Project Title

DNA damage repair systems

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Abstract

DNA, or deoxyribonucleic acid, is the hereditary material in humans and almost all other organisms. Nearly every cell in a person's body has the same DNA. Most DNA is located in the cell nucleus (where it is called nuclear DNA), but a small amount of DNA can also be found in the mitochondria (where it is called mitochondrial DNA or mtDNA). Mitochondria are structures within cells that convert the energy from food in-to a form that cells can use.

Introduction

DNA damage is distinctly different from mutation, although both are types of error in DNA. DNA damage is an abnormal chemical structure in DNA, while a mutation is a change in the sequence of standard base pairs. DNA damages cause changes in the structure of the genetic material and prevents the replication mechanism from function-ing and performing properly. DNA damage and mutation have different biological con-sequences. While most DNA damages can undergo DNA repair, such repair is not 100% efficient. Un-repaired DNA damages accumulate in non-replicating cells, such as cells in the brains or muscles of adult mammals and can cause aging. (Also see DNA damage theory of aging.) In replicating cells, such as cells lining the colon, errors occur upon replication past damages in the template strand of DNA or during repair of DNA damages. These errors can give rise to mutations or epigenetic alterations. Both of these types of alteration can be replicated and passed on to subsequent cell generations. These alterations can change gene function or regulation of gene expression and possi-bly contribute to progression to cancer.

Throughout the cell cycle there are various checkpoints to ensure the cell is in good condi-tion to progress to mitosis. The three main checkpoints are at G1/s, G2/m, and at the spindle assembly checkpoint regulating progression through ana-phase. G1 and G2 checkpoints in-volve scanning for damaged DNA. During S phase the cell is more vulnerable to DNA damage than any other part of the cell cycle. G2 check-point checks for damaged DNA and DNA replication completeness. DNA damage is an alteration in the chemical structure of DNA, such as a break in a strand of DNA, a base missing from the backbone of DNA, or a chemically changed base such as 8-OHdG. DNA damage can occur naturally or via envi-ronmental factors. The DNA dam-age response (DDR) is a complex signal transduction pathway which recognizes when DNA is damaged and initiates the cellular response to the damage.

Project Aim and Outline

1. What is DNA.
2. DNA structure
3. DNA damage
   - 3.1. Sources
   - 3.2 Types
   - 3.3 Nuclear versus mitochondrial
   - 3.4 Senescence and apoptosis
   - 3.5 Mutation
4. DNA repair systems

Results

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. Un-like 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.

Sources

DNA damage can be subdivided into two main types:

1.endogenous damage such as attack by reactive oxygen species produced from normal metabolic byproducts (spontaneous mutation), especially the process of oxidative deamination

1.also includes replication errors

2.exogenous damage caused by external agents such as

1.ultraviolet [UV 200–400 nm] radiation from the sun

2.other radiation frequencies, including x-rays and gamma rays

3.hydrolysis or thermal disruption

4.certain plant toxins

5.human-made mutagenic chemicals, especially aromatic compounds that act as DNA intercalating agents

6.viruses

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 car-ry mutations from which the original DNA sequence is unrecoverable (except in the rare case of a back mutation, for example, through gene conversion).

Types:

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

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

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

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

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

5.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.

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 causes crosslinking between adjacent cytosine and thymine bases creating py-rimidine dimers. This is called direct DNA damage.

2.UV-A light creates mostly free radicals. The damage caused by free radicals is called indi-rect DNA damage.

3.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.

4.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.

5.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. Constitutive (spontaneous) DNA damage caused by en-dogenous oxidants can be detected as a low level of histone H2AX phos-phorylation in un-treated cells.

Nuclear versus mitochondrial

In human cells, and eukaryotic cells in general, DNA is found in two cellular locations – in-side the nucleus and inside the mitochondria. Nuclear DNA (nDNA) exists as chromatin during non-replicative stages of the cell cycle and is condensed into aggre-gate 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 chromo-somal 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 or-ganelles, exists in multiple copies, and is also tightly associated with a number of proteins to form a complex known as the nucleoid. Inside mitochon-dria, reactive oxygen species (ROS), or free radicals, byproducts of the constant pro-duction of adenosine triphosphate (ATP) via oxidative phosphorylation, create a highly oxidative environment that is known to damage mtDNA. A critical enzyme in counter-acting the toxicity of these species is superoxide dismutase, which is present in both the mitochondria and cytoplasm of eukaryot-ic 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). Senes-cence 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 in-appropriately 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 or-ganism. Therefore, the induction of senescence and apoptosis is considered to be part of a strategy of protection against cancer.

Mutation

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 re-sults in physical abnormalities in the DNA, such as single- and double-strand breaks, 8-hydroxydeoxyguanosine residues, and polycyclic aromatic hydrocarbon adducts. DNA damage can be recognized by enzymes, and thus can be correctly repaired if redundant in-formation, 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 fre-quency ac-cording 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 re-pair; 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, unre-paired 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 neu-tral in their effect are deleterious to a cell's survival. Thus, in a population of cells com-posing a tissue with replicating cells, mutant cells will tend to be lost. However, infre-quent 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.

Conclusions

DNA repair, any of several mechanisms by which a cell maintains the integrity of its genetic code. DNA repair ensures the survival of a species by enabling parental DNA to be inherited as faithfully as possible by offspring. It also preserves the health of an in-dividual. Mutations in the genetic code can lead to cancer and other genetic diseases.

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Successful DNA replication requires that the two purine bases, adenine (A) and guanine (G), pair with their pyrimidine counterparts, thymine (T) and cytosine (C). Different types of damage, however, can prevent correct base pairing, among them spontaneous mutations, replication errors, and chemical modification. Spontaneous mutations occur when DNA bases react with their environment, such as when water hydrolyzes a base and changes its structure, causing it to pair with an incorrect base. Replication errors are minimized when the DNA replication machinery “proofreads” its own synthesis, but sometimes mismatched

base pairs escape proofreading. Chemical agents modify bases and interfere with DNA replication. Nitrosamines, which are found in products such as beer and pickled foods, can cause DNA alkylation (the addition of an alkyl group). Oxidizing agents and ionizing radiation create free radicals in the cell that oxi-dize bases, especially guanine. Ultraviolet (UV) rays can result in the production of damaging free radicals and can fuse adjacent py-rimidines, creating pyrimidine dimers that prevent DNA replication. Ionizing radiation and certain drugs, such as the chemo-therapeutic agent bleomycin, can also block replication, by creating double-strand breaks in the DNA. (These agents can also create single-strand breaks, though this form of damage often is easier for cells to overcome.) Base analogs and intercalating agents can cause abnormal insertions and deletions in the sequence.

There are three types of repair mechanisms: direct reversal of the damage, excision re-pair, and postreplication repair. Direct reversal repair is specific to the damage. For ex-ample, in a process called photoreactivation, pyrimidine bases fused by UV light are separated by DNA photolyase (a light-driven enzyme). For direct reversal of alkylation events, a DNA methyltransferase or DNA glycosylase detects and removes the alkyl group. Excision repair can be specific or nonspecific. In base excision repair, DNA gly-cosylases specifically iden-tify and remove the mismatched base. In nucleotide excision repair, the repair machinery recognizes a wide array of distortions in the double helix caused by mismatched bases; in this form of repair, the entire distorted region is ex-cised. Postreplication repair occurs downstream of the lesion, because replication is blocked at the actual site of damage. In order for replication to occur, short segments of DNA called Okazaki fragments are synthesized. The gap left at the damaged site is filled in through recombination repair, which uses the sequence from an undamaged sister chromosome to repair the damaged one, or through error-prone repair, which uses the damaged strand as a sequence template. Error-prone repair tends to be inaccurate and subject to mutation.

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