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Energetic and Genetic Mechanisms of Transformation of Normal Cells into Malignant Cells

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1. Abstract

1.1. Background: P-53 gene mutation is the most common genetic abnormality of cancers regarding low survival and non-response to classical conventional chemotherapy in treatments of patients.

1.2. Method: Identifying P-53 gene mutation with the p-53 protein isoform was detected by the ELISA method to patients with Chronic Lymphocytic Leukemia, (CLL). Also, levels of energy in cells, especially in CLL, due to the dis-regulation of P-53 genes, were measured using the bio-luminescence method, with adenozin-three-phosphate, (ATP), kits, running an Analyzer of bio-luminescence LKB.

1.3. Results: Genetic changes within the neoplastic included the mutation of P-53 gene on the short arm of chromosome 17p in CLL and high levels of energy of malignant cells and high concentrations of ATP.

1.4. Conclusion: Maturational state of the clonal tumor and the prognosis of patients with CLL is dependent of anaerobe metabolism with isoform p-53 proteins.

2. Introduction

2.1. Aim: The aim of this paper was to highlight the stages of Chronic Lymphocytic Leukemia of type B, (CLL-B), which did not meet the standard treatment criteria for malignant hematological diseases due to mutations in the P-53 gene, with progression to Richter Syndrome. Also, following this information, forward aim of this work was to emphasis and levels of energy in cells, in types of malignant disease, especially in CLL-B, due to the dysregulation of genes, using the bioluminescence method, running an Analyzer of bioluminescence LKB.

3. Main Text

3.1. Participants of Inclusion Criteria: Chronic lymphocytic leukemia, (also known as “chronic lymphoid leukemia” or CLL), is a pe of leukemia or cancer of the white blood cells, lymphocytes. The cells accumulate mainly in the bone marrow and blood. Morphologically, these cells resemble mature lymphocytes in the peripheral blood. In the majority of patients with chronic CLL the cells are clonal B cells arrested in the B-cell differentiation pathway between pre-B cells and mature B cells.

Only 2-5% of patients with chronic CLL exhibit a T-cell phenotype. In CLL the DNA of B cells is mutated so that it can’t fight infection, but it grows out of control and crowds out the healthy blood cells that can fight infection. The study encompassed cases of patients with CLL with > 5000 lymphocytes in absolute value, present at the cytological examination of the blood smear, from the peripheral blood, and LLC with less than 10% prolymphocytes based on the peripheral blood smears, May-Grunwald Giemsa, stained**,** (Figure 1).

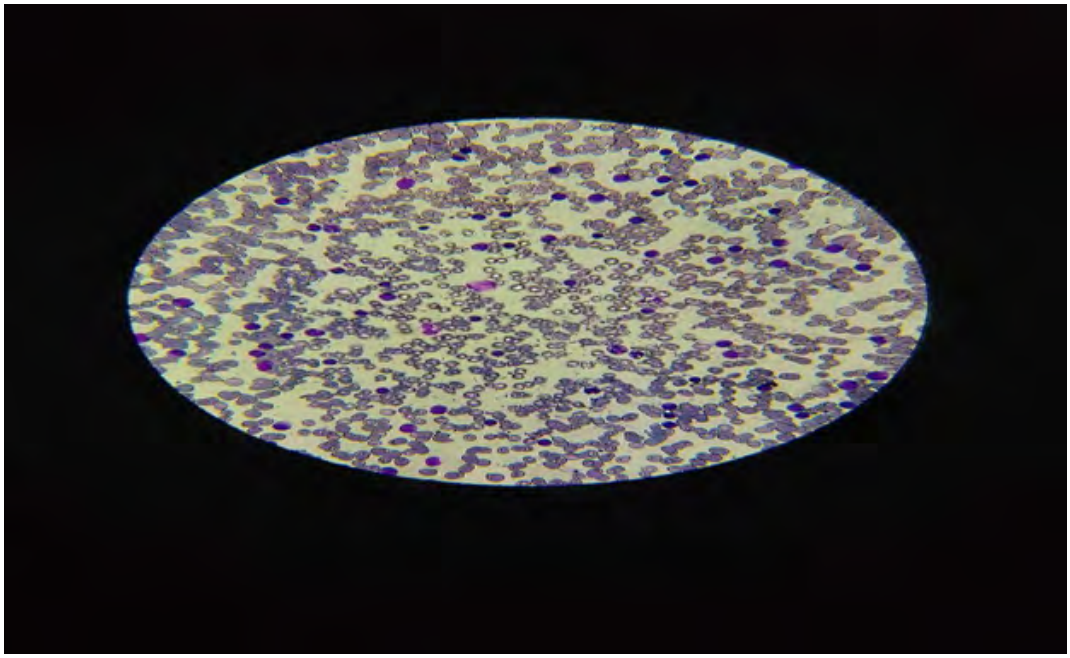


Figure 1: Lymphocytes with Gumprecht nuclear shadows, in CLL on peripheral smear, colored with May-Grunwald Giemsa

3.2. Immunophenotyping of CLL-B Cells: The diagnosis of CLL-B was confirmed by immune phenotyping. All samples that entered the study were lymphocytes with positive $CD19^{+}$, $CD20^{+-}$, $CD5^{+}$ and $CD23^{+}$ cell receptors. The CD38+ receptor was considered positive if the distinct lymphocytes of the population showed a higher intensity of staining than the granulocytes in the sample and was associated with the presence of protein ZAP-70, with pure prognostic of treatment in LLC.

3.3. Participant Type: Patients diagnosed with CLL-B who were hospitalized in the Hematology departments of the Oncology Institute between November 2016 and September 2019. Age group**:** Senior Gender Both**;** Target number of participants 20; Recruitment start date**;** 01/11/2016**;** Recruitment end date**;** 01/09/2019**;** Locations**;** Countries of recruitment Romania.

3.4. Material and Method used on Elisa Line: In full study was used the research with sandwich ELISA quantitative method, for direct detection of p-53 isoform protein, product of Gene P-53**:** Specificity: human p53 protein (aa20-25); Format: Purified product: Monoclonal antibody clone: Isotype DO-1: IgG2a. The antibody is suitable for the techniques: ICC / IF and ELISA. The research PAb 240 antibody bind specifically to denatured p-53 protein, in conformity with reference, (Wang PL and all. 2001}.

3.5. Compatible Sample Types: Cell Culture Supernatants, Plasma, Serum; **Solid Support:** 96-well Microplate;

3.6. The Principle of the ELISA Method: This analysis is based on the sandwich ELISA principle. Each well of the microtiter plate was pre-coated with a specific target capture antibody. Standards or samples are added to the wells and the target antigen, in this case the p-53 protein, binds to the capture antibody.

3.7. Protocol of ELISA Work

1**.**Prepare all reagents, samples and standards as instructed in the manual.

2.Add 100 µl of standard or sample to each well.

3.Incubate 2.5 h at room temperature, (RT), or past night, at 4°C.

4.Add 100 µl of prepared biotin antibody to each well.

5.Incubate 1 h at RT.

6.Add 100 µl of prepared Streptavidin solution to each well.

7.Incubate 45 min at RT.

8.Add 100 µl of TMB One-Step Substrate Reagent to each well.

9.Incubate 30 min at RT.

10.Add 50 µl of Stop Solution to each well.

11.Read at 450 nm immediately on Analyzer Elisa.

3.8. Results Obtained by the ELISA Method: After analyzing the 85 LLC samples, in different stages of disease evolution, starting with stage zero, (stay and watch), and up to stage IV, only 20 patients were selected, eligible for this study, to be investigated for the detection of p-53 protein isoforms responsible for resistance to oncological treatments of the disease with Rituximab, Cyclophosphamide, Doxorubicin hydrochloride , Vincristine sulfate (Oncovin), and Prednisone, (R-CHOP), after 2 cycles of relapses, representing a group of 16 men and 4 women aged 39-85 years.

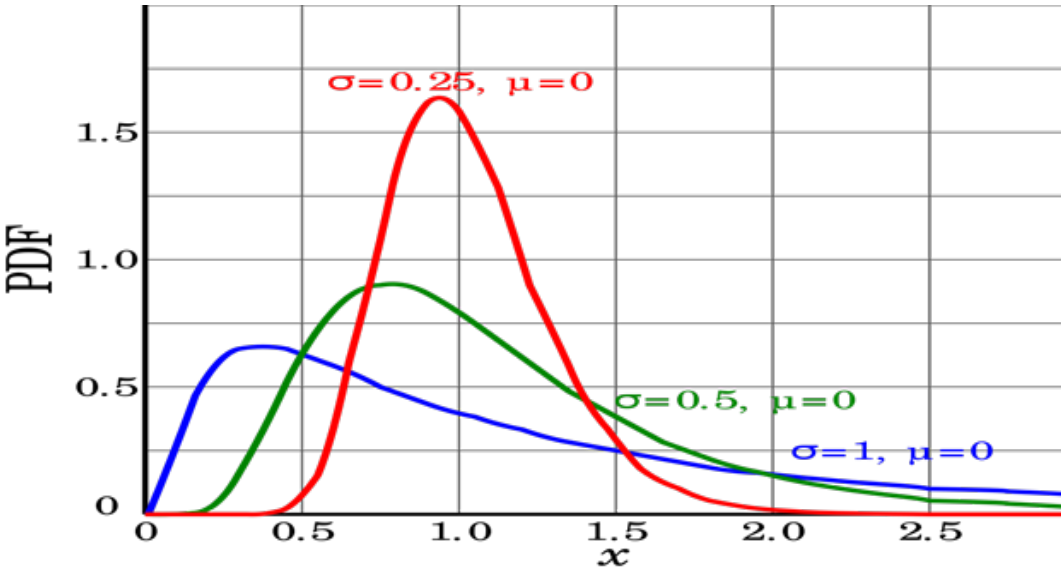
3.9. Male Results: Protein concentration in p-53 / µg / dL: 20, 15, 18, **40**, 10, 12, 14, **60,** 30, 10, 13, 15, 5, 10, 15, 12. **3.10. Women's Results**; Protein concentration p-53 / µg / dL: **140**, 30, 13, 10.

3.11. Normal Values of Normal Cell Lines on Equipment: ELISA = 0.25-0.5 µg / dL, or 2.5- 5ng/ml.

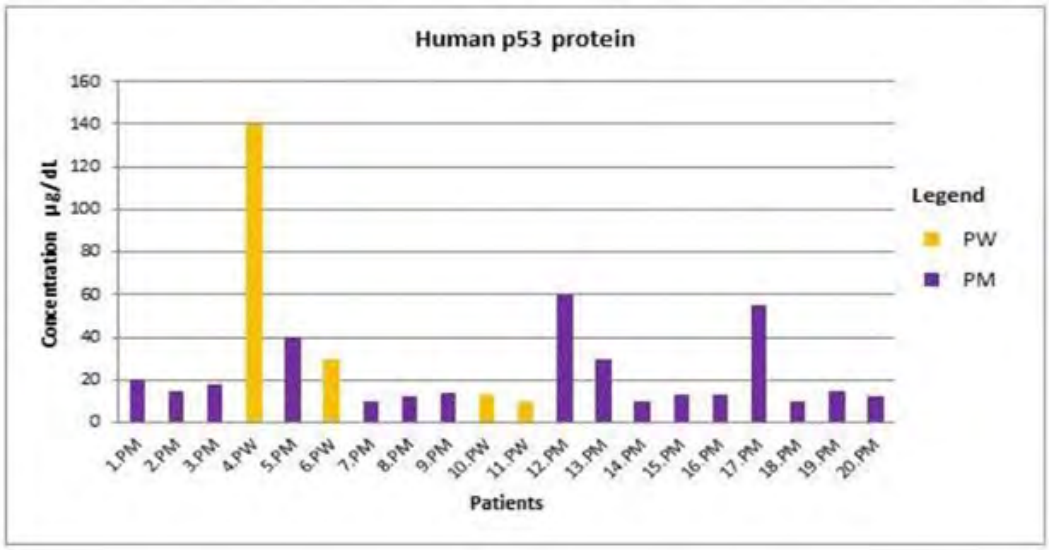
3.12. Statistical Interpretations: Concentration of the p-53 isoform protein representing the P-53 mutant gene in 17 cases, after excluding the 3 out-line cases present in the study, was calculated at the mean value of 14.8 µg / dL, with Standard Deviation, ST-

DEV = 6.46, CV = 0.4% and the probability index (NORMDIST), "p" was calculated in the value of p = 0.079. Multivariate (MA) analyzes were performed for OS on any significant variables at the level of p <0.20 at univariate analysis, with the gradual elimination of insignificant variables. The presence of protein isoforms in the studied group was calculated as a percentage of 17%, and the unfavorable evolution and transformation Chronic Lymphocytic Leukemia in the stages studied in Diffuse Large Lymphoma was calculated to be in a percentage of 3.5% of the studied cases, as in the meta-analyzes from the specialized literature, Diffuse Large lymphoma is considered a rare disease. The comparison between the categorical variables and the numerical variables was performed using the exact Fisher test.

3.13. Fisher Test: Number of patients in the study group = 85; Eligible 20 a + b = 3 + 17; Ineligible 65. c + d = 5 + 60**.** Total a + c b + d a + b + c + d (= n) = 85; p = {a + b} \ {a} x {c + d} \ {c}: [{n} \ {a + c}] = 20 / 3x65 / 5 / 8,125 = 10.2 = 1.1 log in base 10, result that we indicate that all statements are true. {\ frac {(a + b)! (c + d)! (a + c)! (b + d)!} [a! b! c! d! n!], in the calculations made by the statistical software where, (n / k), is the binomial coefficient and the symbol "!" show that factorial**,** (Graph 1). Calculation of frequency of isomorph p-53 protein by ANOVA test positive, in value 1.1 and indicates a linear relationship between the 2 variables, (Table 1). Very high pathological values in the 3 cases of p-53 were calculated in 2 men in the value of 60 µg / dL, respectively at 40 µg / dL, and in the case of females it calculated in the amount of 140 µg / dL, the frequency chronic lymphocytic leukemia with transformation into Diffuse Large Lymphoma, (DLL), (Graph 2). The pathological values in the 3 cases of highly elevated p-53, reflecting the concentration of p-53 protein mutant, were calculated in 2 men in the amount of 60 µg / dl, respectively in 50 µg / dl, and in the female case, it was calculated in the amount of 140 µg / dl, the frequency of chronic lymphocytic leukemia being higher in men than in women, in ratio 2/1, in accordance with the data from the specialized literature. The overall frequency of positivity of the p53 protein, in the increased number of CLL cases studied, was 15% (3 out of 20 cases). The expression of the high-concentration p53 proteins in stage 2/3 of the disease was associated with a significantly weaker response to chemotherapy (p = 0.034) (Table 2). The main stimulus for malignant tumor is hypoxia from predominant anaerobe metabolism. Following this information aim of this work was to emphasis levels of energy in cells, in types of malignant disease, due to the dis-regulation of genes, using the bio-luminescence method, running an Luminometer Analyzer with bio-luminescence LKB. The measurement of ATP was made by standard principle of bioluminescence on automatic analyzer LKB, using ATP monitoring reagent, ATP Standard, (10^6 Mol ATP/ml), buffer solution Tris-EDTA, TCA-EDTA lyse. All results were statistically analyzed by Excel program.



Graph 1: All expressions under the sign of the logarithm are indicated as positive which is under the sign of the logarithm and as a basis, the remaining expression below the logarithm is Frequency of p-53 isoform protein in cohort of study was evaluated with ANOVA test, [**Table 1].**



Graph 2: Very high pathological values in the 3 cases of p-53 were calculated in 2 men with the value of 60 µg / dl, respectively at 40 µg / dl, and in the case of females it was calculated in the amount of 140 µg / dl, the frequency of Chronic Lymphocytic Leukemia with transformation into Diffuse Large Lymphoma, (DLL).

Table 1: Calculation of frequency of isomorph p-53 protein

The interval of concentration (i)	The middle classes (m)	Frequency of concentration (f)
30-32	31	1
27-29	28	0
24-26	25	0
21-23	22	0
18-20	19	2
15-17	16	2
14-Dec	13	8
11-Sep	10	4
8-Jun	7	0
5-Mar	4	1 17%

Table 2: Expression of hemogram parameters and p-53 protein concentration in different stages of CLL-B

CLL – Age patients	CLL stage I/II, (n=17 patients) P-53 protein concentration in reactive limfocytes B	CLL stage III/IV (n = 3 patients] Percentage of p53 izoform proteins	p value
The age of patients with LLC, ranging from 39 to 85 years.	The average p-53 protein concentration in CLL, 16.76 µg / dL	P-5 izofoorm proteins with elevated values was present in 15% (3 of 20 cases 2 Men = 50µg / dL and 60µg / dL, respectively 1 Female = 140µg / dL	0.034
Hematological parameters in peripheral blood	Mean values of haemogram: No. Leukocytes = 35-50 x 10^3/µL ; Hb = 11.8g / dL; Platelet = 140 x 10^3/µL;Lymphocytes = 65-80%	No. Leucocytes = 250-500 x 10^3/µL,Hb = 8.6g / dL,Thrombocytosis = 45x10^3/µL,Limphocytes = 85-90%	0.05

3.14. The Principle of the Reaction: ATP + luciferin + O2----> oxyluciferin + AMP + PPi + CO2 + Light,

reaction catalyzed by the enzyme luciferase from the ATP research kit.

3.15. Working Technique: Lymphocytes were obtained from the peripheral blood of healthy individual and from hospitalized patients with selected diseases from the departments of Oncology Plasma was collected from patient samples using vacutainers with EDTA or heparin as an anticoagulant by centrifuging the samples for 15 minutes at

4500 rpm (280 G). After the blood sample has been centrifuged and its plasma has been separated from red blood cells, the plasma is fractionated into four distinct fractions placed on a layer of white blood cells(lymphocytes).

With a pipet, a quantity of 100µL is extracted from the lymphocyte ring. The extracted lymphocytes are introduced into 25 ml cuvettes with 3 ml Wash Buffer medium for washing the lymphocytes, (Figure 2). Washing is done 3 times, once after 10 minutes, at 1500 revolutions / minute and twice, 10 minutes at 1000 revolutions / minute. Lysis of washed lymphocytes is done with a micro-wave device, Mini Wave Smart Laboratory microwave. Activated B lymphocytes were defined as $CD19^{+}$ cells, $CD20^{+-}$, $CD21^{+}$, and $CD23^{+}$ and or $CD138^{+}$ surface marker. Activated T cells were identified with CD7, CD5, CD3, CD2, CD4, CD8 and CD45RO. The phenotype suggestive of B-CLL or monoclonal B cell lymphocytes was approximately equal numbers of $CD5^{+}$ and $CD19^{+}$ lymphocytes. Concentration analysis of ATP in mean values, (x^{-}) with Standard Deviation, (SD) : -ATP in normal T Cells, x^{-}= 1.39 µM ATP, (SD = 0.41); ATP in normal B cels, x^{-}=0.35 µM ATP, (SD =0.42); ATP in T cells of malignant diseases, x^{-}= 0.17 µM ATP, (SD = 0.46); -ATP in B cells of malignant disease=, x^{-} =3.06 µM ATP, (SD = 0.45); -ATP in B cells of Leukemia, x^{-}= 4.33 µM ATP, (SD =1.5); - ATP in T cells of Leukemia, x^{-}= 0.09 µM ATP, (SD=1.7), (Table 3). Regarding the study of malignant diseases, was noted the increased measured values: 4.30 - 4.55 µM ATP for chronic lymphatic leukemia and respectively 3.20 - 3.65 micromoles ATP for neoplasms or with bone metastases. Ongoing research has highlighted the fact that the direction of the synthesis reactions ADP + Pi>---<ATP + H2O can be controlled in "vitro", depending on the concentration of system factors, pH and ionic strength, making it likely that a functional energy control exists by creating weak bonds between the chemical complexes of the newly formed biologically active substances.

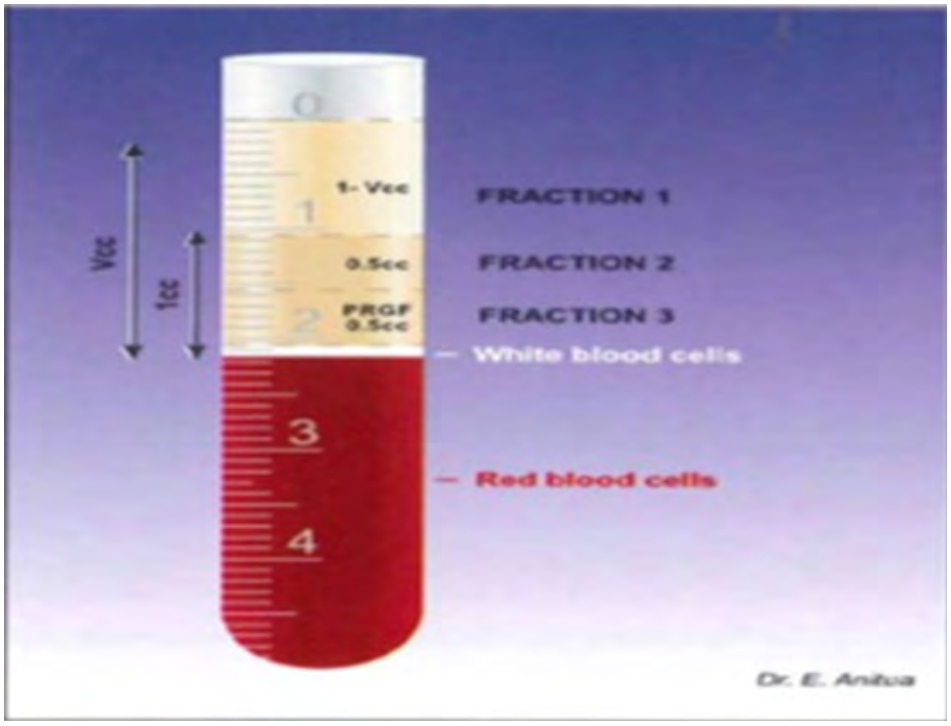


Figure 2: Lymphocyte layer required for drop 100µL in 3 ml Wash Buffer medium.

Table 3: Concentration of micromoles, µM ATP, into malignant diseases were determined with Bio-luminescence

Normal conc. ATP in T Cells	Normal conc. ATP in B cells	Conc. ATP in T cells, malignant diseases	Conc. ATP in B cells, malignant disease	Conc. ATP in B cells, CLL	Conc. ATP in T cells, CLL
x^{-}= 1.39	x^{-}=0.35	x^{-}== 3.06	x^{-}= 0.17	x^{-}=4.33	x^{-}= 0.09
SD = 0.41	SD = 0.42	SD = 0.46	SD = 0.45	SD =1.5	SD=1.7

4. Discussion

Deletion in the short arm of chromosome 17 is associated with rapid progression, short remission, and

decreased overall survival in chronic CLL. The 17p13 deletions are associated with loss of function of the

tumor suppressor gene *p53* and deletions of bands 11q22-q23, associated with extensive lymph node,

involvement aggressive disease and shorter survival. The structural and biochemical changes in malignant cells will influence the development of characteristic bioenergetics processes that at their level will condition the expression of cellular oncogenes. The p53 protein is an oligomeric transcription factor of 393 residues and is organized into 5 structural and functional regions, (Scheme 1). Three-dimensional structure of isomorf p-53 protein in tetrameric form. Restoring p53 function can induce cell death, apoptosis Consistent with this role, the activity of the p53 protein is compromised to a greater or lesser extent in all types of cancer, either by mutation of the P-53 gene

which encodes p53) or changes in the modulating state of the p53 protein. The 3-D structure of p53 is

shown in the figure below, (Figure 3), [1]. The identification of mutations of the P-53 gene present in neoplasms is important, because these mutations have an impact on the clinical evolution of patients and require a adjustment of the therapeutic attitude, appropriate. [2], (Scheme 2).

Theoretical studies have suggested that elevated concentration of adenosine-triphosphate (ATP) in malignant

B cells lymphocytes from CLL impair P53 gene to induce apoptosis of cells. Apoptosis is regulated by a

cascade of proteins called caspases that are present in all cells forms as pro-form. After cleavage, caspases

become active and initiate pathways leading to apoptosis. The pro-apoptotic proteins Bax, Bad, Bak and

Bid induce programmed cell death initially un mitochondria of cells. Death resistance of hypoxia takes place

on at least two levels, within mitochondria and the cytosol. Accumulation of Bax in the mitochondria causes

the release of cytochrome C in cytosol that is strongly reduced under hypoxic environment conditions, [3]. Apoptosis, performed within the extrinsic pathway, is initiated by death ligands, such as Fas ligand or tumor necrosis factor (TNF), which ultimately leads to the activation of caspases 8 and 3 and the activation of apoptosis protein activating factor (APAF). All hematopoietic cells, especially lymphoid cells, express Bcl-2, mainly in the nucleus and endoplasm reticulum. The oncogene Bcl-2 may be a general suppressor of genes that directly regulate apoptosis, [4]. Each cell needs energy to maintain its vital structure, for the synthesis of reserve substances and for the exercise of various specific cellular functions and various movement processes; plasma movement, nuclear division and cell synthesis. As in normal cells, the energy-generating substances are primarily Carbohydrates, then Fats and Proteins. The phenomenon is particularly prevalent in aggressive malignancies, most of which are also hypoxic. Hypoxia induces a stochastic imbalance between the numbers of reduced mitochondrial species vs. available oxygen, resulting in increased reactive oxygen species (ROS) whose toxicity can lead to apoptotic cell death**,** [5], (Scheme 3).

The alteration of the physiological processes of oxidative phosphorylation, the decrease of the respiratory level and the increase of anaerobic glycolysis in the processes of malignancy is accompanied by the increase in the intensity of cellular bioluminescence. Bioluminescence thus appears as an intrinsic component of metabolism and not as the product of specialized photogenic organs. All living cells contain the macro-energetic molecule, adenosine triphosphate (ATP), which is present in a fairly constant amount for each cell type and is rapidly lost after cell death. It was found that the electrical charge of the cell membrane varies relatively little around the value of 0.85eV, in resting conditions. If the energy charge decreases below 0.85 eV, (ATP (<1.75 μM in a cell), the ATP-generating sequences are accelerated by the response of the respective regulatory components, according to the metabolic needs, [6]. ATP is the energy base of DNA-polymerase and DNA-ligase enzymes, enzymes that repair altered DNA nucleotides under the influence of cellular aggression induced by intracellular (free radicals) or extracellular (physical, chemical and biological) toxic factors. The p-53 protein, the product of the P-53 gene, has additional roles, which may overlap with its suppressive capacity, in tumor processes, including the response to DNA damage, aging metabolism and stem cell differentiation, [7].

Following this information, we can say that a certain type of malignant disease is due to the dysregulation of genes in a certain time and way of life. The structural and biochemical changes in malignant cells will influence the development of characteristic bioenergetic processes that at their level will condition the expression of cellular oncogenes to the detriment of anti-oncogenes that are expressed up to now, normally in an aerobic metabolism, [8], (Scheme 4). Ongoing research has highlighted the fact that the direction of the synthesis reactions ADP + Pi>---<ATP + H2O can be reproducibly controlled in vitro, depending on the concentration of system factors, pH and ionic strength, making it likely that a functional energy control exists by creating weak bonds between the chemical complexes of the newly formed biologically active substances, (Scheme 5). Otto Warburg observed that many cancers lose their capacity for mitochondrial respiration, limiting ATP production to anaerobic glycolytic pathways [9]

Mechanism involves inhibition of glycolytic ATP production via a Randle-like cycle while increased uncoupling renders cancers unable to produce compensatory ATP from respiration-generation

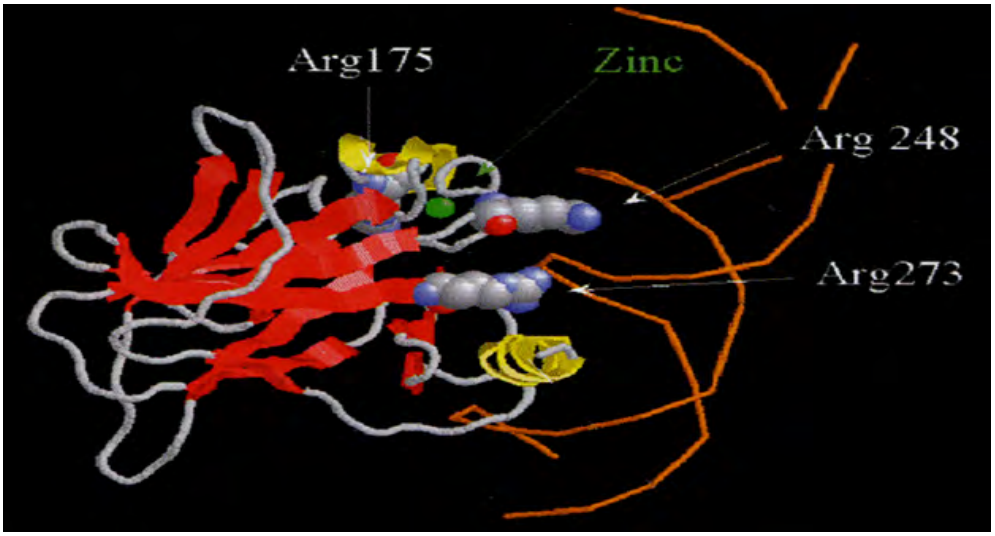
in presence of intact tricarboxylic acid (TCA) enzyme. One mitochondrial adaptation to increased ROS is over-expression of the uncoupling protein 2 (UCP2) that has been reported in multiple human cancer cell lines [10, 11]. Increased UCP2 expression was also associated with reduced ATP production in malignant oxyphilic mouse leukemia and human lymphoma cell lines. Hypoxia reduces the ability of cells to maintain their energy levels, because less ATP is obtained from glycolysis than from oxidative phosphorylation. Cells adapt to hypoxia by activating the expression of mutant genes in glycolysis. Severe hypoxia causes a high mutation rate, resulting in point mutations that may be explained by reduced DNA mismatch repairing activity, [12]. The most direct induction of apoptosis caused by hypoxia is determined by the inhibition of the electron carrier chain from the inner membrane of the mitochondria. The lack of oxygen inhibits the transport of protons and thereby causes a decrease in membrane potential. Cell survival under conditions of mild hypoxia is mediated by phosphoinositide-3 kinase (PIK3) using severe hypoxia or anoxia, and then cells initiate a cascade of events that lead to apoptosis. After DNA damage, a very important regulator of apoptosis is the p53 protein. This tumor suppressor gene has mutations in over 60% of human tumors and acts as a suppressor of cell division. The genetic changes can be identified by fluorescent probes to chromosomal using a technique referred to as fluorescent in situ hybridization (FISH, [13]. Chromosomal evaluation using FISH can identify certain chromosomal abnormalities of CLL that have prognostic significance. Deletion of part of the short arm of chromosome 17 (del 17 q), with target the cell cycle regulating protein p53, is particularly deleterious, [14], (Figure 4,5).

This abnormality is found in 10% of patients with CCL and has a pure prognosis. Deletion of long arm of chromosome 13(del 13q) is the most common genetic abnormality in CLL with roughly 50% of patients exhibiting this effect. These patients have the best prognosis and most will live many years without the need for therapy.

Agents damaging DNA may increase the expression of p53 and its trans-activation activity, suggesting that p53 acts to protect cells against the accumulation of mutants and their subsequent conversion to a malignant status, [15].

Also, hypoxia itself ca also prevent apoptosis by inducing the expression of the anti-apoptotic protein IAP-2. A typical response to the hypoxic environment, by hypoxia inducible factor 1 for example, is expression of insulin-independent GLUT triggered by HIF 1α insuring maximum glucose uptake for glycolytic ATP generation, [16, 17]. Protein p53, in its normal form, acts in stopping the cell division whenever damage to a cell's DNA is detected, thus giving the cells the possibility of repairing DNA before the errors would duplicate and be passed on to the daughter cells. Over-expression of normal p53 protein can result either in G1 arrest, mediated by p21 protein [or in the induction of apoptosis [18].

The p53 protein is becoming an attractive therapeutic target for anticancer drug discovery. Three classes of p53-targeting compounds have been identified and characterized. The first class are compounds that activate or restore wild-type p53 function and can be used in human cancers, such as Nutlin-1, a cis-imidazole analog. The second class, PKI-587, a dual competitive ATP inhibitor, which is a therapeutic target targeting PI3K, (PI3K-α, PI3K-γ) and mTOR, being an orally bioavailable inhibitor that rescues the p-53 protein isomorph carrying a mutation. of the P-53 gene. The third-in-class heterocyclic compound WYE-354 is a bi-ATP-competitive kinase inhibitor that selectively blocks m-TORC1/2 activities, [19], Antibodies to human p53 have been detected in patients with cancer. These antibodies are highly specific for malignant diseases and are rarely detected in healthy donors or patients having benign diseases. This immune response is correlated with the presence of a p53 gene mutation, leading to the accumulation of an ineffective p53 protein in tumor cells with either tridimensional structure, [20, 21].



Scheme 1: The three-dimensional shape of the p-53 protein structure in the isomorphic state. Five P-53 gene mutations have been identified in hereditary cancer. A mutation screening of cancer cases identified a carrier of the Arginine mutation, (Arg-282).

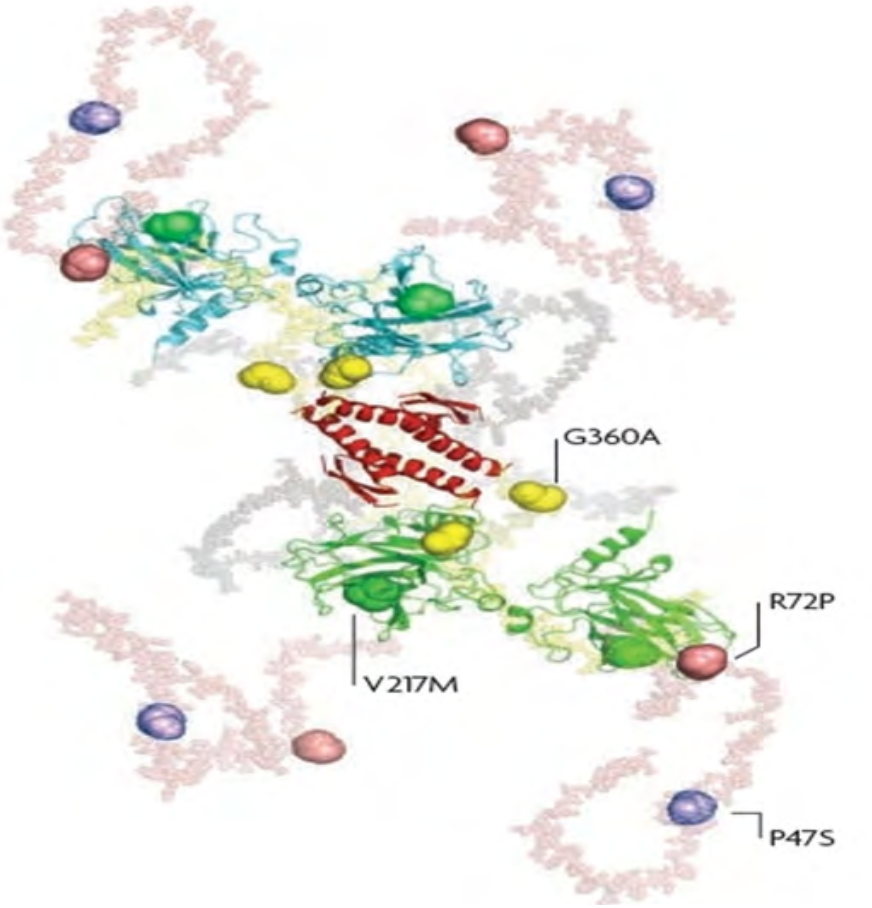
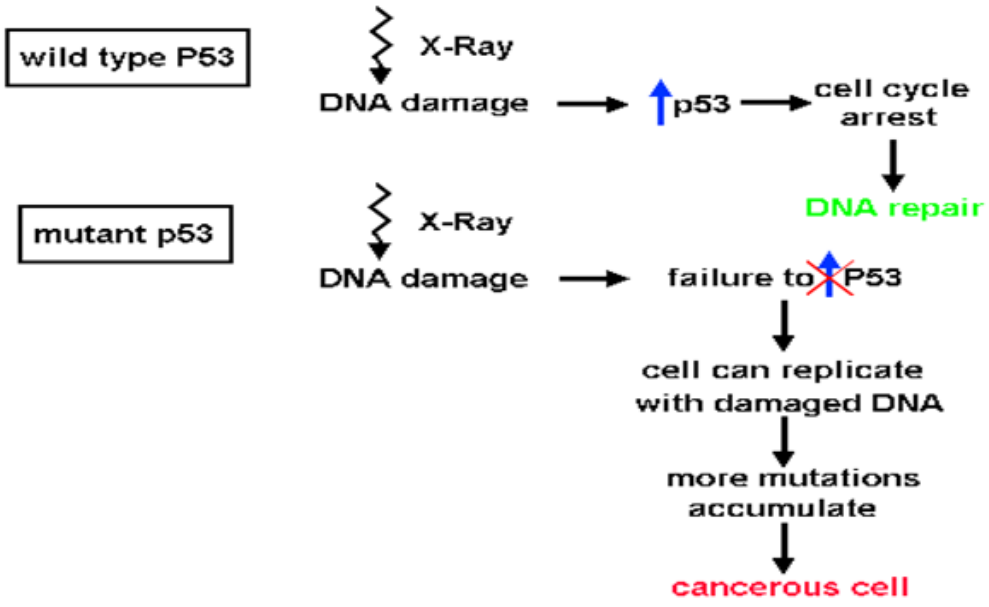
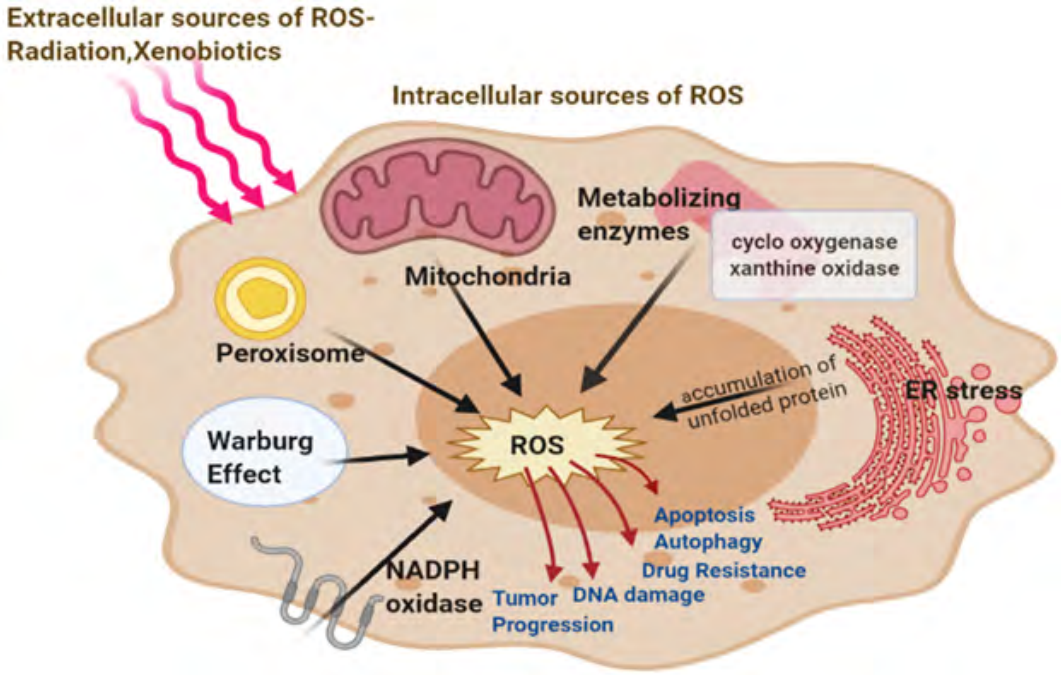


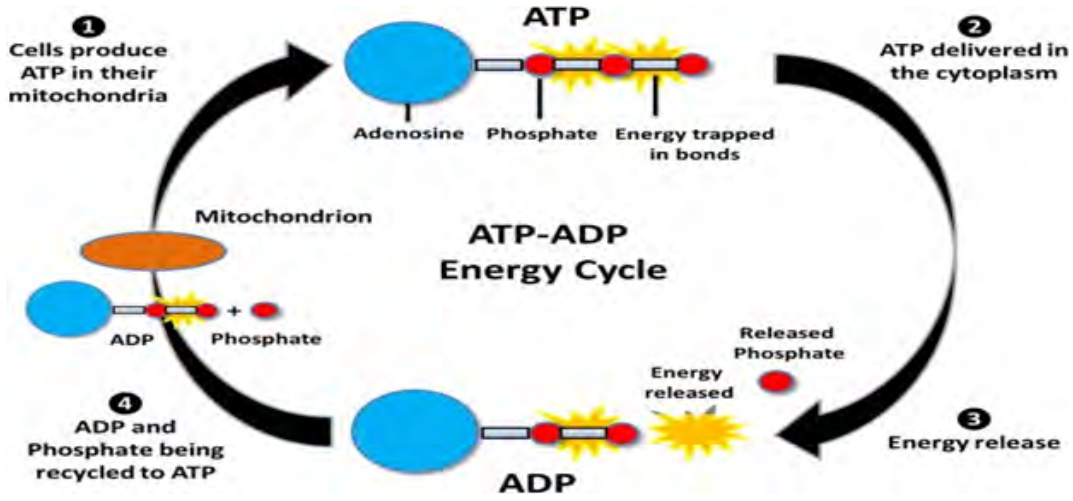
Figure 3: Three-Dimensional structure of p53 in its tetrameric form. The four coding sequence polymorphisms discussed in the text are indicated. Glycine: 360(polymorphic variant is alanine) is displayed in yellow; valine 217(polymorphic variant is methionine) is displayed in green; arginine 72(polymorphic variant in Proline) is displayed in pink; prolone 47(polymorphic variant is serine) is shown in purple. Figure is modified with permission from [160] (C) (2007) National Academy of sciences, USA. Figure courtest of A. Fersht, University of Cambridge, UK.



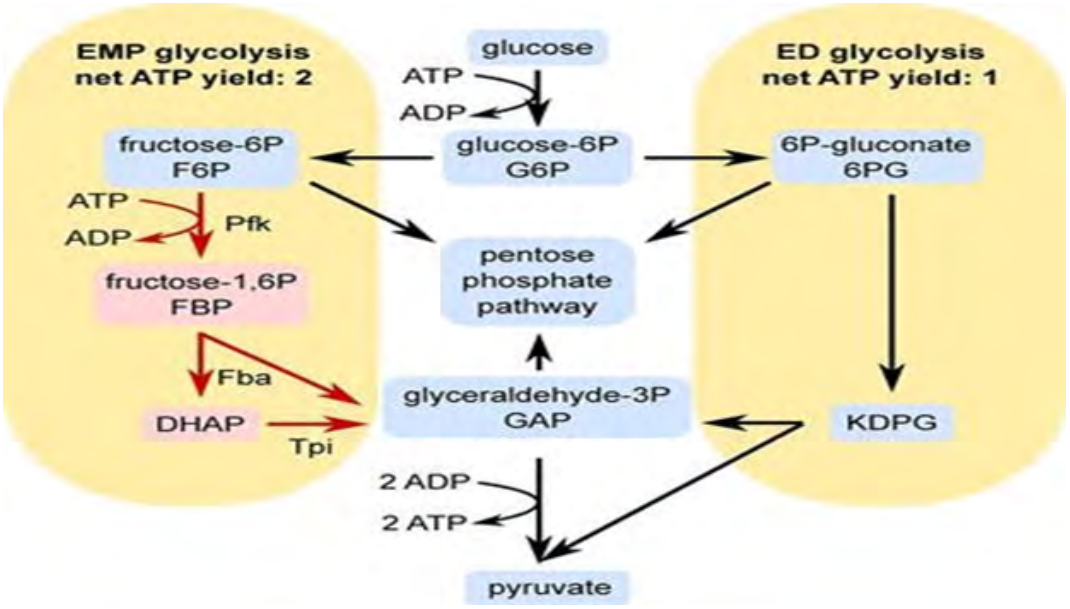
Scheme 2: P-53 isoform protein altered can induce cancer in cells.



Scheme 3: Free oxygen radicals (ROS) of metabolism from various dietary factors may be a major cause of carcinogenesis.



Scheme 4: Cytoplasmic phosphorylation pathways in a cell with predominantly anaerobic metabolism.



Scheme 5: Pathways of ATP production in anaerobic glycolytic pathways.

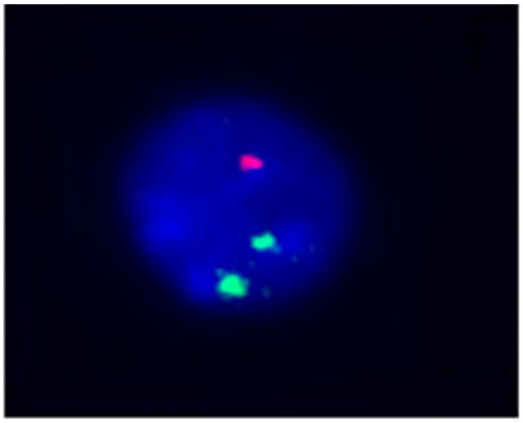


Figure 4: Absence of a specific signal marked with red fluorochrome (TP53 locus) and the presence of two specific signals marked with green fluorochrome (ATM locus), model compatible with the deletion of the TP53 locus.

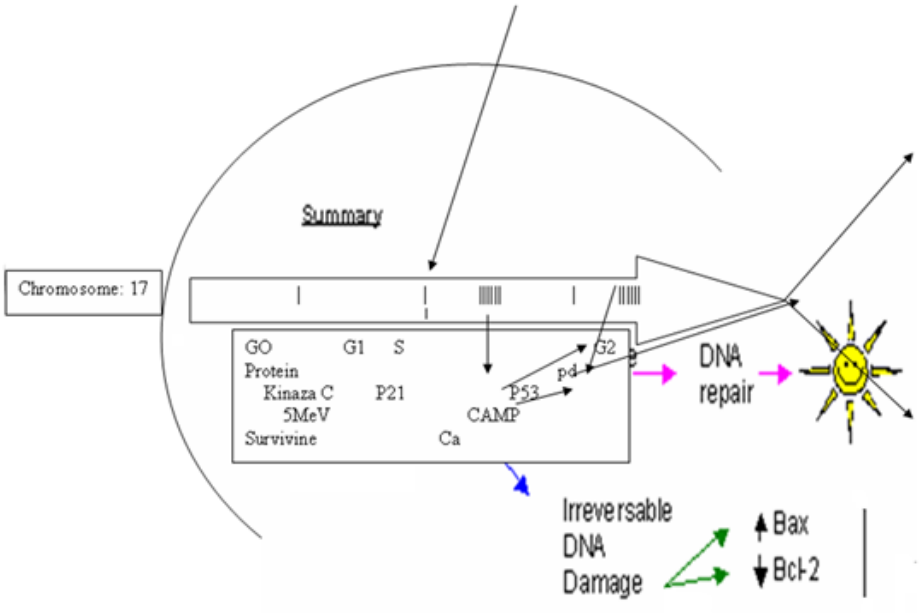


Figure 5: Protein p21 is a cyclin-dependent kinase inhibitor that prevents cell cycle progression at G1. It is induced by wild-type p53 following DNA damage; and p21-null cells are deficient in DNA damage-induced, p53-mediated G1 arrest.

5. Conclusion

Gene mutations, deletions and translocations can be classified as biomarkers of the individual proteomic and genomic profile for all types of cancer. The structural and biochemical changes in malignant cells will influence the development of characteristic bio-energetic processes that at their level will condition the expression of cellular oncogenes to the detriment of anti-oncogenes that are expressed up to now, normally in an aerobic metabolism. Blocked apoptosis from malignant diseases may be due to high ATP concentration originating from anaerobic metabolism initiate suppression of anti-oncogene proteins, specially p53 protein. Further studies are necessary to detect to patients with high concentrations of ATP the mutations, translocations or deletions of the p53 gene that is located on chromosome 17, using FISH technology.

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