PREDICTION OF CANCER POSSIBILITY BY PATTERN RECOGNITION AND STATISTICAL STUDY OF EXPRESSION OF GENE LEVEL OF CANCER CELLS"

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ABSTRACT

The activity of the p53 tumor-suppressor protein has a key role in controlling both cancer and aging: under activity encourages the growth of cancer, and over activity can accelerate the aging process. The p53 protein is a tumor suppressor encoded by a gene whose disruption is associated with approximately 50 to 55 percent of human cancers. The p53 protein acts as a checkpoint in the cell cycle, either preventing or initiating programmed cell death (Apoptosis). p53 regulating genes MDM2,PARP, Oncogenic ras, p21 etc play crucial role in tumor suppression.

KEYWORDS: Apoptosis, p53, p21, MDM2, tumor-suppressor.

DISCUSSION

Why do we get cancer if tumor suppressor is present ?

The p53 gene has been mapped to chromosome 17. In the cell, p53 protein binds DNA, which in turn stimulates another gene to produce a protein called p21 that interacts with a cell division-stimulating protein (cdk2). When p21 is complexed with cdk2 the cell cannot pass through to the next stage of cell division. Mutant p53 can no longer bind DNA in an effective way, and as a consequence the p21 protein is not made available to act as the 'stop signal' for cell division. Thus cells divide uncontrollably, and form tumors.

In most tumor cells, the p53 protein is inactivated by mutation, whereas in some others its function is blocked in other ways. The p53 molecule can be inactivated in several ways. In some human families, for example, p53 mutations are inherited, and family members have a high incidence of cancer. More often, the molecule is inactivated by an outside source. DNA tumor viruses, such as the human adenovirus and the human papilloma virus, can bind to and inactivate the p53 protein function, altering cells and initiating tumor growth. In addition, some sarcomas amplify another gene, called mdm-2, which produces a protein that binds to p53 and inactivates it, much the way the DNA tumor viruses do.

INTRODUCTION

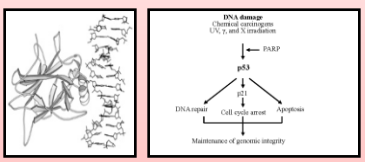
TP53 GENE and p53 PROTEIN

The tumour suppressor protein p53 was first described in 1979 and ten years later identified as a tumour suppressor. In human, the TP53 gene that contains 11 exons is located in chromosome 17p13.1, while the mouse gene, which also contains 11 exons, is located in chromosome 11. In both human and mouse, the coded protein is approximately 53 kDa in size, the human protein containing 393 amino acids and mouse protein 390 amino acids. The p53 protein consists of an acidic N-terminus with a transactivation domain, a hydrophobic central DNA-binding core and a basic C-terminus with regulatory and oligomerisation domains. The DNA-binding domain of the p53 protein is composed of two beta-sheets and a zinc atom which stabilizes the structure .

REGULATORY PROTEIN

MODE OF ACTION OF P53:

The tumor-suppressing p53 protein (left) can bind to target sequences on the DNA double helix to activate genes that prevent cell growth.



THE p53 PATHWAY

FUNCTIONS

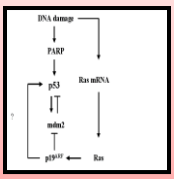
- Inhibition of cell growth i.e. APOPTOSIS.
- Transcrptional activation of cell cycle gene.
- Induction of cell arrest of cell.
- Preventing the fixation of of damaged DNA as mutation.

Aberrations of p53 function

- There are many ways in which the p53 function may be altered in human cancers.
- p53 can be inactivated indirectly through binding to viral proteins, as a result of alterations in the *mdm2* or *p19ARF* genes or by localization of the p53 protein to the cytoplasm.
- Other factors that prevent normal folding of the p53 protein, such as cadmium, may influence its DNA-binding capacity.

Mdm2 PROTEIN

The **murine double minute 2** (*mdm2, hdm2* in human) gene encodes a 90 kDa protein (97 kDa in human) ,a dominant transforming oncogene. The *mdm2* gene has been found to be amplified in human cancers. The combination of over expressed mdm2 and p53 gives a worse prognosis than either one of them alone. Deletion of the *mdm2* gene in mice is embryonically lethal, probably due to increased accumulation of p53, but this lethality can be counter-acted by deletion of the TP53 gene. The p53-mdm2 relationship is vital in the regulation of cell growth and death.



PROTEIN INVOLVED IN THE REGULATION OF THE DNA DAMAGE - INDUCED p53 PROTEIN.

Poly(ADP-ribose)polymerase :

Poly (ADP-ribose) polymerase (PARP) has long been known to play a role in the recognition of DNA damage and in DNA repair. The PARP protein detects DNA strand breaks and catalyzes the attachment of ADP-ribose units from NAD to itself and to other proteins. The substrates of PARP can then influence the architecture of chromatin or act in DNA metabolism. PARP plays a positive role in the activation and upregulation of p53.

Oncogenic Ras :

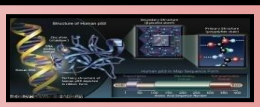
Mammalian *ras* genes are considered crucial in the regulation of cell proliferation. In mammals, the *ras* family consists of three genes located in different chromosomes, encoding the homologous 21 kDa proteins H-Ras, N-Ras and K-Ras. It has been estimated that 30% of all human cancers express mutated forms of *ras*. *Ras* regulates MAPK which in turn regulates p53.. Ras induces $p19^{ARF}$ in murine fibroblasts.

p21 :

p21 play role in the inhibition of CDK-cyclin activity and directly inhibit DNA replication. The gene is transcriptionally upregulated by wild-type p53 .The activation of p53 causes induction of p21, which in turn inhibits CDK-cyclin activity and arrests the cell cycle at the G1 or G2 cell cycle checkpoint. This gives time for DNA repair before replication or mitosis and thus links p21 directly to the tumour suppressor function of p53.

METHOD

Following P53 databases were downloaded from the website.
->p53 mutations in tumors only
->p53 mutations in cell lines
->Germline p53 mutations



Using the mutation data in the website, statistical calculations were performed using the SPSS (Statistical Package for the Social Sciences) software. **The Microsoft excel software was used to distribute the data to gain the insight for mutations at all the codon sites on the p53 gene. The frequencies of all the 393 codons were tabulated.**

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RESULTS

p53 mutations are common in lung cancer and range from 33% in adenocarcinomas to 70% in small cell lung cancers. These mutations are mostly GC to TA transversions, with a rate of transition mutations lower than in other cancers. A strong correlation has been detected between the frequency of these GC to TA transversions and lifetime cigarette smoking. *benzo(a)pyrene,a* carcinogen in tobacco is responsible for GC to TA transversions and causes damage at codon 157,248 and 273 in p53 gene. A large proportion of all mutations in TP53 are single base substitutions. Of all mutations, approximately 30% occur in *six codons (175, 245, 248, 249, 273 and 282) which are called the hotspot codons .Thus p53 gene* is target of carcinogen found in tobacco.