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Signification of protein p-53 isoforms and immune therapeutic success in chronic lymphocytic leukemia

Udristioiu Aurelian[a], Nica-Badea Delia[b,*]

[a] Molecular Biology, Faculty of Medicine, Titu Maiorescu University, Bucharest, Romania
[b] Constantin Brancusi University, Faculty of Medical Science and Behaviors, Târgu Jiu, Romania

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ABSTRACT

In the past few years has used thetechnique for analyzing deletions of genes, its rearrangements, cross-reactivity or multiplications in human genome affected of genetic diseases. Was proved that, 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.

1. 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 [1].

2. Protein p-53 isoforms and cancer

In last researches were 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), [2].

In this context, the nuclear p-53 protein was showed that protects 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 needs 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 impairs DNA damage and is extending from mild to severe cancer phenotype [4], (Fig. 1).

Ser-15 phosphorylation protein p-53 also triggers a series of sequential events and additional phosphorylation in p-53 protein (including phosphorylation Ser-9-46-20 and Thr-18), contributes to the induction of p53 and its 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 the partial failure of p53 to inhibit cell cycle progression. In this context, the nuclear protein p-53 showed that protects the cells of a malignant process, and only the cytoplasmic protein p-53, in its modified isoforms, in cytoplasmic medium with a high concentration of anaerobic ATP, leads to cancer, [5].

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). Also, by the Warburg

* Corresponding author at: Faculty of Medical and Behavioral Sciences, Constantin Brancusi University, Eroilor Street No. 30, CP 210135, Târgu-Jiu, Romania.
E-mail address: nicabadeadelia@yahoo.com (D. Nica-Badea).

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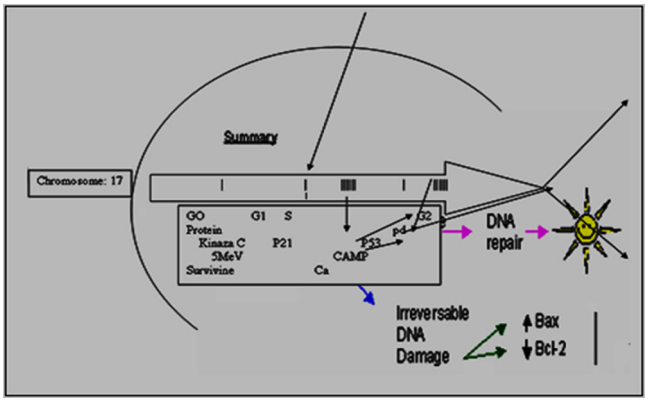

Fig. 1. The p21 protein as regulator of cells cycle progression at G1 to S phase is controlled by the tumor protein p53 [4].

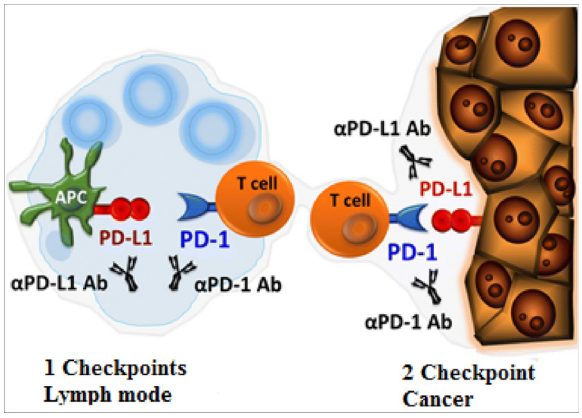

Fig. 2. Programmed death (PD)-1 inhibitors in cancer [27].
(Abbreviations: Ab, antibody; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein 1 ligand).

Table 1
PD-1 and PD-L1 Antibodies in Clinical Development.

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

Abbreviations: Ab, antibody; IgG, immunoglobulin G; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein 1 ligand.

effect, glucose maintains stability mutant P-53 gene and promotes cancer cells.

.Most researches seem to indicate that, in line with its role as tumor suppressor, p53 is able to fall glycolysis. The mTORc2/Akt complex control the 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 seem 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.

Also, the protein p-53 plays an important role in the regulation of glycolysis that is proven experimentally [8]. Of major concern, the p53 protein has been identified as an important regulator of glucose transport and has been demonstrated transcriptional repression of both receptors GLUT1 and GLUT4. By contrast, the mutant p-53 does not affects the GLUT1 and GLUT4 receptor activity, diving to malignant cell [9,10].

2.1. 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 mediates the p53- protein dependent cell cycle G1, phase arrest in response to a variety of stress signals. 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. In this kind, the cells divided uncontrollably and form tumors [11]. Protein p-53 isoforms can downregulate p53 transcriptional activity of suppressor genes in carcinogenesis processes [12].

2.2. The effect of Aurora-kinase A and B Aurora kinases

Aurora-kinase A and B family 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 critically for tumor suppressor pathways mediated by the p53 protein family, often disrupted during oncogenic transformation process.

Recent research has demonstrated that Phosphorylation of p53 at level serine-106 inhibits p53 interaction with MDM2 and p53 protein has half-life [13]. It was found that Aurora-B kinase interacts with p53 protein and phosphorylates multiple residues in the DNA binding domain, blocking apoptosis process. In contrast with the effect of phosphorylation of p53 made of Aurora A, Aurora-B kinase phosphorylates amio-acids serine-269 and threonine- 284 and inhibits 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 the cancer patients appear antibodies anti-p53 protein and these researches are included in clinical trial studies [16,17].

3. 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-2 A, (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 enzyme is an