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IMPORTANCE OF HPV IN DEVELOPMENT OF CANCER: MINI REVIEW

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INTRODUCTION

HPV enters the skin or mucosa through breaks in the surface (even those not visible to the naked eye). Once inside, HPV infects host epithelial cells, it produces new viruses. In the process of healthy cell replacement, the infected cells are shed, releasing viral particles. Although this is not a normal part of the HPV life cycle, high risk strains of HPV can combine viral DNA into the host genome. Infected host cells get a selective advantage from viral integration leading to a longer infection time. As long as the infection lasts, the more time there is for cancer to develop. The human papillomaviruses (HPV) have a heterogeneous group of more than 130 epitheliotropic genotypes, 16 of which are considered "high-risk" types and linked with the development of malignant disease. HPV 16 and HPV 18, are high-risk types, with the main etiological agents of cervical cancer. HPV 16 is involved in about half of all cases of cancer.[1] HPV are responsible for approximately half a million new cervical cancer with Head and neck squamous cell carcinoma as the eighth most common cancer.[2] Almost 250,000 deaths per year, occur in developing countries.[1]

Life Cycle of Papillomaviruses

The HPV genome is a double-stranded circular DNA molecule of 8,000 base pairs (bp) that encodes up to ten proteins. Only one DNA strand is transcribed into mRNA. The genome is divided into three portions: a ~4,000 bp region that encodes proteins primarily involved in

viral DNA replication and cell transformation; a ~3,000 bp region that encodes the structural proteins of the virus particles; and a ~1,000 bp non coding region that contains the origin of viral DNA replication and transcriptional regulatory elements. The dominance of HPV 16 prevails in both the cervical and oral squamous cell carcinoma. The rate of spontaneous mutagenesis in normal human cells is exceedingly low, but the expression of high-risk HPV E6/E7 proteins dramatically augments genomic instability.[2]

Risk Factors

1. Exposition to exogenic carcinogens.
2. Number of sexual partners.
3. Weakened immune systems
4. Genetic factors

How HPV is responsible in causing cancer?

The development of normal human cells mostly depends on the information contained in the cells chromosomes. Chromosomes are large molecules of DNA. DNA is the chemical that carries the instructions for nearly everything our cells do. As we usually look like our parents because they are the source of our DNA. However, DNA affects more than the way we look.

Some genes (packets of our DNA) have commands for resting while our cells grow and divide. *Oncogenes* promote cell division. Others that slow down cell division or cause cells to cease at the right time are called *tumor suppressor genes*. Cancers can be resulting from DNA mutations (gene defects) that turn on oncogenes or turn off tumor suppressor genes.

HPV causes the production of 2 proteins known as E6 and E7 which turn off some tumor suppressor genes. This could allow the cervical lining cells to grow too much and to expand modifications in additional genes, which in some cases will result to cancer.

Evidence from laboratory and epidemiological studies has shown an association between human papillomavirus (HPV) infection and both cervical cancer and pre-cancerous neoplasias. High-risk HPV types like HPV 16 and 18 have been strongly linked to cervical carcinoma. In addition to HPV 16[3] being common in the general population, it remains among the most prevalent individual type in cervical neoplasias.

Viral integration promotes the disruption of the HPV E2 gene leading to unregulated increases in the E6 and E7 proteins. These viral proteins of oncogenic HPVs inactivate the

products of p53 and Rb tumor suppressor genes, respectively. The tumor suppressor gene functions include regulation of the cell cycle and the cellular response to DNA damage, initiation of DNA repair status of viral DNA and p53 gene alterations. In most cervical immortalized cells, high risk HPV DNA often integrates into the cellular genome. The integration is processed throughout the E2 gene by disrupting some part of it and causing over expression of the E6 and E7 proteins. This results in the loss of anti oncogenic function in p53 and Rb proteins.[4] The p53 gene mutation is induced by various etiological agents and threat factors with its implications towards HNSCC.[5]

Infection with high-risk human papillomavirus types is frequent among sexually active women, with incidence ranging from 15 to 40%.[3] However, the majority of the infections are found to be transient because most individuals develop a specific immune response. When the infection persists, precancer lesions may develop. About 1% of the general population presents genital warts and 4% of all women have cervical precancerous lesions. Another remarkable finding is the high rate of HIV-positive women who are infected with human papillomavirus heterosexual transmission without using a condom is the main route to female human immunodeficiency virus infection. The presence of other sexually transmitted diseases, such as human papillomavirus infection, promotes breaks in the genital tract and increases the susceptibility to acquiring the human immunodeficiency virus.[4] Likewise head and neck squamous cell carcinoma (HNSCC) is the fifth most prevalent cancer worldwide. Apart from various known clinicopathogical factors, it is still a major concern as many genetic and epigenetic alterations bring about the possibility of this deadly disease.[5]

Impact on DNA damage with Genetic polymorphisms and repair

Every cell of human is exposed to spontaneous oxidative damages to approximately 10000 bases. Cell death or mutations and malignant transformation causing cancer are due to failure of the cell's response to DNA damage. Cells are equipped with a number of efficient DNA repair systems evolutionary to maintain genomic integrity. Various pathways[5] are shown below:

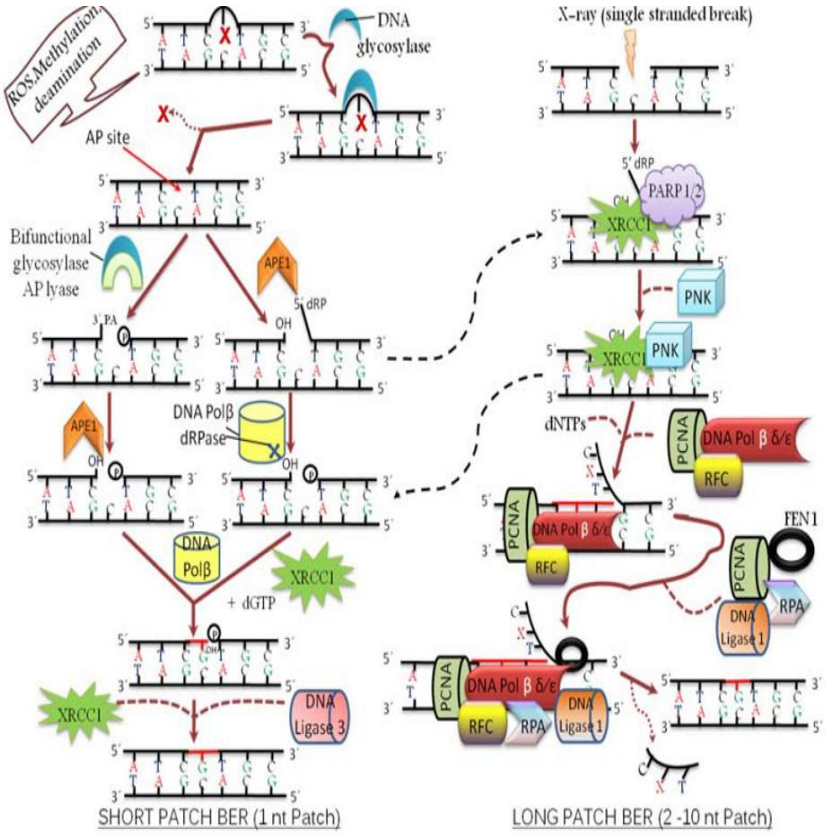

Figure 1. (Base excision repair) BER pathway.

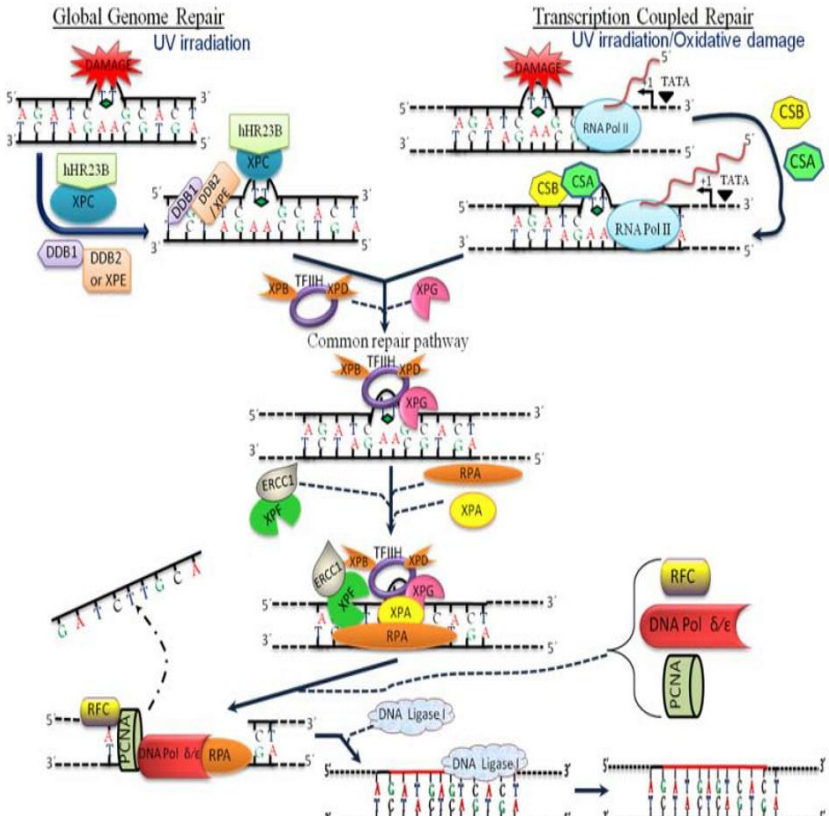

Figure 2. (Nucleotide excision repair) NER pathway.

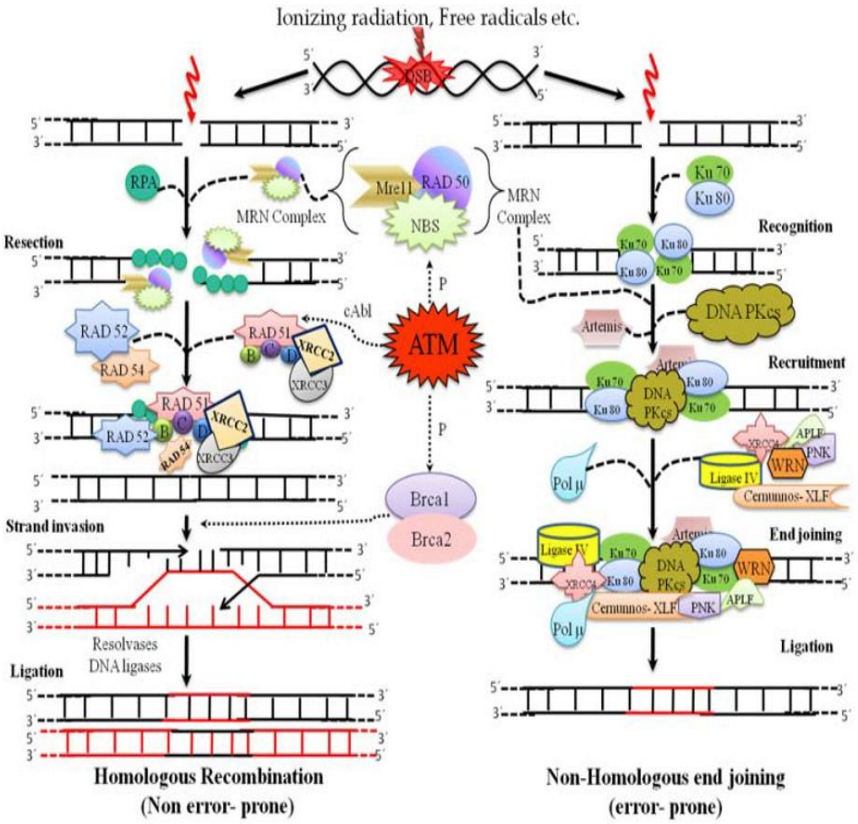

Figure 3. (DNA double strand breaks) DSB repair pathway.

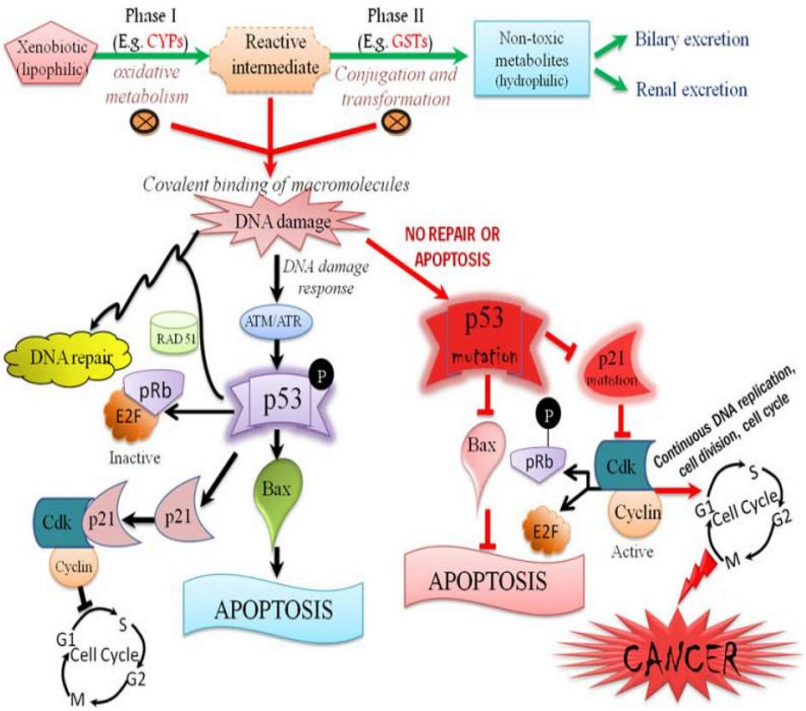

Figure 4. A schematic representation of the p53 pathway and its mechanism of action during DNA damage repair and cell cycle progression.

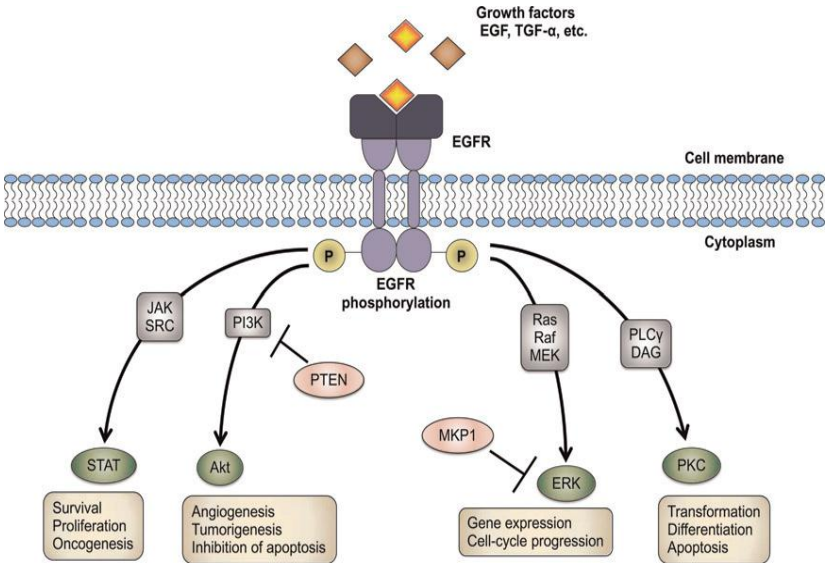

Figure 5. The EGFR signaling pathway.[6]

Novel Strategies in the Treatment of Patients with Head and Neck Squamous Cell Carcinoma[7]

1. Targeting the Epidermal Growth Factor Receptor Pathway
2. Vaccine Strategies

CONCLUSION

Due to lack of clear symptoms the first phase of cancer is often misidentified, but with the advent of powerful bioinformatic tools like proteomics, genomics, transcriptomics, metabolomics, peptidomics, glycomics and lipidomics have helped to fight the cancer. The pre-detection of cancer, development of biomarkers, identification of cell growth signals, cell death by apoptosis, and cellular metabolism can be easily established, thereby providing a helping hand.[3]

Early detection of cancer increases a patient's survival rate by five year with standard therapy alone. As a result, current research in therapeutics for advanced, cancer patients have been focused on new treatment modalities that exploit biological differences between tumor and normal cells. These therapies include vaccination, monoclonal antibodies, molecular inhibitors, gene therapy and photodynamic therapy.

Apart from a sound knowledge of all such measures, cancer therapeutics is still in their infancy and further research along with increased public awareness is needed.

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