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Review Article

A Systematic Review on Leukemogenesis: Is there any Pitfall in Human Health

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Abstract

Leukemia is a monoclonal disease that arises when the normal hematopoietic stem cells are replaced by the leukemic cells. The proliferation of the immature cells of the hematopoietic system leads to leukemogenesis. It is an evolutionary process that includes numerous self-governing genetic and epigenetic factors. These changes are accompanied by specified pattern of clonal cytogenetic anomalies. The description of these clonal chromosomal abnormalities, along with detected modifications in other growth promoting factors, provides a vital outline to study leukemogenesis and to understand the occurrence and development of leukemia overall. There is no cure for these dreadful diseases, even with advances in medical technology. Research is ongoing to find the cause of leukemia and its cure, but there is no elixir. This review underlines the leukemogenesis of cancer in an individual highlighting the different risk factors, various transcription factors and pathways that are altered during leukemogenesis and resulting in leukemia.

Keywords: Leukemia; Transcription factors; Leukemogenesis; TKI; Epigenetics

Introduction

Human health is a comprehensive state that includes physical, social, and intellectual wellness. According to Ayurveda, the human frame is made of five elements, which blend together in a scientific way (Figure 1). Leukemogenesis is a multistep process caused by mutations to the DNA of a single lymph-or blood-forming stem cell. Patients suffering from leukemia have severe anemia, bleeding, and reduced ability to protect against infections [1]. Oncogenes and tumor suppressor genes have a significant impact on tumor growth, invasiveness, and metastasis, leading to leukemia.

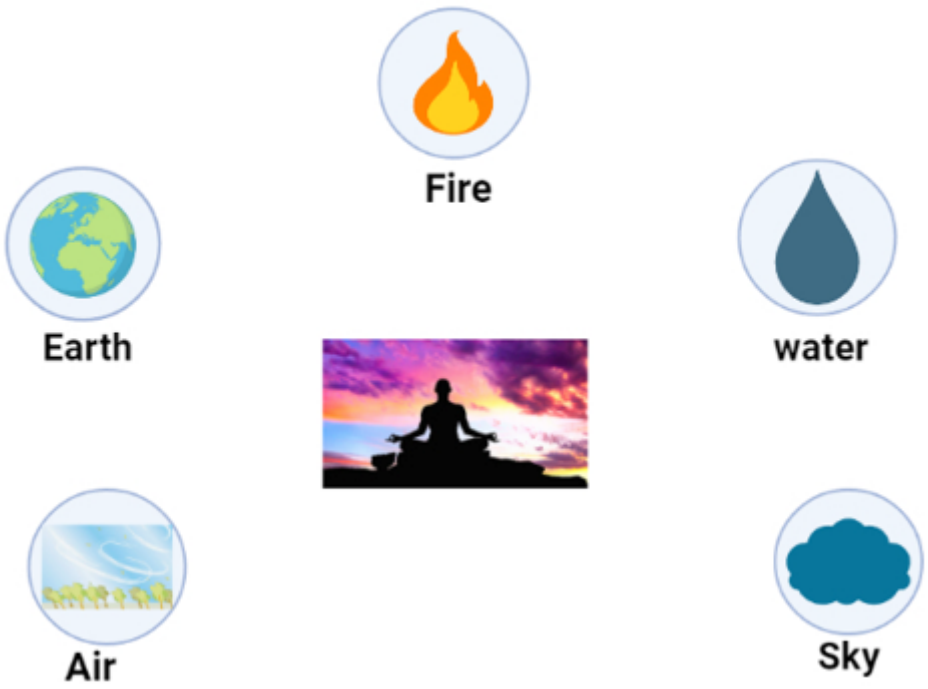

Figure 1: The five elements of human framework.

Method

Systematic Literature Review

In accordance with a predetermined methodology, we used a procedure consistent with the 2009 Preferred Reporting Items for Systematic Reviews (PRISMA) standards to systematically review published research. In order to find human studies written in English and published between December 01, 1992, and March 20, 2021. Several databases including PubMed, Google scholar, Cleveland Clinic and Embase were searched to collect the data. Additional searches were made for conference proceedings from the European Haematology Association (EHA), American Society of Clinical Oncology (ASCO), American Society of Haematology (ASH), and the European Society of Medical Oncology (ESMO) that were released between 2012 and 2021.

Data extraction and screening

Initial searches turned up titles or abstracts, which were then compared to the predetermined inclusion standards (Online Supplementary Methods). For studies whose eligibility was questioned during the title/abstract screening as well as for studies whose eligibility was determined, the full texts were retrieved. Two reviewers separately went through the complete texts to determine which research should be included. A third reviewer settled any disagreements. The Online Supplementary Methods include information on data extraction.

Risk Factors for Leukemogenesis

There are few recognized risk factors for leukemia. One can't control every threat of leukemia, but there are some that can be controlled with life-style management (Figure 2).

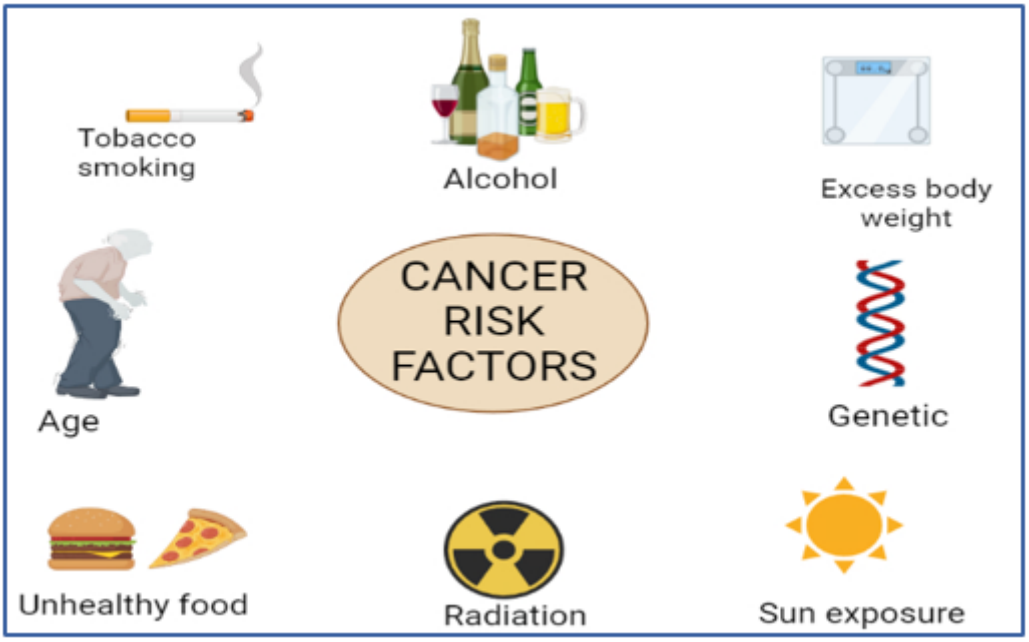

Figure 2: Risk factors associated with cancer.

Risk elements you can have control over includes:

Habit of smoking and alcohol consumption: Cigarette smoking and drinking alcohol may be a risk factor for leukemia and may lead to leukemia of specific morphologic and chromosomal types. They have a negative impact on survival and progression of disease in patients. Thus, the patients should be encouraged to quit smoking and alcohol so that their chance of recovery from disease is more likely in their favour.

Uptake of nutritionally balanced diet: Patients suffering from leukemia need a healthy balanced diet to boost their immune response and to resist infections. The food enriched with antioxidants, proteins and good fat like pulses, whole grains and low-fat proteins such as fish, eggs, fruits and vegetables.

It ought to be noticed that the eating routine of leukemia patients rely upon a lot of factors, such as, severity or the disease stage, age, therapy he/she is going through and other basic physical and medical ailments of the patient.

Avoid exposure to chemical compounds: Exposure to harmful chemicals like, benzene, ethylene oxide, and formaldehyde increases the risk of leukemogenesis. These chemical substances influence the bone marrow and can cause decline in red blood cells, causing anemia. It can also result in extreme blood loss and might influence the immune system, thereby increasing the chances for infection.

Yoga and meditation: Yoga is a mind–body therapy that might end up being useful to individuals manage disease side effects or unfavourable impacts of medicines and work on their personal satisfaction, though reflection is a vital component of yoga.

For individuals managing deadly disease, with all the psychological and emotional mess, meditation unleashes to calm one's mind. It helps with anxiety, depression, distress, stress and sleep disturbances in people with cancer and leads to increased tolerance to pain and trauma thereby relaxing the mind and body.

Risk elements you cannot control include:

Age: Leukemia is most common in kids however, the risk of rising these cases is quite often with age. The age of 65 years is perceived in Acute Myeloid Leukemia (AML), Chronic Myeloid Leukemia (CML), or Chronic Lymphocytic Leukemia (CLL). Nonetheless, most occurrences of intense lymphocytic leukemia (ALL) emerge in people under 20 years of age. The middle age of an ALL-patient ranges between 15-50 years.

Gender: Leukemia occurrence is slightly greater in men than women. A physician-researcher who researches the genetics of leukemia and potential remedies for the treatment, Andrew Lane, assistant professor of medication and a researcher at the Dana-Farber Cancer Institute explains that "It's something intrinsic in the male and female machine." Lane says that he and others noted that men with positive kinds of leukemia regularly possess mutations on genes placed on the X chromosome. These mutations damage tumor-suppressor genes, which typically halt the rampant cell division that triggers most cancers. Lane initially reasoned that woman, who've X chromosomes, could be much less vulnerable to these cancers because they've copies of every tumor suppressor gene. In assessment, males have an X and a Y chromosome—or simply one copy of the protecting genes, which may be "taken out" via mutation.

Genes: Leukemia doesn't always run-in families. But the chromosomal mutations which are thought to cause leukemia might be inherited in some cases [2]. However, in case you are a first-degree relative of a most cancers affected person, like a sibling or parent or if you have an identical twin that's had leukemia have more risk for developing blood cancer.

Previous cancer treatment with chemotherapy and radiation: One is at higher chance for leukemia if they've been handled with chemotherapy or radiation in the past. Previous cancer treatment with chemotherapy drugs is likewise a risk issue for leukemia. These drugs encompass: alkylating agents, platinum agents, topoisomerase II inhibitors, and many others. The low blood cell counts, bleeding, and serious infections occur due to high concentration of chemicals in chemotherapy drugs that can damage the bone marrow. Thus, the complete risks of radiation are nevertheless being studied.

Treatment with immune-suppressing drugs: The organ transplantation is a life-saving approach for the patients having last stage disease, it also puts the recipients at an increased risk for developing cancer. As the medication administered while the treatment suppresses the immune system and prevents rejection of the organ can lead to leukemia. Drugs such as Dasatinib, Gleevec (Imatinib Mesylate), Nelarabine, Dexamethasone, Busulfan, Hydroxyurea, Scemblix (Asciminib Hydrochloride), etc. suppresses the immune system, thereby increasing the chances for the occurrence of leukemogenesis.

Down syndrome and other genetic syndromes: Certain genetic situations could make you much more likely to develop leukemia. This consists of:

Down syndrome- It has been seen that children with Down syndrome have a greater chance of developing leukemia mainly acute megakaryoblast leukemia (AMKL) and acute lymphoblastic leukemia (DS-ALL). Researchers estimate that approximately 2.8 percent of children with Down syndrome develop leukemia [3,4].

Klinefelter syndrome: Klinefelter syndrome- The link with malignant haematological issues [2] has also been mentioned in various reviews. Welborn et al. after reviewing literature found that there were 66 instances of KS associated with haematological cancers. In literature the most frequently reported cases were of non-hodgkin lymphoma (23%), acute myeloid leukemia (23%), acute lymphocytic leukemia (18%) and myelodysplastic syndrome (17%) [5-8].

Fanconi anemia (FA): The physical abnormalities, bone marrow failure, and increased risk for malignancy are specific characteristics of Fanconi Anemia (FA). It has been reported that more than four hundred FA positive patients out of 2000 possess a certain type of malignancy. The significant intricacies are aplastic anemia, acute myeloid leukemia (AML), myelodysplastic disorder (MDS), and explicit solid cancers. A severe subset, because of changes in FANCD1/BRCA2 genes, has a total frequency of malignant growth of 97% by age 7 years; the diseases are AML, brain cancers, and Wilms growth, etc. [9,10].

Bloom syndrome: Bloom syndrome is an autosomal recessive disease described with short height, inclination to the development of malignant growth, and genomic instability. Bloom syndrome is because of changes in the BLM quality that is a member of RecQ DNA helicase family [11]. They additionally have an increased risk of growing cancer at an early age, in particular squamous cell skin cancers, leukemia, lymphoma, and gastrointestinal tract cancer. Bloom syndrome patients have an excessive risk of developing hematopoietic cancers. This review mainly focusses on how leukemogenesis results in leukemia, a neoplastic proliferation of immature cells of the bone marrow and the lymphatic system.

Leukemia begins when a single cell DNA within the bone marrow mutates and can't grow and function normally. Treatments for leukemia depend upon the type of leukemia one suffers from, individual's age and average fitness, and different stages (if the leukemia has spread to different organs or tissues).

Leukemia classifications

Leukemia is a malignant fast spreading cancer in which the bone marrow and other blood-forming organs yield large number of undeveloped or atypical leukocytes. This results in the suppression of healthy blood cells, causing anemia and other symptoms.

Leukemia is categorized into two groups firstly on the basis of how quickly it advances and deteriorates, and secondly on the types of blood cells involved (Table 1). These groups are undermentioned respectively:

I (a) **Acute leukemia:** It is a type of leukemia that progresses fast producing abnormal blood cells which doesn't develop and function efficiently.

I (b) **Chronic leukemia:** This type of leukemia progresses gradually. It occurs when there are fewer immature cells, yet others are normal and can function in a manner they ought to. It becomes bad more slowly than the acute ones.

II (a) **Lymphocytic/Lymphoblastic leukemia:** This includes bone marrow cells that develop into lymphocytes, a sort of white blood cell such as, T-lymphocytes, B-lymphocytes and natural killer cells.

II (b) **Myelogenous/Myeloid leukemia:** This includes the marrow cells that consist of red blood cells, and different types of WBCs such as granulocytes, macrophages, monocytes, neutrophils, etc.

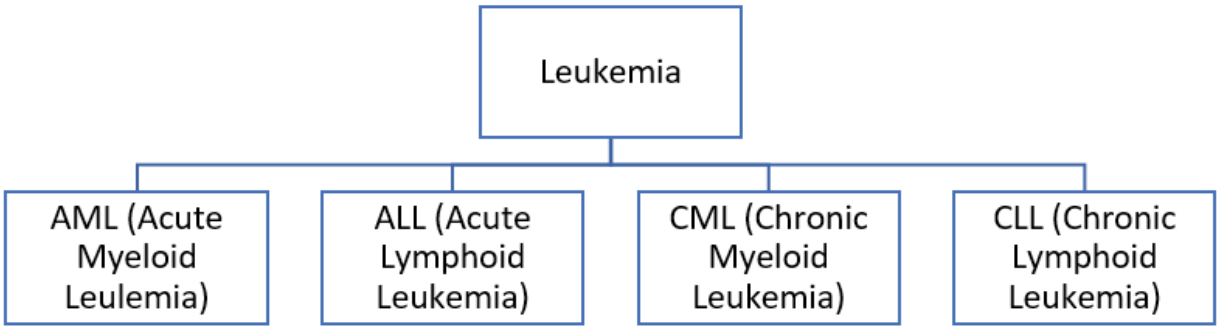

Table 1: Types of Leukemias.

Types of leukemia

They are mainly four types of leukemia are, mentioned as follows:

1. Acute lymphocytic leukemia (ALL) is most common in juvenile. ALL advances quickly, changing healthy cells producing functional lymphocytes with leukemic cells, i.e., immature cells that functions inefficiently. When mutations in DNA occur, that make the bone marrow produce an excessive number of abnormal lymphocytes. This spreads on lymph nodes and central nervous system.
2. Acute myelogenous leukemia (AML) is relatively common in children and one of the most familiar types for grown-ups. In AML the bone marrow overproduces immature white blood cells, overcrowding the healthy blood cells and disturbs the individual's ability to combat against infections.
3. Chronic lymphocytic leukemia (CLL) is a slow developing cancer that activates lymphocytes in the bone marrow and stretches out into the blood stream. It might moreover spread to lymphatic system and other organs including, the liver and spleen. CLL progresses while an excessive number of abnormal lymphocytes develop, crowding out healthy cells and making it difficult for the body to fight infections.
4. Chronic myelogenous leukemia (CML) starts inside the blood-forming cells (BFU) of the bone marrow and gradually invades in to blood stream. In due course, the leukemia spreads to different parts of the body. This blood cancer is slow-growing, yet when it progresses it results in symptoms, comprising of weariness, fever, weight decrease and an enlarged spleen. Blood assessment is considered as a distinguished method to diagnose CML.

Some scientists believe that leukemia results from an as-of-yet undetermined fusion of genetic and environmental factors that could cause mutations within the cells of the bone marrow. These mutations, called leukemic changes, cause the cells to grow and divide very unexpectedly.

Pathways Begetting Leukemogenesis

The objective of this review is to evaluate the phenomenon of leukemogenesis in various forms of leukemia focusing on different signalling pathways and highlighting areas of crosstalk between various signalling pathways and the impact it incorporates on our knowledge of the development of disease and treatment plans. Our main focus can be the below mentioned pathways:

PI3K/ AKT/ mTOR pathway: The processes involving cell proliferation, autophagy, angiogenesis, drug resistance and apoptosis are being regulated by mammalian target of rapamycin (mTOR) in collaboration with couple of signalling pathways in the body. It has been found that the mTOR signaling pathway is linked with cancer, osteoporosis, arthritis, insulin resistance, and other diseases [12,13]. The protein kinase B (AKT)/phosphoinositide-3-kinase (PI3K), adenosine 5′-monophosphate-actuated protein kinase (AMPK) are signalling pathways associated with mTOR pathway [14]. The process of transcription and protein synthesis are influenced by the mTOR, as it directs various signal stimulation, leading to apoptosis, growth, and autophagy of cells [15]. Tyrosine kinase receptors (RTKs), a growth factor that promotes Phosphatidylinositol 3-kinase (PI3K) activation with the help of chemokines via RAS family proteins / G-protein coupled receptors (GPCRs). When Akt is activated, it results in increased leukemic cell viability and up- regulation of antiapoptotic proteins such as Bcl-xL, Mcl-1, and X-linked inhibitor of apoptosis protein (XIAP), thus impacting the effects of sustained BCR stimulation [16]. PI3K is a heterodimer consist of the regulatory subunit and the catalytic subunit i.e., p85 and p110 respectively [17,18]. Akt is a serine/ threonine kinase present in three isoforms: Akt 1, 2 and 3. Among the three Akt 1 and 2 are expressed exceedingly in hematopoietic stem cells (HSCs) [19]. mTOR is a serine threonine protein kinase that regulates various nutrients, stress signals, hormones and growth factors thereby influencing the growth and survival of normal cells. Among all, mTOR possess a major role in tumor tumorigenesis and progression. Many studies have illustrated that tumor growth over activates the AKT/mTOR signaling pathway [20,21]. Therefore, mTOR suppressor is utilized in targeted tumor therapy, organ transplantation and other diseases. The purpose of the present review is to clarify the connection between mTOR signaling pathway and cancer development in an individual. mTOR signaling act as important regulator of cell growth and

division under normal conditions. However, mTOR is abnormally activated in cancer cells that tend to send signals to tumor cells to multiply and metastasize, and invade new healthy cells [22]. It has been reported that when PI3K/ AKT/ mTOR pathway are inhibited have a beneficial effect in leukemia, examined both in-vitro and in-vivo [23].

This pathway is linked to leukaemia because it is crucial to the development of the disease and can be used as a therapeutic target. Targeting the PI3K/Akt/mTOR pathway may have an impact on the anti-proliferative and apoptotic effects in haematological malignancies, according to earlier studies [24, 25]. According to research, AMPK is a key player in regulating the survival of cancerous cells, so killing this protein with modulators could be a very effective way to kill leukemic cells.

Wnt/ β catenin pathway: It is likewise identified as the established Wnt signaling pathway. It involves physiological processes, differentiation, proliferation, migration, invasion, apoptosis and tissue homeostasis [26]. The binding of Wnt protein to the N-terminal extracellular cysteine rich region of frizzled (Fz) receptor, triggers the Wnt signaling pathway. The Fz family receptor is a distinct component of G- protein coupled receptors (GPCRs). The early onset of leukemogenesis is being regulated by the transcription factor β-catenin [27-29]. The absence of Wnt protein causes phosphorylation of β catenin resulting in ubiquitylation and subsequent proteasomal degradation that is mediated by glycogen synthase kinase 3β (GSK3β) and casein kinase 1α (CK1α) within the degradation complex. In reference to ligand-receptor, receptor-receptor and receptor-co-receptor interactions the transduction of Wnt signals across the cell's plasma membrane involves a confounding amount of complexity and diversity [30].

The addition of secreted cysteine-rich glycoprotein ligands Wnts to the lipoprotein receptor-related protein (LRP)-5/6 receptors and Frizzled (FZD) receptors is begun by β-catenin-dependent signaling pathway. The Wnt co-receptors and its interaction with main components of the Wnt signaling pathway has been considered in understanding its significance in cancer biology and as therapeutic biomarker as well. The recent studies have demonstrated that LRP-5/6 is potential cancer-causing proteins. Thus, by blocking LRP56 function it might lead to novel approaches in cancer treatment [31]. In the presence of Wnt protein, the attachment of Wnt ligand and receptors at the cell surface induces disheveled (DVL), inflicting the accumulation of the complex (AXIN, GSK3β, CK1, APC) to the receptor [32]. The sequence-specific DNA-binding and context-dependent interactions of T-cell factor/lymphoid enhancer factor (TCF/LEF) are multifunctional proteins that specify which genes will be regulated by Wnts. The dysregulation of Wnt/β-catenin pathway is intently linked to the commencement and development of many kinds of tumors resulting in the activation of p53, a key tumor suppressor marker.

For its stimulating function in adult HSC maintenance and self-renewal, the Wnt signalling pathway has been well characterized [33,34]. There is conflicting evidence about the impact of β-catenin signalling on the HSC population, despite the conserved importance of WNT signalling in controlling HSC self-renewal. WNT signalling is not required for HSC function, as shown by knockout studies [35,36]. For instance, deletion of β-catenin did not affect differentiation or self-renewal in bone marrow progenitors [37].

The WNT signalling pathway is required for self-renewal and survival, it has been demonstrated that the WNT signalling pathway also plays significant roles in LSCs. It has been demonstrated that β -catenin is localized in nucleus in human Chronic Myelogenous Leukemia (CML) LSCs, and that production of AXIN can decrease in vitro LSC activity [38].

Importantly, it has been shown that BCR-ABL activation of the PI3K pathway, which in turn stimulates β -catenin activity, causes CML to progress from the chronic phase to the blast crisis. β -catenin levels are lowered when BCR-ABL or the PI3K pathway are inhibited.

Inferring that PI3K pathway and WNT pathway crosstalk is essential for LSC maintenance in CML, in vivo blockade of this system delays the progression of CML and lowers the potential for CML LSCs to form tumours following subsequent transplantation [39].

A further indication of the significance of the WNT signalling system in LSCs is the elevated expression of β-catenin and WNT pathway-associated genes in CML and AML LSC populations compared to healthy HSCs [40,41].

Notch pathway: Notch signaling pathway is an evolutionarily signalling pathway and engaged in the normal regulation of cell endurance, multiplication, differentiation, programmed cell death and other physiological processes. It manages self-renewal and differentiation of various tissues and cell types. The cell fate commitment that is achieved by the formation of cell type-specific transcriptional programs, has been governed by Notch pathways. Its hyperactivation has been intent as oncogenic in various malignant growths alongside breast diseases and Lymphocyte intense lymphoblastic leukemia (T-ALL) [42]. In vertebrates, there are four receptors, Notch 1~4, and five ligands, delta(δ)-like ligand 1 (DLL1), delta(δ)-like ligand 3 (DLL3), delta(δ)-like ligand 4 (DLL4), Jagged-1 (JAG1) and Jagged-2 (JAG2) [43]. When a notch receptor binds with a ligand this signaling pathway is initiated. The gamma (γ) secretase complex cleaves the notch receptor after ligand binds to it, thereby translocating the receptor into the nucleus. Transcriptional activation of Notch target genes is regulated by collaborated intracellular domain of Notch (NICD) and coactivator proteins e.g., Centromere Binding Factor 1 (CBF-1) and MAML1. It has been noticed that notch signaling act as either tumor suppressor or oncogenic in LSCs. Notch signaling plays an acknowledged part in proceeding myeloid differentiation by upregulating the transcription factor PU.1[44]. It has been described in previous studies that Notch 1 is expressed feebly in AML cell lines and have a correlation with a reduced PU.1-mediated differentiation, signifying that Notch signaling might be accountable for sustaining the immature myeloid compartment

observed in leukemia [45]. There is no significant difference between the mutated notch receptor genes in recognized tumor cell lines and those of established oncogenes and tumor suppressors. The Notch signaling pathway is quite significant in cellular development, differentiation and to maintain homeostasis [46]. The improper functioning of this pathway has negative impact on several cancers, such as T-cell leukemia, breast cancers, prostate cancer, colorectal cancers and lung cancer in addition to central nervous system (CNS) tumors [47].

Depending on the lineage setting, Notch signalling has been shown to play either a tumour suppressor or an oncogenic role in LSCs, raising questions about the Notch pathway's functions in LSCs. In the setting of T-ALL and CLL, where Notch signalling is thought to be oncogenic, the roles of Notch signalling in LSCs have been well investigated [42]. The overwhelming body of data points to the critical functions that Notch signalling plays in tumour progression and carcinogenesis, including in T-cell leukaemia and breast cancer [48,49]. In T-cell acute lymphoblastic leukaemia (T-ALL), hypoxia/HIF-1 mediated Notch1 signalling increases cell proliferation, invasion, and chemoresistance [50].

JAK/STAT pathway: The most outstanding signaling pathways in cell biology is the Janus kinase/signal transducers and activators of transcription (JAK-STAT) [51]. The proliferation and self-renewal of hematopoietic stem cells (HSCs) has been regulated by active JAK-STAT pathways. It leads to phosphorylation of members of the STAT family. The defects in HSCs and hematologic malignancies might occur due to alterations in gene elements of the JAK-STAT pathway. Recent studies illustrated that various malignancies have been associated with deregulation of the JAK-STAT pathway [52]. The transcription factor signals transducers and activators of transcription 5 (STAT5) has a significant and remarkable role in Breakpoint Cluster Region - Abelson 1 (BCR-ABL1). The existence and growth of CML cells is maintained by STAT5 signaling network. The major functions such as differentiation, propagation, survival, programmed cell death, and migration are controlled by JAK-STAT pathway [53].

This review discusses the functions of the oncoproteins JAK/STAT and BCR-ABL in leukemogenesis as well as their significance in the control of cell cycle progression and apoptosis. Regulation proteins have developed in these pathways to restrict their proliferative and antiapoptotic effects [54]. For the treatment of leukaemia, small molecular weight, cell membrane-permeable medicines that target these pathways have been created. Cytokines engage with receptors on the surface of cells to start signalling cascades that encourage cell division and expansion while blocking the pathways leading to apoptotic cell death. Many cytokines that either enhance or inhibit hematopoiesis activate the JAK/STAT, Raf/MEK/ERK, and PI3K/Akt signalling pathways [55]. These include type I interferons, IL-3, IL-7, SCF, G-CSF, and TGF-b. JAK-STAT activation causes the phosphorylation of STAT family members, which controls HSC proliferation, survival, and self-renewal. Defects in HSCs and hematologic malignancies are associated with mutations in JAK-STAT pathway components.

TGF-β pathway: The Transforming Growth Factor Beta (TGFB) signaling pathway is engaged in numerous cell pathways in both adults and foetus, like cellular development, cell differentiation, cell movement, apoptosis, cellular homeostasis and different cell function [56]. The transforming growth factor β (TGFβ) superfamily comprising secreted polypeptides, along with Bone Morphogenetic Proteins (BMPs), TGFβ1, 2, 3, activins, inhibins and nodal, and growth differentiation factors (GDFs) [57]. The depletion and overproduction of HSCs is balanced by the signals that promote quiescence and stimulation of inducers that causes proliferation and differentiation. Any disturbance in the regulation of these transforming growth factors results in blood disorders that include bone marrow failure or leukemia.

TGF1, TGF2, and TGF3 are the three ligands that make up the TGF family. They all communicate with type I and type II Serine/Threonine kinase membrane receptors [58]. ALK5 (activin receptor-like kinase [ALK1-7]), also known as TRI, is the main type I receptor for TGF, while TRII is the only type II receptor.

TGF-β signalling is a key mechanism that is intricately controlled and plays a significant role in human development and adult life. It has extensive connections to various signalling pathways. Additionally, it contributes to the development of haematological and solid tumour cancers. TGF- is paradoxically both a tumour promoter and a tumour suppressor. The anti-proliferative and apoptotic effects of the tumour suppressor activities are frequently used terms. It is common for tumors to circumvent the tumor-suppressive effects of TGF-β by either developing mutations in signalling components or by blocking its anti-proliferative response during the course of cancer. This "switch" aids the tumor's utilization of TGF-β as an oncogenic factor that promotes tumour motility, invasion, metastasis, and the change from epithelial to mesenchymal tissue.

There is a great desire to target TGF-β signaling in cancer therapy as a result of developments in the research of molecular processes that explain the carcinogenic actions of TGF-β. However, more information needs to be provided regarding the precise mechanisms underlying TGF-β transformation into cancer. Only then will it be possible to create effective therapy plans and offer fresh therapeutic targets to bring back the normal TGF-β function. In healthy epithelium, TGF-β functions as a tumour suppressor by preventing cell growth and inducing apoptosis. However, as a tumour develops, sensitivity to these TGF-β effects is frequently lost, and later on, TGF-β signalling has an oncogenic effect. TGF-β has been shown to engage in a number of actions that would promote tumour growth [59]. Human myeloid leukemia cells are effectively inhibited by TGF-β [60].

Tumor suppressor genes and oncogenes inflicting leukemogenesis

Proteins produced by tumour suppressor genes regulate cell growth and aid in preventing leukemogenesis. Antioncogenes, also known as loss-of-function genes, are another name for tumour suppressor genes. These genes' primary roles include inhibiting

unneeded cell division and expansion, promoting cell death, and supporting DNA repair in order to preserve cellular homeostasis. Tumour suppressor genes function as "brakes" to stop cells in their tracks before they can start along the path to cancer in this fashion. TSG is rendered inactive by proteasomal degradation via ubiquitination, cellular localization, and transcription [61]. There are five categories for TSGs: 1) Genes encoding secreted hormone receptors or signal transducers that prevent cell proliferation, such as transforming growth factor (TGF)- and adenomatous polyposis coli (APC), [62]; 2) Genes encoding intracellular proteins, such as pRB and p16, that control development into a particular stage of the cell cycle [63]; 3) Genes encoding proteins that initiate apoptosis [64]; and 5) Genes encoding proteins involved in the DNA repair process [e.g., p53 and DNA mismatch repair protein 2 (MSH2)]. [65] 4) Checkpoint-control protein-encoding genes that cause cell cycle arrest in response to DNA damage or chromosomal abnormalities (BRCA1, p16, and p14, for example) [66].

Many malignancies result in the deactivation of the p53 TSG (TP53), which negatively regulates the chain of events involved in cell cycle control and linked to genome equilibrium and angiogenesis [67,68]. P53 is induced by DNA damage, which prompts the Cdk inhibitor p21's transcription to increase. The inhibitor p21 prevents DNA replication by binding to PCNA (proliferating cell nuclear antigen), functioning as a general inhibitor of Cdk/cyclin complexes, and blocking the progression of the cell cycle. During the cell cycle arrest, the damaged DNA is repaired before replication [69,70]. The TSG acts as inhibitors of cell proliferation and tumor development on the unlike of cell growth. In most cancers, due to multifactorial reasons these genes are lost or deactivated, thus eliminating undesirable cell production and leading to the irregular spread of cancer cells.

Epigenetic factors

The study of genetic phenotype alterations that do not comprise modifications in the DNA sequence is called as Epigenetics. It depicts how genes might be changed biochemically and influences the expression of the genes without changing the original DNA. It's not only the changes in the genomes that matters, however modifying the way genes are expressed without hereditary changes. These epigenetic factors have an important role in cancer. The possible changes in the environment of our tissues also affect the "expression" of tumor suppressor genes. Epigenetics is yet not explored in depth with respect to translational clinical practice. The initial examination in clinics laid emphasis on cytogenetic studies, classifying illness based on genetic disorders and biomarkers, and treating the patients accordingly. The most significant aspect of epigenetic beginning of disease is that a portion of these modifications in DNA expression might be preventable or even reversible. It additionally is turning out to be progressively certain that some acquired epigenetic changes that incline toward disease can be spread through the germline from parent to kid. Leukemia oncogenesis is a consequence of hereditary and epigenetic aspects, wherein hematopoietic pathways are disturbed and leukemia cells are able to avoid heredity obligation. This relationship between altered genes and gene regulation is fundamental in cancer growth. The different epigenetic factors that can result in leukemogenesis involve histone deacetylation, DNA methylation, histone modifications and others.

Epigenetic defects and genetic mutations are attained during the life of an individual and accumulate with aging. Both types of events, either individually or in collaboration, can result in the loss of control over cell growth and development of cancer [71]. Even though the epigenetic silencing of some genes is critical throughout life, still the DNA sequence data is considered more reliable than the epigenetic information that may change over a lifetime.

Conclusion

Our ability to treat individuals with certain diseases will significantly improve as our understanding of the specific genes altered in malignancies advances. A transcription factor or enzyme needed for growth control may occasionally change in function and/or regulation as a result of a reciprocal translocation. In certain instances, the swapped chromosomal pieces come together to create a brand-new genetic framework. Occasionally, such an entity can give rise to a fusion protein with novel functions that disrupt the control of cellular homeostasis.

Hopefully, we will be able to target the specific gene(s) in the affected pathway(s). Numerous signal transduction pathways may be affected by the genetic mutation, according to earlier studies. It could be necessary to create particular therapies that focus on multiple pathways. Moreover, targeting various pathways may also be more effective because it can stop or slow the growth of the tumour.

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