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BIOCHEMISTRY

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1. MUTAGENESIS

Mutagenesis is a process by which the genetic information of an organism is changed, resulting in a mutation. It may occur spontaneously in nature or as a result of exposure to mutagens. It can also be achieved experimentally using laboratory procedures. In nature mutagenesis can lead to cancer and various heritable diseases, but it is also a driving force of evolution. Mutagenesis may occur endogenously, for example, through spontaneous hydrolysis, or through normal cellular processes that can generate reactive oxygen species and DNA adducts, or through error in replication and repair. Mutagenesis may also arise as a result of the presence of environmental mutagens that induce changes to the DNA. The mechanism by which mutation arises varies according to the causative agent, the mutagen, involved. Most mutagens act either directly or indirectly via mutagenic metabolites, on the DNA producing lesions. Some, however, may affect the replication or chromosomal partition mechanism, and other cellular processes.

Many chemical mutagens require biological activation to become mutagenic. An important group of enzymes involved in the generation of mutagenic metabolites is cytochrome P450. Other enzymes that may also produce mutagenic metabolites include glutathione S-transferase and microsomal epoxide hydrolase. Mutagens that are not mutagenic by themselves but require biological activation are called promutagens.

Many mutations arise as a result of problems caused by DNA lesions during replication, resulting in errors in replication. In bacteria, extensive damage to DNA due to mutagens results in single-stranded DNA gaps during replication. This induces the SOS response, an emergency repair process that is also error-prone, thereby generating mutations. In mammalian cells, stalling of replication at damaged sites induces a number of rescue mechanisms that help bypass DNA lesions, but which also may result in errors. The Y family of DNA polymerases specializes in DNA lesion bypass in a process termed translesion synthesis (TLS) whereby these lesion-bypass polymerases replace the stalled high-fidelity replicative DNA polymerase, transit the lesion and extend the DNA until the lesion has been passed.

In genetics, a mutagen is a physical or chemical agent that changes the genetic material, usually DNA, of an organism and thus increases the frequency of mutations above the natural background level. As many mutations can cause cancer, mutagens are therefore also likely to be carcinogens, although not always necessarily so. Some chemicals only become mutagenic through cellular processes. Not all mutations are caused by mutagens. So-called "spontaneous mutations" occur due to spontaneous hydrolysis, errors in DNA replication, repair and recombination. so that normal replication can resume. These processes may be error-prone or error-free.

1. MUTATION

A mutation is the permanent alteration of the nucleotide sequence of the genome of an organism, virus, or extra chromosomal DNA or other genetic elements.

Mutations result from errors during DNA replication or other types of damage to DNA (such as may be caused by exposure to radiation or carcinogens), which then may undergo error-prone repair (especially microhomology-mediated end joining), or cause an error during other forms of repair or else may cause an error during replication (translesion synthesis). Mutations may also result from insertion or deletion of segments of DNA due to mobile genetic elements. Mutations may or may not produce discernible changes in the observable characteristics (phenotype) of an organism. Mutations play a part in both normal and abnormal biological processes including: evolution, cancer, and the development of the immune system, including junctional diversity.

The genomes of RNA viruses are based on RNA rather than DNA. The RNA viral genome can be double stranded (as in DNA) or single stranded. In some of these viruses (such as the single stranded human immunodeficiency virus) replication occurs quickly and there are no mechanisms to check the genome for accuracy. This error-prone process often results in mutations.

Mutation can result in many different types of change in sequences. Mutations in genes can have no effect, alter the product of a gene, or prevent the gene from functioning properly or completely. Mutations can also occur in non-genic regions. One study on genetic variations between different species of Drosophila suggests that, if a mutation changes a protein produced by a gene, the result is likely to be harmful, with an estimated 70% of amino acid polymorphisms that have damaging effects, and the remainder being either neutral or marginally beneficial. Due to the damaging effects that mutations can have on genes, organisms have mechanisms such as DNA repair to prevent or correct mutations by reverting the mutated sequence back to its original state.