Human Gene Replication - BRCA1

The human body is incredible in its biological reactions that are constantly occurring within us to keep us alive and functioning well. A crucially important combination of processes in molecular genetics can be explained through the concept of the Central Dogma. This includes DNA replication, transcription and translation. It is necessary to understand them because they play a significant role in the existence of diseases and disorders. Using the gene BRCA1 as an example, let's take a look at the general journey of this gene.

BRCA1 is a gene found on the human chromosome seventeen (BRCA1 gene, 2018). It is found in breast epithelial cells, and codes for a protein made up of one thousand eighteen hundred sixty three amino acids in humans (Deng, 2006). In order to be converted into its gene product of a functioning protein, the gene must first be replicated. Thus, the first step in the process is DNA replication which takes place within the nucleus of the cell.

Before the replication can begin, the DNA strands must be unwinded slightly first, which is done by the enzyme gyrase. Once this happens, helicase is another vital enzyme that quickly comes in to separate the double helix and create a replication fork by breaking apart the hydrogen bonds between them.

Single Strand Binding Proteins (SSBs) are present to ensure the strands do not come back together. Once the strands are separated, primase produces RNA primers that initiates DNA Polymerase function to start replicating. Since DNA Polymerase 3 only builds in the 5' to 3' direction, this creates a leading and a lagging strand. The leading strand is the one that goes in the 5' to 3' direction, and thus builds continuously by having complementary bases added by the DNA Polymerase 3. On the opposite hand, the lagging strand is constructed discontinuously by binding to numerous primers, forming what are known as Okazaki fragments. Another enzyme called DNA Polymerase 1 replaces the RNA primers with their complementary bases, and proof reads for any errors during the end of the replication. The removal of the primers allows for ligase to connect the Okazaki fragments by creating phosphodiester bonds between them. In the final step, replication is stopped when the protein TUS (termination utilization substance) binds

to the terminator sequences in order to prohibit helicase from unwinding the DNA any more (Basic requirements for DNA synthesis, n.d).

The next step in the Central Dogma to turn the gene into the protein is transcription. This also occurs in the nucleus. During this, the DNA is turned into RNA in order to move it out of the nucleus and to the ribosome. The original copy of the DNA cannot be sent out because it is too valuable to be exposed to any harm in the cytoplasm. RNA polymerase is the main enzyme here that is responsible to copy the part of the DNA that contains the BRCA1 gene into RNA. The original DNA strand going in the 5' to 3' direction becomes the template strand from which the new RNA strand is built using complementary bases. This copied strand is identical to the coding strand, with the exception of thymine being replaced with uracil. The RNA Polymerase binds to the specific BRCA1 promoter, which essentially directs the enzyme to the right location to begin transcribing the gene once a transcription bubble is formed (Stages of transcription, n.d). Once transcription has started, elongation takes place where the new strands gets longer and longer as a result of adding nucleotides. Transcription keeps going until it reaches a specific DNA sequence that signals a stop, known as the terminator sequence. The end product of this process is mRNA, which will go through some post transcriptional modifications. Since BRCA1 has twenty four exons, they are separated from introns through splicing by specific enzymes called spliceosomes (Deng, 2006). However, before the mRNA is sent out of the nucleus, it is provided with a poly A tail on the 3' end and a GTP cap on its 5' end for protection against degradation or damage from the cytoplasm.

Now the mRNA is ready to be translated into a protein at the ribosome. The mRNA has nucleotides that are known as "codon" each of which represent an amino acid. Three bases are read at a time to build the appropriate protein. The process of translation is started with the AUG codon that codes for start. The tRNA is critical here, as it transports amino acids to the mRNA. This is made possible because of the three nucleotides at the other end of the tRNA that are anticodons which attach themselves to specific codons on the mRNA (Overview of translation, n.d). The first step is initiation: this is where the ribosome encircles the mRNA and the tRNA

binds to the start codon which codes to the amino acid called methionine. The second step is elongation; here amino acids are added to keep the chain growing and this causes a shift in the position of codons, one at a time. The ribosome contains three spots that the tRNA moves through to transport the amino acids (tRNAs and ribosomes, n.d). The landing location is known as the A-site, or the acceptor site where peptide bonds are formed. The P-site is where peptide chain keeps growing, and the E-site is where the tRNA exits after carrying the transported amino acids (Burkhardt, Junemann, Spahn, Nierhaus, 2008). Next is translocation, where the tRNA moves through the different sites and the ribosome is translocated from the 5' to 3' end. And finally, the final step is termination. At this point, the 'stop' codon must be processed, and the polypeptide chain is released from the ribosome.

Many proteins also undergo additional chemical changes after translation to achieve the mature protein product. These are known as post-translational modifications, which are catalyzed by enzymes that recognize target sequences in certain proteins. This is also important in supervising the three dimensional folds of the protein (Burkle, 2001). For the BRCA1 gene, it undergoes several post-translational modifications such as phosphorylation, ubiquitination and SUMOylation (Henderson, 2012). The gene product of BRCA1 is a tumor suppressor, whose protein product works with other proteins to repair damaged DNA and maintains stability in the cell's genetic information. As a tumor suppressor, it prevents rapid and uncontrolled cell growth. Any mutations on this gene increase chances of developing breast cancer as the suppressor is unable to perform its duty properly (BRCA1 gene, 2018). Therefore, this gene is incredibly important as it holds the outcome of a fatal disease, and its mutations can be recognized through different screening tests.

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