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New Principles of Treatments in Malignant Hematological Diseases, as Acute and Chronic Lymphocytic Leukemia or Multiple Myeloma

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Abstract: Aim of this study is to present the latest researches in the field of molecular medicine, in terms of treatments in malignant hemopathies, emerged from the P53 gene deletion in human lymphoma genome. Method: In recent years proved that the best techniques in the investigation of malignant lymphocytes are the Flow Cytometry, Elisa, ICT and Fluorescence in Situ Hybridization (FISH). This method is used as an alternative to chromosomal banding, a conventional application in molecular medicine. Discussion: 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, Apoptosis, Fluorescence in Situ Hybridization, Phosphatase-Tensin Homolog, Tumor Necrosis Factor Receptor, Antigen Presenting Cells

1. Introduction

B-cell chronic lymphocytic leukemia (B-CLL) is one of the most common hematologic malignant diseases which had especially to the elderly. It is particularly interesting that, although known as a pathological entity and studied for decades, CLL remains an incurable disease in patients who require therapeutic intervention. While some patients had quickly disease evolution and with a final immediately, other patients can survive for years without even require treatment. In the normal cells, the flux of glucose is directed in a path lipogenic de novo, which is regulated in part by the enzyme phosphoinositol-3 kinase (PI-3K) activation dependent on the ATP-citrate lyase (ACL), which is a cytosolic enzyme which catalyzes the production of acetyl CoA citrate. Inhibition of ACL leads to a loss of B cell growth and viability of the cell [1].

Phosphatase-tensin homolog (PTEN) is a tumor suppressor protein that regulates enzyme phosphoinositol-3 kinase (PI-3K). Several mutations or loss of function of PTEN affects lipid phosphatase activity which leads to development of a variety of cancers. Of the three residues of component PTEN, residue R-335 was observed as important to interact with the membrane cellular, in common with several other mutations in the germ line and was associated with cancers inherited [Figure 1], [2].

Also, the cytosolic NADPH may be limited to cell proliferation, since its level is essential to reduce the equivalents of fatty acid and cholesterol biosynthesis, and for the modulation of the oxidative stress [Figure 2].

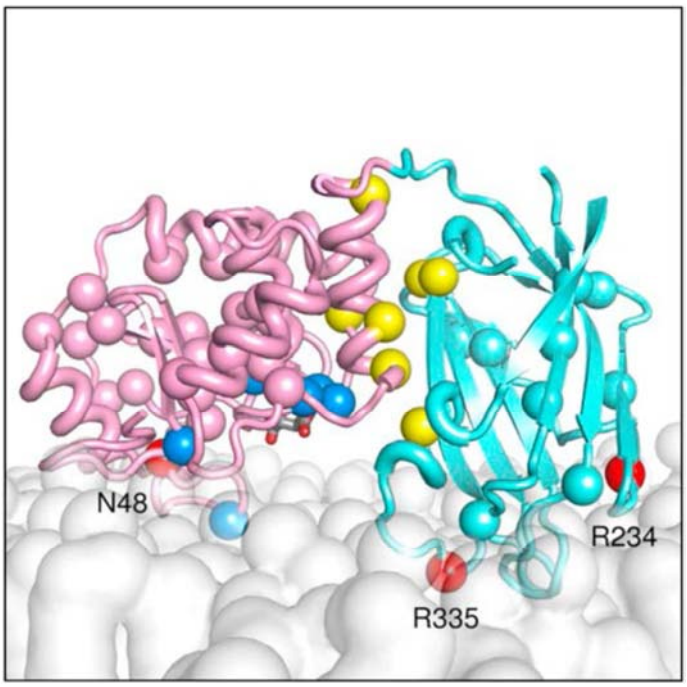

Figure 1. *Phosphatase-tensin homolog (PTEN) enquired in the membrane locations that interact with receptors which will expresses clinical mutations. (Defining the Membrane-Associated State of the PTEN Tumor Suppressor Protein. Biophys J, 2013).*

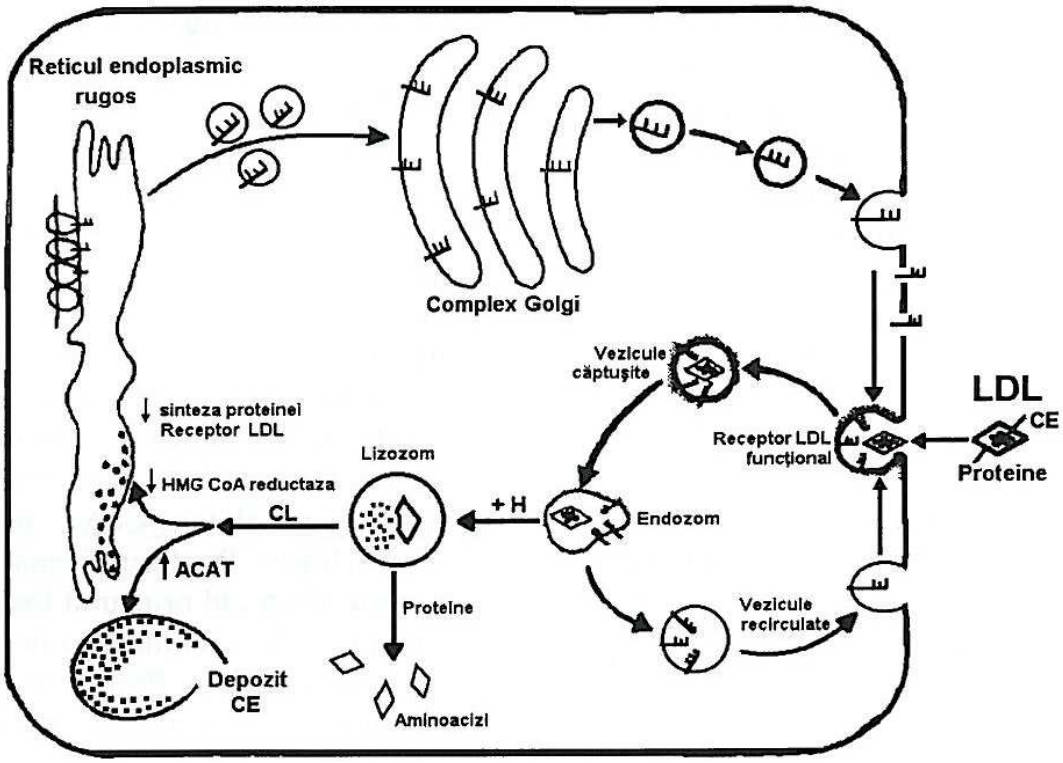

Figure 2. *Metabolism of LDL-Co with cholesterol biosynthesis and modulating oxidative stress.(Cutting edge: distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4+ T cell subsets. J. Immunol 2011}.*

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 or translocations in human lymphoma genome and the prognostic and treatment of this diseases, in function of damages of P53 gene.

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, MGG). 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.

4. Previous International Researcher

It is know from experimental studies that metformin, an anti-hyperglycemic agent induces apoptosis in CLL cells. The main effect of this drug in the biguanide family, is to reduce acute hepatic glucose production, particularly by a transient inhibition of mitochondrial respiratory chain. It has been suggested that metformin may inhibit the growth of cancer cells by reducing cellular energy state [3]. In cancer metabolism research in the past decade, increased understanding of the importance of glycolysis associated with cell growth and proliferation. Development of hypoxia in tumors is accompanied by a significant accumulation of nucleoside adenosine (ADO) in the range of 50-100 μM. [4]. By contrast, ADO levels in normal tissues have been found to be 10-50 μM. It has been proven that ADO can directly boost tumor cell proliferation and angiogenesis [4].

Latest studies have shown that signaling lymphocyte B cell receptor (BCR) is regulated in part by the amount of cholesterol in the cell membrane. It has been found that statins (Lovostatin), pharmacological inhibitors of cholesterol synthesis, induce apoptosis of CLL cells in vitro and in vivo. In addition, ectopic expression of CD5 in B-cell line stimulates the transcription of genes involved in cholesterol synthesis [5]. B lymphocytes express a variety of specific surface antigens which can be targets for the chimeric antigen receptor (CAR) that destroy leukemia cells [Figure 3].

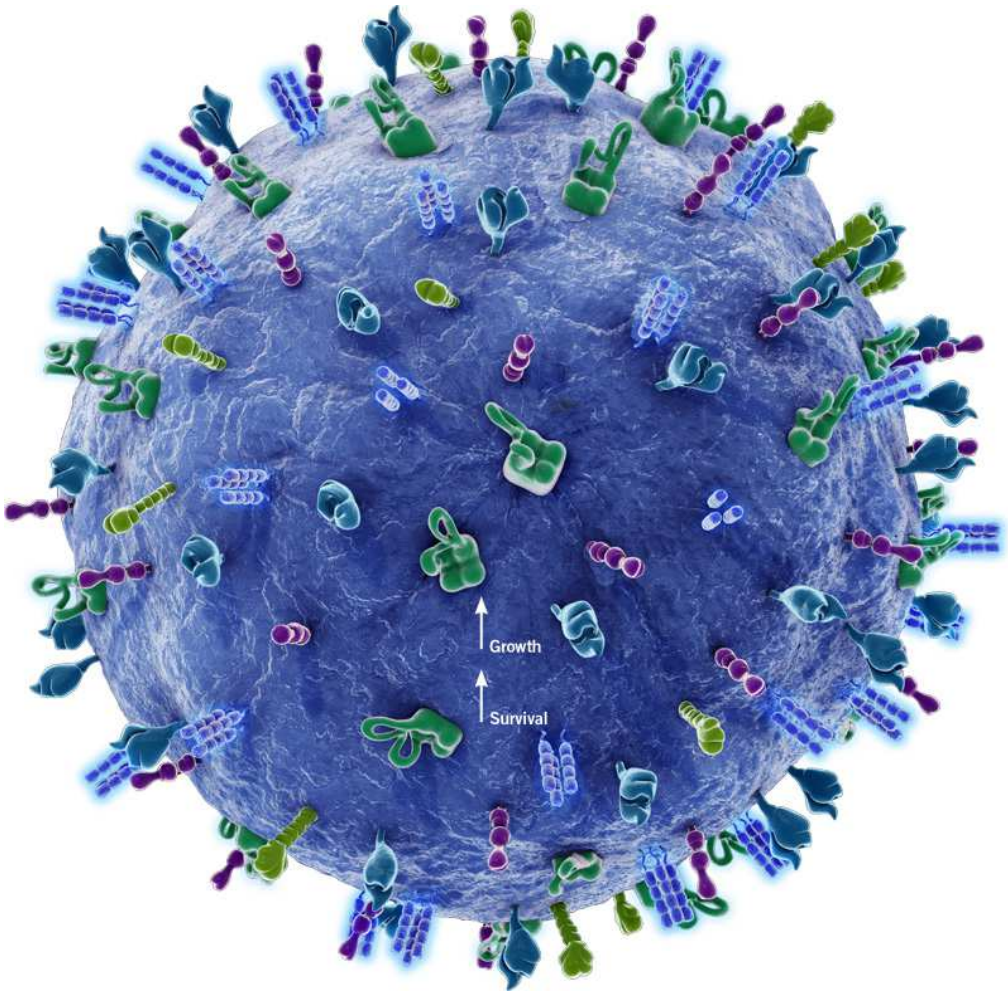

Figure 3. *Overexpression of the cell receptor on the cell surface of malignant B cells express a variety of specific surface antigens that could theoretically act as targets for the chimeric antigen receptor (CAR), [Cloning and Genetic Modification. Association of Reproductive Health Officials 2013}.*

CD40 receptor, a tumor necrosis factor receptor (TNF), TNFRSF5 product gene sequence, expressed during the development of B-lymphocytes and plays an important role in the activation of T cells mediated a high level of CD40 expression has been detected in a wide range of malignant cells, including lymphocytes neoplasm type B. However, the primary pathogenic event leading to the growth, proliferation and survival of B-lymphocytes in CLL it is difficult to determine. Molecules involved in B cell receptor (BCR) signaling pathways constitutes rise to cytoplasmic survival factors, acting in concert to confer resistance to apoptosis [6].

CD44 receptor is a molecule multi-structural and multifunctional surface of cells involved in cell proliferation, cell differentiation, cell migration, angiogenesis, presentation of cytokines, chemokines, and growth factors and receptors that signal for cell survival. All these biological properties are essential for physiological activities of normal cells, but they are also associated with pathological activity of cancer cells, according associated manifestations. The experiments in recent years have shown that targeting anti-CD-44 antibody for cancer cells significantly reduces the activities of various malignant neoplasm [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. 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 [8].

Increasing of amount p53 protein seems a solution for preventing or treating their tumors spread. However, this is not a useful treatment method, as this of can lead to premature aging. Restoring normal function of endogenous p53 some holds promise. Research has shown that this restoration of function of the protein p-53 of can result in regression of cancer cells certain without damaging other cells. The dynamics of p53 protein, together with its MDM-2 antagonist, indicates that p-53 protein levels, in units of normal concentration, vary in function of time. Mathematical models indicated the concentration of p53 also oscillates much faster once with the expose to the theratogens such as UV radiation. Current model also was useful for modeling protein isoforms p53 mutations and their pharmacological effects of oscillation could the promote drug discovery in the treatment of CLL chemotherapy [9].

Pharmaceutical products, Nutlinii, are a group of analogs of cis-imidazoline having a high binding potency and selectivity for MDM2. Recent data have shown that NUTLINE-3, mimicked the remains of three helical region of the area of trans-activation of p53 (Phe19, Trp23 and Leu26), which are conserved across species and critical for MDM2 binding. NUTLINE-3 displaces p53 by MDM2 compete for binding. Also, it has been found that strong NUTLINE-3 induces apoptosis in cell lines derived from hematological malignancies and B-cell CLL, with frequent translocations 14q32- 17p with a good therapeutic response [10].

5. Discussions

The most common form of therapy using chromosomal DNA using a 53 P-functional gene to replace it with a P-53 mutant gene of the DNA chain of the polymer molecule and is packaged in a "vector" target. In recent research has included this method to treat (LLC) [11]. The molecular complex, Toso, has been described as a marker over-expressed in CLL cells as a new anti-apoptotic factor in the pathogenesis of CLL by stromal interaction with the CD40 molecule. In recent years shows that the Toso is associated with progressive disease and proliferative in leukemia CD38 + subset of CLL prognosis is poor. It also found that the receptor CD150 thus could trigger cascading PI3K / Akt (phosphatidylinositol 3 kinase Akt-mediated protein kinase B) signaling pathway) in malignant B cells [12].

Activated mTOR complex, especially mTORC1, best known for action in protein synthesis, as a transcription factor, it was also involved in the development of oxidative stress in the endoplasmic reticol (ER) oxidative. Activation of the PI3K / Akt is perhaps the most common spontaneous lesion in human cancers. Activated PI3K / Akt leads to excess glucose uptake and increase anaerobic glycolysis. Like PI3K, Akt and mTORC1 as the onco-gene myc transcription factor is important metabolic roles beyond increased glycolysis and carcinogenic progression. Myc proto-oncogene is involved in the synthesis of nucleotides and amino acids, as well as by adjusting direct transcription and by increasing the synthesis of precursors of mitochondrial metabolites, the metabolism of malignant cells. [Figure 4], [13].

PI3K / AK T / mTOR usually activated in human cancers, is a key regulator in cell survival, protein synthesis and glucose metabolism. AKT, which is downstream of PI3K, and stimulates glycolysis by increasing the expression of membrane translocation of glucose transporters and glycolytic phosphorylation of key enzymes, such as hexokinase, the increasing glucose uptake Glut1 transporter, and increases the flow of glycolysis. Activated Akt, also ACL, promotes the conversion of citrate into acetyl-CoA for lipid synthesis.

The drug Crizotinib, a tyrosine kinase inhibitor targeting the AKT showed a significant increase in progression-free survival of leukemia, but the reality remains that most patients treated with these drugs will obtain clinical responses in the short term to possible development of resistance mechanisms that lead to disease progression and moarte. lor. Micro ribonucleic acid, miRNA, acts as a regulator of genes similar as a transcription factors and determine gene expression patterns in the cell. This is an interesting observation because miR-34 RNA was identified

as a target goal of P53 gene to aid in its pro-apoptotic functions [14]. Various mechanisms of resistance to apoptosis in CLL have been described, such as receptor over-expression of BCL2-mediated depletion of inhibitors of miR-15 and miR-16.3, [15].

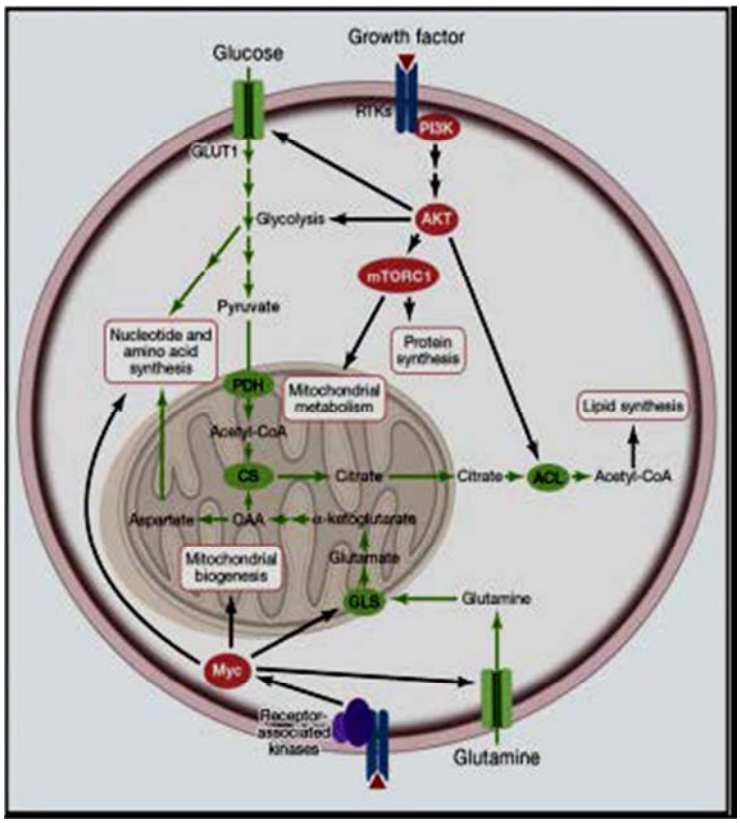

Figure 4. *Alterations in oncogenes classical cells with neoplastic transformation. (Aerobic Glycolysis: Meeting the Metabolic Requirements of Cell Proliferation. Annual Review of Cell and Developmental Biology 2011}.*

The T cell activation leads to increased glucose uptake, glycolysis and lipid synthesis to support growth and proliferation [16]. Activated T cells were identified with Membrane T receptors (TCR), CD7, CD5, CD3, CD2, CD4, CD8 and CD45-RO. At the same time, the expression of CD95 and its ligand cause death or the apoptotic cells through autocrine and paracrine mechanism during inflammation by interleukin induce of IL1-β and interferon-1α. Glut1 glucose transporter over-expression leads to increased glucose uptake and glycolysis and the Glut1 transgene expression in T cells results in an increase in T cell proliferation, survival and cytokine production [17]. CD28 receptor is a co-stimulating action to further activate the cascade PI3K / Akt / mTOR pathway, in particular, and provides a signal to the Glut1 expression. The control mechanisms T reprogramming cellular metabolic are now light, and many of these oncogenes are also crucial to drive the metabolic conversion of T cells, most notably the stimulation of proto-oncogene Myc, hypoxia, factor-inducible hypoxia, (HIF) the mTOR pathway [18].

Recently, it turned out that proto-oncogene Myc as playing an essential role to induce glycolytic metabolism and gene expression of glutamine in the initial hours of T cell activation In a similar way, HIF1 transcription factor-a, can up-regulate gene glycolytic to allow cancer cells to survive hypoxic conditions. Recently, CD73 was investigated as a potential diagnostic marker for T-type leukemia CD73 has been shown to be over-CLL T Expressed and on a subset of clones with a more aggressive clinical behavior and proliferation [19].

Their findings with regard to the regulation of T cell responses principles key provided on the control points of the immune system. T cells express receptors that recognize antigen complexes of cell surface MHC molecules and peptides taken from them almost all proteins in the cell. Recognition at the same time the antigen / MHC ligands co-stimulators of T cells initiate a complex set of genetic programs leading to the production of cytokines, cell cycle progression and the production of factors, anti-apoptotic which results in proliferation and functional differentiation of the cells T.

Thus, T cell activation, as a result of receptor signaling antigen and CD28 co-stimulation of the dendridic cells is followed not only by the induction of genetic programs leading to proliferation and functional differentiation, but also by inducing a program inhibitor mediated receptor CTLA-4, which will eventually stop proliferation [20]. Consistent with the observation that CD28 and CTLA-4 had an effect on T cell responses, it was found that blocking antibody to CD28 and block the antibodies to CTLA-4, improved responses anti-tumor program check point (Leach et al., 1996) [Figure 5].

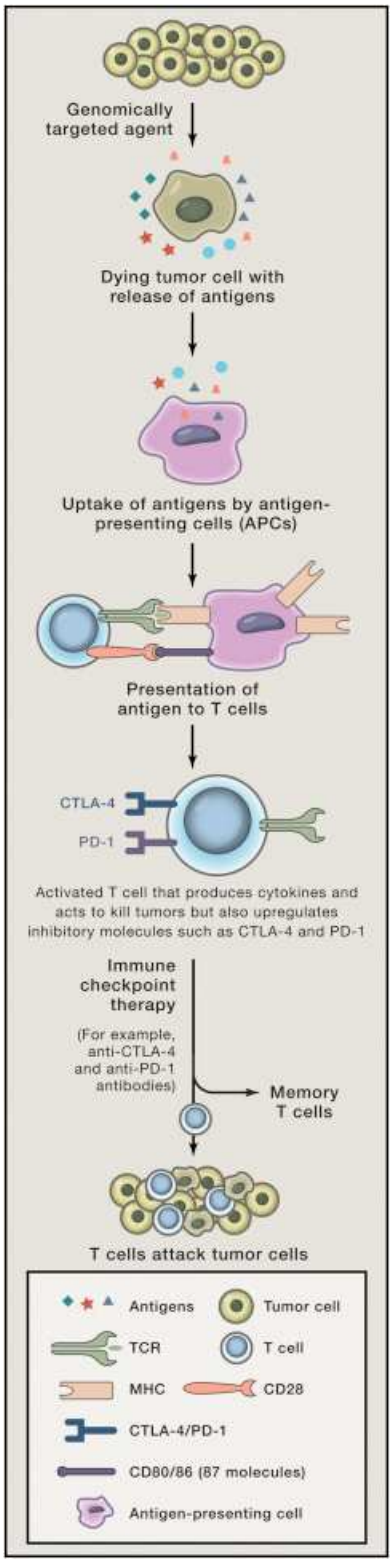

Figure 5. *Another way of inhibiting cell identified after the CTLA-4 receptor is represented by PD-1 (programmed to the pH) and PD-L1, or ligand. Like CTLA-4, PD-1 is expressed only in activated T cells to stop their proliferation at a time, limiting the production of memory T lifocvite type. However, in contrast to CTLA-4, PD-1 inhibits T cell responses by interfering with T cell receptor signaling, as opposed to out-Competing CD28. There are ongoing clinical trials with anti-CTLA-4 (ipilimumab, Med-Immune / Astra-Zeneca) plus anti-PD-1 or anti-PD-L1 in other types of tumors with preliminary data showing promising results (Abstract. Callahan et al 2014, J. Clin Oncol).*

6. Immune Therapeutic Success

After the chimiotherapy treatment, the tumor antigens are taken up by antigen presenting cells (APC) and are presented in the context of co-stimulatory molecules B7. T cells recognize antigens to become activated. T cells can differentiate into memory T cells that can be reactivated in the presence of recurrent tumor. Another way of inhibiting cell identified after the CTLA-4 receptor is represented by PD-1 (programmed to the pH) and PD-L1, or ligand. Like CTLA-4, PD-1 is expressed only in activated T cells to stop their proliferation at a time, limiting the production of memory T lymphocyte type. However, in contrast to CTLA-4, PD-1 inhibits T cell responses by interfering with T cell receptor signaling, as opposed to out-competing CD28. There are ongoing clinical trials with anti-CTLA-4 (Ipilimumab, Med-Immune / Astra-Zeneca) plus anti-PD-1 or anti-PD-L1 in other types of tumors with preliminary data showing promising results (Abstract. Callahan et al 2014, J. Clin Oncol).

7. Conclusion

We conclude that the most important cellular mechanisms for regulating the metabolic pathways of energy in malignant B cells and T are receptors on the cell membrane, in relation to caspases, Bcl-2 family of proto-oncogenes, tumor suppressor gene P-53, TNF and recent Micro (miRNAs), which acts on the posttranscriptional level to regulate the expression of the protein [21, 22, 23, 24].

Combination therapy can improve the anti-tumor responses. Recently, somatic gene therapy is based on climate science and therapeutic. DNA (either integrated into the genome plasmid or external) is used experimentally to treat a disease that occurs due to mutations in chromosomal regions. In recent years, this method has been included in the treatment of CLL, acute lymphocytic leukemia [ALL], or multiple myeloma [MM]. The mutant genes and frequency its deletions in CLL can be regarded as biomarkers proteomic and genomic profile individual in this type of leukemia that can be put in place to treat the patient in personalized medicine.

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