
Review Article

Signaling Pathways in Leukemia: Any Role for Medicinal Plants in Leukemia Therapy

Paul Takam Kamga¹, Armel Herve Nwabo Kamdje²

¹Department of Medicine, Section of Hematology, Stem Cell Research Laboratory, University of Verona, 37129, Verona, Italy

²Department of Biomedical Sciences, Faculty of Sciences, University of Ngaoundere, Ngaoundere, Cameroon

Email address:

takoumba@yahoo.fr (P. T. Kamga), kamdjewa@yahoo.fr (A. H. N. Kamdje), armel.nwabo@gmail.com (A. H. N. Kamdje)

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Abstracts: Leukemia is a cancer of the early blood-forming cells. Most often, leukemia is a cancer of the white blood cells, but some leukemias start in other blood cell types. Scientists in the U.S. believe they have identified a new pathway in the progression of chronic myelogenous leukemia (CML). They have also discovered that an extract from the root of a common ornamental plant can suppress the process. Drug discovery from natural sources involve a multifaceted approach combining botanical, phytochemical, biological, and molecular techniques. Accordingly, medicinal-plant-based drug discovery still remains an important area, hitherto unexplored, where a systematic search may definitely provide important leads against various pharmacological targets. Ironically, the potential benefits of plant-based medicines have led to unscientific exploitation of the natural resources, a phenomenon that is being observed globally. This decline in biodiversity is largely the result of the rise in the global population, rapid and sometimes unplanned industrialization, indiscriminate deforestation, and overexploitation of natural resources, pollution, and finally global climate change. Therefore, it is of utmost importance that plant biodiversity be preserved, to provide future structural diversity and lead compounds for the sustainable development of human civilization at large. This becomes even more important for developing nations, where well-planned bioprospecting coupled with nondestructive commercialization could help in the conservation of biodiversity, ultimately benefiting mankind in the long run. Based on these findings, the present review is an attempt to update our knowledge about the role of signaling pathways and medicinal plants in Leukemia therapy.

Keywords: Leukemia, Signaling Pathways, Medicinal Plants, Therapy

1. Introduction

Leukemia is a cancer of the early blood-forming cells. Most often, leukemia is a cancer of the white blood cells, but some leukemias start in other blood cell types. Leukemia is often described as being either acute (fast growing) or chronic (slow growing). Different types of leukemia have different treatment options and outlooks. Many pathways have been reported to promote the development of leukemic cells such as Notch, Wnt, SHH and others. The overexpression of Wnt signaling is also common in many hematological malignancies, and solid tumors. Clinical and experimental evidence suggests that Wnt/ β -catenin activation is critical for cancer development, angiogenesis, migration and invasion [1] [2] [3]. Antagonists of Wnt pathway such as Wnt inhibitory factor 1 (WIF-1),

Dickkopf proteins (Dkks), the secreted frizzled-related proteins (sFRPs), and Dishevelled-axin domain containing 1 (DIXDC1), mitigated tumorigenic and metastatic processes of various cancer types in vitro and in vivo [4] [5] [6]. As Notch and Wnt pathways, hedgehog is an evolutionary and developmental pathway involved in cellular differentiation, but also in physiological and tumorigenic control of postnatal cellular events such as proliferation, cell death, motility, migration and invasion [2] [3]. Notch family of transmembrane proteins encompasses four receptors (Notch1-4), and five ligands (Jagged1/2, Dll-1/3/4). Notch receptors are activated when they bind to a ligand expressed on the membrane of an adjacent cell. Then, the receptors undergo two proteolytic cleavages at S2 and S3 sites performed by ADAM10/17 metalloprotease and gamma

secretase complex, respectively. These two proteolytic events result in the release of an intracellular active form of the receptors called Notch intracellular domain (NICD). Subsequently, NICD domains enter the nucleus where they form a transcriptional activation complex with MALM1 and RBP-jk proteins. This complex will promote the expression of various genes involved in cell fate determination, including for instance *myc*, *cyclinD* and genes of the helix basic family such as *hes1*, and *hey1*. Functionally, products of this transcription will control cell proliferation, cell death, adhesion, invasion, and migration [7]. In a more recent report by Shao and collaborators (2015) Jagged1-induced Notch signaling triggered, migration, invasion, and a Slug-dependent EMT transition in breast cancer cells. All these effects were abrogated by Notch silencing [7], underlining the potential of Notch targeting for the modulation of tumor cell motility. Furthermore, Rho-GTPase upregulation is common in patients diagnosed with T-cell acute lymphoblastic leukemia (T-ALL), a hematological malignancy where Notch activating mutations are observed in more than 50% of cases [8]. Scientists in the U. S. believe they have identified a new pathway in the progression of leukemia. They have also discovered that an extract from the root of a common ornamental plant can suppress the process. The exciting new extract is forskolin, which comes from the root of the plant *coleus forskohlii*, a native of India that is used in the U. S. as an ornamental plant. Natural substances have long served as sources of therapeutic drugs, where drugs including digitalis (from foxglove), ergotamine (from contaminated rye), quinine (from cinchona), and salicylates (willow bark) can be cited as some classical examples. The present review is an attempt to update our knowledge about the the role of signaling pathways and medicinal plants in Leukemia therapy.

2. Common Garden Plant May Hold Cure for Leukemia: Signaling Pathway

2.1. Chronic Myelogenous Leukemia (CML)

Scientists in the U. S. believe they have identified a new pathway in the progression of chronic myelogenous leukemia (CML). They have also discovered that an extract from the root of a common ornamental plant can suppress the process¹. The exciting new extract is forskolin, which comes from the root of the plant *coleus forskohlii*, a native of India that is used in the U. S. as an ornamental plant. Their findings may suggest new treatment options for the estimated 4,600 people in the United States who are expected to develop CML this year, in particular those in the advanced stages of the disease, or those who become resistant to the commonly used drug Gleevec. Early results on CML patient cells both in culture and in mice have apparently shown that forskolin reduced the cancer cells' ability to grow by up to 90 percent [1]. Danilo Perrotti, a member of the OSU Comprehensive Cancer Center's Molecular Biology and Cancer Genetics Program and an assistant professor in the department of molecular virology,

immunology and medical genetics, says the findings are significant. He believes they have uncovered a key process that underlies progression in CML and identified an agent that can block it. They have also shown, he says, that forskolin can reinstate normal cell functioning, even in Gleevec-resistant cells that do not respond to any current treatment. CML arises when two chromosomes mistakenly exchange genetic material during cell division. This action creates a new, fused gene that produces a cancer-causing enzyme called Bcr-Abl. This enzyme permanently "turns on" cell growth signals that are normally held in check by molecules called phosphatases, and the result is the uncontrolled production of white blood cells, the hallmark of CML. Apparently patients with the earliest form of the disease may not even be aware they are sick. If discovered early the disease almost always responds to the drug Gleevec, which puts the brakes on Bcr-Abl activity. The Food and Drug Administration (FDA) approved Gleevec as a treatment for CML about five years ago and it was initially hailed as the first "wonder drug" for cancer. But since then, a significant minority of patients who initially responded well to Gleevec developed resistance to the drug. In these patients, white blood cells continue to proliferate and if left unchecked, it leads to the final, acute stage, called the blast crisis, where immature white blood cells infiltrate the blood and the bone marrow. Although doctors easily recognise the signs and symptoms of the different stages of CML, until now, they have had few clues about what actually causes the disease to progress. Perrotti says his studies show that it may be due to the increased activity of Bcr-Abl itself. Perrotti discovered by extensive chemical and genetic tests, conducted in collaboration with an international group of researchers, that Bcr-Abl stimulates a protein called SET, which, in turn, inhibits the phosphatase PP2A. When PP2A isn't working properly, cancer cells are free to grow and spread. It seems that while PP2A suppression occurs in other forms of cancer, Perrotti said their tests reveal that in CML, it only occurs in the blast crisis, and in the initial, chronic phase of the disease. Perrotti remembered from earlier studies that forskolin could restore PP2A function; however although forskolin is currently used in Japan as a broncho- and vaso-dilator and has been tested and found safe in clinical trials in Austria among patients with asthma, it has not been approved by the FDA for use in the United States. In their research Perrotti and his team tested the effects of forskolin on normal, Gleevec -sensitive and Gleevec-resistant CML cells, and discovered that the extract restored normal PP2A function, reduced the cancer cells' ability to grow by up to 90 percent and induced leukemic cell death and differentiation [1]. In the meantime it had no adverse effects upon normal cells. The team found that when leukemic mice which had been treated with forskolin then stopped getting the treatment, some died of leukemia and others showed evidence of Bcr-Abl activity. But once the forskolin treatment was resumed, even weeks after the initial treatment had stopped, Bcr-Abl activity was blocked and normal cell functioning was reinstated. Perrotti says forskolin may well be an additional or potential treatment for patients with CML who have already advanced to the blast phase, but

more pre-clinical and pharmacologic studies need to be done to assess the therapeutic relevance of forskolin in patients with leukemia [9].

2.2. Chronic Lymphocytic Leukemia (CLL)

A multi-center, international, randomized, Phase III study of older untreated patients with chronic lymphocytic leukemia (CLL) demonstrated that ibrutinib, a kinase inhibitor, is significantly more effective than traditional chemotherapy with chlorambucil [10]. The study, which followed 269 patients, revealed a 24-month overall survival rate of 97.8 percent for patients taking ibrutinib versus 85.3 percent for those on chlorambucil. Minor adverse effects were reported [10]. Results from the study, led by Jan Burger, M. D., Ph.D. from The University of Texas MD Anderson Cancer Center, were published in today's online issue of the *New England Journal of Medicine*. "Ibrutinib was superior to chlorambucil in CLL patients with no prior treatment, as measured by progression-free survival, overall survival, and response" said Burger, an associate professor in Leukemia. "The study also revealed significant improvements in hemoglobin and platelet levels." Ibrutinib, marketed as IMBRUVICA® by its developer, Pharmacyclics, an AbbVie Company, was previously FDA-approved for treating mantle cell lymphoma and CLL patients who had relapsed after prior treatments. "CLL is the most common adult leukemia in western countries, and primarily affects older patients with a median age of 72 years at diagnosis," said Burger. "In many countries, chlorambucil has remained the standard first-line therapy for such patients since the 1960s. This study CLL is a disease of B lymphocytes, immune cells that originate in the bone marrow, develop in the lymph nodes, and which fight infection by producing antibodies. In patients with CLL, B cells continuously grow and accumulate in the lymph nodes, bone marrow, and blood, where they crowd out healthy blood cells. CLL cell growth is driven by the B cell receptor (BCR), a molecule on the surface of the leukemia cells, which transmits growth signals into the cells using enzymes, including Bruton's tyrosine kinase (BTK). Ibrutinib attaches itself to BTK, and thereby blocks BTK function, shutting down the growth signals and consequently leading to CLL cell death. Ibrutinib also disables tissue anchor signals on the leukemia cells, removing CLL cells from the lymph nodes' nurturing environment, causing them to starve. Patients were randomly assigned to receive either ibrutinib or chlorambucil, both oral medications. Median age of study patients was 72 years, and 44 percent had advanced stage disease. The median follow-up was 18.4 months, with 87 percent of ibrutinib-treated patients still continuing their treatment at the time of analysis. Side effects occurred in 20 percent of patients and included diarrhea, fatigue, cough and nausea [10].

2.3. Acute Myeloid Leukemia (AML)

New treatment options are badly needed for acute myeloid leukemia, a relatively rare form of cancer. The malignancy begins in the bone marrow, and from there can spread rapidly

to the bloodstream, depriving the body of the essential blood cells that carry oxygen and fight infections¹¹. Now, new work from a team lead by Rockefeller University researchers has revealed a potential genetic weakness of the disease, offering insights into the molecular mechanisms behind acute myeloid leukemia and suggesting a new target for drug development¹¹. Previously, researchers identified a variety of mutations associated with this disease, including a DNA rearrangement found in about 15 percent of patients [3]. The abnormal DNA-binding protein produced as a result of this mutation takes on entirely new functions, dramatically altering a set of genes that are turned on in a cell to promote the cancer. But how this mutation affects these changes has remained mysterious [11]. In their new work published on October 21 in *Genes and Development*, the researchers describe how they identified the molecular mechanism behind this gene activation. The researchers, led by Robert G. Roeder, Arnold and Mabel Beckman Professor and head of Rockefeller's Laboratory of Biochemistry and Molecular Biology, began by searching for proteins that interact with the mutant protein, known as AE, produced by a DNA rearrangement. Their screen identified JMJD1C, an enzyme that removes chemical tags, known as methyl groups, from histones, which are proteins contained in chromosomes. These tags serve as repressive marks, indicating that genes in the associated region should be turned off. To investigate the relationship between JMJD1C and AE, the team first explored the broader effects of removing JMJD1C. "We found that numerous genes were down-regulated upon loss of JMJD1C, and the set overlaps significantly with the genes that are normally activated by AE," explains first author Mo Chen, a postdoc in Roeder's lab. The loss of gene expression turns out to have dramatic consequences for the disease. The team found that acute myeloid leukemia cells are addicted to the presence of JMJD1C, and without it they cannot survive. "In fact, these cells were very sensitive to depletion of JMJD1C," says Chen. "We see an increase in apoptosis, a sort of cellular suicide." The team confirmed that JMJD1C interacts with AE, and demonstrated that the enzyme is required for AE to exert its cancer-promoting effects [11]. But they also found that JMJD1C plays an even a broader role in acute myeloid leukemia, beyond its interaction with AE. "We were very surprised to find that JMJD1C is required for the proliferation of other acute myeloid leukemia cell lines, which do not have AE, so we looked for other proteins that might be responsible for JMJD1C addiction," says Chen. The team found at least two other proteins that can recruit JMJD1C to target genes in diseased cells that lack AE, fueling leukemia growth. These results suggest that JMJD1C may play a general role in promoting growth in myeloid leukemias, according to the researchers. "We are excited because this type of general phenomena is an ideal target for drug development," Roeder says. There are already small molecules that inhibit this class of enzymes. "Our work will facilitate the development of selective inhibitors against JMJD1C, which is a highly promising therapeutic target for multiple types of leukemia," Roeder adds [11].

3. Conclusion

Results from many studies have shown that several pathways play a pivotal role in the development of Leukemic cells such as Notch, Wnt, HSS and others. Some medicinal plants contain the inhibitors of the above pathways. Scientists in the U. S. believe they have identified a new pathway in the progression of chronic myelogenous leukemia (CML). They have also discovered that an extract from the root of a common ornamental plant can suppress the process. The discovery of new medicinal plants with anti-Leukemia activity than harmful leukemic cells and leave leukemia cells unharmed should be consider as the new way to fighting against leukemia and cancer.

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