Genetic mutations result in faulty proteins

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The DNA sequence codes for a particular gene which is then copied into a protein sequence code. Protein is found in every cell in human body and has a vital role in cell growth and tissue repair. The amino acids are the building blocks of proteins which are arranged in a specific order to determine the protein’s shape and function.

The incorrect amino acid sequence leads to harmful consequences because it can lead to the formation of faulty proteins which can cause disruption in metabolic and regulatory pathways which cause genetic disorders (1).

Genetic mutation is a change in genomic sequence which encodes DNA. It can be either inherited or somatic mutation. Somatic mutations are introduced either during DNA replication or when the DNA repair process fails.

Agents which damage DNA are frequent carcinogens. Most carcinogenic agents are mutagens. There are two classes of mutations caused by mutagens. The first class is spontaneous mutations caused by depurination, deamination and demethylation(3). The second class is induced mutations

caused by ionizing radiation, chemical mutagens and ultra violet radiation(3).

Mutation during DNA replication

Before cell divides, cell duplicates its entire DNA sequence. To start DNA replication, the DNA helicase separates the DNA molecule into two strands. Then DNA polymerase copies each strand of DNA in order to create two double-stranded DNA molecules. Somatic mutation occurs when this DNA polymerase makes an error in copying which takes place once every 100, 000, 000 bases (4).

Mutation effects

Single base substitution: The consequences of single base substitution mutation depend on the location of the protein which can lead to either silent mutation, missense mutation or a non-sense mutation.

Silent mutations are those which don’t produce any change in an amino acid sequence of a protein. They occur in that region that either doesn’t code for a protein or doesn’t alter the final sequence of amino acid chain. For example GCA codon turns into GCG codon as in result of single nucleotide replacement because both GCA and GCG codons mean arginine in mRNA (8).

Missense mutations involve a change in a single nucleotide to cause substitution of a different amino acid. This can result into a non-functional protein. Sickle cell anemia is an example of missense mutation where CTC in the DNA sense strand specifies glutamate residue get altered with GUG in the mRNA which results in a Valine residue in the protein causing sickle-cell anemia (8).

Non-sense mutations are those which results in a premature stop codon leading to the formation of a non-functional protein. An example for non-sense mutation is a single nucleotide replacement from C to T in codon CAG which forms a stop codon TAG. This incorrect sequence causes the shortening of protein (8).

Frameshift mutation: This mutation is the result of an insertion or a deletion of one or more nucleotides from the DNA sequence but not in multiples of three because bases in set of three forms a codon which provides the code for an amino acid sequence of the protein. So as DNA polymerase read the triplet nature of codon so an insertion or a deletion can disrupt its reading frame which results into a completely different translation done by the DNA polymerase (8+6).

Chromosome mutation: Any change either in structure or arrangement of chromosomes is a chromosome mutation which frequently occurs in meiosis during crossing over. The different types of chromosome mutation are:-

Translocation: In this mutation, a piece of one chromosome gets transferred to a non-homologous chromosome. For example when translocation between chromosomes 9 and 22 takes place, an abnormal gene forms which codes for an abnormal faulty protein resulting the development of leukaemia (8).

Inversion: During this mutation, a DNA region on a chromosome flips its orientation leading the formation of an abnormal gene which then codes for a faulty abnormal protein.

Deletion: In this mutation, a chromosome section gets deleted which results in the loss of genes (6).

Duplication: During this mutation, some genes get duplicate and get read twice by the DNA polymerase on the same chromosome resulting in the formation of a faulty abnormal protein (6).

Non-disjunction: This is when chromosomes don’t separate successfully to opposite poles at anaphase stage during meiosis which allows the presence of an extra chromosome in one of the daughter cells. Downs syndrome is an example of non-disjunction which occurs in chromosome 21 of a human egg cell (8).

Removal of faulty proteins

In eukaryotic cells, faulty proteins are recognized and degraded very rapidly in cells to prevent any harmful consequences. The two major faulty protein destruction pathways are:-

Ubiquitin-proteasome pathway for faulty intracellular proteins:

In the case of formation of faulty proteins which are defective get ejected into the proteasome from the endoplasmic reticulum through channels called retrotranslocons.

Proteasome is a large multi-catalytic protein complex found in all eukaryotes which is located in nucleus and cytoplasm. It is responsible to degrade faulty intracellular proteins through proteolysis(2). The enzymes which carry out proteolysis are known as proteases. Those intracellular proteins which need to go under degradation get tagged with another small protein called

ubiquitin(2). Ubiquitin binds to the amino group of the side chain of a lysine residue. This tagging process is catalyzed by ubiquitin ligase. Once the protein gets tagged, a signal gets released to other ligases allowing more ubiquitin molecules to attach to form a poly-ubiquitin chain. Poly-ubiquitin chain then bound by the 26s proteasome complex which leads to the degradation of tagged protein(7). Ubiquitin does get released which that can be reused in next cycle. However ATP is used for the attachment of ubiquitin and for the degradation of tagged proteins (5).

Lysosomal proteolysis for faulty extracellular proteins:

Lysosomes are membrane-enclosed cellular organelles in animals containing digestive enzymes and proteases. They have important roles in cell metabolism including the digestion of extracellular proteins taken up through endocytosis.

So during this protein degradation pathway, the protein is uptaken by lysosomes through the formation of vesicles derived from endoplasmic reticulum called “ autophagosomes”. Then these autophagosomes fuse with lysosomes so in result the digestive lysosomal enzymes digest their contents (5).