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Tumor Suppressor Genes and Its Role in Cancer – A Review.

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ABSTRACT

Cancer as commonly used synonym for malignant neoplasm is a family of diseases concerned with up-regulation of cell growth involving multiple mutations at both the genetic as well as phenotypic levels. The tumor suppressor genes are one of the most important of the normal regulatory genes which are highly mutated and plays main role in carcinogenesis. The most commonly mutated tumor suppressor genes are P53 gene and RB gene. Some of the other tumor suppressor genes are APC, BRCA1, BRCA2 etc. This review helps in understanding the tumor suppressor genes and their role in cancer.

Key words: Cancer, Tumor suppressor gene, P53 gene, RB gene

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INTRODUCTION

Cancer has been a major source of mortality in Global population affecting millions of people every year. The most common cancers are the breast, lung, brain, pancreatic and head and neck cancer today. The mechanism of these different types of cancer is almost the same involving basics steps of DNA damage, mutations and alterations in all the normal regulatory genes leading to clonal expansion and tumor progression. The 6 main hall marks of carcinogenesis include self sufficiency in growth signals, insensitivity to anti-growth signals, limitless replicative potential, sustained angiogenesis, evading apoptosis and tissue invasion and metastasis [1]. Tumor suppressor genes are the proteins which are mainly responsible for the regulation of cell cycle. The most commonly mutated genes are the p53 or TP53 and Retinoblastoma (RB) gene. Some other examples of tumor suppressor genes include APC, BRCA1, BRCA2, CD95, ST5, ST7, ST14, PTCH, NF1, NF2 etc. These genes are essential for the continuing of cell cycle by inhibiting cell division.

P53 Gene

The p53 tumor suppressor gene was first identified in 1979 as a transformation related protein and a cellular protein accumulating in the nuclei of cancer cells [2-5]. With subsequent studies in the past, p53 became the most commonly mutated gene in almost all human cancers with the main functions of cell-cycle regulation, induction of apoptosis, gene amplification and cellular senescence. Hence, based on various research and studies in the past on wild-type p53 (wt p53), it was rightfully designated as “guardian of the genome” and presently they can be identified in more than 50% of all human cancer [2, 6, 7.]

The p53 tumor suppressor gene actually belongs to a unique protein family that includes three members: p53, p63 and p73 and among which the p53 seems to have evolved in higher organisms for the prevention against tumor development[8-10]. Human p53 is a protein which has a molecular weight of 53kDa and located on the small arm (p) of chromosome 17 [11, 12]. It can induce cell cycle arrest in G_1, G_2 and S phases of the cell cycle [13]. There are 2 key initiators of DNA damage in the form of protein kinases: ataxia-telangiectasia mutated (ATM) and ataxia-telangiectasia mutated related (ATR). However, the types of damage sensed by both are different but with a similar activation pathways. The p53 senses this DNA damage and helps in its repair by causing G_1 arrest and inducing DNA repair genes. If the DNA damage cannot be repaired, p53 induces cellular senescence or apoptosis [1] (Figure 1).

Cell with loss of p53, when undergo DNA damage fails to repair due to inactivation of p53 and with the help of multiple mutation lead to malignant tumor. In most all cases, inactivation of mutations affects both *p53* alleles which are acquired in somatic cells. However, in some individuals, they inherit a mutant *p53* allele causing the disease called Li-Fraumeni syndrome which develop at a relatively younger age leading to multiple tumors [1]. This p53 gene status in human tumors can be analyzed by four methods. They are by molecular analysis, immunohistochemical analysis, serological analysis and functional analysis [14].

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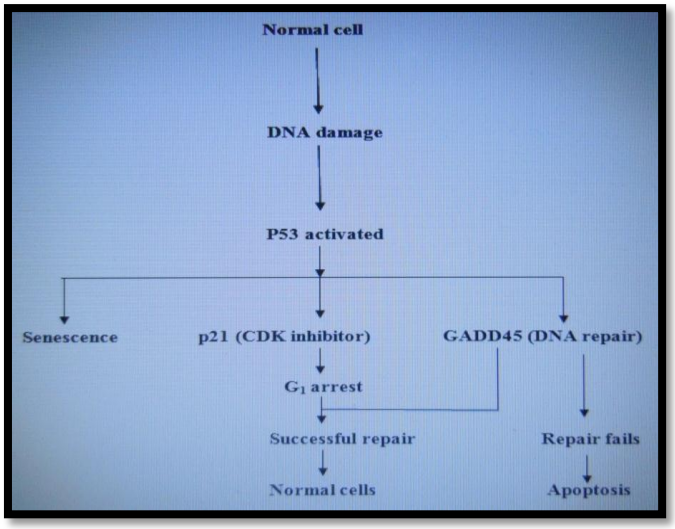

Figure 1: DIAGRAMMATIC REPRESENTATION OF ROLE OF P53 IN MAINTAINING THE INTEGRITY OF THE GENOME

RB Gene

The Retinoblastoma gene (RB gene) was the first tumor suppressor gene to be discovered and identified. The pRB (protein product of RB gene) is essential for retinal development in human. Retinoblastoma is a rare malignancy of developing retina affecting mainly children [15]. According to Knudson (1974), two mutations (hits) are required to produce retinoblastoma. In familial cases, it develops when the normal RB gene is lost in retinoblasts due to somatic mutations in them and in sporadic cases; both the normal RB alleles are lost by somatic mutations in one of the retinoblasts. A tumor develops only when it loses heterozygosity of the normal RB gene [1]. The pRB is a nuclear transcription factor which is generally regulated by phosphorylation through the cell cycle [15].

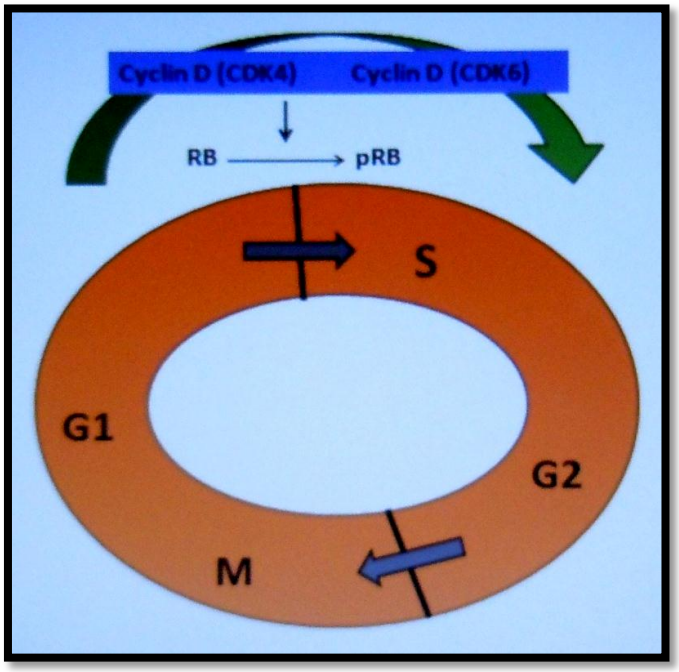

Figure 2: G_1 – S TRANSITION BY PHOSPHORYLATION OF RB PROTEIN (pRB)

The Human RB gene contains 27 exons within the 180 kb of genomic DNA and is located on chromosome 13q14 [1, 15]. The RB gene exists in an active hypophosphorylated and inactive hyperphosphorylated state. It exerts antiproliferative effects by controlling the transition of G_1 – S phase in the cell cycle. If there is a loss in cell cycle control, there is a chance of malignant transformation. Disabling of the G_1 checkpoint is seen in almost all cancer, by mutation the RB gene or the genes that affect its function such as cyclin D, CDK4 and CDKIs [1]. Cyclin D has an important role for the cell cycle regulation in RB positive cells and pRB is the major target for D-CDK4/6 [15](Figure 2). It is generally accepted that at least one of the 4 key regulators of the cell cycle i.e. CDKN2A, cyclin D, CDK4 and RB is mutated in most of the human cancers. However, there are many oncogenic DNA virus ex. HPV (E7) which binds to the RB and makes it nonfunctional [1].

There are other tumor suppressor genes which are involved in various human cancers such as the BRCA1 and BRCA2, which are involved in familial breast cancer and APC, which are responsible for sporadic colorectal cancer, however, the still most commonly mutated genes are the p53 (about 50% in all cancers) and RB1 (Retinoblastoma susceptibility gene) [16].

CONCLUSION

Genetic damage remains the main basis of carcinogenesis. Such genetic damage or so-called mutations can be due to various factors such as the carcinogens, radiations or viruses. Tumor suppressor genes play the major role in carcinogenesis by sensing the genetic (DNA) damage and subsequently act in the repair of it. A basic knowledge on these tumor suppressor genes can provide assistance for the readers on the actual molecular pathogenesis on various cancers.

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