**DNA damage response with in the Cell.**

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**Abstract:**

DNA is constantly replicating in the living cells. These cells replicate under several conditions that might in turn influence the DNA and cause mutations. These mutated genome cells give rise to cancer cells lines. Apart from other DNA damage repair pathways so far studied, another aspect of damage repair has been found. This is called the self-destruction of the mutated cells or apoptosis.p53 a tumor suppressor protein in involved in the damage repair system. However on mutation it lacks the repairing ability. Another long noncoding RNA(lncRNA) molecule has been discovered known as DINO that stabilizes the p53 and starts apoptosis when the cell is accumulated with sufficient damage.

**Introduction:**

Living cells have evolved a series of enzymatic systems that repair the DNA damage in a variety of ways. Failure of these mechanisms leads to an extremely higher number of mutations that a cell can under go. A number of human diseases can be attributed to the defects in the DNA repair system. Some enzymatic systems involve the direct neutralization of the mutation/damage causing chemicals like the super oxide dismutase catalyze the conversion of the super oxide radicles to hydrogen peroxide and the enzyme catalase in turn convert hydrogen peroxide in to water thus safeguarding the DNA from getting damaged.

Other pathways involve the direct reversal of the damage which is sometimes not possible since some of the damages are irreversible. One case is a mutagenic photodimer caused by the UV light. The photo reactivating enzyme (PRE) repairs the damage made by the UV. It only works in the light therefore other complementary pathways are needed to rectify the damage. Alkyl transferases are also involved in the direct reversal of the genomic lesion.

The excision and repair method is another option for repairing of the damaged part of the DNA. This involves the specific endonucleases to perform the task at the damaged site. There are also post replication methods of removing the mismatched base pairs. However it is very essential for the cellular machinery to identify the damage because the cells with the damaged genome at times begin to defy the standard rules for growth and become cancerous. Certain cellular components have been identified which are involved in the genomic correction. Eventually they safe guard the cell from becoming cancerous.

**Recent Progress:**

Now researchers have discovered a new candidate in this game of genome rectification in the form of unique regulatory RNA that has been named DINO (Damage Induce Noncoding). DINO is a member of a group of RNA known as lncRNAs (long noncoding RNAs). These molecules have been associated with a mounting number of critical regulatory roles in the cell. This is the first time that lncRNA has been shown in the association with DNA damage repair because being an RNA, it is synthesized in the nucleus where p53 is active. This lncRNA (long noncoding RNA, transcribed from DNA but does not get translated) molecule binds to p53 a well-known tumor suppressor protein and stabilize it. This protein when mutated, results in one of the most potent tumor causing protein. It is therefore essential to keep track of the culprit genes and mutations in the cell.

However this seems to be a problem for the cells to remain in constant check which may halter the normal growth of the cell. This can ultimately result in the cell apoptosis. This DINO protein is the integral part of the decision making process. To elaborate the results, human fibroblast cells were examined in control and experimental conditions by exposing some of the cells to DNA-damaging chemotherapy drug doxorubicin. This resulted in the production of RNA DINO in large quantities almost up to 100 folds. Once the cell accumulated a sufficient amount of genomic damage, the DINO RNA comes into action and stabilizes the p53 protein so that it can initiate the process of apoptosis.

The expression and function of this DINO RNA is being explored in order to understand the flip and switch model of the DNA damage repair. Because there are several small mutations that are being developed in a cell that are usually harmless, therefore the cell cannot initiate apoptosis every time. On the same time if an abnormal cell left unchecked in to the body will develop into a cancer cell line.

In further experiments with mice, it was found that on exposure to a lethal dose of radiations, mice lacking DINO (the mouse version of the lncRNA) lived longer as compared to the normal mice that expressed DINO. This indicated that their cells were taking longer to detect the damage caused by the radiation exposure. Although they died eventually after exposure. The alteration of the damage response in this situation is captivating for its potential use in radiation therapy for cancer treatment. Mutations are recognized by the cell immediately and rectified. p53 plays its essential role at this stage. It responds to the DNA damage by increasing the expression of the genes that are involved in the repair mechanism, hence acting as a tumor suppressor. Once mutated, p53 loses its ability to control the cell’s damage repair system.

It is concluded from the above conducted research that the DINO expression allows the cell to fine tune its response to the DNA damage and respond appropriately. It may provide a major rapid, accurate and precise response to the DNA damage as compared to the regulatory protein which would be synthesized in cytoplasm.

It is also believed that this DINO may play a role in cancer development and possibly premature aging by modulating how a cell responds to DNA damage. This DINO association with the tumor suppressor p53 and subsequent apoptosis of the cancerous cells in a positive feedback loop has given hope for future advancement in cancer treatment.

**Discussion:**

The overall DNA damage repair system of the cell plays a vital role in the maintenance of a specific cell line. It promotes genomic stability. Loss of large number of damage repair genes result in increased frequencies of cancer. DNA damage repair is also relevant to the effectiveness of classic therapeutic treatments such as radio therapy and chemotherapy. This is because these therapies are based upon the induction of DNA damage. This induction triggers DNA damage repair- dependent cell death especially in proliferating cells. As many tumors become defective in some aspect of the DNA damage repair, they turn out to be more dependent on other repair components. Cancer treatments aimed for inhibiting key components are being evaluated in clinical trials.

Another crucial aspect of DNA damage repair is when somatic cells exceed their intended proliferated lifetime as in cancer cells. In these cells telomeric ends of the chromosomes get shorten and are sensed as DNA damage. Thus DNA damage repair system is activated. The cell is informed to undergo apoptosis or differentiation. Both are tumor suppressive mechanisms. Hence DNA damage repair acts as a barrier to tumorigenesis. It also acts to promote aging and aging related diseases.

The basic concept of correcting the mutation right at the point is very important. Development in the related field is leading to the understanding of the mechanism in detail. Positive feedback loops are utilized in many applications including engineering, to increase the sensitivity of systems and apply inceptions for action.

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