Teaching Session

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P53 ALTERATIONS IN HUMANS: BASIC INFORMATION AND CLINICAL APPLICATIONS

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The tumor-suppressor gene p53 is one of the most important discoveries of recent years in the field of cancer biology. p53 is located on chromosome 17 and in its wild form is involved in the control of cell proliferation. p53 mutations, which are the most diffuse gene alterations among human tumors, occur at different times of the cell transformation process and tumor progression in the various tumor types. Molecular, and more recently, immunohistochemical procedures compatible with paraffin-embedded samples have been used to detect p53 mutation and P53 protein expression. Basic studies have evidenced a role of p53 in biological functions other than proliferation control, such as programmed cell death, or apoptosis. Several studies have demonstrated a clinical relevance of P53 expression. P53 alterations have a pathogenetic role in some human tumor types and are prognostically relevant, sometimes independent of other consolidated biologic and pathologic factors, with a diversified predictive power as a function of the time of appearance during preneoplastic or neoplastic progression. Recent discoveries on the role of p53 in promoting apoptosis suggest a direct involvement of the tumor-suppressor gene in clinical response to chemotherapy and radiotherapy. Such evidence is also supported by the association between p53 and genes involved in cellular response to DNA damage and by its modulated expression in the different cell cycle phases.

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MULTIFACTORIAL ANALYSIS OF P53 ALTERATION IN HUMAN CANCER

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p53 alterations are involved in the majority of human malignancies. Three approaches can be used to test p53 condition in human tumor: molecular, immunocytochemical and serological diagnosis.

(i) Molecular analysis: DNA sequencing led to the determination of the exact mutational event which modified the p53 gene. More than 3000 p53 point mutations have been described in a large panel of human malignancies. Extensive analysis of these mutations led to the demonstration that p53 gene is an informative model useful to study the molecular mechanisms of mutagenesis in the human genome.

(ii) Immunocytochemical analysis: p53 mutations induce a change in the conformation of the p53 protein leading to the stabilization and the accumulation of p53 in the nucleus of tumoral cell. This observation has encouraged an intensive study of the expression of p53 protein by immunohistochemistry in a large panel of tumors, since there seems to be a good correlation between p53 gene mutation and protein accumulation.

(iii) Serological analysis: It has been shown that p53 accumulation can lead to production of p53 antibodies in the sera of patient with various types of cancer. Detection of these antibodies by ELISA has shown a very good correlation between p53 mutation, p53 antibodies and prognostic factors.

The use of these three approaches on clinical diagnostic will be discussed.

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P53-INDUCED APOPTOSIS: A CELLULAR RESPONSE TO DNA DAMAGE

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p53 is the most frequently mutated gene in human cancer. The p53 protein can block cell cycle progression in the G1 phase, and induce cell suicide or apoptosis. p53 levels are normally low but rise after DNA damage. This allows DNA repair prior to DNA replication or elimination of cells with DNA damage. p53 is a transcription factor that binds to a specific DNA sequence and transactivates genes such as WAF1, MDM2, and GADD45. However, p53 can also interact with single stranded DNA ends in a sequence independent fashion through its C-terminal tail. This may trigger a conformational change in the p53 molecule that activates specific DNA binding. Thus, p53 acts as a sensor of DNA strand breaks *in vivo*.

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THE ROLE OF P53 IN THE CONTROL OF CELL DEATH

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The rate of growth of a cell population is dictated by the balance between proliferation on the one hand, and terminal differentiation and cell death on the other hand. Genes controlling either of these processes are likely to affect cancer development. In line with this notion, the p53 tumor suppressor gene was found to be a positive regulator of cell death.

In certain cancer cells, reactivation of functional wild type (wt) p53 can trigger cell death, with distinctive features of apoptosis. Furthermore, wt p53 is required in many cases for the efficient induction of apoptosis by DNA damage or by deprivation of survival factors.

We have developed an assay for the analysis of apoptosis in transfected HeLa cells. Using this assay, it was shown that wt p53, but not tumor-derived p53 mutants, can serve as a potent inducer of apoptosis. The pRB, the product of another tumor suppressor, can protect HeLa cells from p53-mediated apoptosis. This suggests an inverse relationship between certain growth inhibitory signals and cell death. Further experiments in the HeLa assay suggest that p53, despite being primarily a transcriptional activator, can induce apoptosis without the need to activate target genes. The relationship of these findings to the tumor suppressor effects of p53 will be discussed.