream and downstream of damage by endonucleases , and resynthesis of removed DNA region . NER is a highly evolutionarily conserved repair mechanism and is used in nearly all eukaryotic and prokaryotic cells . In prokaryotes , NER is mediated by Uvr proteins . In eukaryotes , many more proteins are involved , although the general strategy is the same .

Mismatch repair systems are present in essentially all cells to correct errors that are not corrected by proofreading . These systems consist of at least two proteins . One detects the mismatch , and the other recruits an endonuclease that cleaves the newly synthesized DNA strand close to the region of damage . In E. coli , the proteins involved are the Mut class proteins . This is followed by removal of damaged region by an exonuclease , resynthesis by DNA polymerase , and nick sealing by DNA ligase .

= = = Double @-@ strand breaks = = =

Double @-@ strand breaks , in which both strands in the double helix are severed , are particularly hazardous to the cell because they can lead to genome rearrangements . Three mechanisms exist to repair double @-@ strand breaks (DSBs) : non @-@ homologous end joining (NHEJ) , microhomology @-@ mediated end joining (MMEJ) , and homologous recombination . PVN Acharya noted that double @-@ strand breaks and a " cross @-@ linkage joining both strands at the same point is irreparable because neither strand can then serve as a template for repair . The cell will die in the next mitosis or in some rare instances , mutate . "

In NHEJ , DNA Ligase IV , a specialized DNA ligase that forms a complex with the cofactor XRCC4

, directly joins the two ends . To guide accurate repair , NHEJ relies on short homologous sequences called microhomologies present on the single @-@ stranded tails of the DNA ends to be joined . If these overhangs are compatible , repair is usually accurate . NHEJ can also introduce mutations during repair . Loss of damaged nucleotides at the break site can lead to deletions , and joining of nonmatching termini forms insertions or translocations . NHEJ is especially important before the cell has replicated its DNA , since there is no template available for repair by homologous recombination . There are " backup " NHEJ pathways in higher eukaryotes . Besides its role as a genome caretaker , NHEJ is required for joining hairpin @-@ capped double @-@ strand breaks induced during V (D) J recombination , the process that generates diversity in B @-@ cell and T @-@ cell receptors in the vertebrate immune system .

MMEJ starts with short @-@ range end resection by MRE11 nuclease on either side of a double @-@ strand break to reveal microhomology regions . In further steps , PARP1 is required and may be an early step in MMEJ . There is pairing of microhomology regions followed by recruitment of flap structure @-@ specific endonuclease 1 (FEN1) to remove overhanging flaps . This is followed by recruitment of XRCC1 ? LIG3 to the site for ligating the DNA ends , leading to an intact DNA .

DNA double strand breaks in mammalian cells are primarily repaired by homologous recombination (HR) and non @-@ homologous end joining (NHEJ) . In an in vitro system , MMEJ occurred in mammalian cells at the levels of 10 ? 20 % of HR when both HR and NHEJ mechanisms were also available . MMEJ is always accompanied by a deletion , so that MMEJ is a mutagenic pathway for DNA repair .

Homologous recombination requires the presence of an identical or nearly identical sequence to be used as a template for repair of the break . The enzymatic machinery responsible for this repair process is nearly identical to the machinery responsible for chromosomal crossover during meiosis . This pathway allows a damaged chromosome to be repaired using a sister chromatid (available in G2 after DNA replication) or a homologous chromosome as a template . DSBs caused by the replication machinery attempting to synthesize across a single @-@ strand break or unrepaired lesion cause collapse of the replication fork and are typically repaired by recombination .

Topoisomerases introduce both single- and double @-@ strand breaks in the course of changing the DNA 's state of supercoiling , which is especially common in regions near an open replication fork . Such breaks are not considered DNA damage because they are a natural intermediate in the topoisomerase biochemical mechanism and are immediately repaired by the enzymes that created them .

A team of French researchers bombarded Deinococcus radiodurans to study the mechanism of double @-@ strand break DNA repair in that bacterium . At least two copies of the genome , with random DNA breaks , can form DNA fragments through annealing . Partially overlapping fragments are then used for synthesis of homologous regions through a moving D @-@ loop that can continue extension until they find complementary partner strands . In the final step there is crossover by means of RecA @-@ dependent homologous recombination .

= = = Translesion synthesis = = =

Translesion synthesis (TLS) is a DNA damage tolerance process that allows the DNA replication machinery to replicate past DNA lesions such as thymine dimers or AP sites . It involves switching out regular DNA polymerases for specialized translesion polymerases (i.e. DNA polymerase IV or V , from the Y Polymerase family) , often with larger active sites that can facilitate the insertion of bases opposite damaged nucleotides . The polymerase switching is thought to be mediated by , among other factors , the post @-@ translational modification of the replication processivity factor PCNA . Translesion synthesis polymerases often have low fidelity (high propensity to insert wrong bases) on undamaged templates relative to regular polymerases . However , many are extremely efficient at inserting correct bases opposite specific types of damage . For example , Pol ? mediates error @-@ free bypass of lesions induced by UV irradiation , whereas Pol ? introduces mutations at these sites . Pol ? is known to add the first adenine across the T ^ T photodimer using Watson @-@ Crick base pairing and the second adenine will be added in its syn conformation using Hoogsteen

base pairing . From a cellular perspective , risking the introduction of point mutations during translesion synthesis may be preferable to resorting to more drastic mechanisms of DNA repair , which may cause gross chromosomal aberrations or cell death . In short , the process involves specialized polymerases either bypassing or repairing lesions at locations of stalled DNA replication . For example , Human DNA polymerase eta can bypass complex DNA lesions like guanine @-@ thymine intra @-@ strand crosslink , G [8 @,@ 5 @-@ Me] T , although can cause targeted and semi @-@ targeted mutations . Paromita Raychaudhury and Ashis Basu studied the toxicity and mutagenesis of the same lesion in Escherichia coli by replicating a G [8 @,@ 5 @-@ Me] T @-@ modified plasmid in E. coli with specific DNA polymerase knockouts . Viability was very low in a strain lacking pol II , pol IV , and pol V , the three SOS @-@ inducible DNA polymerases , indicating that translesion synthesis is conducted primarily by these specialized DNA polymerases . A bypass platform is provided to these polymerases by Proliferating cell nuclear antigen (PCNA) . Under normal circumstances , PCNA bound to polymerases replicates the DNA . At a site of lesion , PCNA is ubiquitinated , or modified , by the RAD6 / RAD18 proteins to provide a platform for the specialized polymerases to bypass the lesion and resume DNA replication . After translesion synthesis , extension is required . This extension can be carried out by a replicative polymerase if the TLS is error @-@ free , as in the case of Pol ? , yet if TLS results in a mismatch , a specialized polymerase is needed to extend it ; Pol ? . Pol ? is unique in that it can extend terminal mismatches , whereas more processive polymerases cannot . So when a lesion is encountered , the replication fork will stall , PCNA will switch from a processive polymerase to a TLS polymerase such as Pol ? to fix the lesion , then PCNA may switch to Pol ? to extend the mismatch , and last PCNA will switch to the processive polymerase to continue replication .

= = Global response to DNA damage = =

Cells exposed to ionizing radiation , ultraviolet light or chemicals are prone to acquire multiple sites of bulky DNA lesions and double @-@ strand breaks . Moreover , DNA damaging agents can damage other biomolecules such as proteins , carbohydrates , lipids , and RNA . The accumulation of damage , to be specific , double @-@ strand breaks or adducts stalling the replication forks , are among known stimulation signals for a global response to DNA damage . The global response to damage is an act directed toward the cells ' own preservation and triggers multiple pathways of macromolecular repair , lesion bypass , tolerance , or apoptosis . The common features of global response are induction of multiple genes , cell cycle arrest , and inhibition of cell division .

= = = DNA damage checkpoints = = =

After DNA damage , cell cycle checkpoints are activated . Checkpoint activation pauses the cell cycle and gives the cell time to repair the damage before continuing to divide . DNA damage checkpoints occur at the G1 / S and G2 / M boundaries . An intra @-@ S checkpoint also exists . Checkpoint activation is controlled by two master kinases , ATM and ATR . ATM responds to DNA double @-@ strand breaks and disruptions in chromatin structure , whereas ATR primarily responds to stalled replication forks . These kinases phosphorylate downstream targets in a signal transduction cascade , eventually leading to cell cycle arrest . A class of checkpoint mediator proteins including BRCA1 , MDC1 , and 53BP1 has also been identified . These proteins seem to be required for transmitting the checkpoint activation signal to downstream proteins .
DNA damage checkpoint is a signal transduction pathway that blocks cell cycle progression in G1 , G2 and metaphase and slows down the rate of S phase progression when DNA is damaged . It leads to a pause in cell cycle allowing the cell time to repair the damage before continuing to divide .

Checkpoint Proteins can be separated into four groups : phosphatidylinositol 3 @-@ kinase (PI3K) -like protein kinase , proliferating cell nuclear antigen (PCNA) -like group , two serine / threonine (S / T) kinases and their adaptors . Central to all DNA damage induced checkpoints responses is a pair of large protein kinases belonging to the first group of PI3K @-@ like protein kinases @-@ the

ATM (Ataxia telangiectasia mutated) and ATR (Ataxia- and Rad @-@ related) kinases , whose sequence and functions have been well conserved in evolution . All DNA damage response requires either ATM or ATR because they have the ability to bind to the chromosomes at the site of DNA damage , together with accessory proteins that are platforms on which DNA damage response components and DNA repair complexes can be assembled .

An important downstream target of ATM and ATR is p53 , as it is required for inducing apoptosis following DNA damage . The cyclin @-@ dependent kinase inhibitor p21 is induced by both p53 @-@ dependent and p53 @-@ independent mechanisms and can arrest the cell cycle at the G1 / S and G2 / M checkpoints by deactivating cyclin / cyclin @-@ dependent kinase complexes .

= = = The prokaryotic SOS response = = =

The SOS response is the changes in gene expression in Escherichia coli and other bacteria in response to extensive DNA damage . The prokaryotic SOS system is regulated by two key proteins : LexA and RecA . The LexA homodimer is a transcriptional repressor that binds to operator sequences commonly referred to as SOS boxes . In Escherichia coli it is known that LexA regulates transcription of approximately 48 genes including the lexA and recA genes . The SOS response is known to be widespread in the Bacteria domain , but it is mostly absent in some bacterial phyla , like the Spirochetes . The most common cellular signals activating the SOS response are regions of single @-@ stranded DNA (ssDNA) , arising from stalled replication forks or double @-@ strand breaks , which are processed by DNA helicase to separate the two DNA strands . In the initiation step , RecA protein binds to ssDNA in an ATP hydrolysis driven reaction creating RecA ? ssDNA filaments . RecA ? ssDNA filaments activate LexA autoprotease activity , which ultimately leads to cleavage of LexA dimer and subsequent LexA degradation . The loss of LexA repressor induces transcription of the SOS genes and allows for further signal induction , inhibition of cell division and an increase in levels of proteins responsible for damage processing .

In Escherichia coli , SOS boxes are 20 @-@ nucleotide long sequences near promoters with palindromic structure and a high degree of sequence conservation . In other classes and phyla , the sequence of SOS boxes varies considerably , with different length and composition , but it is always highly conserved and one of the strongest short signals in the genome . The high information content of SOS boxes permits differential binding of LexA to different promoters and allows for timing of the SOS response . The lesion repair genes are induced at the beginning of SOS response . The error @-@ prone translesion polymerases , for example , UmuCD ' 2 (also called DNA polymerase V) , are induced later on as a last resort . Once the DNA damage is repaired or bypassed using polymerases or through recombination , the amount of single @-@ stranded DNA in cells is decreased , lowering the amounts of RecA filaments decreases cleavage activity of LexA homodimer , which then binds to the SOS boxes near promoters and restores normal gene expression .

= = = Eukaryotic transcriptional responses to DNA damage = = =

Eukaryotic cells exposed to DNA damaging agents also activate important defensive pathways by inducing multiple proteins involved in DNA repair , cell cycle checkpoint control , protein trafficking and degradation . Such genome wide transcriptional response is very complex and tightly regulated , thus allowing coordinated global response to damage . Exposure of yeast Saccharomyces cerevisiae to DNA damaging agents results in overlapping but distinct transcriptional profiles . Similarities to environmental shock response indicates that a general global stress response pathway exist at the level of transcriptional activation . In contrast , different human cell types respond to damage differently indicating an absence of a common global response . The probable explanation for this difference between yeast and human cells may be in the heterogeneity of mammalian cells . In an animal different types of cells are distributed among different organs that have evolved different sensitivities to DNA damage .

In general global response to DNA damage involves expression of multiple genes responsible for

postreplication repair , homologous recombination , nucleotide excision repair , DNA damage checkpoint , global transcriptional activation , genes controlling mRNA decay , and many others . A large amount of damage to a cell leaves it with an important decision : undergo apoptosis and die , or survive at the cost of living with a modified genome . An increase in tolerance to damage can lead to an increased rate of survival that will allow a greater accumulation of mutations . Yeast Rev1 and human polymerase ? are members of [Y family translesion DNA polymerases present during global response to DNA damage and are responsible for enhanced mutagenesis during a global response to DNA damage in eukaryotes .

= = DNA repair and aging = =

= = = Pathological effects of poor DNA repair = = =

Experimental animals with genetic deficiencies in DNA repair often show decreased life span and increased cancer incidence . For example , mice deficient in the dominant NHEJ pathway and in telomere maintenance mechanisms get lymphoma and infections more often , and , as a consequence , have shorter lifespans than wild @-@ type mice . In similar manner , mice deficient in a key repair and transcription protein that unwinds DNA helices have premature onset of aging @-@ related diseases and consequent shortening of lifespan . However , not every DNA repair deficiency creates exactly the predicted effects ; mice deficient in the NER pathway exhibited shortened life span without correspondingly higher rates of mutation .

If the rate of DNA damage exceeds the capacity of the cell to repair it , the accumulation of errors can overwhelm the cell and result in early senescence , apoptosis , or cancer . Inherited diseases associated with faulty DNA repair functioning result in premature aging , increased sensitivity to carcinogens , and correspondingly increased cancer risk (see below) . On the other hand , organisms with enhanced DNA repair systems , such as Deinococcus radiodurans , the most radiation @-@ resistant known organism , exhibit remarkable resistance to the double @-@ strand break @-@ inducing effects of radioactivity , likely due to enhanced efficiency of DNA repair and especially NHEJ .

= = = Longevity and caloric restriction = = =

A number of individual genes have been identified as influencing variations in life span within a population of organisms . The effects of these genes is strongly dependent on the environment , in particular , on the organism 's diet . Caloric restriction reproducibly results in extended lifespan in a variety of organisms , likely via nutrient sensing pathways and decreased metabolic rate . The molecular mechanisms by which such restriction results in lengthened lifespan are as yet unclear (see for some discussion) ; however , the behavior of many genes known to be involved in DNA repair is altered under conditions of caloric restriction .

For example , increasing the gene dosage of the gene SIR @-@ 2 , which regulates DNA packaging in the nematode worm Caenorhabditis elegans , can significantly extend lifespan . The mammalian homolog of SIR @-@ 2 is known to induce downstream DNA repair factors involved in NHEJ , an activity that is especially promoted under conditions of caloric restriction . Caloric restriction has been closely linked to the rate of base excision repair in the nuclear DNA of rodents , although similar effects have not been observed in mitochondrial DNA .

It is interesting to note that the C. elegans gene AGE @-@ 1 , an upstream effector of DNA repair pathways , confers dramatically extended life span under free @-@ feeding conditions but leads to a decrease in reproductive fitness under conditions of caloric restriction . This observation supports the pleiotropy theory of the biological origins of aging , which suggests that genes conferring a large survival advantage early in life will be selected for even if they carry a corresponding disadvantage late in life .

= = Medicine and DNA repair modulation = =

= = = Hereditary DNA repair disorders = = =

Defects in the NER mechanism are responsible for several genetic disorders , including :
Xeroderma pigmentosum : hypersensitivity to sunlight / UV , resulting in increased skin cancer incidence and premature aging
Cockayne syndrome : hypersensitivity to UV and chemical agents
Trichothiodystrophy : sensitive skin , brittle hair and nails
Mental retardation often accompanies the latter two disorders , suggesting increased vulnerability of developmental neurons .
Other DNA repair disorders include :
Werner 's syndrome : premature aging and retarded growth
Bloom 's syndrome : sunlight hypersensitivity , high incidence of malignancies (especially leukemias) .
Ataxia telangiectasia : sensitivity to ionizing radiation and some chemical agents
All of the above diseases are often called " segmental progerias " (" accelerated aging diseases ") because their victims appear elderly and suffer from aging @-@ related diseases at an abnormally young age , while not manifesting all the symptoms of old age .
Other diseases associated with reduced DNA repair function include Fanconi anemia , hereditary breast cancer and hereditary colon cancer .

= = DNA repair and cancer = =

Because of inherent limitations in the DNA repair mechanisms , if humans lived long enough , they would all eventually develop cancer . There are at least 34 Inherited human DNA repair gene mutations that increase cancer risk . Many of these mutations cause DNA repair to be less effective than normal . In particular , Hereditary nonpolyposis colorectal cancer (HNPCC) is strongly associated with specific mutations in the DNA mismatch repair pathway . BRCA1 and BRCA2 , two famous genes whose mutations confer a hugely increased risk of breast cancer on carriers , are both associated with a large number of DNA repair pathways , especially NHEJ and homologous recombination .
Cancer therapy procedures such as chemotherapy and radiotherapy work by overwhelming the capacity of the cell to repair DNA damage , resulting in cell death . Cells that are most rapidly dividing ? most typically cancer cells ? are preferentially affected . The side @-@ effect is that other non @-@ cancerous but rapidly dividing cells such as progenitor cells in the gut , skin , and hematopoietic system are also affected . Modern cancer treatments attempt to localize the DNA damage to cells and tissues only associated with cancer , either by physical means (concentrating the therapeutic agent in the region of the tumor) or by biochemical means (exploiting a feature unique to cancer cells in the body) .

= = = Epigenetic DNA repair defects in cancer = = =

Classically , cancer has been viewed as a set of diseases that are driven by progressive genetic abnormalities that include mutations in tumour @-@ suppressor genes and oncogenes , and chromosomal aberrations . However , it has become apparent that cancer is also driven by epigenetic alterations .
Epigenetic alterations refer to functionally relevant modifications to the genome that do not involve a change in the nucleotide sequence . Examples of such modifications are changes in DNA methylation (hypermethylation and hypomethylation) and histone modification , changes in chromosomal architecture (caused by inappropriate expression of proteins such as HMGA2 or HMGA1) and changes caused by microRNAs . Each of these epigenetic alterations serves to

regulate gene expression without altering the underlying DNA sequence . These changes usually remain through cell divisions , last for multiple cell generations , and can be considered to be epimutations (equivalent to mutations) .

While large numbers of epigenetic alterations are found in cancers , the epigenetic alterations in DNA repair genes , causing reduced expression of DNA repair proteins , appear to be particularly important . Such alterations are thought to occur early in progression to cancer and to be a likely cause of the genetic instability characteristic of cancers .

Reduced expression of DNA repair genes causes deficient DNA repair . When DNA repair is deficient DNA damages remain in cells at a higher than usual level and these excess damages cause increased frequencies of mutation or epimutation . Mutation rates increase substantially in cells defective in DNA mismatch repair or in homologous recombinational repair (HRR) . Chromosomal rearrangements and aneuploidy also increase in HRR defective cells .

Higher levels of DNA damage not only cause increased mutation , but also cause increased epimutation . During repair of DNA double strand breaks , or repair of other DNA damages , incompletely cleared sites of repair can cause epigenetic gene silencing .

Deficient expression of DNA repair proteins due to an inherited mutation can cause increased risk of cancer . Individuals with an inherited impairment in any of 34 DNA repair genes (see article DNA repair @-@ deficiency disorder) have an increased risk of cancer , with some defects causing up to a 100 % lifetime chance of cancer (e.g. p53 mutations) . However , such germline mutations (which cause highly penetrant cancer syndromes) are the cause of only about 1 percent of cancers .

= = = Frequencies of epimutations in DNA repair genes = = =

Deficiencies in DNA repair enzymes are occasionally caused by a newly arising somatic mutation in a DNA repair gene , but are much more frequently caused by epigenetic alterations that reduce or silence expression of DNA repair genes . For example , when 113 colorectal cancers were examined in sequence , only four had a missense mutation in the DNA repair gene MGMT , while the majority had reduced MGMT expression due to methylation of the MGMT promoter region (an epigenetic alteration) . Five different studies found that between 40 % and 90 % of colorectal cancers have reduced MGMT expression due to methylation of the MGMT promoter region .

Similarly , out of 119 cases of mismatch repair @-@ deficient colorectal cancers that lacked DNA repair gene PMS2 expression , PMS2 was deficient in 6 due to mutations in the PMS2 gene , while in 103 cases PMS2 expression was deficient because its pairing partner MLH1 was repressed due to promoter methylation (PMS2 protein is unstable in the absence of MLH1) . In the other 10 cases , loss of PMS2 expression was likely due to epigenetic overexpression of the microRNA , miR @-@ 155 , which down @-@ regulates MLH1 .

In further examples (tabulated in Cancer epigenetics) , epigenetic defects were found at frequencies of between 13 % -100 % for the DNA repair genes BRCA1 , WRN , FANCB , FANCF , MGMT , MLH1 , MSH2 , MSH4 , ERCC1 , XPF , NEIL1 and ATM . These epigenetic defects occurred in various cancers (e.g. breast , ovarian , colorectal and head and neck) . Two or three deficiencies in the expression of ERCC1 , XPF or PMS2 occur simultaneously in the majority of the 49 colon cancers evaluated by Facista et al .

The chart in this section shows some frequent DNA damaging agents , examples of DNA lesions they cause , and the pathways that deal with these DNA damages . At least 169 enzymes are either directly employed in DNA repair or influence DNA repair processes . Of these , 83 are directly employed in the 5 types of DNA repair processes illustrated in the chart . The more well studied genes central to these repair processes are also shown in the chart . As indicated by the DNA repair genes shown in red , many of the genes in these repair pathways are regulated by epigenetic mechanisms , and these are frequently reduced or silent in various cancers (marked by an asterisk) . Two review articles , and two broad experimental survey articles document most of these epigenetic DNA repair deficiencies .

It appears that epigenetic repression of DNA repair genes in accurate DNA repair pathways are

central to carcinogenesis . However microhomology @-@ mediated end joining (MMEJ) is an additional error @-@ prone repair pathway for double @-@ strand breaks . In MMEJ repair of a double @-@ strand break , an homology of 5 - 25 complementary base pairs on both strands is identified and used as a basis to align the strands , but with mismatched ends . MMEJ removes extra nucleotides (flaps) where strands are joined , then ligates the strands to create an intact DNA double helix . MMEJ always involves at least a small deletion , so that it is a mutagenic pathway . FEN1 , the flap endonuclease in MMEJ , is epigenetically increased by promoter hypomethylation and is over @-@ expressed in the majority of cancers of the breast , prostate , stomach , neuroblastomas , pancreatic , and lung . Other genes in the MMEJ pathway are also over @-@ expressed in a number of cancers (see MMEJ for summary) , and are shown in cyan (blue) in the chart in this section .

= = DNA repair and evolution = =

The basic processes of DNA repair are highly conserved among both prokaryotes and eukaryotes and even among bacteriophage (viruses that infect bacteria) ; however , more complex organisms with more complex genomes have correspondingly more complex repair mechanisms . The ability of a large number of protein structural motifs to catalyze relevant chemical reactions has played a significant role in the elaboration of repair mechanisms during evolution . For an extremely detailed review of hypotheses relating to the evolution of DNA repair , see .

The fossil record indicates that single @-@ cell life began to proliferate on the planet at some point during the Precambrian period , although exactly when recognizably modern life first emerged is unclear . Nucleic acids became the sole and universal means of encoding genetic information , requiring DNA repair mechanisms that in their basic form have been inherited by all extant life forms from their common ancestor . The emergence of Earth 's oxygen @-@ rich atmosphere (known as the " oxygen catastrophe ") due to photosynthetic organisms , as well as the presence of potentially damaging free radicals in the cell due to oxidative phosphorylation , necessitated the evolution of DNA repair mechanisms that act specifically to counter the types of damage induced by oxidative stress .

= = = Rate of evolutionary change = = =

On some occasions , DNA damage is not repaired , or is repaired by an error @-@ prone mechanism that results in a change from the original sequence . When this occurs , mutations may propagate into the genomes of the cell 's progeny . Should such an event occur in a germ line cell that will eventually produce a gamete , the mutation has the potential to be passed on to the organism 's offspring . The rate of evolution in a particular species (or , in a particular gene) is a function of the rate of mutation . As a consequence , the rate and accuracy of DNA repair mechanisms have an influence over the process of evolutionary change . Since the normal adaptation of populations of organisms to changing circumstances (for instance the adaptation of the beaks of a population of finches to the changing presence of hard seeds or insects) proceeds by gene regulation and the recombination and selection of gene variations ? alleles ? and not by passing on irreparable DNA damages to the offspring , DNA damage protection and repair does not influence the rate of adaptation by gene regulation and by recombination and selection of alleles . On the other hand , DNA damage repair and protection does influence the rate of accumulation of irreparable , advantageous , code expanding , inheritable mutations , and slows down the evolutionary mechanism for expansion of the genome of organisms with new functionalities . The tension between evolvability and mutation repair and protection needs further investigation .

= = DNA repair technology = =

A technology named clustered regularly interspaced short palindromic repeat shortened to CRISPR @-@ Cas9 was discovered in 2012 . The new technology allows anyone with molecular biology

training to alter the genes of any species with precision .