

REVIEW ARTICLE

Oxidative stress in leukemogenesis: Mechanistic insights and chemotherapeutic approaches

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Abstract

There is compelling evidence that reactive oxygen species (ROS) generation regulates a network of intracellular signals that may have negative consequences, such as cellular damage and aberrant physiological processes. Commonly, the term “oxidative stress” relates to a shift in redox status, for instance, an instability in the proportions of antioxidant enzymes. A thorough literature review was conducted across PubMed, Scopus, Web of Science, and Google Scholar, focusing on oxidative stress, leukemia biology, and ROS-targeted therapies. Data from studies published from 2006 to 2026 were prioritized, and important landmark studies were included for scientific context. Acute and chronic leukemogenesis, among other hematological cancers, have been linked to oxidative stress. High rates of hematopoietic blast cell proliferation and aberrant differentiation are characteristic of leukemogenesis in acute myeloid leukemia. Hyperleukocytosis, medullary illness, and aberrant thrombosis are all linked to this aberrant expansion and differentiation of blast cells. It is necessary to examine the molecular pathways underlying the onset, progression, and evolution of leukemogenesis driven by oxidative stress. Therefore, a thorough understanding of ROS production in leukemia can open new avenues for efficient therapeutic interventions, such as chemical, radiation, immunological, and targeted therapies targeting oncogenes and tumor suppressor genes. These diverse potential treatments aim to prevent leukemia recurrence and progression by targeting signal transduction pathways. This article discusses current research on the putative role in leukemia etiology, prospective treatments, and clinical trials that specifically target redox status in cancer.

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1. Introduction

Leukemia is a serious public health problem worldwide. Acute leukemia is a clonal disease of the poorly differentiated hematopoietic cell populations in bone marrow. According to the American Cancer Society, there will be an estimated 67,790 (39,070 men and 28,720 women) new cases resulting in 23,910 (13,900 men and 10,010 women) deaths from leukemia cancer in 2026. Specifically, acute myeloid leukemia (AML) is expected to account for 22,720 new cases (12,160 in men and 10,560 in women) and 11,500 deaths (6,520 in men and 4,980 in women); chronic myeloid leukemia accounts for 9,650 new cases and 1,170 deaths; acute lymphocytic leukemia is expected to account for 6,250 new cases and 1,600 deaths; and chronic lymphocytic leukemia accounts for

22,760 new cases and 4,350 deaths.¹

The modulation of biochemical functions, signal transduction, and their regulation is largely regulated by diverse reactive chemical signaling mediators, such as reactive oxygen species (ROS).^{2,3} ROS has been reported to regulate cell cycle progression and growth by controlling enzymes and genes involved in cancer progression, as well as by mediating redox-sensitive transcriptional factors in various cell types. The primary source of ROS is superoxide (O_2^-), which is predominantly produced by mitochondria or by the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.^{2,3} Research has demonstrated that ROS at optimal or low levels have positive effects; they upregulate cell growth and proliferation by regulating cell survival mechanisms. Usually, an antioxidant protection system or an enzymatic substrate interface with mechanisms that regulate excessive ROS generation maintains an appropriate equilibrium between ROS production and elimination, thereby preserving cellular redox homeostasis and preventing oxidative damage. According to studies, excessive ROS generation contributes to oxidative stress, which damages DNA and alters regulatory proteins that promote cancer growth and progression.²

Although there is significant evidence that oxidative stress leads to the aberrant proliferation and development of leukemia cells, the exact mechanism by which oxidative stress causes cancer remains unknown.^{3,4} According to research, both active granulocytes and tumor cells have the capacity to produce abundant ROS, which might result in oncogenesis and a bad prognosis. These ROS contribute to leukemogenesis by inducing DNA damage, promoting genetic instability, and altering signal transduction, thereby influencing cell populations and differentiation. Thus, manipulating ROS levels could be a therapeutic approach to inhibit AML progression. In the early stages of AML, inhibition of ROS could exert an antitumor effect, and at late stages, targeting oxidative stress might contribute to the eradication of leukemia stem cells (LSCs).^{4,5}

Novel pharmacological approaches that specifically target leukemic cells are the most crucial requirement, as they imply that existing therapeutic approaches have reached the limit of their potential efficacy. Recent investigations have shown that impaired antioxidant status is a distinctive hallmark of AML, and reactive oxygen species levels were substantially higher in cancerous cells than in healthy leucocytes in blasts from individuals with different types of leukemia.^{5,6} The acute form of myeloid leukemogenesis is prompted by enhanced production of both intracellular and extracellular ROS. On the other hand, malignant cells seem to be able to withstand

persistent oxidative stress (intrinsic), which triggers the upregulation of cellular defense pathways aimed at restoring redox balance and preventing damage, as well as encouraging drug tolerance.⁷ An expanding body of literature and research points to a link connecting cancer metabolic routes with an overabundance of ROS generation. Cancerous cells may become more vulnerable to metabolic anomalies, highlighting a potential for innovative treatment strategies.⁸

Accumulating evidence indicates that persistent oxidative stress initiates inflammatory signaling, a hallmark of inflammatory and infectious illnesses, cancer, cardiovascular, endocrine, neurodegenerative, and respiratory conditions. This study summarizes recent data on the roles of intrinsic and extrinsic ROS in leukemia development, which are recognized as significant in leukemia initiation, progression, and therapeutic resistance. The review also discusses ROS-mediated signaling pathways involved in cellular proliferation, apoptosis, metabolic reprogramming, and redox regulation in leukemic cells. Furthermore, the manuscript emphasizes the translational significance of redox biology and explores new therapeutic avenues targeting redox homeostasis to improve therapeutic outcomes in leukemia.

2. Leukemogenesis and aberrant oxidative stress

Aberrant and negative oxidative stress will disrupt free radical formation, thereby negatively modulating the expression of signal-mediated genes.⁹ The mitochondrial respiratory chain in cells is primarily responsible for producing ROS. According to studies, aberrant oxidative stress triggers the proliferation of leukemia cells, hence leading to leukemia.¹⁰ The distortion in the shape of the cell and its functionality, which is caused by ROS formation, is continuously created under conditions of oxidative stress, for a specific period. Therefore, hematopoietic cells undergo somatic and neoplastic mutations.¹¹ Oxidative stress exerts both tumor-promoting and tumor-suppressive effects, while physiological levels of reactive ROS are essential for the self-renewal, proliferation, and differentiation of hematopoietic stem cells (HSCs). HSCs reside within hypoxic bone marrow niches that maintain low mitochondrial activity and membrane potential, thereby limiting ROS generation.⁹ In their quiescent state, HSCs predominantly rely on anaerobic glycolysis for energy production, which minimizes oxidative stress. To further regulate ROS homeostasis, HSCs employ antioxidant defense systems comprising molecules such as glutathione, thioredoxin, and NADPH, together with enzymes such as catalase, superoxide dismutase, and

glutathione peroxidase.⁶

Intracellular ROS levels also vary among AML cell populations. AML blasts generate high levels of oxygen-derived radicals and often exhibit impaired antioxidant defenses, leading to persistent oxidative stress, DNA damage, and mutagenesis. Superoxide anion ($O_2^{\cdot-}$) represents the predominant ROS species in AML cells, and altered glutathione metabolism further contributes to leukemogenesis. Reduced catalase expression promotes hydrogen peroxide (H_2O_2) accumulation, while constitutive activation of NADPH oxidase 2 (NOX2), observed in more than half of AML patients, enhances ROS overproduction.^{2,4,5} In contrast, AML LSCs are characterized by low oxidative status and aberrant overexpression of the anti-apoptotic *BCL2* gene. Targeting *BCL2* can suppress enhanced mitochondrial oxidative phosphorylation and selectively eliminate quiescent LSCs. Overall, low ROS levels are associated with LSC quiescence and survival, whereas elevated ROS levels support AML blast proliferation and disease progression. Overall, understanding how oxidative stress is dysregulated in leukemogenesis provides important mechanistic insights and a solid basis for new redox-targeted therapeutic approaches in leukemia management. Consequently, low ROS levels favor HSC quiescence and self-renewal, whereas moderate ROS levels promote differentiation.^{3,6,10} However, excessive ROS accumulation disrupts cellular integrity and function, leading to abnormal hematopoiesis, cell death, and malignant transformation of HSCs into LSCs, a critical event in the development and progression of AML. Additional regulatory mechanisms include interactions with the bone marrow microenvironment and mitophagy, which preserves mitochondrial quality and quantity.

3. Genomic instabilities induced by oxidative stress leading to leukemogenesis

As oxidative stress triggers DNA anomalies, including double-strand breaks (DSBs), chromosomal aberrations, and increased proliferation of leukemic cells, these anomalies have been linked to the initiation and progression of cancer.¹² Genetic variability introduced by mutations in DNA and a malfunctioning DNA repair mechanism leads to the onset of both genetic and sporadic forms of human leukemias.¹³ Under physiological conditions, HSCs maintain the balance of the hematopoietic system by tightly regulating oxidative stress; however, excessive or persistent ROS accumulation can severely impair HSC function by altering their metabolic state and disrupting cellular homeostasis. ROS-induced changes in the hematopoietic microenvironment can promote HSC senescence or apoptosis. Because HSCs

residing within specialized niches normally exhibit lower ROS levels than most other tissues, they are particularly sensitive to fluctuations in ROS and genetic alterations. Key transcription factors, including forkhead box O3 (FOXO3) and ataxia-telangiectasia mutated kinase (ATM), are critically involved in ROS regulation within HSCs. Importantly, different ROS levels exert distinct biological effects on HSCs: low ROS levels maintain HSC quiescence by regulating adhesion molecules within the hematopoietic niche, moderate ROS levels promote cell-cycle progression and proliferation through oxidative modification of signaling molecules, whereas high ROS levels induce HSC aging, metabolic dysregulation, and functional decline. Consequently, prolonged exposure of mature and differentiating HSCs to elevated ROS levels can lead to senescence, metabolic reprogramming, and loss of hematopoietic function, ultimately contributing to leukemogenesis. During carcinogenesis, elevated ROS levels may trigger transcription factors and their associated genes to become constitutively active, which, in turn, activate gene variants associated with malignancy.^{12,14} The oxidation-reduction equilibrium in leukemic cells can be shifted by a variety of oncogenes, some of which are named as *NFE2L2*, *KRAS*, nuclear factor (NF)- κ B signaling components, *MYC*, and *BCR::ABL*.¹⁵

Preleukemic fusion genes (PFGs) result from DNA damage and chromosomal translocations in HSCs or hematopoietic progenitor cells (HSPCs) and are significant clinical markers for leukemia diagnosis and therapy. The most common PFGs are *BCR::ABL* and *ETV6::RUNX1*.¹⁶ ROS-mediated DNA DSBs are thought to play a role in fusion gene formation, and ROS-mediated PFG expression may also disrupt DNA repair capacity, thereby promoting genomic instability. In line with this, Somsedikova *et al.*¹⁷ investigated DSB levels in acute lymphoblastic leukemia cells with *BCR::ABL* and *ETV6::RUNX* fusion genes, revealing significantly higher DSB levels in cells containing PFGs than in those without PFGs. Furthermore, Sallmyr *et al.*¹⁸ showed that *FLT3* internal tandem duplication (ITD) mutations create a vicious cycle of genomic instability characterized by elevated ROS levels, increased DSBs, and impaired DNA repair. Thus, AML patients with PFGs and associated genetic mutations tend to have higher genomic instability and worse prognosis. Additionally, almost 25% of newly diagnosed AML patients had *FLT3*-ITD receptor mutations. In both murine (Ba-F3 and 32D) and leukemia cells (MOLM-14 and MV4-11), alterations in *FLT3*-ITD receptors have been observed to cause significant ROS production.¹⁹ This shows that ROS plays a crucial role in modulating *FLT3*-mutated AML. Oxidative stress-mediated genomic instability is therefore a central mechanism in leukemogenesis, leading to DNA damage,

chromosomal abnormalities, and a diminished capacity to repair DNA, and makes oxidative stress a promising biomarker and a potential therapeutic target for the prevention, diagnosis, and treatment of leukemia.

4. Reactive oxygen species-induced inflammation leads to leukemia progression

A physiological response to adverse conditions, such as infection and tissue damage, is called inflammation. Inflammatory cells (mast and leucocyte cells) trigger an increase in oxygen absorption, inducing an oxidative burst that leads to an upsurge in ROS production and deposition at the affected area.^{20,21} Contrarily, soluble regulators such as cytokines, chemokines, and arachidonic acid precursors are also released by inflammatory cells. Numerous transcription factors are activated by oxidative stress, such as NF- κ B, nuclear respiratory factor 1 (Nrf1), nuclear factor erythroid 2-related factor (Nrf) 2, and Nrf3, activating protein-1 (AP-1), p53, hypoxia-inducible factor-1 α (HIF-1 α), peroxisome proliferator-activated receptor- γ (PPAR- γ), signal transducer and activator of transcription (STAT) 3, protein kinase B (AKT), forkhead box O (FOXO), and BTB (broad-complex, tramtrack and bric-à-brac) and CNC (cap 'n' collar) homology proteins 1 and 2 (BACH1 and BACH2). Some of these transcription factors are known to play important roles in both oxidative stress in erythropoiesis and leukemogenesis. Some act as regulators of antioxidant defense, and others promote tumor cell survival by protecting them from oxidative damage. Redox-sensitive transcription factors can regulate the expression of over 500 genes involved in various cellular processes, including growth factor signaling, inflammatory cytokine and chemokine production, cell-cycle control, and anti-inflammatory responses. As a result, factors that regulate cellular transcription in response to ROS and redox-sensitive signaling pathways have become important factors involved in the pathogenesis of leukemia and are emerging as targets for cancer prevention and therapeutic intervention. These mediators induce excessive ROS production by attracting other inflammatory cells to damaged areas.^{15,21,22} These mediators also activate signaling pathways and orchestrate the cellular activities triggered by stress mechanisms. Oxidative stress-induced inflammation causes multiple molecular and cellular changes, including the expression of the cyclooxygenase-2 (COX-2) enzyme, overexpression of nitric oxide synthase, and increased levels of tumor necrosis factor, interleukin (IL)-1, IL-6, and IL-8. Oxidative stress-mediated inflammation also correlates with changes in the expression of the CXC chemokine receptor 4 (CXCR4) and microRNAs, which, in turn, regulate inflammatory signaling pathways.²¹ The

sustained oxidative environment establishes a vicious cycle that damages normal epithelial and stromal cells, eventually leading to the initiation of carcinogenesis.²² Numerous hematological malignancies, as well as tumor angiogenesis, have been linked to COX-2. Preliminary studies using cancer models have reported that blocking COX-2 exhibits notable anti-cancer activity.²³ Current investigative analysis reported that COX-2 expression was identified in both lymphocyte types (T and B cells), that unstimulated cell lines showed minimal to no expression, and that in AML cell lines, it is nearly always present and easy to detect.²⁴ Overall, ROS-mediated inflammatory signaling is believed to be the key mechanism supporting the progression of leukemia, through the maintenance of a pro-tumorigenic microenvironment and the identification of redox pathways associated with inflammation as potential therapeutic targets.

5. Oxidative stress-mediated cellular signaling cascades implicated in leukemogenesis

Several signaling pathways are commonly linked to leukemia and are directly dependent on elevated oxidative stress. The overproduction of ROS intermediates can destabilize important macromolecules, the molecular basis of inflammatory processes, cardiovascular disease, cancer, and other diseases. In addition, ROS can activate several tumor growth signaling pathways, such as NF- κ B, phosphatidylinositol-3-kinase (PI3K), and mitogen-activated protein kinase (MAPK). MAPKs influence signal transduction by regulating numerous functional proteins and modulating cell fate. Alterations in cellular redox homeostasis have been shown to activate extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK subfamilies. The imbalance between free radicals and ROS leads to oxidative stress, and its effects are depicted in [Figure 1](#). First, oxidative stress can regulate the signaling pathways related to cell survival, proliferation, and apoptosis, and then it can promote tumor cell survival, induce cell proliferation, and protect cells from apoptosis further to promote cancers⁷; second, oxidative stress metabolic disorder participates in inflammation processes, thus promoting inflammation and affecting the immune system^{8,9}; third, oxidative stress can also trigger secondary messengers between cells, thus destroying essential biomolecules (such as lipids, proteins, and DNA) and damaging important structures and functions of cells.^{1,7} It can induce poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP)-mediated poly(ADP)-ribosylation of chromatin-associated proteins and consequent DNA damage, leading to activation of DNA damage response signaling and kinase pathways.

This is followed by mitochondrial dysfunction, including loss of mitochondrial membrane potential, leading to the activation and translocation of pro-apoptotic proteins, down-regulation of anti-apoptotic proteins, and ultimately the induction of apoptosis, thereby contributing to carcinogenesis.⁵ In conclusion, oxidative stress is involved in oncogenesis and cancer progression. Specifically, oxidative stressors, such as H_2O_2 , and inflammation can stimulate AP-1 activation, predominantly through the JNK and p38 signaling cascades.^{23,24} Upon activation, JNK protein migrates to the nucleus, where they activate c-Jun and transcription factor-2 (ATF-2), thereby amplifying gene transcription. Excessive ROS overwhelms the antioxidant buffering capacity, leading to mitochondrial dysfunction, DNA damage, lipid peroxidation, and apoptosis. Various factors that activate the oxidative stress-induced signaling cascade leading to leukemia are shown in Figure 1.

5.1. Oxidative stress and mitogen-activated protein kinase-mediated pathway

Among the various activators of the MAPK signaling cascade is ROS. ROS activates receptor tyrosine kinases, initiating a cascade that activates rapidly accelerated fibrosarcoma kinase (Raf) isoforms, which subsequently phosphorylate mitogen-activated protein kinase kinase (MEK), leading to the activation of ERK through serial phosphorylation.²⁴ Most cancer-related abnormalities that upregulate ERK signaling include changes in tyrosine kinase receptor expression, alterations in tyrosine kinase receptors, and mutations in *BRAF* and rat sarcoma viral oncogene homolog (Ras). ERK signaling can activate a wide range of cellular activities, including translocation, angiogenesis, transcriptional regulation, viability, differentiation, and proliferation, depending on the specific cell type.^{25,26} Recent findings indicate

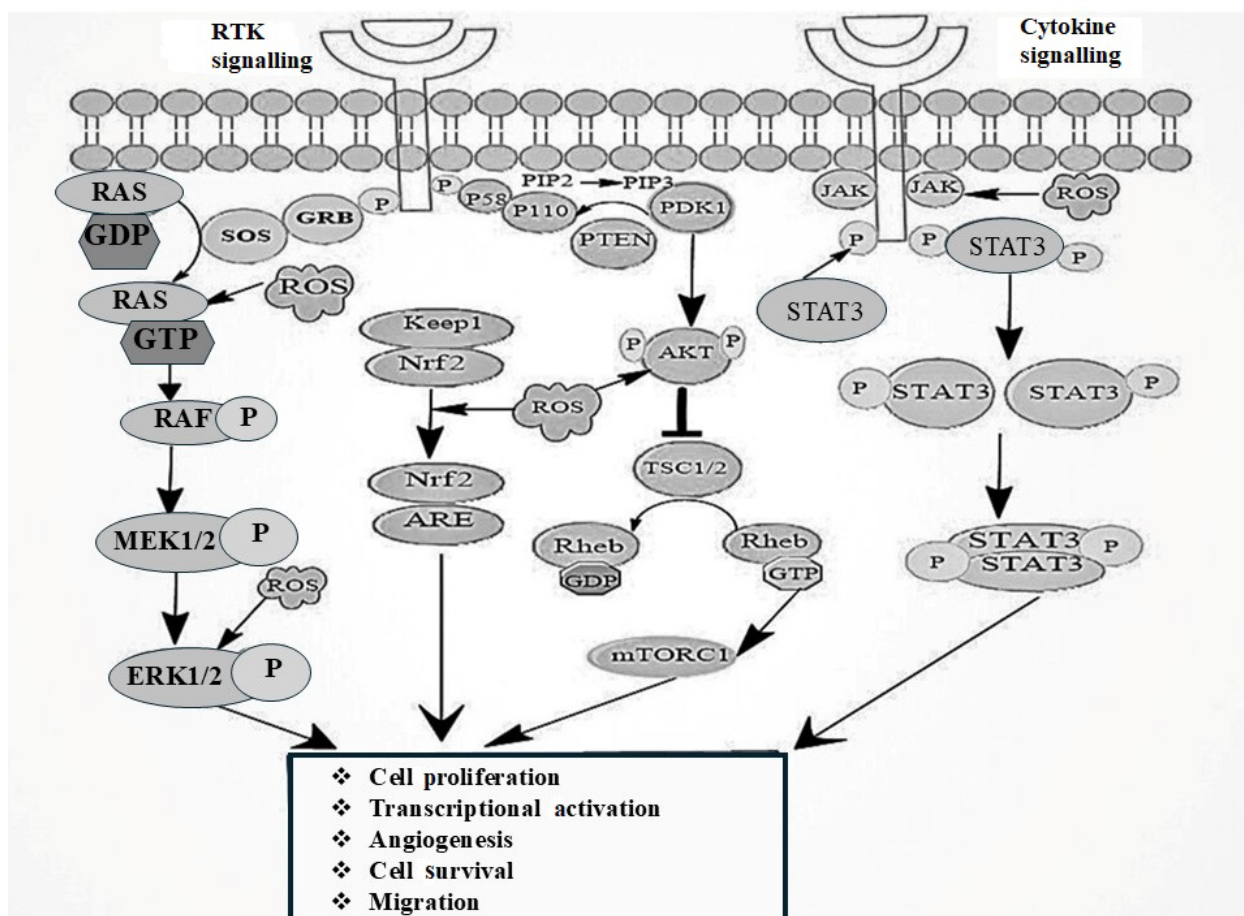


Figure 1. Schematic demonstration of signaling pathways that are mediated by reactive oxygen species (ROS). ROS are important modulators of intracellular transduction signaling. Through a protein redox-sensor process, ROS can activate diverse signaling pathways, such as mitogen-activated protein kinase, Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, protein kinase B (AKT)-mechanistic target of rapamycin (mTOR), and the redox-sensitive nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, which modulate transcriptional factors and several genes involved in the cell's proliferation, survival, angiogenesis, and migration in leukemia development.

that prolonged exposure to H_2O_2 in fibroblastic cells can stimulate matrix metalloproteinase-2 (MMP-2) activity, thereby enhancing cellular invasiveness.²⁰ Oxidative stress is also known to influence MMP-2 expressions through multiple mechanisms, including activation of the Ras oncogenic pathway, direct stimulation of ERK1/2, p38, and JNK, as well as inhibition of phosphatases responsible for regulating these signaling proteins.²⁷ As previously reported, 30% of AML patients hold defective *FLT3*, which ultimately increases relapses and reduces survival rates. Like 90-95% chronic myeloid leukemia patients can also undergo dysregulated activation of the *BCR::ABL* fusion.^{28,29} Finally, oxidative stress-induced activation of the MAPK signaling pathway is an important pathway that promotes leukemogenic cell survival and proliferative capacity, suggesting this pathway as a therapeutic target for redox-mediated therapy in leukemia.

5.2. Oxidative stress and Janus kinase-signal transducer and activator of transcription signaling pathway

Cytoplasmic transcriptional regulators, particularly the STAT family, are activated by signaling mediators, including hormones, enzymes, and inflammatory stimuli. Activated STAT proteins mediate multiple biological activities, including proliferation, maturation, and survival.³⁰ Oxidative stress activates the JAK-STAT pathways either by triggering in the receptor's intracellular domain by the interaction of ligands to their subsequent receptors or by upregulation of IL-6.³¹ This binding will further lead to receptor oligomerization. Activation of the signaling cascade is also achieved by upregulating JAK tyrosine kinases or sarcoma (Rous sarcoma virus) proto-oncogene (Src) family kinases.^{32,33} The STAT proteins' tyrosine residues are directly phosphorylated upon stimulation of this kinase signaling cascade, which is preceded by dimerization of the STAT protein. Following translocation to the nucleus, the homo- or heterodimerized STAT proteins form a complex with the promoter sequence of certain genes to activate transcription of those genes.

According to reports, STAT3 modulates the transcription of p27Kip1, an inhibitor of cyclin-dependent kinases, leading to cell cycle inhibition. By augmenting CCAAT/enhancer-binding protein (C/EBP) expression and transcriptional activity, STAT3 promotes myeloid cell differentiation.³⁴ By boosting its transcription, STAT5 may also regulate the function of anti-apoptotic proteins (Bcl-2 and Bcl-xL), which inhibit apoptosis, thereby promoting cell survival and progenitor cell development. In contrast to STAT3 and STAT5, all-trans retinoic acid triggers the induction and activation of STAT1 during the myeloid differentiation process in various leukemia cell

lines.³⁵ It is clear that oxidative stress-induced JAK-STAT signaling activation plays a major role in leukemogenesis by regulating cell proliferation and survival, and therefore represents a pertinent target for redox-based therapeutic approaches in leukemia.

5.3. Oxidative stress and phosphatidylinositol-3-kinase downstream signaling

The PI3K and mTOR signaling pathways play important roles in both normal and malignant hematopoiesis. ROS oxidizes and inactivates the phosphatase and tensin homolog (PTEN) that triggers the PI3K signal transduction.³⁶ Erythropoiesis is regulated by PI3K activity, which mediates proliferation and survival. Myelopoiesis is regulated by the AKT pathway through modulation of the transcription factor C/EBP α . When AKT activity is suppressed, glycogen synthase kinase-3 becomes active, leading to the phosphorylation and subsequent inactivation of C/EBP α , thereby promoting eosinophilic differentiation. While activating AKT, it activates C/EBP α and the progression of neutrophil development. Therefore, irregularities in the PI3K/AKT signaling pathway influence leukemia growth.³⁷

When PI3K is activated, the level of phosphatidylinositol (PI3,4,5-triphosphate) is regulated by PI3K and PTEN. AKT (protein kinase B) is activated downstream of PI3K through phosphorylation at key serine and threonine residues by phosphoinositide-dependent kinase-1 (PDK1). AKT regulates multiple cellular processes, including glucose transport, metabolism, and cell survival. AKT promotes cell survival by phosphorylating downstream targets involved in apoptotic regulation, thereby inhibiting apoptosis. In previous studies, arsenic trioxide (As_2O_3) failed to induce cell death in a PI3K/Akt cloned HL-60 resistant cell as compared to wild-type cells.^{38,39} This study concluded that upregulation of the PI3K pathway protects cells against apoptosis, and that chemotherapy using As_2O_3 -induced ROS could trigger apoptosis in leukemic cells. Experiments showing that short interfering RNA-based suppression of AKT stimulates As_2O_3 -induced cell death in leukemia and T lymphoblast cell lines. Glutathione peroxidase (GPx) participates in the reduction of lipid hydroperoxides and H_2O_2 , and As_2O_3 induces apoptosis by inhibiting GPx.³⁸ Overall, oxidative stress-modulated PI3K downstream signaling is important for leukemic cell survival, metabolic rewiring, and resistance, and thus a promising target for redox-based therapeutic intervention.

5.4. Oxidative stress and nuclear factor erythroid 2-related factor-mediated pathway

The NRF2 detects the oxidative stress level by sensing ROS and electrophilic agents. The increase in ROS levels activates

NRF2 by modifying cysteine residues on the Kelch-like *Echinocloa* homolog-associated protein 1 (Keap1), thereby deactivating NRF2.⁴⁰ As per reports, malignant blasts extracted from AML patients' blood have been reported to have constitutively activated NRF2, which promotes cancer development and protection against chemotherapy. Similar observations have been reported in patients with CLL. In addition, NRF2's persistent activation appears to lead to the activation of NF- κ B downstream targets. NRF2 can control the enzymes that regulate glutathione (reduced form; GSH) production by activating the antioxidant response element. According to studies, compared with healthy CD34+ cells, AML cells exhibit higher levels of GSH-metabolizing enzymes, such as glutamate-cysteine ligase and glutathione S-transferase.^{41,42} Further evidence that leukemic cells use abnormal stimulation of the NRF2 signaling to counteract the increased oxidative stress due to GSH to its oxidized form (GSSG), regulated by GPx. Because GSH is also linked to chemoresistance, the association between GSH and NRF2 is critical for treating and preventing hematological cancers.⁴³ Overall, NRF2-mediated antioxidant signaling plays a key role in oxidative stress-related adaptive mechanisms in leukemogenesis, and its dysregulation is associated with survival and resistance to treatment in leukemic cells, indicating its potential as a therapeutic target for redox-based therapies depending on the cell type.

6. Treatment approaches for leukemia

Oxidative stress emerges as a complex, context-dependent mechanism in the initiation and progression of leukemia. ROS levels contribute to genomic instability, potentially driving disease progression and resistance to tyrosine kinase inhibitors. High levels of oxidative stress can promote the fate of leukemic cells, offering a paradoxical therapeutic angle. This duality advocates the demand for a deep understanding of redox biology in leukemia. Future research should aim to untangle these opposing effects and explore how modulating oxidative stress could be strategically leveraged to prevent drug resistance upgrade and improve cancer management. Chemotherapy, radiation therapy, and stem cell transplantation are the most common traditional therapeutic options for preventing relapses of leukemia.^{43,44} Combination therapies are commonly used to achieve faster remission and reduce the risk of resistance. Consolidation and maintenance strategies aim to prevent cancer relapse.

A common component of consolidation therapy is the resumption of intensified chemotherapy or the escalation of chemotherapy by adding synergistic agents. Conversely, maintenance therapy doses are lower than those used in the initiation phase. Refractory or relapsed leukemia

may be treated with high-dosage chemotherapy, which is subsequently followed by autologous or allogeneic hematopoietic stem cell transplantation (HSCT) for bone-marrow rescue.⁴⁵ Allogeneic HSCT induces graft-versus-leukemia effects, thereby suppressing leukemia. Donor lymphocyte infusion can be favorable in case of post-HSCT recurrence.⁴⁶ However, the lack of appropriate donors and transplant-related mortality and morbidity limit allogeneic transplantation. Various inhibitors targeting all the major signaling cascades to prevent leukemogenesis are shown in Figure 2.

6.1. Potent inhibitors of the rapidly accelerated fibrosarcoma kinase-extracellular signal-regulated kinase signaling axis

To stop activation of the Raf-ERK signaling axis, it is important to know the underlying genetic alteration driving its dysregulation. It is still unclear what type of major mutation (or mutations) triggers at least 50% of AMLs and other types of cancer to develop malignantly. There are compelling reports regarding the transitional development of B-rapidly accelerated fibrosarcoma kinase (BRAF) and MEK inhibitors. Nevertheless, their long-term effectiveness is often undermined by the emergence of acquired resistance, largely driven by tumor heterogeneity and genomic instability. To improve leukemia therapy, small-molecule MEK inhibitors (ARRY-142886, AZD6244) are under investigation in combination with agents that block other signaling pathways and target anti-apoptotic proteins.⁴⁷

Sorafenib has been approved as a Raf inhibitor and is being investigated for consideration in leukemia trials. Small-molecule Raf inhibitors selectively bind to the ATP-competitive domain of the Raf kinase. These drugs include sorafenib (L-779,450, ZM 336372, and Bay 43-9006), which binds to the Raf kinase domain, thereby inhibiting kinase activation.^{48,49} In addition to Raf, Sorafenib has been shown to inhibit several other kinases, including vascular endothelial growth factor receptor 2 and 3, platelet-derived growth factor receptor beta (PDGFR-beta), CD117, and feline McDonough sarcoma virus-like tyrosine kinase 3 (FLT-3). Determining *RAF* gene mutations or overexpression in specific leukemia subtypes can be essential for guiding personalized therapy. Patients exhibiting *RAF* overexpression may respond more effectively to inhibitors targeting that Raf isoform. As a result, designing both selective and broad-spectrum Raf inhibitors could offer therapeutic advantages in the management of leukemia.^{50,51} Another strategy for inhibiting Raf is to suppress the enzymes and phosphatases that activate it, preventing its activation by targeting upstream regulators, such as p21-activated kinase (PAK)

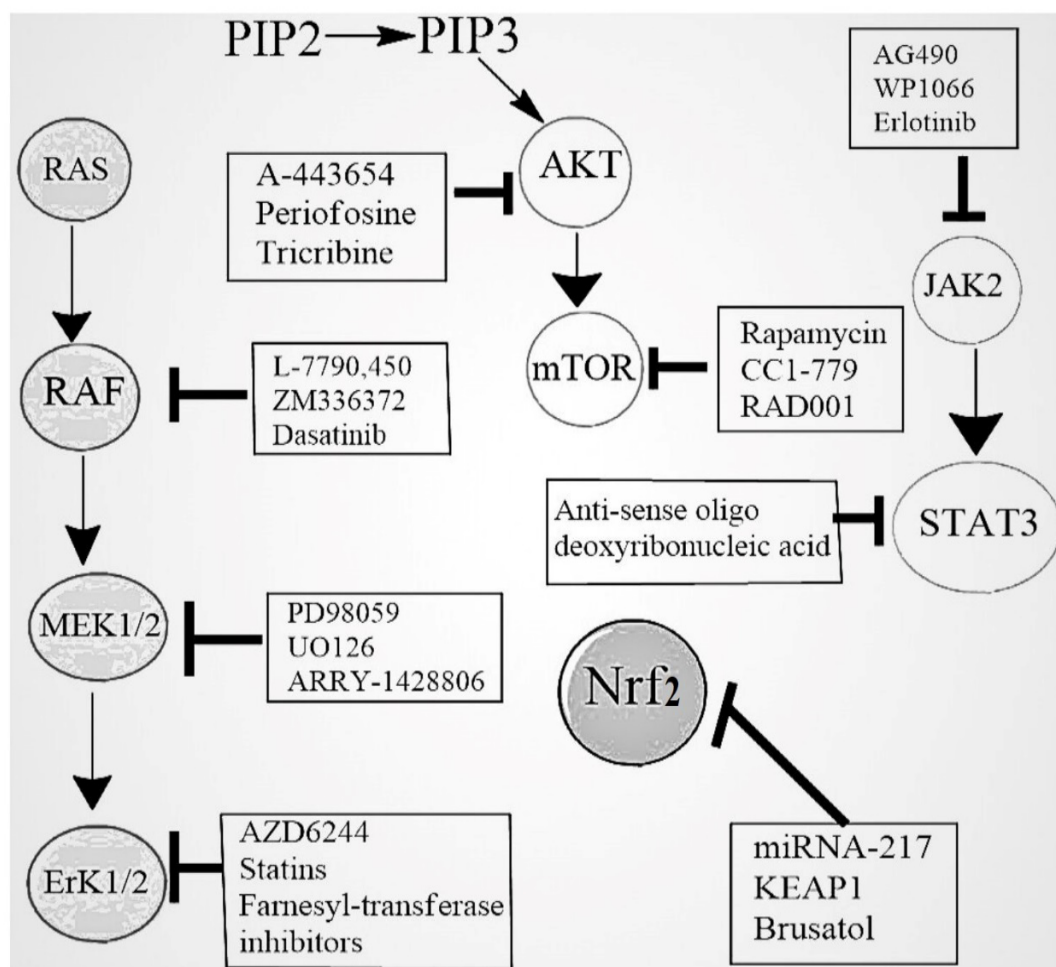


Figure 2. Inhibitors of stress-induced signaling pathways that lead to leukemia. Specific inhibitors have been shown to block the abrupt reactive oxygen species-mediated signaling in leukemia.

and protein phosphatase 2A (PP2A). Some Src kinase inhibitors, like dasatinib, are expected to prevent Src from activating Raf-1, preventing Raf from being activated.^{48,52}

Owing to constitutively active upstream tyrosine kinases, including *BCR::ABL*, PDGFR- β , CD117, FLT3, and colony-stimulating factor 1 receptor, the Raf/MEK/ERK signaling pathway is aberrantly activated in many leukemias. MEK-specific inhibitors such as PD98059, U0126, and PD184352 (also known as CI1040) have shown promising results in treating leukemia.^{53,54} Leukemic cell proliferation was significantly reduced by the MEK inhibitor AZD6244, which disrupts signal transduction through ERK1/2. In both AML primary blasts and AML cell lines, cholesterol-lowering drug statins can also inhibit activation of ERK, which may promote apoptosis. Farnesyl transferase inhibitors, which block the post-translational modification of Ras GTPases, have shown

efficacy in treating several cancers, including lymphoma and leukemia.^{55,56}

6.2. Potent Inhibitors of phosphatidylinositol-3-kinase and downstream targets

Several small molecules have the potential to inhibit PI3K and its downstream signaling pathways. Downstream mTOR can be blocked with drugs like rapamycin and tailored isoforms such as CCI-779 and RAD001, PI3K with LY294002, and PX-866. In line with this, PDK1 can be suppressed with OSU-03012, celecoxib, and Akt can be blocked with A-443654, perifosine, and tricribine.^{52,57} These molecules are persistently active in AML blast cells and play key roles in promoting leukemic cell growth, survival, and resistance to chemotherapy. Apoptosis is induced immediately upon PI3K inhibition, indicating that inhibitors of this pathway can be effective therapeutics

for the management and prevention of leukemia.^{58,59}

6.3. Targeting Janus kinase-signal transducer and activator of transcription pathway

In leukemias and lymphomas, STAT proteins are widely expressed and regulate various processes, including apoptosis, signaling, and angiogenesis. According to studies, leukemia has an overexpression of many STAT isoforms. STAT1 protein is expressed in leukemia. The STAT3 protein is activated in AML, while STAT5 expression has been observed across various hematologic malignancies, including AML and myeloproliferative disorders (MPDs).⁶⁰ Several studies have shown that several oncogenes activate STAT during genetic transformations. T cells infected with HTLV-I also exhibit active STATs, rendering them resistant to apoptosis.^{61,62}

Several strategies under development target STAT proteins. By lowering STAT protein expression, these strategies regulated it. For example, antisense oligodeoxyribonucleotides can block STAT3 expression, inhibiting the growth of leukemias and lymphomas *in*

vitro. *BCR::ABL*, an oncogene that can be suppressed by RNA interference, activates STAT5. An alternative strategy for inhibiting STAT proteins includes using peptide or oligonucleotide decoys.^{61,62}

6.4. Potent inhibitors of Janus kinase 2

Given the critical role of JAK2 in various proliferative disorders, efforts are underway to develop specific inhibitors that target this kinase. One such inhibitor is AG490, which prevents leukemia cell proliferation both *in vivo* and *in vitro* while having no negative effects on hematopoiesis in healthy tissues. Protein kinase inhibitor AG490 is a member of the tyrphostin family.⁶³ WP1066 has the potential to inhibit JAK2 isoforms, including the JAK2 V617F mutation, which is commonly associated with erythroid leukemia. Additionally, the endothelial growth factor receptor inhibitor erlotinib has proven efficacy in restraining JAK2-mutated HSPCs. Patients at high risk of developing MPDs are not eligible for these therapies, as they remain under investigation in Phase I clinical trials.⁶⁴ Various inhibitors targeting distinct pathways and inhibiting cancer progression are listed in Table 1.

Table 1. Mechanism of common inhibitors of reactive oxygen species in leukemia

No.	Signaling molecule	Inhibitors	Functions
1	Raf	L-779,450	Inhibit B-Raf activity
		ZM 336372	Inhibit C-Raf activity
		Bay 43-9006	Both C and B-Raf inhibitors
		Dasatinib	Block Raf-1 activity
2	Mek	PD98059	Prevent activation of Mek1
		U0126	Inhibit MAPK activity
		PD184352	Prevent phosphorylation of Mek 2
		PD-0325901	Downregulate Mek and suppress Erk phosphorylation
3	Erk	ARRY-142886	Inhibit the enzymatic activity of Mek1
		AZD6244	Downregulate Mek and suppress Erk phosphorylation
		Statins and farnesyl transferase inhibitors	Inhibit the phosphorylation of Erk 1/2
4	PI3K	LY294002	Competitive substrate for the ATP-binding site of PI3K
		PX-866	Inhibit the production of PIP3 secondary messenger for PI3K activation
5	AKT	A-443654	Prevent AKT activity by phosphorylation of AKT
		Perifosi	It targets the AKT homology domain, thereby preventing its translocation to the plasma membrane.
		Tricribine	It suppresses AKT phosphorylation and kinase activity.
6	mTOR	Rapamycin	It destabilizes the MTOR rector complex.
		CCI-779	It inhibits the kinase activity.
		RAD001	Inhibit MTOR by preventing P21 translation.

(Cont'd...)

Table 1. (Continued)

No.	Signaling molecule	Inhibitors	Functions
7	STAT	Antisense oligodeoxyribonucleic acid	It blocks the <i>STAT3</i> gene.
8	JAK2	AG490	It downregulates phosphorylation of JAK2
		Wp1066	It targets JAK2 V617 F isoform.

Abbreviations: AKT: Protein kinase B; Erk: Extracellular signal-regulated kinase; JAK: Janus kinase; MAPK: Mitogen-activated protein kinase; Mek: Mitogen-activated protein kinase kinase; mTOR: Mechanistic target of rapamycin; PI3K: Phosphatidylinositol-3-kinase; Raf: Rapidly accelerated fibrosarcoma kinase; STAT: Signal transducer and activator of transcription.

7. Clinical trials

The ROS show double functions in cancer, promoting proliferation at low levels but triggering cell death at specific concentrations. Clinical trials exploring the antioxidant activity of leukemia have shown its potential as a complementary agent to conventional treatment. ROS promote leukemogenesis and disease progression by inducing DNA damage, driving cellular proliferation, and inhibiting apoptosis. Several synthetic and natural antioxidants were tested in patients with acute and chronic leukemia for their antioxidant properties and efficacy in

improving treatment outcomes. These trials have shown positive outcomes, including modulation of ROS, increased antioxidant enzyme activity, improved quality of life, and reduced chemotherapy-induced toxicity. Antioxidants have also been found to have synergistic effects with several anticancer drugs, in that they sensitize leukemic cells to apoptosis while sparing normal hematopoietic cells from oxidative damage. But clinical results have not been consistent across studies with different designs, antioxidant doses, leukemia types, and treatment regimens. [Table 2](#) summarizes recent clinical trials of oxidative stress-mediated therapies in leukemia.

Table 2. Clinical trials of ROS-modulated drugs in hematological cancers

No	Drugs	Mechanism	Disease/phase/status	Ref/identifier no
1	Minnelide	Inhibits HSP70, induces ROS, and downregulates c-Myc	AML/Phase 1/withdrawn	NCT03347994
2	Nicosamide	Inhibit CREB, NF- κ B signaling, and modulate oxidative stress	AML/Phase 1	NCT05188170
3	Karonudib	Inhibit MTH1, oxidative stress, and microtubule polymerization	Leukemia/Phase 1	NCT04077307
4	Navitoclax, Venetoclax, Decitabine	Inhibit Bcl-2, Bcl-xL, DNMT, and exploit oxidative stress	Advanced myeloid neoplasms/Phase 1	NCT05222984, NCT05455294
5	Hydroxychloroquine mitoxantrone etoposide	Inhibit MDR p170 protein, tolerable dose	Leukemia, acute myelogenous/Phase 1	NCT02631252
6	Fenretinide	Induces cell death, ROS generation, and ceramide	Refractory or relapsed leukemia/Phase 1/completed	NCT00104923
7	Fenretinide cytarabine methotrexate	Caused cell death, ROS generation, and DNA damage	Recurrent/resistant ALL, AML, and NHL/Phase 1/terminated	NCT01187810
8	Azacitidine chidamide	Inhibit DNA methyltransferases and histone deacetylase and modulate ROS, JAK2/STAT3	AML/Phase 1, 2/ongoing	NCT05270200
9	Chidamide	cell cycle arrest, apoptosis, and block mitochondrial OXPHOS	AML/Phase 1, 2/ongoing	NCT05682755
10	DCHA as post-remission therapy	Modulation of epigenetic and ROS generation	Leukemia chemotherapy/Phase 1/unknown	NCT03453255
11	Azacitidine cytarabine aclamycin, chidamide, venetoclax granulocyte	Inhibit Bcl-2, OXPHOS, DNA, and correct oxidative imbalance	Relapsed AML/Phase 1/ongoing	NCT05659992

(Cont'd...)

Table 2. (Continued)

No	Drugs	Mechanism	Disease/phase/status	Ref/identifier no
12	VCA	Inhibit Bcl-2, HDAC, OXPHOS, and correct oxidative imbalance	Refractory leukemia, relapsed AML/Phase 2/ongoing	NCT05305859
13	VCA regimen and dicitabine combined with liposome mitoxantrone, cytarabine, and G-CSF (DMAG)	Inhibiting Bcl-2, HDAC, is safe and tolerable, and the accumulation of ROS generation	Leukemia, myeloid, acute AML stage/Phase 2/recruiting	NCT05603884
14	Chidamide cladribine	Inhibit HDAC2, c-Myc, RCC1 Axis	AML/Phase 2/ongoing	NCT05330364
15	Chidamide cytarabine	Inhibit MYC-RRP9 axis	AML/Phase 1, 2/unknown	NCT03031262
16	CDIAG regimen	Inhibit DNA methyltransferases and HDAC	AML/Phase 2/completed	NCT03985007
17	CAHAG regimen, placebo regimen	Inhibit DNA topoisomerase II, and Immune checkpoint inhibitors	AML/Phase 2/active	NCT05029141

Abbreviations: AML: Acute myeloid leukemia; CREB: Cyclic adenosine monophosphate response element-binding protein; DNMT: DNA methyltransferase; HDAC: Histone deacetylase; HSP70: Heat shock protein 70; JAK2: Janus kinase2; MDR: Multidrug resistance; MTH1: MutT homolog 1; NF- κ B: Nuclear factor κ B; OXPHOS: Oxidative phosphorylation; RCC1: Regulator of chromosome condensation 1; ROS: Reactive oxygen species; RRP9: Ribosomal RNA processing protein 9; STAT3: Signal transducer and activator of transcription 3; VCA: Venetoclax combining chidamide and azacitidine.

The clinical results with ROS-targeting agents in leukemia remain variable, with some agents showing promising preclinical and early-stage clinical activity, while others have yielded mixed or limited results. This heterogeneity is significantly associated with leukemia type, disease stage, and the underlying redox state. Though the potential therapeutic benefits are promising, there are important limitations to ROS-based strategies, including a narrow therapeutic window, adaptive antioxidant defenses in leukemic cells, and off-target toxicities in normal hematopoietic tissues. Furthermore, there is considerable heterogeneity among leukemia subtypes, making the standardization of treatments difficult, as these differences can create distinct genetic and metabolic environments that affect the degree of redox dependency. Deficiencies in the development of robust, well-validated biomarkers for patient stratification and treatment monitoring exacerbate these challenges.

A major constraint is the difficulty of implementing a biomarker-guided approach to treatment, hindered by the lack of large-scale randomized clinical trials and limited incorporation of redox profiling into the clinic. Therapies were further categorized by mechanism of action, including direct ROS-modulating agents, indirect ROS-modulating pathway effectors, and agents with strong versus preliminary clinical evidence. Together, these factors highlight the importance of larger randomized trials and present new opportunities for precision redox therapeutics tailored to each patient's leukemic cells' redox landscape.

8. Conclusion

Recent developments in the biology of AML have improved the ability to detect genomic and heritable alterations as well as redox-mediated hematological cancers. Different types of leukemia exhibit abnormal ROS levels, which are the primary focus for the discovery of new anti-cancer medications. Redox modulation of cancer cells is a very fine-scale therapeutic approach. The most significant difference between normal and diseased tissues is that basal ROS levels are higher in malignancies, thereby providing a clear vulnerability target for pro-oxidant agents; however, the risk of indiscriminate oxidative tissue damage is a formidable obstacle to clinical implementation. The approach to this challenge is to move beyond a general strategy of countering systemic oxidative stress towards very targeted strategies. Specific antioxidant pathway inhibitors, combination drug regimens, and stimuli-responsive drug delivery systems can be used to maximize cancer-cell lethality while protecting healthy tissues by exploiting the narrow therapeutic window of tumor cells. Finally, optimizing these selective strategies will be instrumental in achieving a shift from the highly effective cell-killing effects of pro-oxidant therapeutics to the safer, more predictable, and survival-extending effects in the clinic for patients with cancer.

Redox biomarkers, monitoring of the GSH/GSSG and NADPH/NADP⁺ ratios, mitochondrial metabolic profiling, and redox-responsive genomic and transcriptomic signatures are expected to be developed as

new tools for precision redox medicine and will be used in the therapeutic management of leukemia in the future. New techniques, such as single-cell redox analysis, and combination therapies, including ROS modulation and targeted therapy/immunotherapy, could further improve treatment efficacy and selectivity. Furthermore, patient-specific redox profiling, real-time monitoring of oxidative stress, and personalized dosing regimens will play an important role in reducing toxicity while simultaneously enhancing the vulnerabilities of leukemic cells, thereby supporting the translation of these redox therapeutic interventions.

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