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REVIEW ARTICLE

A possible novel therapeutic targets of selinexor in acute lymphoblastic leukemia: a comprehensive review

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ABSTRACT

Background and Aim: Acute lymphoblastic leukemia (ALL) presents a formidable challenge in pediatric and adolescent healthcare due to its aggressive nature and high relapse rates. Despite therapeutic advancements, the demand for more effective treatments remains pressing. In the realm of hematologic malignancies, selective inhibitors of nuclear export (SINE) have emerged as promising agents, particularly in evading resistance observed with conventional chemotherapy in acute myeloid leukemia (AML). Selinexor, a prominent SINE compound, has exhibited promising anti-leukemic effects in murine models of AML, laying the foundation for its clinical evaluation. Furthermore, selinexor has been utilized in clinical trials both as a single-agent therapy and in combination with established regimens for a wide range of solid and liquid tumors. However, the precise impact of selinexor in the context of ALL, specifically as a single agent or in combination therapies, remains unexplored. Unraveling the mechanistic intricacies underlying selinexor's actions in ALL holds the key to optimizing its efficacy either as a monotherapy or in combination therapies. Notably, within the intricate landscape of ALL pathogenesis, critical factors including the mammalian target of rapamycin signaling cascade, aberrations in cancer glucose metabolism, occurrences of alternative splicing, perturbed expressions of dysregulated long noncoding RNAs, and impaired autophagic processes have emerged as pivotal determinants. This comprehensive review undertakes a systematic exploration of potential therapeutic targets that hold the promise of augmenting selinexor's efficacy within the unique landscape of ALL.

Relevance for Patients: This study highlights the possible therapeutic targets of selinexor in ALL. Understanding the intricate molecular mechanisms, the rational refinement of selinexor's administration, both as a single agent and as a synergistic component in combination therapies could lead to new avenues for improving the treatment outcomes in ALL patients.

1. Introduction

Acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) represent two distinct forms of acute leukemia, which are fast-growing blood cancers that originate in the bone marrow and affect the white blood cells [1,2]. However, they differ in terms of the specific types of white blood cells they affect, their prevalence across various age groups, treatment strategies, and certain genetic and clinical attributes. AML primarily affects myeloid cells, responsible for producing various types of mature blood cells including red blood cells, platelets, and certain white blood cell varieties [3]. AML is linked to several genetic mutations (FLT3, NPM1, and IDH1/IDH2 mutations) that can impact treatment

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response and prognosis [3]. On the other hand, ALL predominantly target lymphoblasts, immature white blood cells belonging to the lymphoid lineage [4]. In the United States, approximately 6,540 new cases of ALL were diagnosed in the year 2023, resulting in over 1,390 deaths from the disease (American Cancer Society). ALL is characterized by specific genetic abnormalities, including chromosomal translocations such as the Philadelphia chromosome (Ph+), which is associated with a more adverse prognosis [3,4]. Among the spectrum of ALL, a distinctive subtype called B-cell precursor ALL (B-pre-ALL) emerges. Moreover, this subtype specifically targets B-cell precursors or immature B-lymphocytes, rendering it the most widespread variant of ALL, particularly prevalent among children [4,5]. In managing both AML and ALL, various therapeutic strategies are employed, including chemotherapy, immunotherapy, targeted therapy (like monoclonal antibodies), or allogeneic stem cell transplantation [6]. Due to a higher tendency of central nervous system (CNS) involvement in ALL as compared to AML, treatments with a specific focus on the CNS (such as intrathecal chemotherapy or cranial radiation) are frequently integrated into ALL treatment protocols [7]. Despite advancements in the therapeutic process, relapsed cases of ALL remain a significant challenge, exhibiting unfavorable prognoses. Thus, a critical need exists to develop effective therapies for treating relapsed ALL and to explore novel combinatorial therapeutic regimens with chemotherapy to enhance outcomes in newly diagnosed patients [8]. Elucidating the underlying molecular mechanisms that contribute to *de novo* or acquired drug resistance presents a ubiquitous obstacle in cancer therapeutics [9]. This underscores the imperative to explore novel targeted therapeutic strategies, specifically directed toward ALL [10]. Noticeably, selective inhibitors of nuclear export (SINE) are emerging as a potential therapeutic approach to overcome drug resistance in the context of AML [11].

Selinexor, an inhibitor of nuclear export, was recently demonstrated to bind reversibly and inhibit the nuclear export protein exportin-1 (XPO1), leading to the accumulation of cargo proteins inside the cell nucleus [12]. Selinexor exerts its effects on multiple myeloma by inhibiting nuclear factor kappa B (NF-kB) signaling, reactivating various tumor suppressor proteins, and reducing c-myc levels [13,14]. A recent study has indicated that selinexor treatment led to the downregulation of the mammalian (or mechanistic) target of rapamycin (mTOR) signaling pathway in sensitive and resistant AML cell lines [13]. Selinexor exhibited synergistic antimyeloma effects when combined with glucocorticoids, proteasome inhibitors (PIs), and immunomodulators in preclinical studies [14,15]. Notably, the combination of selinexor and dexamethasone (DEX) has received approval in the United States for treating patients with penta-refractory multiple myeloma [16]. Moreover, the selinexor-bortezomib-dexamethasone combination has also been approved for patients who have received ≥1 prior therapy in multiple myeloma patients [16]. The clinical trial of selinexor, either as a monotherapy or in combination, for AML patients has been shown in Table 1. However, the impact of selinexor treatment on ALL as a single agent or in combination therapies has not been explored. Gaining insights into selinexor's mechanism of action within the context of ALL is crucial for optimizing its efficacy as a standalone treatment or in synergy with combination therapies. In this review, we discuss the possible targets of selinexor in ALL, such as mTOR signaling, glucose metabolism, alternative splicing, long non-coding RNA expression, and autophagy, all of which may play critical roles in determining the pathogenesis of the disease and the effectiveness of chemotherapy. We have provided the descriptions of clinical and preclinical studies of selinexor in various cancers (Tables 1 and 2).

2. mTOR

mTOR is a conserved serine/threonine kinase that belongs to the PI3K-related kinase family and exists in two distinct signaling complexes known as mTORC1 and mTORC2 [23,24]. mTORC1 plays a significant role in mRNA translation and protein synthesis, whereas mTORC2 substantially contributes to cell survival and migration [23,24]. The mTOR pathway occupies a central position in sensing environmental cues and monitoring virtually all facets of metabolism, spanning from the cellular to the organismal level [25]. Dysregulated mTOR signaling is linked to cancer and diabetes progression, along with the aging process [26]. Given that the activation of the PI3K/Akt/mTOR network is frequently linked to a poor prognosis and chemoresistance in ALL, there remains an ongoing demand to identify novel inhibitors for the effective treatment of this disease. This is particularly relevant given the mounting evidence indicating mTOR dysregulation's association with metastatic potential, cell proliferation, and angiogenesis. [27,28]. Moreover, B-pre-ALL is characterized by constitutive activation of the PI3K/Akt/mTOR network, which is known to significantly impact cell growth and survival [29].

The application of selinexor to AML cell lines led to the reduction of mTOR activity [13]. Moreover, selinexor demonstrates synergistic effects with dexamethasone to suppress mTORC1 signaling and promote cell death in multiple myeloma [16] (Table 2). Consequently, investigating the impact of selinexor treatment on mTOR signaling in the context of ALL holds significant therapeutic importance (Figure 1A). This endeavor is pivotal for assessing the efficacy of selinexor in ALL treatments.

3. Reprogrammed Glucose Metabolism in Cancer

Aberrant glucose metabolism has emerged as a major type of metabolic reprogramming in cancer, discovered by Otto Warburg in the late 1920s [30]. The uncontrolled proliferation of cancer cells induces a heightened demand for nutrients, creating an environment of limited nutrient availability. In response to this increased nutritional stress, cancer cells undergo metabolic adaptations. Cancer cells exhibit a preference for utilizing glycolysis as their primary pathway for glucose metabolism even in oxygen-abundant conditions, rather than relying on the more efficient mitochondrial oxidative phosphorylation for ATP production [30,31]. Moreover, the cancer cells exploit elevated levels of glucose as a primary carbon source to fuel

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Table 1. Clinical trial studies of selinexor alone or in combination with chemotherapeutic drugs in AML

Drugs	Type of leukemia	Phases	Outcome	References
Selinexor	AML	Phase I	Selinexor is safe as a monotherapy in patients with relapsed or refractory AML	[17]
Selinexor + Venetoclax	AML	Phase I	This combination is a safe regimen for AML patients	NCT04898894
Selinexor + Daunorubicin + Cytarabine	AML	Phase I	This combination is a safe regimen for newly diagnosed poor-risk AML patients	[18]
Selinexor + Mitoxantrone (M) + Etoposide (E) + Cytarabine (C)	AML	Phase I	Selinexor plus MEC is a feasible treatment for patients with R/R AML	NCT02299518
Selinexor + Cytarabine + Idarubicin	AML	Phase II	Selinexor, cytarabine, and idarubicin result in a high remission rate in patients with R/R AML	[19]

AML: Acute myeloid leukemia

Table 2. Preclinical studies of selinexor alone or in combination with chemotherapeutic drugs in various cancers and their altered pathways

Drugs	*In vitro/In vivo* studies	Altered pathways	References
Selinexor	AML cell line	Downregulation of mTOR signaling; regulate p53 pathway	[13]
Selinexor + Dexamethasone	Multiple myeloma cell line and multiple myeloma mice models	Suppress mTORC1 signaling and inhibits tumor growth in both *in vitro* and *in vivo* studies	[20]
Selinexor + Azacitidine	AML cell line	Inhibit XPO1/eIF4E/c-MYC signaling	[21]
Selinexor	Gall bladder cancer cell line and mice models	Autophagy-dependent apoptosis by activating the p53/ mTOR pathway	[22]

AML: Acute myeloid leukemia; mTOR: Mammalian target of rapamycin

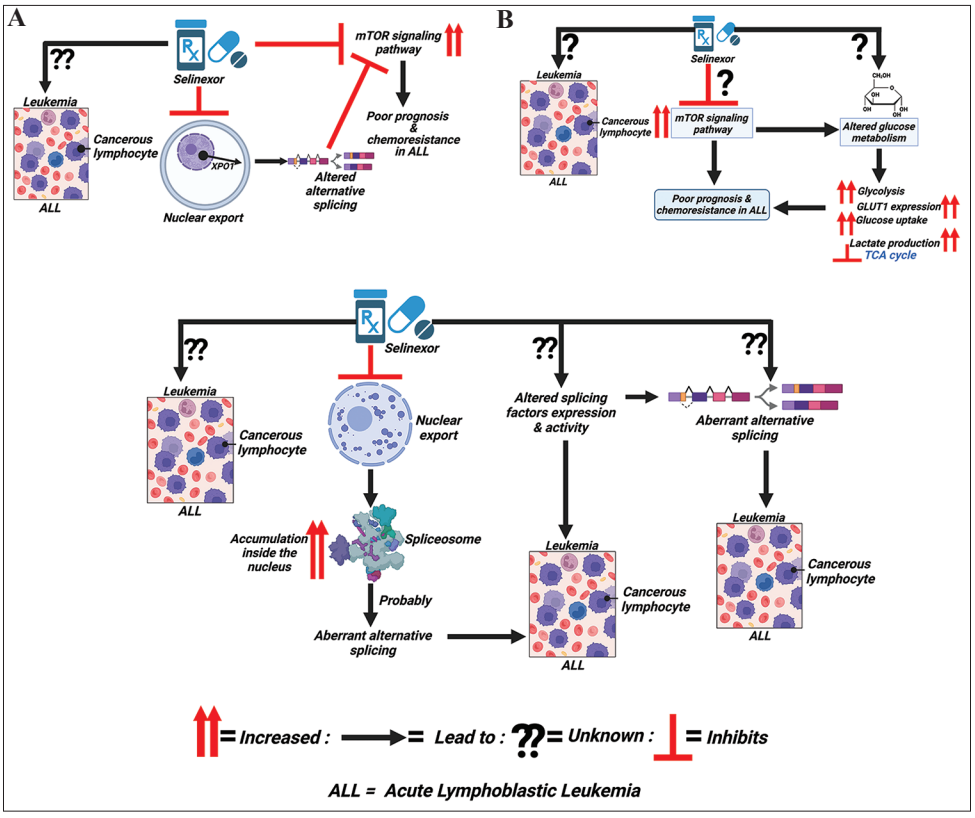

Figure 1. Mammalian target of rapamycin (mTOR) Signaling, cancer glucose metabolism, and alternative splicing as possible therapeutic targets of selinexor. **(A)** This schematic provides an overview of the potential therapeutic targets of selinexor, an inhibitor of nuclear export, in the regulation of the mTOR signaling pathway in childhood acute lymphoblastic leukemia (ALL). It also illustrates the established consequences of dysregulated mTOR signaling in ALL. **(B)** This diagram explores the potential impact of selinexor on the regulation of cancer glucose metabolism in ALL. It also highlights the regulation and consequences of altered glucose metabolism in ALL. **(C)** Alternative splicing emerges as a promising therapeutic target of selinexor in ALL. The figure portrays the various potential mechanisms by which selinexor may influence alternative splicing in ALL. The "???" in the figure represents areas that remain unexplored or unanswered.

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anabolic reactions. These reactions play pivotal roles in various aspects of cancer, including initiation, progression, metastasis, cell survival, and the development of resistance against anti-tumor therapies [32,33]. Indeed, the complete metabolic network undergoes significant reprogramming under the influence of oncogenes and tumor suppressor genes [32]. This restructuring also encompasses a redefinition of nutrient flow within metabolic networks during the process of tumor formation. In recent years, there has been a growing interest in glucose metabolism of cancer cells, which has now become an integral part of cancer biology [32]. Moreover, both mTORC1 and mTORC2 complexes play a significant role in the regulation of metabolism [34]. Gene expression profiling of pediatric patients diagnosed with ALL revealed the activation of genes that promote glycolysis, alongside the downregulation of genes associated with the tricarboxylic acid cycle [35]. Functional analysis conducted on pediatric patients with ALL demonstrated elevated expression of the glucose transport protein and glucose transporter 1 [35]. Furthermore, cell lines derived from ALL exhibited heightened lactate production and a notable susceptibility to the glycolysis inhibitor, 2-deoxy-D-glucose [35]. Mutations in genes that encode transcription factors responsible for regulating glucose metabolism, such as PAX5 and IKZF1, have been observed in more than 80% of cases of pre-B-cell ALL [36]. Notably, the combined utilization of selinexor and azacitidine exhibited synergistic effects by targeting XPO1/eIF4E/c-MYC signaling pathways in AML, offering encouraging preclinical data that suggest its potential for future clinical application [21] **(**Table 2**)**.

In preclinical models of triple-negative breast cancer, selinexor exhibits notable anti-tumor efficacy [21,37]. Selinexor treatment induces distinct alterations in AKT signaling and the expression of genes associated with metabolism in breast cancer cell lines including BT474 and MCF-7 [38]. Moreover, the combination of selinexor with tamoxifen resulted in a marked reduction in AKT signaling, and seahorse metabolic profiling revealed a significant shift in the metabolic profile of breast cancer cells. This transition shifted the cells from an energetic state to a quiescent state [38]. Notably, both the glycolytic and mitochondrial pathways were concurrently inhibited, thereby inducing autophagy [38]. In addition, selinexor induces autophagy-dependent apoptosis in gallbladder cancer by activating the p53/mTOR pathway, both *in vitro* and *in vivo* [22]. Interestingly, the inhibition of the glycolytic pathway plays a crucial role in modulating autophagy, exerting a significant impact on the survival of leukemia cells [39]. Consequently, there exists a potential for selinexor to modulate the glycolytic pathway in ALL. However, the precise effect of selinexor on cancer glucose metabolism in the context of ALL remains unknown (Figure 1B). The significance of conducting experiments aimed at evaluating the impact of selinexor treatment on the expression of PAX5 and IKZF1 cannot be overstated. These investigations will provide crucial insights into the potential effects of selinexor on these genes and their relevance in the context of ALL treatments.

4. Autophagy

Christian De Duve first coined the term “autophagy” in 1963 to describe the process of self-eating that he had discovered while studying lysosomes [40]. Since then, the role of autophagy has been explored in numerous research areas including cancer, diabetes, infectious diseases, and neurodegenerative disorders [40]. Autophagy is a multistep catabolic signaling cascade that orchestrates cytoplasmic content in a double-membrane vesicle and fuses with lysosomes, involved in the degradation of damaged organelles such as mitochondria (mitophagy), lipids, and proteins, that maintains cellular homeostasis under normal circumstances [40]. Autophagy has a multifaceted role in cancer, with well-established roles for autophagy in promoting tumor cell survival by providing recycled nutrients and modulating mitochondrial function through mitophagy, or intriguing new roles in tumor cell migration and invasion through control of focal adhesion turnover and secretion of pro-migratory cytokines/chemokines [41]. Conversely, autophagy acts as a tumor suppressor by preventing malignant transformation in mouse models defective for autophagy [42]. Therefore, autophagy has both tumor-suppressive and tumor-promoting effects in cancer depending on tumor genetics, host variables, and tumor stage [41,43]. Due to its contradictory effects, autophagy has been considered a double-edged sword in cancer, challenging researchers to further investigate how to modulate autophagy in the context of cancer therapies [43,44]. Autophagy has emerged as one of the critical molecular mechanisms involved in drug resistance. Chemotherapeutic agents are well known to induce autophagy in cancer cells [45]. The P38 stress response pathway has also been linked to therapeutic resistance and regulation of autophagy [46]. Therefore, autophagy may be exploited as a promising strategy for the therapeutic sensitization of cancer cell [43,44,47].

Selinexor treatment of sensitive AML cell lines resulted in a heightened DNA damage response [13]. Conversely, in resistant AML cell lines, the administration of selinexor led to the activation of increased stress response pathways [13]. Moreover, in the context of wild type p53 resistant cell line, selinexor treatment upregulated the autophagy pathway, while in mutant p53-resistant cells, selinexor treatment triggered an enhanced p38 stress response pathway [13]. It is worth noting that selinexor has been shown to induce autophagy-dependent apoptosis in gastric cancer [22]. Hence, based on this evidence, we propose that selinexor might have the capacity to modulate autophagy in the treatment of childhood ALL (Figure 2B).

5. Alternative Splicing

Alternative splicing is a pivotal mechanism governing the regulation of gene expression [48,49]. It entails the excision of introns from messenger RNAs, allowing exons to join together [48,49]. This process of alternative splicing is widely deregulated in various cancers, leading to the emergence of cancer-specific splicing experiences widespread dysregulation across diverse cancers, resulting in the emergence of splicing

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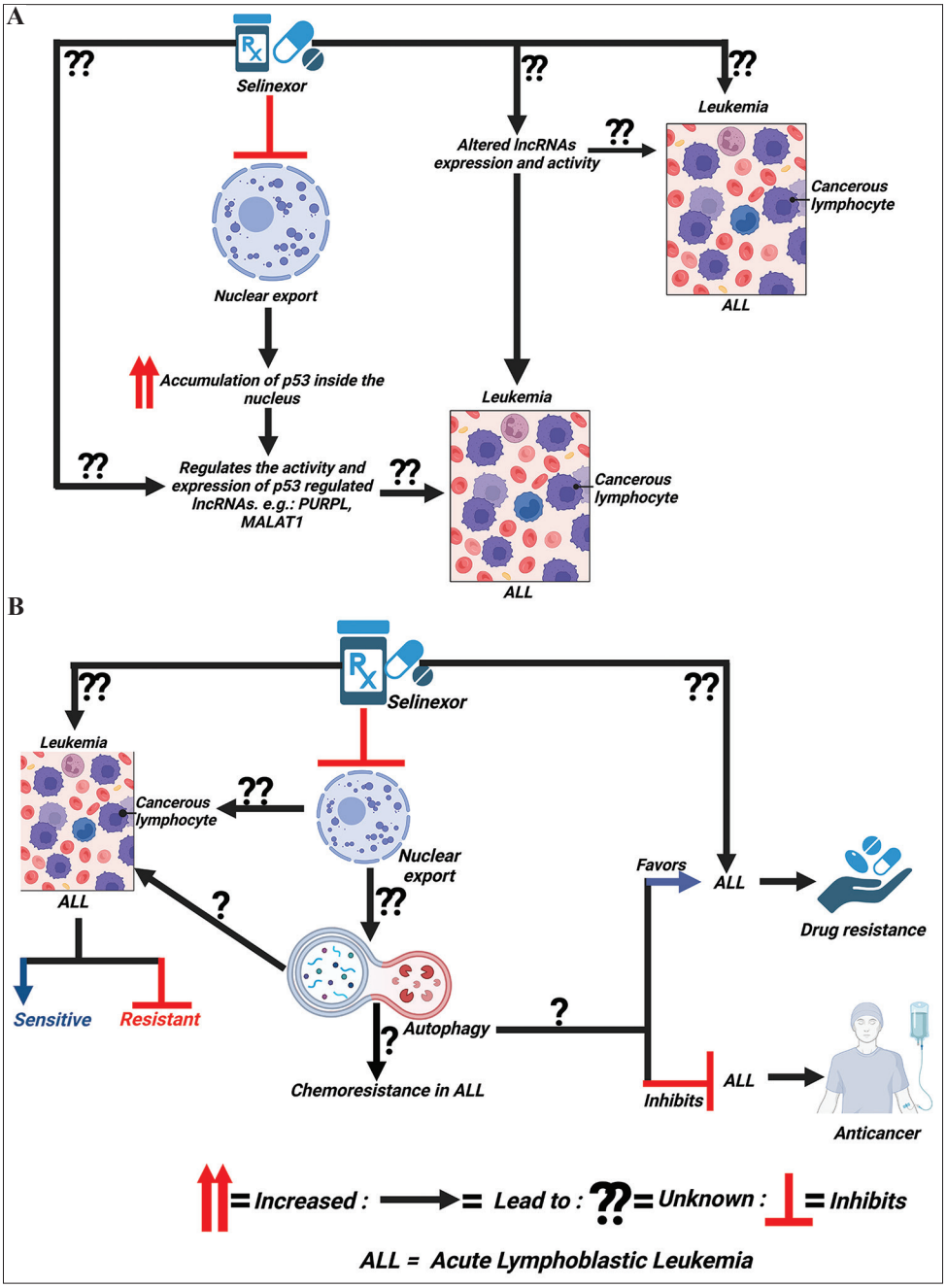

Figure 2. Long non-coding RNAs (lncRNAs) and autophagy as possible therapeutic targets of selinexor. (**A**) This schematic provides an overview of the potential therapeutic targeting of long non-coding RNAs (lncRNAs) by selinexor. It also illustrates the regulation and implications of altered lncRNA expression in acute lymphoblastic leukemia (ALL). (**B**) This diagram outlines the role of autophagy in the selinexor-mediated response in ALL. It emphasizes the significance of autophagy in ALL. The "???" in the figure symbolizes areas that remain unexplored or unanswered.

isoforms that are unique to cancer and display either absence or distinctive expression levels when contrasted with their equivalents in healthy tissue [50]. Significantly, a considerable proportion of these transcripts encompass pivotal oncogenes and tumor suppressor genes [50,51]. Among the proteins that are translocated to the nucleus in selinexor-sensitive cells, there was a notable over-presentation of KEGG terms associated with spliceosome [13]. The spliceosome holds a significant function in governing alternative splicing regulation [52]. Alternative splicing plays a pivotal role in enhancing the intricacy of proteins within the human system [34]. This intricate process is under the regulation of splicing factors [49,53], which exert control over alternative splicing. It is evident that a strong correlation exists between numerous diseases and the disruptions and errors in splicing regulation caused by these splicing factors [50,51,53]. These crucial regulatory elements, known as splicing factors, belong to

the category of trans-acting RNA binding proteins [51,53]. It is worth noting that only a limited number of RNA-binding proteins have been associated with childhood ALL. In addition, their precise contributions to childhood ALL are still emerging. The phenomenon of alternative splicing is deregulated in AML [22]. Aberrant spliced Isoforms of IKZF1 have been detected not only in leukemic cell lines but also in samples derived from patients with ALL [54]. Furthermore, the splicing patterns of IKZF1 have been associated with the development of resistance to receptor tyrosine kinase inhibitors among samples from ALL patients [55]. Likewise, a connection has been established between the splicing of isoforms in the N terminus of p53 and its involvement in ALL [56]. In AML, a particularly noteworthy aspect involves the recurrence of mutations within the machinery responsible for splicing, leading to widespread instances of irregular splicing events across the entire genome [57]. Studies looking at the role of spliceosome machinery and aberrant splicing have not been studied extensively in childhood ALL. One of the most critical challenges in contemporary cancer treatment is the emergence of resistance to therapeutic medications, ultimately culminating in the failure of treatment endeavors [10,58]. Importantly, alternative splicing holds the capacity to significantly alter the coding region of drug targets [57].

Several reports have identified significant alternative splicing events that take place in different types of cancers and contribute to resistance against cancer therapies [59]. In the context of Phase II clinical trials targeting patients with myelodysplastic syndrome (MDS), the administration of selinexor resulted in mixed outcomes, with some patients showing a positive response while others did not respond [19]. Genetic investigations have revealed a strong connection between the response to selinexor and the presence of hotspot mutations within the core RNA splicing factor SF3B1 [60]. Notably, SF3B1 mutations are frequently found in MDS and render cells more vulnerable to the impairment of normal splicing functions in remaining wild-type genes. This interplay between SF3B1 mutations and the response to selinexor is particularly significant, given SF3B1's established association with MDS and the essential role of XPO1 in the nuclear export and maturation of RNA spliceosome components [61]. After selinexor treatment, comprehensive transcriptomic sequencing of alternative splicing events in bone marrow specimens taken before and after treatment unveiled a distinct pattern [61]. Patients who achieved marrow complete remission (mCR) displayed a widespread disruption in RNA splicing, characterized by heightened intron retention (IR) in post-treatment samples compared to their pre-treatment counterparts. In contrast, those who did not achieve mCR exhibited less pronounced IR [61].

Interestingly, selinexor induced significant IR, notably in the Inhibitor of NF-kB Kinase Subunit Beta gene. This led to the inclusion of a premature stop codon, subsequently triggering nonsense-mediated decay and disrupting the NF-kB signaling pathway [61]. These observations became apparent when closely examining the most prominent instances of IR among selinexor responders [61]. Considering the above observations, it would be intriguing to explore the role of alternative splicing in the drug response of selinexor (Figure 1C). The objective would be to investigate how aberrant alternative splicing impacts the effectiveness of selinexor in the treatment of childhood ALL.

6. Long Noncoding RNAs

Long non-coding RNAs (lncRNAs: longer than 200 nucleotides) play a crucial role in regulating various aspects of gene expression. They are involved in processes such as chromatin remodeling, transcriptional control, regulation of splicing, mRNA stability, mRNA translation, miRNA processing, and protein stability [62]. Recently, a study has shed light on the involvement of lncRNAs in the etiology, progression, and treatment response of childhood ALL [63]. In addition, MALAT1, a specific long noncoding RNAs has been linked to poor prognosis in childhood AML [64]**.** Multiple studies have also implicated MALAT1 in drug resistance of various cancer types [65-70]. It would be intriguing to investigate the expression of MALAT1 in response to selinexor exposure in childhood ALL cell lines and patient samples. This raises the question of whether MALAT1 plays a role in determining the sensitivity of selinexor. Furthermore, it is worth noting that MALAT1 is a nuclear-localized lncRNA, while selinexor acts as an inhibitor of nuclear export. The impact of selinexor on MALAT1 expression, function, and regulation remains unknown.

p53, a well-studied tumor suppressor protein, has been demonstrated to govern the expression of several lncRNAs, including lncRNA-p21 [71], PANDA [72], DINO [73], and PURPL (p53 upregulated regulator of p53 levels), [74]. PURPL is an intergenic lncRNA that was identified by RNA sequencing (RNA-seq) in multiple colorectal cancer (CRC) lines [74]. The loss of PURPL has been linked to elevated basal levels of p53 and an impairment of cell growth both *in vitro* and *in vivo* [74]. Recent research has shown that PURPL production is transcriptionally regulated by the transcription factor p53, which tends to be elevated in senescent conditions [75]. Given the dependency of selinexor sensitivity on p53 levels observed in AML [13], it becomes intriguing to investigate the levels of p53-regulated lncRNAs in ALL. In addition, selinexor treatment has been shown to lead to an increased accumulation of p53 inside the nucleus [13]. However, the impact of selinexor on well-established p53-targeted lncRNAs such as lncRNA-p21, PANDA, DINO, and, PURPL, in terms of their expression, function, and regulation, remains largely unknown (Figure 2A). In addition, the role of p53-regulated noncoding RNAs in childhood ALL remains unexplored.

7. Summary and Future Prospectives

Due to the extensive disruption of nuclear transport in cancer and its pivotal involvement at the crossroads of crucial signal transduction pathways, there has been a significant focus on exploring exportins as a prime target in cancer-related research. A plethora of small molecules targeting XPO1 inhibition have been discovered. In preclinical investigations, the administration of selinexor leads to the suppression of XPO1, leading to the accumulation of its target molecules within the nucleus. The potential alternations in mTOR signaling, cancer glucose

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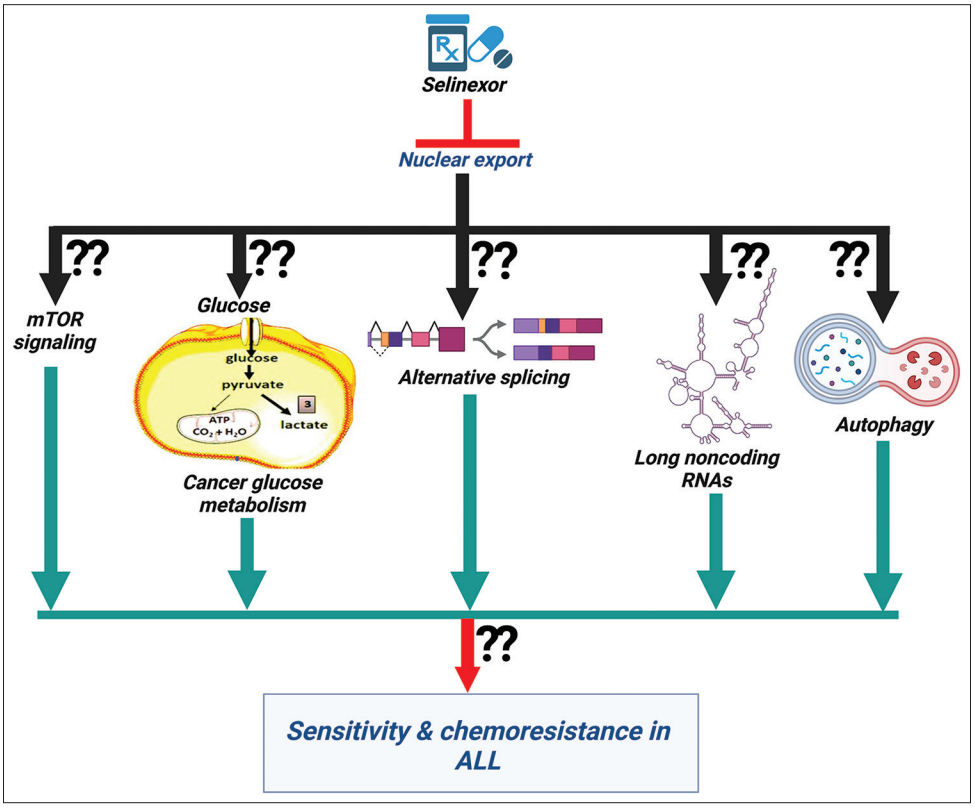

Figure 3. This diagram illustrates the multifaceted therapeutic targets of selinexor and its role in determining the effectiveness of acute lymphoblastic leukemia (ALL) treatments. Red lines represent direct effects, indicating targets directly impacted by selinexor. Black lines signify pathways that can be modulated due to selinexor's inhibition of nuclear export. Light green lines indicate the diverse responses of selinexor in ALL resulting from its interactions with different potential therapeutic targets. The "???" in the figure symbolizes areas that remain unexplored or unanswered.

metabolism, autophagy, lncRNAs expression, and alternative splicing on selinexor treatment could be employed to understand the detailed molecular mechanism of action. In instances where selinexor treatment induces heightened autophagic activity within resistant cellular lineages, the co-administration of selinexor with autophagy inhibitors holds promise for augmenting its efficacy against cell populations manifesting a resistant phenotype. Theoretically, if ALL cell lines or patient samples demonstrate certain dysregulated alternative splicing or lncRNA expression, the application of selinexor treatment in conjunction with a precise inhibitor for lncRNA expression or a splicing regulator could offer a corrective approach for specific aberrant splicing events. Further investigations are required to validate the responsiveness of selinexor in combination with mTORC1 inhibitors on both cell lines and patient samples.

Overall, we anticipate that the knowledge gained from this study can be effectively integrated into the development of innovative therapies targeting childhood ALL. These therapies hold the promise of not only prolonging the lifespan and enhancing the quality of life for ALL patients by postponing the onset of drug resistance but also serving as chemo-preventative agents to decrease the occurrence of ALL. Collectively, such focused research endeavors will significantly enhance our comprehension of the underlying factors driving childhood ALL and offer valuable pathways for its therapeutic management (Figure 3).

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Conflicts of Interest

The authors declare no competing interests.

References

[1] Chen J, Huang C, Zhu Y, Dong L, Cao W, Sun L, *et al*. Identification of Similarities and Differences Between Myeloid and Lymphoid Acute Leukemias using a Gene-gene Interaction Network. Pathol Res Pract 2015;211:789-96.

[2] Catovsky D. Symposium: Classification of Leukemia. 1. The Classification of Acute Leukemia. Pathology 1982;14:277-81.

[3] Di Nardo CD, Cortes JE. Mutations in AML: Prognostic and Therapeutic Implications. Hematology Am Soc

Hematol Educ Program 2016;2016:348-55.

[4] Cortes JE, Kantarjian HM. Acute Lymphoblastic Leukemia. A Comprehensive Review with Emphasis on Biology and Therapy. Cancer 1995;76:2393-417.

[5] Faderl S, Jeha S, Kantarjian HM. The Biology and Therapy of Adult Acute Lymphoblastic Leukemia. Cancer 2003;98:1337-54.

[6] Debela DT, Muzazu SG, Heraro KD, Ndalama MT, Mesele BW, Haile DC, *et al*. New Approaches and Procedures for Cancer Treatment: Current Perspectives. SAGE Open Med 2021;9:20503121211034366.

[7] Deak D, Gorcea-Andronic N, Sas V, Teodorescu P, Constantinescu C, Iluta S, *et al*. A Narrative Review of Central Nervous System Involvement in Acute Leukemias. Ann Transl Med 2021;9:68.

[8] Fullmer A, O'Brien S, Kantarjian H, Jabbour E. Novel Therapies for Relapsed Acute Lymphoblastic Leukemia. Curr Hematol Malig Rep 2009;4:148-56.

[9] Hamid AB, Petreaca RC. Secondary Resistant Mutations to Small Molecule Inhibitors in Cancer Cells. Cancers (Basel) 2020;12:927.

[10] Mansoori B, Mohammadi A, Davudian S, Shirjang S, Baradaran B. The Different Mechanisms of Cancer Drug Resistance: A Brief Review. Adv Pharm Bull 2017;7:339-48.

[11] Balasubramanian SK, Azmi AS, Maciejewski J. Selective Inhibition of Nuclear Export: A Promising Approach in the Shifting Treatment Paradigms for Hematological Neoplasms. Leukemia 2022;36:601-12.

[12] Fung HY, Chook YM. Atomic Basis of CRM1-cargo Recognition, Release and Inhibition. Semin Cancer Biol 2014;27:52-61.

[13] Emdal KB, Palacio-Escat N, Wigerup C, Eguchi A, Nilsson H, Bekker-Jensen DB, *et al*. Phosphoproteomics of Primary AML Patient Samples Reveals Rationale for AKT Combination Therapy and p53 Context to Overcome Selinexor Resistance. Cell Rep 2022;40:111177.

[14] Sellin M, Berg S, Hagen P, Zhang J. The Molecular Mechanism and Challenge of Targeting XPO1 in Treatment of Relapsed and Refractory Myeloma. Transl Oncol 2022;22:101448.

[15] Pinto V, Bergantim R, Caires HR, Seca H, Guimarães JE, Vasconcelos MH. Multiple Myeloma: Available Therapies and Causes of Drug Resistance. Cancers (Basel) 2020;12:407.

[16] Mo CC, Yee AJ, Midha S, Hartley-Brown MA, Nadeem O, O'Donnel EK, *et al*. Selinexor: Targeting a Novel Pathway in Multiple Myeloma. EJHaem 2023;4:792-810.

[17] Garzon R, Savona M, Baz R, Andreeff M, Gabrail N, Gutierrez M, *et al*. A Phase 1 Clinical Trial of Single-agent Selinexor in Acute Myeloid Leukemia. Blood 2017;129:3165-74.

[18] Sweet K, Komrokji R, Padron E, Cubitt CL, Turner JG, Zhou J, *et al*. Phase I Clinical Trial of Selinexor in Combination with Daunorubicin and Cytarabine in Previously Untreated Poor-risk Acute Myeloid Leukemia. Clin Cancer Res 2020;26:54-60.

[19] Fiedler W, Chromik J, Amberg S, Kebenko M, Thol F, Schlipfenbacher V, *et al*. A Phase II Study of Selinexor Plus Cytarabine and Idarubicin in Patients with Relapsed/Refractory Acute Myeloid Leukaemia. Br J Haematol 2020;190:e169-73.

[20] Argueta C, Kashyap T, Klebanov B, Unger TJ, Guo C, Harrington S, *et al*. Selinexor Synergizes with Dexamethasone to Repress mTORC1 Signaling and Induce Multiple Myeloma Cell Death. Oncotarget 2018;9:25529-44.

[21] Long H, Hou Y, Li J, Song C, Ge Z. Azacitidine is Synergistically Lethal with XPO1 Inhibitor Selinexor in Acute Myeloid Leukemia by Targeting XPO1/eIF4E/c-MYC Signaling. Int J Mol Sci 2023;24:6816.

[22] Zhao C, Yang ZY, Zhang J, Li O, Liu SL, Cai C, *et al*. Inhibition of XPO1 with KPT-330 Induces Autophagy-dependent Apoptosis in Gallbladder Cancer by Activating the p53/mTOR Pathway. J Transl Med 2022;20:434.

[23] Saxton RA, Sabatini DM. mTOR Signaling in Growth, Metabolism, and Disease. Cell 2017;168:960-76.

[24] Laplante M, Sabatini DM. mTOR Signaling at a Glance. J Cell Sci 2009;122:3589-94.

[25] Zoncu R, Efeyan A, Sabatini DM. mTOR: From Growth Signal Integration to Cancer, Diabetes and Ageing. Nat Rev Mol Cell Biol 2011;12:21-35.

[26] Linke M, Fritsch SD, Sukhbaatar N, Hengstschläger M, Weichhart T. mTORC1 and mTORC2 as Regulators of Cell Metabolism in Immunity. FEBS Lett 2017;591:3089-103.

[27] Fruman DA. mTOR Signaling: New Networks for ALL. Blood 2016;127:2658-9.

[28] Simioni C, Martelli AM, Zauli G, Melloni E, Neri LM. Targeting mTOR in Acute Lymphoblastic Leukemia. Cells 2019;8:190.

[29] Neri LM, Cani A, Martelli AM, Simioni C, Junghanss C, Tabellini G, *et al*. Targeting the PI3K/Akt/mTOR Signaling Pathway in B-precursor Acute Lymphoblastic Leukemia and its Therapeutic Potential. Leukemia 2014;28:739-48.

[30] Liberti MV, Locasale JW. The Warburg Effect: How does it Benefit Cancer Cells? Trends Biochem Sci 2016;41:211-8.

[31] Zheng J. Energy Metabolism of Cancer: Glycolysis Versus Oxidative Phosphorylation (Review). Oncol Lett 2012;4:1151-7.

[32] Hay N. Reprogramming Glucose Metabolism in Cancer: Can it be Exploited for Cancer Therapy? Nat Rev Cancer 2016;16:635-49.

[33] Fadaka A, Ajiboye B, Ojo O, Adewale O, Olayide I, Emuowhochere R. Biology of Glucose Metabolization in

Cancer Cells. J Oncol Sci 2017;3:45-51.

[34] Szwed A, Kim E, Jacinto E. Regulation and Metabolic Functions of mTORC1 and mTORC2. Physiol Rev 2021;101:1371-426.

[35] Boag JM, Beesley AH, Firth MJ, Freitas JR, Ford J, Hoffmann K, *et al*. Altered Glucose Metabolism in Childhood Pre-B Acute Lymphoblastic Leukaemia. Leukemia 2006;20:1731-7.

[36] Chan LN, Chen Z, Braas D, Lee JW, Xiao G, Geng H, *et al*. Metabolic Gatekeeper Function of B-lymphoid Transcription Factors. Nature 2017;542:479-83.

[37] Arango NP, Yuca E, Zhao M, Evans KW, Scott S, Kim C, *et al*. Selinexor (KPT-330) Demonstrates Anti-tumor Efficacy in Preclinical Models of Triple-negative Breast Cancer. Breast Cancer Res 2017;19:93.

[38] Kulkoyluoglu-Cotul E, Smith BP, Wrobel K, Zhao YC, Chen KL, Hieronymi K, *et al*. Combined Targeting of Estrogen Receptor Alpha and XPO1 Prevent Akt Activation, Remodel Metabolic Pathways and Induce Autophagy to Overcome Tamoxifen Resistance. Cancers (Basel) 2019;11:479.

[39] Kawaguchi M, Aoki S, Hirao T, Morita M, Ito K. Autophagy is an Important Metabolic Pathway to Determine Leukemia Cell Survival Following Suppression of the Glycolytic Pathway. Biochem Biophys Res Commun 2016;474:188-92.

[40] Glick D, Barth S, Macleod KF. Autophagy: Cellular and Molecular Mechanisms. J Pathol 2010;221:3-12.

[41] Rosenfeldt MT, Ryan KM. The Multiple Roles of Autophagy in Cancer. Carcinogenesis 2011;32:955-63.

[42] Galluzzi L, Pietrocola F, Pedro JM, Amaravadi RK, Baehrecke EH, Cecconi F, *et al*. Autophagy in Malignant Transformation and Cancer Progression. EMBO J 2015;34:856-80.

[43] Yang ZJ, Chee CE, Huang S, Sinicrope FA. The Role of Autophagy in Cancer: Therapeutic Implications. Mol Cancer Ther 2011;10:1533-41.

[44] Chen N, Karantza V. Autophagy as a Therapeutic Target in Cancer. Cancer Biol Ther 2011;11:157-68.

[45] Sui X, Chen R, Wang Z, Huang Z, Kong N, Zhang M, *et al*. Autophagy and Chemotherapy Resistance: A Promising Therapeutic Target for Cancer Treatment. Cell Death Dis 2013;4:e838.

[46] Losa JH, Cobo CP, Viniegra JG, Lobo VJ, Cajal SR, Sánchez-Prieto R. Role of the p38 MAPK Pathway in Cisplatin-based Therapy. Oncogene 2003;22:3998-4006.

[47] Levy JM, Towers CG, Thorburn A. Targeting Autophagy in Cancer. Nat Rev Cancer 2017;17:528-42.

[48] Nilsen TW, Graveley BR. Expansion of the Eukaryotic Proteome by Alternative Splicing. Nature 2010;463:457-63.

[49] Wang Y, Liu J, Huang BO, Xu YM, Li J, Huang LF, *et al*. Mechanism of Alternative Splicing and its Regulation. Biomed Rep 2015;3:152-8.

[50] Urbanski LM, Leclair N, Anczuków O. Alternative-splicing Defects in Cancer: Splicing Regulators and their Downstream Targets, Guiding the Way to Novel Cancer Therapeutics. Wiley Interdiscip Rev RNA 2018;9:e1476.

[51] Anczukow O, Krainer AR. Splicing-factor Alterations in Cancers. RNA 2016;22:1285-301.

[52] Will CL, Lührmann R. Spliceosome Structure and Function. Cold Spring Harb Perspect Biol 2011;3:a003707.

[53] Fredericks AM, Cygan KJ, Brown BA, Fairbrother WG. RNA-binding Proteins: Splicing Factors and Disease. Biomolecules 2015;5:893-909.

[54] Zhao W, Li Y, Yao C, Zhang G, Zhao KY, Chen W, *et al*. Detection of Pathogenic Isoforms of IKZF1 in Leukemic Cell Lines and Acute Lymphoblastic Leukemia Samples: Identification of a Novel Truncated IKZF1 Transcript in SUP-B15. Cancers (Basel) 2020;12:3161.

[55] Lacobucci I, Lonetti A, Messa F, Cilloni D, Arruga F, Ottaviani E, *et al*. Expression of Spliced Oncogenic Ikaros Isoforms in Philadelphia-positive Acute Lymphoblastic Leukemia Patients Treated with Tyrosine Kinase Inhibitors: Implications for a New Mechanism of Resistance. Blood 2008;112:3847-55.

[56] Oh L, Hainaut P, Blanchet S, Ariffin H. Expression of p53 N-terminal Isoforms in B-cell Precursor Acute Lymphoblastic Leukemia and its Correlation with Clinicopathological Profiles. BMC Cancer 2020;20:110.

[57] De Necochea-Campion R, Shouse GP, Zhou Q, Mirshahidi S, Chen CS. Aberrant Splicing and Drug Resistance in AML. J Hematol Oncol 2016;9:85.

[58] Housman G, Byler S, Heerboth S, Lapinska K, Longacre M, Snyder N, *et al*. Drug Resistance in Cancer: An Overview. Cancers (Basel) 2014;6:1769-92.

[59] Siegfried Z, Karni R. The Role of Alternative Splicing in Cancer Drug Resistance. Curr Opin Genet Dev 2018;48:16-21.

[60] Jeromin S, Weissmann S, Haferlach C, Dicker F, Bayer K, Grossmann V, *et al*. SF3B1 Mutations Correlated to Cytogenetics and Mutations in NOTCH1, FBXW7, MYD88, XPO1 and TP53 in 1160 Untreated CLL Patients. Leukemia 2013;28:108-17.

[61] Taylor J, Mi X, Penson AV, Paffenholz SV, Alvarez K, Sigler A, *et al*. Safety and Activity of Selinexor in Patients with Myelodysplastic Syndromes or Oligoblastic Acute Myeloid Leukaemia Refractory to Hypomethylating Agents: A Single-centre, Single-arm, Phase 2 Trial. Lancet Haematol 2020;7:e566-74.

[62] Malakar P, Shilo A, Mogilevsky A, Stein I, Pikarsky E, Nevo Y, *et al*. Long Noncoding RNA MALAT1 Promotes Hepatocellular Carcinoma Development by SRSF1 Upregulation and mTOR Activation. Cancer Res 2017;77:1155-67.

[63] Ouimet M, Drouin S, Lajoie M, Caron M, St-Onge P, Gioia R,

et al. A Childhood Acute Lymphoblastic Leukemia-specific lncRNA Implicated in Prednisolone Resistance, Cell Proliferation, and Migration. Oncotarget 2017;8:7477-88.

[64] Pouyanrad S, Rahgozar S, Ghodousi ES. Dysregulation of miR-335-3p, Targeted by NEAT1 and MALAT1 Long Non-coding RNAs, is Associated with Poor Prognosis in Childhood Acute Lymphoblastic Leukemia. Gene 2019;692:35-43.

[65] Chen W, Zhao W, Zhang L, Wang L, Wang J, Wan Z, *et al*. MALAT1-miR-101-SOX9 Feedback Loop Modulates the Chemo-resistance of Lung Cancer Cell to DDP via Wnt Signaling Pathway. Oncotarget 2017;8:94317-29.

[66] Chen W, Tan X, Yang Q, Fang Z, Xu Y. MALAT1 Enhances Gemcitabine Resistance in Non-small Cell Lung Cancer Cells by Directly Affecting miR-27a-5p/PBOV1 Axis. Cell Signal 2022;94:110326.

[67] Feng C, Zhao Y, Li Y, Zhang T, Ma Y, Liu Y. LncRNA MALAT1 Promotes Lung Cancer Proliferation and Gefitinib Resistance by Acting as a miR-200a Sponge. Arch Bronconeumol (Engl Ed) 2019;55:627-33.

[68] Fang Z, Chen W, Yuan Z, Liu X, Jiang H. LncRNA-MALAT1 Contributes to the Cisplatin-resistance of Lung Cancer by Upregulating MRP1 and MDR1 via STAT3 Activation. Biomed Pharmacother 2018;101:536-42.

[69] Jiang Q, Liu S, Hou L, Guan Y, Yang S, Luo Z. The Implication of LncRNA MALAT1 in Promoting Chemo-resistance of Laryngeal Squamous Cell Carcinoma Cells. J Clin Lab Anal 2020;34:e23116.

[70] Shi C, Ren S, Zhao X, Li Q. lncRNA MALAT1 Regulates the Resistance of Breast Cancer Cells to Paclitaxel via the miR-497-5p/SHOC2 Axis. Pharmacogenomics 2022;23:973-85.

[71] Huarte M, Guttman M, Feldser D, Garber M, Koziol MJ, Kenzelmann-Broz D, *et al*. A Large Intergenic Noncoding RNA Induced by p53 Mediates Global Gene Repression in the p53 Response. Cell 2010;142:409-19.

[72] Hung T, Wang Y, Lin MF, Koegel AK, Kotake Y, Grant GD, *et al*. Extensive and Coordinated Transcription of Noncoding RNAs within Cell-cycle Promoters. Nat Genet 2011;43:621-9.

[73] Schmitt AM, Garcia JT, Hung T, Flynn RA, Shen Y, Qu K, *et al*. An Inducible Long Noncoding RNA Amplifies DNA Damage Signaling. Nat Genet 2016;48:1370-6.

[74] Li XL, Subramanian M, Jones MF, Chaudhary R, Singh DK, Zong X, *et al*. Long Noncoding RNA PURPL Suppresses Basal p53 Levels and Promotes Tumorigenicity in Colorectal Cancer. Cell Rep 2017;20:2408-23.

[75] Casella G, Munk R, Kim KM, Piao Y, De S, Abdelmohsen K, *et al*. Transcriptome Signature of Cellular Senescence. Nucleic Acids Res 2019;47:7294-305.

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