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Role of P53 Gene in Oncogenesis from Chronic Lymphocytic Leukemia

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Abstract: Objective of this study is to present the latest researches in the field of molecular medicine, in terms of Chronic Lymphocytic Leukemia (CLL), emerged from the P53 gene deletion in human lymphoma genome. *Method* In recent years proved that the best technique in the investigation of malignant lymphocytes is the Fluorescence in situ hybridization (FISH). This method is used as an alternative to chromosomal banding, a conventional application in molecular medicine. *Previous Results:* In the literature it was registered, in previous years, on an international study, conducted on 109 cases of CLL, 79 cases (72.5%) who had more genetic abnormalities; the remaining 30 cases (27.5%) had normal results, using the technique Florescence in situ Hybridization, (FISH). The majority of patients, 67% (53.79) had a single anomaly and the remaining 33% had two or three genetic abnormalities. The band 14q32 /17p translocations in LLC genome, which appeared similar to some common, had demonstrated abnormalities involving IGH gene, located on chromosome14q32. *Discussions:* Identification of P53 gene mutations in regions of 17 chromosome of hematological neoplasm is important because these mutations have an impact on the clinical course of patients and requires an attitude adjustment therapeutic adequate. Restoring function to p53 can induce lymphoma, apoptosis. Recent, endogenous somatic gene therapy research is a basic of trial clinical and therapeutic trial. The DNA, is used to treat a disease arising as a result of mutations in chromosomal regions. In the past few years, this method has been included in the treatment of CLL, acute lymphocytic leukemia, [ALL], or multiple myeloma [MM]. *Conclusion:* The frequencies of P53 gene mutations and deletion in CLL can be categorized as individual biomarkers in proteomic and genomic profile for this type of leukemia that can be implemented in targeted patient treatment of personalized medicine.

Keywords: P-53 Gene, Lymphocytic Leukemia, Apoptosis, Fluorescence in Situ Hybridization

1. Introduction

Chronic lymphocytic leukemia, (CLL), is a heterogeneous disease, clinically characterized by the accumulation and expansion of a clone population of mature B lymphocytes in blood, bone marrow and lymphoid organs. Initial, genetic events are primarily responsible for the first stage of malignancy transformation and the processes of development and progression of CLL clone are considered to be modulated by signals of different micro-cellular environment, which regulates cell proliferation and survival of malignant B cells.

In the most forms of CLL, the cells are inert and arrested in G0/G1 of the cell cycle and there is only a small proliferative compartment; however, the progressive accumulation of malignant cells will ultimately lead to symptomatic diseases [1].

The diagnosis of CLL can be established initially by optical microscopy morphology combined with immune-phenotyping: monoclonal antibodies in the panel receptors CD5 +, CD20 + and CD23 +, CD28 + B lymphocytes, to intensely positive for CD20, FMC7 and / or CD79b, or coloring negative for CD23 immune-phenotyping, which was seen as an atypical LLC. The receptor CD38+ is considered positive if population distinct lymphocytes exhibit a greater intensity of staining than granulocytes in the sample and is in association with proteins ζ model (ZAP-70). The protein ZAP-70 is a member of the protein-tyrosinekinase family. ZAP70 is normally expressed in T cells and natural killer cells, and has a critical role in the initiation of T-cell signaling. ZAP70 in B cells is used as a prognostic marker in identifying different forms of chronic lymphocytic leukemia

(CLL), with a poor prognostic [2].

Various biological and genetic markers also have prognostic values. Patients with a del. (17p) chromosome or P-53 gene mutation are refractory to repeated chemo-immuno-therapies [3]. In the human body, the *TP53* gene is located on the short arm of chromosome 17. The product of gene P53, protein p53 can arrests the growth cells by holding the cell cycle at the G1/S regulation point on DNA damage recognition. If the *P-53* gene is damaged, tumor suppression is severely compromised. People who inherit only one functional copy of the *P53* gene will most likely develop tumors in early adulthood, a disorder known as Li-Fraumeni syndrome [4].

P-53 gene may also be altered by mutagens (chemicals, radiation or viruses), increasing the likelihood of uncontrolled cell division. Through experimental research demonstrated that more than 50 percent of human tumors contain a mutation or deletion of P53 gene. Loss of function gene p53 creates genomic instability, which often leads to aneuploidy [5].

2. Aim

The objective of this study is to present the latest researches in the field of molecular medicine, in terms of CLL, emerged from the P53 gene with deletions, translocations or mutations in human lymphoma genome and, the prognostic and treatment of this diseases, in function of damages of P53 gene. Also, are following the correlations between characteristics CLL disease and response to treatment with tyrosinekinase inhibitor treatment until the indication of alogenic stem transplantation.

3. Method

In recent years was proved that the best technique in the investigation of malignant lymphocytes is the Fluorescence in situ hybridization (FISH). The method is a gene analysis technique (recombinant DNA technology) and consists of coupling a fluorescent-labeled nucleic acid probes with a specific chromosomal region, (In situ hybridization with digoxigenin or fluorescent classical dye). The method is used to identify the chromosomal abnormalities and its numerical and structural sites.

The principle of this method consists in attaching to the target sequence a single-stranded DNA probes (about 40 kb) fluorescently labeled on the basis of the complementary with a target sequence of a chromosome. Hybridization of the probe with the cellular DNA is visualized in the fluorescence microscope equipped with excitation and emission filters, which enables the reading target as a specific signal. FISH technique allows the detection and chromosomal rearrangements complex. By FISH-engineering, can be detected the chromosome deletions: 7q, 13q, 11q, 14q and 17p, from peripheral blood leukocytes or bone morrow. This test requires cell culturing and the analysis can be performed only in conditions in which leukocyte count is > 10 x 10^3 /µ L and the percentage of immature cells is on blood smear is > 20%. In this aim have to used more types of sample:

- Centromeric probes that have a role in the identification of a particular chromosome and / or numerical chromosome abnormalities. Chromosome-specific probes allow a "coloring" of the entire chromosome or just a region. By staining of two or more different chromosomes can identify the small rearrangements in which they are involved.

-Telomeric probes and subtelomeric locus, specific probes, to identify submicroscopic deletions or duplications (not visible using conventional karyotype). Absence of appropriate fluorescent probe signal on a specific chromosome deletion means (absent) area.

These probes are used for identification of chromosomal breakpoints in case of translocations (abnormal structure involving an exchange of fragments between two or more multi-chromosomes), (Abnova Kits, http://www.abnova.com). Because the cytogenetic abnormalities detected by FISH have prognostic and predictive values, this examination should be performed before initiating therapy.

4. Previous Results

In the previous literature it was registered, on an international study, conducted on 109 cases of CLL, 79 cases (72.5%) who had more genetic abnormalities; the remaining 30 cases (27.5%) had normal results, using the technique Florescence in situ Hybridization, (FISH). The majority of patients, 67% (53.79) had a single anomaly and the remaining 33% had two or three genetic abnormalities. The band chromosomes 14q32 17p translocations in LLC genome, which appeared similar to some common, had demonstrated abnormalities involving IGH gene, located in 14q32 region [6].

The 90 cases of CLL were analyzed for the presence of lymphocytic membrane receptor of B lymphocytes, CD38 and the 81 cases were placed in groups of prognosis. Nineteen (23%) of 81 were CD38 + with a poor prognostic. A similar percentage of cases CD38 + was present in cases with del. 17q chromosome and 11q (33%), translocation (4q-11q (36%)) and cases results FISH normal were in percentage [33%]). CLL cases with trisomy 12 or isolated 13q- had the lowest percentage of CD38 + cases; 15% and 8%, respectively. ZAP-70 receptor was tested in 36 cases; 10 were positive [7].

Deletions of chromosomal region 13q14 were frequently associated with cases of CLL, and lymphocytosis with monoclonal B cells may precede occasionally CLL or aggressive lymphomas and is suggested that this region contains a tumor suppressor gene, similar to gene P-53 with who combine their work. All this leads us to conclude that the appearance CLL deficiency occurs through a common P-53 gene and chromosomal region 13q14 gene.

CLL and Hodgkin Lymphoma (HL) are particularly dependent on their microenvironment and have associated signaling pathways and deletion of miR15/16 locus, common in

specially, in CLL. Micro-ARN, miR15 and miR16 are located at chromosome 13q14, a region deleted in more than half of B cell chronic lymphocytic leukemia (B-CLL). Detailed deletion and expression analysis shows that miR15 and miR16 are located within a 30-kb region of loss in CLL and that both genes are deleted or down-regulated in the majority (approximately 68%) of CLL cases). Micro-RNA deletions, miR-15a / 16-1, both accelerate the proliferation of human B cells by modulating the expression of genes that control cell cycle progression. These results define the role of the 13q14, with deletions P-53 in the pathogenesis of CLL [8, 9].

5. Discussion

In the normal cells, suppressor gene P53 gene, coding proteins that bind to DNA and regulate the expression of genes, prevents the genome mutations. A mutation of the gene P-53 will inevitably lead to a process of carcinogenesis in which the cell divides endlessly [10]. In recent years proved that the best technique in the investigation of malignant lymphocytes is the FISH technique and this method is used as an alternative to chromosomal banding, a conventional application in molecular medicine [11]. Identification of P53 gene mutations in regions of 17 chromosome of hematological neoplasm is important because these mutations have an impact on the clinical course of patients and requires an attitude adjustment therapeutic adequate [12].

However, the primary pathogenic event that lead to growth, proliferation and survival of B-cells in CLL is difficult to determine. Molecules involved in B cell receptor (BCR) signaling pathways and constitutes rise to cytoplasmic survival factors, acting in concert to confer resistance to apoptosis, [Figure 1].

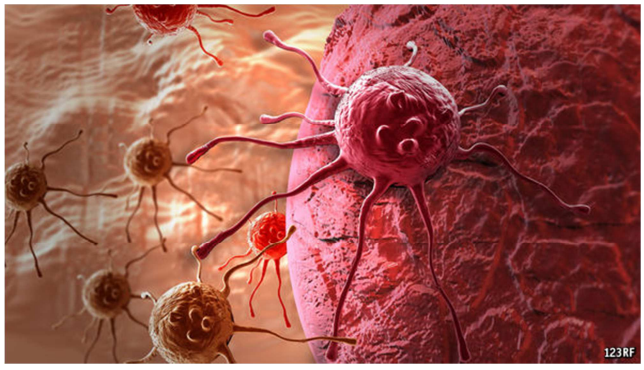

Figure 1. *Malignant cells with BCR receptors in pathways to receptors of tissues.*

Restoring function to p53 can induce lymphoma, apoptosis. Recent, endogenous somatic gene therapy research is a basic of trial clinical and therapeutic trial. The nucleic acid, DNA, is used to treat a disease arising as a result of mutations in chromosomal regions. In the past few years, this method has been included in the treatment of CLL, acute lymphocytic leukemia, [ALL], or multiple myeloma [MM], [13]. Cancer genome sequencing studies confirm that P53 is the most commonly mutated tumor suppressor gene in human cancers. The majority of studies indicate that the presence of mutated P53is associated with bad prognosis in various cancer types. Five new P53 mutations were identified in six pedigrees from hereditary cancer clinics, (17p13.1), [14].

Mutations in the p53 gene are known primarily to inactivate properties onco-suppressor protein p53 wild type, losing the function of transcription (loss-of-function - FOL), and this can arm cancer cells with new oncogenes (gain-of -function - GOF). P5-53 when the gene exerts its function, glucose uptake is enhanced by a GOF producing shunt glucose transporter, Glut-1 on the surface of the cancer cell membrane [15]. Encoded by the mutated gene variants P-53 tumor suppressor proteins p53 isoforms function of onco-proteins they acquire assets, promoting tumor growth and metastasis, [Figure 2].

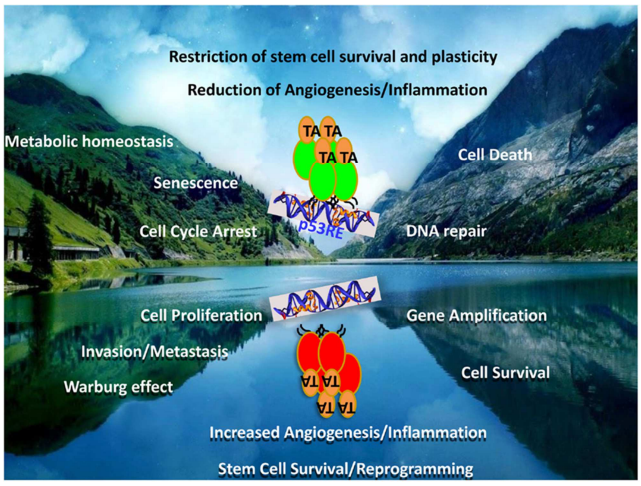

Figure 2. *Many of the functions of the tumor suppressor protein p-53 are emphasis as a mirror image, the functions of oncogenic mutant invasion of metastasis; metabolic homeostasis versus Warburg effect, increase in angiogenesis and inflammation, stem cell reprogramming survival.*

During the development of the transformed cells, the p53 protein derived from the mutated allele P-53 coexists with the wild type (WT) allele of the p53 from the other for different periods of time, until the WT allele is generally lost through loss of -heterozygozity (LOH), resulting solely from the existence of only p53 mutant alleles. Moreover, mutant p53 protein, called "gain-of-function" (GOF), acquires new activities that help cancer aggression. Induction of p53 action is carried out largely by decoupling the p53-MDM2 interaction her, leading to increased levels of p53 [16].

Increasing the amount of p53, in its hyper-phosphorylated state may seem a solution for treating tumors or preventing their spread. However, this is not a useful treatment method, as this can lead to premature aging. The increase in p53 protein level is controlled by two distinct mechanisms: stabilization of the p53 protein caused by the loss of Mdm2 recruitment and an increase in translation of the p53 mRNA [17, 18]. Research has shown that this restoration of function of the protein p-53 can result in regression of certain cancer cells without damaging other cells. For example, restoration of the function of endogenous p-53 can induce apoptosis in lymphoma while cell growth may be reduced to normal levels. Thus the farmacological reactivation of p53 is

presented as a viable treatment option to cancer [19]. The broad spectrum of phenotypes of P53 gene mutations cause cancer is supported by the fact that the p53 protein iso-forms have different cellular mechanisms of prevention against cancer [20], [Figure 3].

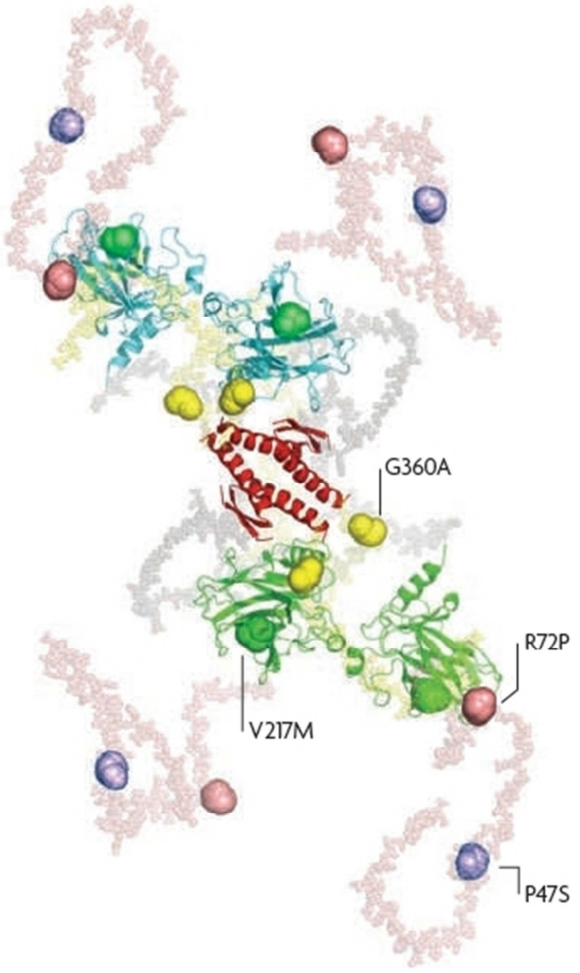

Figure 3. *Mutations in the gene P-53 can give rise to different iso-forms of protein p-53, preventing their functionality overview in different cellular mechanisms and extending thus the phenotype of cancer in mild from to severe.*

Acetylation of p53 is an important means of post-translational modifications and is indispensable for its activation that is a reversible enzymatic process [21]. Both acetylation and deacetylation of p53 are involved in the fine regulation of cellular responses to DNA damage and genotoxic stress [22]. By the Warburg effect, 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, [23]. The broad spectrum of phenotypes of P53 gene mutations cause cancer is supported by the p53 protein isoforms. Mutations in the gene P-53 can give rise to different isoforms of protein p-53, preventing their overview in different cellular functionality Mechanisms and thus extending the phenotypic of cancer from mild to severe [24, 25] [Figure 4].

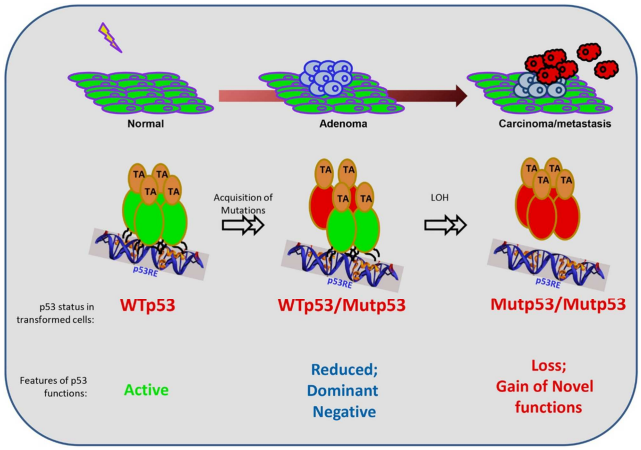

Figura 4. *During the development of function of mutant p53 in a cancer cell, P-53 mutations are not present in normal cases and this induces exposure to a genotoxic allele. Therefore, midway mutant p-53 co-exist with wild-type (WT) p53, before losing the wild-type allele by loss-heterozygozity (LOH). [Sabapathy K, Contribution mutant p53 proteins in oncogenesis. Sci. Re-publication beyond 2015; 5, [23].*

Previous studies have suggested that expression of gene P-53 works like a watch and this has a circadian rhythm. Disruption of the circadian rhythms appears to be associated with accelerating the development of cancer. This "written off" oscillation has been documented clinically and was presented as the mathematical model. Mathematical models indicate also that the concentration of p53 protein oscillate much faster once the exposes to teratogens such as UV radiation. Current models are also useful for modeling protein isoforms of p53 mutations and their effects of oscillation could promote pharmacological drug discovery of chemotherapy in the treatment of CLL [26]. To investigate the patterns of circadian gene P-53, was studied the protein p21 involved in cell division, cyclin D1, CDK1 and cyclin B1 in various stages of carcinogenesis. The profiles were studied a daily by analysis of mRNA of these genes and on these pathways were detect by RT- PCR precancerous lesions chemically induced in normal tissue.

A mutant p53 protein will no longer bind DNA in an effective way, and, as a consequence, the p21 protein will not be available to act as the "stop signal" for cell division [27], [Figure 5].

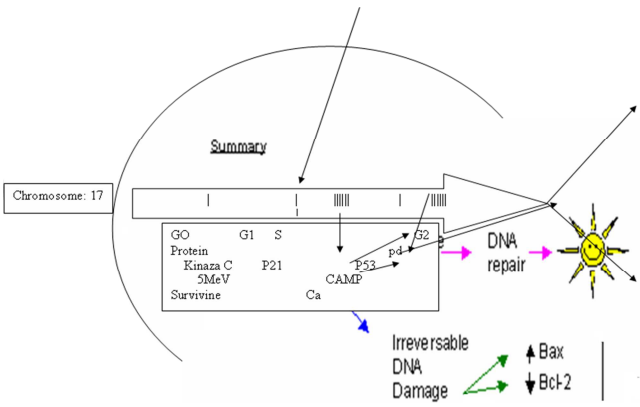

Figure 5. *The p21 protein functions as a regulator of cells cycle progression at G1 to S phase, controlled by the tumor protein p53.*

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, [2].

In the current studies, the investigators described a new mechanism of regulation of p21 by the MTORC1/4E-BPI pathway. Mammalian Target of Rapamicin (mTOR), is a master regulator of proteins synthesis that under ordinary conditions induces cells to grow and divide. However, in cancer cells the mTOR pathway, does not function correctly, and the signals tumor cells to grow, divide, undergo metastasis, and invade new healthy tissues. The 4-EBPI gene encodes, the factor 4E-binding protein, which has function of repressor protein. The current study showed that non-phosphorylated 4E-BPI interact with protein p21 and induces its degradation, thus p21 levels is strongly correlated with m-TOR activity, but not with protein p53 status. The study was published in February 2, 2016, online edition of the Journal Nature Communication (www.cnio.es).

Protein p-53 has an important role in the regulation of glycolysis. Most experimental evidence seems to indicate that, in agreement with its tumor suppressor role, p53 is capable of lowering glycolysis [27]. This activity can be regarded as an attempt by p53 to counter the acquisition of aerobic glycolysis usually associated with cancer cells. Of major interest, p53 has been identified as an important regulator of glucose transport, and wild-type p53 was shown to repress transcription of both *GLUT1* and *GLUT4* promoters in transfection assays ways, such as glycolysis. In contrast, mutant p-53 not impairs activity of GLUT1 and GLUT4 receptors [28]

The dynamics of p53 protein, together with its antagonist MDM-2, show that protein p-53 levels in units of normal concentration, varies in function of time. This "written off" oscillation has been documented clinically and be presented as the mathematical model. Mathematical models indicate also that the concentration of p53 oscillates much faster once to the expose at teratogens such as UV radiation. Current models are also useful for modeling protein isoforms of p53 mutations and their effects of oscillation could promote pharmacological drug discovery in chemotherapy in the treatment of CLL farmatokinetic, [29].

6. New Cancer Therapies

Somatic gene therapy has become a research table in clinical trials using a therapeutic DNA, for the treatment of diseases. In gene therapy, for example, stem cells from peripheral blood are altered by the introduction of functional genes in their genomes. The most common form of therapy DNA encoding uses a functional gene to replace a mutated gene, the polymer molecule is packaged in a "vector" molecule into the genome of the cells, [30]. In recent studies has included the method for the treatment of CLL [31-33], acute lymphocytic leukemia (ALL), and multiple myeloma [MM] [34].

In experimental models, disrupting the MDM2–p53 interaction restored p53 function and sensitized tumors to chemotherapy or radiotherapy. For example in hematologic malignancies, such as multiple myeloma, chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and Hodgkin's disease, the induction of p53 – using a small MDM2-inhibitor molecule, nutlin-3 – can induce the apoptosis of malignant cells [35].

Nutlins are a group of cis-imidazoline analogs which have a high binding potency and selectivity for MDM2. Crystallization data have shown that nutlin-3 mimics the three residues of the helical region of the trans-activation domain of p53 (Phe19, Trp23 and Leu26), which are conserved across species and critical for binding MDM2. Nutlin-3 displaces p53 by competing for MDM2 binding. It has also been found that nutlin-3 potently induces apoptosis in cell lines derived from hematologic malignancies and B-cell CLL with frequent translocation 14q32- 17p, with a good therapeutic response [36].

Some studies showed that patients with cancer make antibodies against p53 proteins, but the frequency and magnitude of this response is still under debate [37]. The most advanced work used a long synthetic peptide mixture derived from p53 (p53-SLP; ISA Pharmaceuticals, Bilthoven, the Netherlands), [38]. The vaccine is delivered in the adjuvant setting and induces T helper type cells. However, the response may not be potent enough to result in clinical benefit as a mono-therapy. Therefore, approaches are being investigated to promote a stronger and more correctly polarized response using both DNA-based and dendritic cell-delivered p53 vaccines.

7. Conclusion

The studies of genotypic and phenotypic chromosomes aberrations by FISH method allow the identification of differential diagnosis at patients with CCL. The frequencies of gene mutations, deletions or translocations of P53, in CLL, can be classified as biomarkers of individual proteomic and genomic profile for this type of leukemia.

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 and requires an attitude adjustment therapeutic adequate.

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