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Signification of Proteins P-53 Isoforms in a CLL

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Abstract

In the past few years has used the technique for analyzing deletions of genes, its rearrangements, cross-reactivity or multiplications in human genome affected of a variety genetic diseases. Was proved, the best techniques in the investigation of malignant lymphocytes are the Flow Cytometry, Elisa, ICT and Fluorescence *in situ* hybridization (FISH). Last method, FISH is used as an alternative to chromosomal banding, a conventional application in molecular medicine and can detect the chromosomal rearrangements and complexes of different genes in malignant diseases, like chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia, (ALL), or multiple myeloma (MM). Identification of *P53* gene deletions and mutations in regions of chromosome 17 in hematological malignancies is important because these mutations have an impact on the clinical management of patients.

Keywords: *P-53* gene; Apoptosis; Fluorescence *in situ* hybridization; p-53 protein isoform; Aurora kinase; TET2 enzyme

Introduction

Chronic lymphocytic leukemia (CLL), occurs on average elderly person and the elderly, affecting men for women in about 2/1. Many patients are asymptomatic, when the disease is diagnosed. Patients with minimal signs of illness, for example, lymphocytosis, is considered to be an early stage of the disease, while those showing the compromise of function of morrow, anemia or thrombocytopenia, are in advanced stages. Research has shown that this restoration function of p-53 protein may lead to recovery activity of cell with regression of cancer cells.

Protein p-53 Isoforms and Cancer

In last researches was shown that the *P-53* gene is a tumor suppressor gene and its activity stops the formation of tumors. The *P-53* gene has been mapped to chromosome 17. In the cell, p53 nuclear protein binds DNA, stimulating another gene, CDKN1A, to produce a protein called p21 that interacts with a cell division stimulating protein (CDK2) [1,2].

In this context the nuclear p-53 protein was showed that protect the cell of a malignant process, and only cytoplasmic p-53 protein, by its isoforms, phosphorylated in multi-sites, into modified cytoplasmic medium, by high concentration of anaerobic ATP, drives at cancer. P-53 protein, in native status, for to become in active status need of acetylation processes, methylation and phosphorylation in multisite. [3].

Assigned that acetylation and deacetylation of protein p-53 are reversible processes and can repair DNA damage in cancer cells. The spectrum of phenotypes of cancer due to mutations in the gene P-53 is also supported by the fact that different isoforms of the protein p53 have different cellular mechanisms in cancer. Altered activity of p-53 protein in isoform status lead impairs DNA damage and is extending from mild to severe cancer phenotype (Figure 1) [4].

Ser-15 phosphorylation protein p-53 also triggers a series of sequential events additional phosphorylation in p-53 protein (including phosphorylation of Ser-9-46-20.0 and Thr-18), which further contributes to the induction of p53 and activation.

These findings suggest that phosphorylation of Ser15, therefore, is an important focal point in p53 activation. Ser15 phosphorylation is necessary to enable the local assigned to histones and loosening of chromatin. Mutation of serum alanine-15 resulted from the partial failure of p53 to inhibit cell cycle progression. In this context, nuclear protein p-53 showed that protect the cells of a malignant process, and only the cytoplasmic protein p-53, to support modified isoforms, cytoplasmic, high concentrations of anaerobic ATP, leading to cancer, [5].

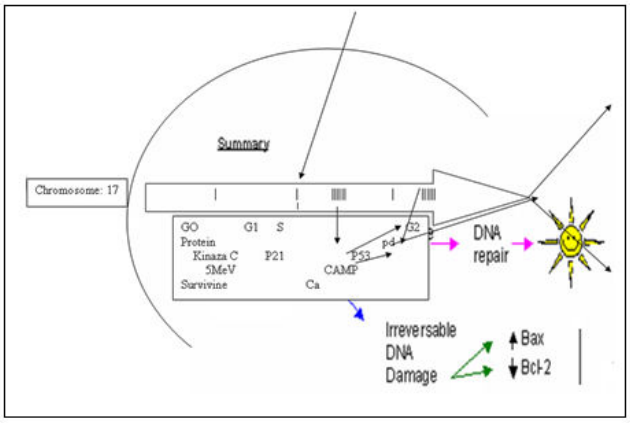

Figure 1: The p21 protein as regulator of cells cycle progression at G1 to S phase, controlled by the tumor protein p53 [4].

The current study showed that the level of p-21 is strongly correlated with the activity of Mammalian Target Rapamycin (m-TOR). The study was published in the February 2, 2016, online edition of the Journal Nature Communication (www.cnio.es). By the Warburg effect, glucose maintains stability mutant *P-53* gene and promotes cancer cell. Most researches seem to indicate that, in line with its role as tumor suppressor p53 is able to fall glycolysis. The mTORc2/Akt complex controls mitochondrial metabolism and physiology, through the phosphorylation of the glycolytic enzyme hexokinase 2, thus promoting cancer cell's aerobic glycolysis (Warburg effect) and preventing mitochondrial apoptosis [6].

P-53 protein plays an important role in the regulation of glycolysis, which was demonstrated experimentally. Most research seems to indicate that, in the light of its role as a tumor suppressor p53 is able to drop Glycolysis [7]. By the Warburg effect, the glucose maintains stability mutant p53 gene promotes cancer cell growth and generating a positive regulatory loop. This appetite for glucose to cancer cell, identify a potential therapy of malignant diseases, which is currently under extensive investigation. The protein p-53 plays an important role in the regulation of glycolysis that is proven, experimentally. Most research seems to indicate that, in line with its role as a tumor suppressor, p53 is able to fall glycolysis [8]. Of major concern, the p53 protein has been identified as an important regulator of glucose transport, and it has been demonstrated transcriptional repression of both receptors GLUT1 and GLUT4. By contrast, the mutant p-53 does not affect the GLUT1 and GLUT4 receptor activity [9,10].

Expression of the Gene that Encodes the Protein CDK

The expression the CDKNIA gene, which encode protein p21, is tightly controlled by the tumor suppressor protein p53, through which this protein mediate the p53-protein dependent cell cycle G1, phase arrest in response to a variety of stress stimuli, When p21 protein forms a complex with CDK2 protein the cell cannot pass through to the next stage of cell division, G1-S.

Mutant gene P-53 products a p-53 protein which cannot 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 [11]. Protein p-53 isoforms can regulate p53 transcriptional activity of genes and its development [12].

The Effect of Aurora-kinase A and B Aurora Kinases

Aurora-kinase A and B enzymes play a critical role in adjusting axial assembly, chromosomal segregation and cytokine to ensure loyalty of segregation of chromosomes during the cell division mitotic cycle. Aberrant expression of the p53 Aurora kinases family of signaling axes may be critical for tumor suppressor pathways mediated by the p53 protein family, often disrupted during the oncogenic transformation process.

Recent research has demonstrated that Phosphorylation of p53 serine-106 inhibit p53 interaction with MDM2 and p53 protein half-life [13]. It was found that Aurora-B kinase interacts with p53 and variously phosphorylates to multiple residues in the DNA binding domain. In contrast to the effect of phosphorylation of p53 of Aurora A, Aurora-B of the p53 at serine-269 and threonine- 284 inhibit p53 transactivation activity, whereas phosphorylation at serine-183, threonine-211, and serine-215 accelerates the degradation of p53 through poly- ubiquitination -mediated proteasome pathway, (MDM2) [14,15]. Some studies have shown that to cancer patients appear antibodies anti-p53 protein and these researches are included in clinical trial studies [16,17].

New Cancer Therapy

About a third of cases (30%) had no recurrent chromosomal mutations, suggesting a high degree of heterogeneity and genetic mutation nor clear drivers of CLL [18]. Consistent with a role in disease initiation, global DNA hypo-methylation and shortened telomeres were found to be significantly associated early-stage CL patient's untreated tumors [19].

Similarly, gene methylation CDKN-2A, (INK4a/ARF) locus protein expression can be epigenetically silenced p14 ARF, and stop activity of oncogenes to stabilize p-53 protein response. A body of work using two mouse models has recently provided strong evidence that the aberrant hypo-methylation promotes development LLC. Thus, Hypo-methylation of a single aberrant promoter can upregulate several micro RNAs, possibly contributing to tumorigenesis. TET2 the enzyme is an enzyme that plays a central role in DNA demethylation to catalyze the conversion of 5-mC into 5-hydroxymethyl cytosine (5-hmC) [20].

Some recent date studies suggested strong cross-talk between histone modifications, translational activity and DNA methylation status of DNMT prior locale [21]. Treatments with methylation-specific agents are used in combination with conventional chemotherapy treatment anti-neoplastic [22]. Nutlings molecules of imidazole analogs and Nutlin-3 moves the MDM2 binding to p53 competing with good response in treatment of CLL with 13-14q translocations [23]. Antibodies specific for p53 and p53 for phosphorylated at three different sites in the field of activation were used in parallel analyses in investigations of CLL treatments [24,25].

Immune Therapeutic Success

After chemotherapy treatment, tumor antigens are taken up by cells presenting antigen (APC) and are presented in the context of the co-stimulatory molecules B7 from dendritic cells. T cells recognize antigens to become activated. T-cells may differentiate into memory T cells that can turn into tumor recurring presence not only through induction of genetic programs, which leads to a proliferation and differentiation, but also to induce receptor inhibitor mediated by CTLA-4 program, which ultimately is going to stop proliferation. As T-cell receptor CTLA-4, T-cell receptors, PD-1 is expressed only in activated T cells to stop their proliferation at a time, limiting the production of a type of memory T lymphocytes. However, unlike the CTLA-4, PD-1 inhibits T-cell responses by interfering with the T cell receptor signaling unlike competing out-CD28.

Interactions between PD-1 and its ligands, PD-L1/PD-L2, are complex and occur in several stages of an immune response (Figure 2). According to Postov and collaborators, there is an activation mechanism in the lymph node where PD-L1/PD-L2 on an antigen presenting cell (dendritic cell) negatively regulates T-cell activity by PD-1 and an interaction between B7 and PD- L1. The PD-1 pathway is also likely to be important in the tumor micromedium where PD-L1 expressed by tumors interact with PD-1 on T cells to suppress effector function of T. MHC cells, a major histocompatibility complex [26].

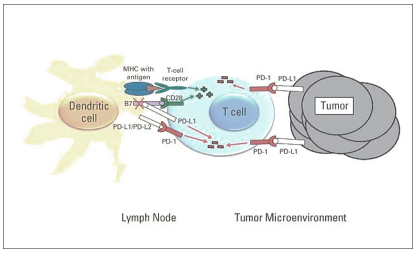

Figure 2: Stages of the immune response within the lymph node-tumor microenvironment.

In many laboratory studies (Table 1), here today are ongoing clinical trials with anti-CTLA-4 and immunological control points, i.e. PD-1/PDL1 [26,27] can improve the prospects of patients with various malignancies.

Target	Agent	Class
PD-1	Nivolumab (MDX1106, BMS-936558)	IgG4 fully human Ab
	Pembrolizumab (MK-3475)	IgG4 engineered humanized Ab
	Pidilizumab (CT-011)	IgG1 humanized Ab
PD-L1	BMS935559 (MDX-1105)	IgG4 fully human Ab
	MPDL3280A	IgG1 engineered fully human Ab
	MEDI4736	IgG1 engineered fully human Ab
	MSB0010718C	IgG1 fully human Ab
PD-1–positive T cells	AMP-224	Fc of human IgG–PD-L2 fusion

Table 1: PD-1 and PD-L1 Antibodies in Clinical Development; Ab-Antibody; IgG- Immunoglobulin G; PD-1-Programmed cell death protein 1; PD-L1-Programmed cell death protein 1 ligand.

Conclusion

The frequencies of *P53* gene mutations, deletions or translocations, in CLL, can be categorized as the individual biomarkers in proteomic and genomic profile for this type of leukemia and can be implemented in chooses of targeted treatments from personalized medicine. Deletion and mutation of the gene p-53 in malignant homeopathies requires therapeutic attitude in a personalized medicine. Personalized treatments to be applied by a combination of diagnostic tools, knowledge databases and therapeutic drug.

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