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PERSPECTIVE

XPO1 as a key regulator in small cell lung cancer: mechanisms, biomarkers, and therapeutic implications

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Introduction

Small cell lung cancer (SCLC) is a highly aggressive malignancy with limited treatment options. Despite advances in immunotherapy, response rates remain low, and the efficacy of current molecular subtyping[1,2] is insufficient to predict therapeutic outcomes[3,4]. A recently identified vulnerability in SCLC involves the dysregulation of nuclear-cytoplasmic transport, particularly through exportin 1 (XPO1)[5-7]. This discovery has led to the identification of a novel SCLC subtype characterized by high histone deacetylase 7 (HDAC7) expression, which correlates with enhanced sensitivity to the XPO1 inhibitor selinexor[8]. XPO1 not only contributes to oncogenic transport but also plays a crucial role in immune surveillance. Recent breakthroughs have identified an XPO1-derived peptide, NAPLVHATL, which activates Killer immunoglobulin-like receptor 2DS2 positive natural killer ($KIR2DS2^+$ NK) cells and offers a promising new strategy for immunotherapy[9]. XPO1's dual role as both a driver of tumor progression and an immune-targetable antigen may open new avenues for personalized immunotherapy in SCLC, with the potential to improve patient outcomes.

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Advancing SCLC subtyping: integrating epigenetic and transport mechanisms into therapeutic stratification

Subtyping of SCLC according to transcription factors, such as achaete-scute homologue 1 (ASCL1), POU class 2 homeobox 3 (POU2F3), neurogenic differentiation factor 1 (NEUROD1), and yes-associated protein 1 (YAP1, or Inflamed)[1,2], has provided valuable insights into the biological heterogeneity of the disease. However, these subtypes do not consistently correlate with therapeutic responses, particularly to immunotherapy[3,4]. Non-negative matrix factorization (NMF)-based proteogenomic analysis has uncovered distinct SCLC subtypes with unique molecular and clinical characteristics, which may enable more personalized therapeutic strategies. Notably, the MYC-high expression subtype is associated with poor prognosis, aggressive behavior, treatment resistance, and dysregulated cell proliferation and metabolism[10]. Although MYC plays an important role in SCLC, targeted therapies against MYC continue to face challenges. Additionally, the infiltration of immune cells within the SCLC tumor microenvironment closely correlates with immunotherapy outcomes, thus emphasizing the importance of immune dynamics in treatment efficacy[3]. Recent studies have highlighted the dysregulation of nuclear-cytoplasmic transport mechanisms, particularly exportin 1 (XPO1), as a key factor driving tumor progression and metastasis in SCLC. Because elevated expression of XPO1 is associated with aggressive tumor phenotypes and poor prognosis, this transport protein may be a promising therapeutic target. Inhibition of XPO1 has demonstrated efficacy in preclinical models and has potential for overcoming

chemoresistance, particularly in HDAC7/MYC-driven SCLC[8]. However, current transcription factor-based subtyping systems do not adequately capture the heterogeneity of therapeutic responses. For instance, HDAC7/MYC-driven tumors, which display aggressive biological features, are found across all subtypes, yet their sensitivity to targeted therapies, such as XPO1 inhibitors, is not effectively addressed by these existing frameworks[8]. Moreover, crucial epigenetic regulators, such as HDACs[11], and components of the nuclear-cytoplasmic transport machinery, such as XPO1[5-8], have not been integrated into the current subtyping systems, despite their critical roles in tumor progression, metastasis, and chemoresistance. This disconnect underscores the urgent need for molecularly driven subtyping systems more precisely aligned with therapeutic vulnerabilities to improve clinical outcomes. Integrating XPO1 as a core component of SCLC subtyping might enhance patient stratification and improve responses to targeted therapies. The development of molecularly informed subtyping systems that incorporate XPO1 inhibition will be critical in advancing personalized treatment approaches for SCLC.

XPO1 in SCLC: a key regulator of oncogenic transport and tumor progression

Mechanistic basis of XPO1 dependency

XPO1 plays a central role in mediating the nuclear export of tumor suppressors such as forkhead box O3a (FOXO3a) and oncogenic factors such as MYC mRNA, which are critical in regulating tumor progression. Dysregulation of XPO1, leading to the mislocalization of tumor suppressors to the cytoplasm, promotes survival and resistance to therapies[12]. Inhibition of XPO1 with agents such as selinexor restores the nuclear localization of FOXO3a, reactivates pro-apoptotic pathways, and substantially decreases tumor proliferation. We have reported that poly-ADP-ribose polymerase (PARP) inhibition induces cytoplasmic sequestration of FOXO3a, a key transcription factor responsible for apoptosis and DNA repair in SCLC[5]. This mislocalization suppresses FOXO3a-dependent transcriptional regulation of pro-apoptotic genes (e.g., BIM), thereby promoting tumor survival and potential chemoresistance. Preclinical models have demonstrated that XPO1 inhibitors, such as selinexor, restore FOXO3a nuclear localization, reactivate apoptotic pathways, and decrease tumor proliferation by approximately 50% in mini-patient-derived xenografts (mini-PDXs)[5] (**Figure 1A**). Subsequent studies by Rudin's team further validated these findings by showing that XPO1 inhibition enhances SCLC sensitivity to chemotherapy, *via* CRISPR-Cas9 screens[6] (**Figure 1B**), and suppresses neuroendocrine transformation through SOX2[7] (**Figure 1C**). Importantly, HDAC7$^+$ SCLC, often characterized by elevated HDAC7, MYC and XPO1 expression, has shown increased sensitivity to XPO1 inhibitors compared to non-HDAC7$^+$ SCLC, thus supporting the therapeutic potential of targeting XPO1 in specific molecular subsets of SCLC. For example, in HDAC7/MYC-overexpressing SCLC patient-derived organoid models, XPO1 inhibition restricts tumor growth by more than 90%, with respect to that in controls[8] (**Figure 1D**). Similarly, in MYC-high hepatocellular carcinoma mouse models, XPO1 inhibition results in a >95% decrease in tumor volume[13]. These findings underscore the therapeutic potential of targeting XPO1 as a standalone treatment in molecularly defined malignancies (**Figure 1**).

Interplay between XPO1 and epigenetic dysregulation

Epigenetic modifications, such as DNA methylation, histone modifications, and chromatin remodeling, profoundly influence gene expression and cellular identity. In SCLC, aggressive phenotypes are closely associated with epigenetic dysregulation[14]. For instance, nuclear factor I/B (NFIB) promotes SCLC metastasis by broadly increasing chromatin accessibility[15], whereas mutations in histone-modifying enzymes, such as lysine methyltransferase 2C (KMT2C) and DNA methyltransferase 3A (DNMT3A), drive metastatic progression and chemoresistance[11]. Functional crosstalk exists between XPO1 and epigenetic dysregulation: for example, HDAC7 overexpression transcriptionally upregulates XPO1 expression, thereby linking histone modification to nuclear transport mechanisms[8]. This interplay suggests that XPO1 inhibition might counteract epigenetically driven malignancy by restoring the nuclear retention of tumor suppressors, thus providing a promising therapeutic strategy.

XPO1 as an NK cell-activating antigen: a paradigm shift

XPO1 plays a critical role in oncogenesis; however, recent studies have revealed its dual function as an immune-activating antigen. A peptide derived from XPO1, NAPLVHATL, has

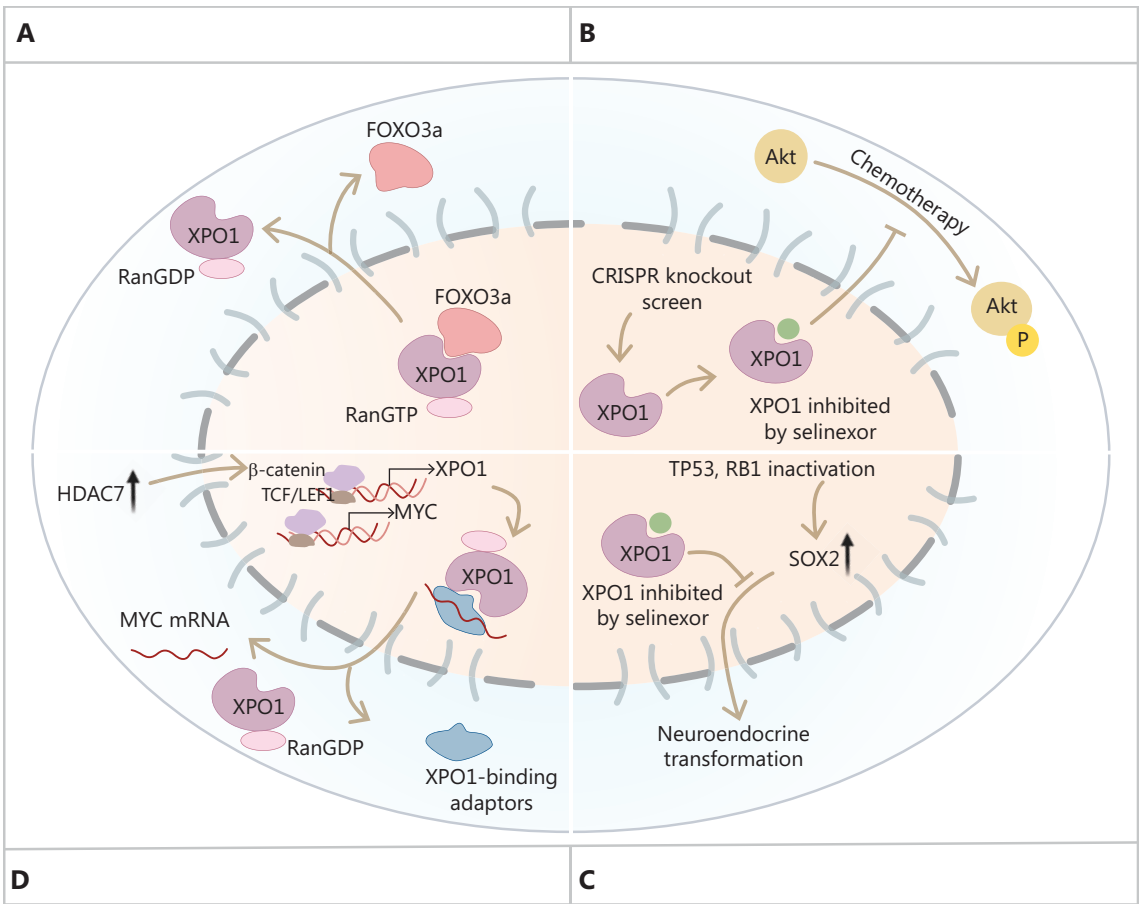


Figure 1 Mechanistic basis of XPO1 dependency. (A) XPO1 inhibitor counteracts PARP1 inhibitor-mediated alterations in FOXO3a nuclear localization. (B) XPO1 inhibitor suppresses chemotherapy-triggered activation of the Akt signaling pathway. (C) XPO1 inhibitor reverses SOX2 elevation-induced neuroendocrine transition. (D) XPO1 inhibitor mitigates HDAC7-driven malignant biological behaviors in the novel SCLC subtype by modulating MYC nuclear export. FOXO3a, forkhead box O3a; HDAC7, histone deacetylase 7; LEF1, lymphoid enhancer-binding factor 1; PARP, poly-ADP-ribose polymerase; RanGDP, Ran guanosine diphosphate; RanGTP, Ran guanosine triphosphate; RB1, retinoblastoma 1; TCF, T-cell factor; XPO1, exportin 1.

been identified through peptide library screening targeting the XPO1 protein complex and subsequently validated by structural analysis. This peptide is specifically recognized by KIR2DS2$^+$ NK cells in the context of HLA-C*01:02, and subsequently triggers NK cell activation and enhances their cytotoxicity against tumor cells. Importantly, although high XPO1 expression is generally associated with poor prognosis across multiple cancer types, its association with NK cell infiltration, particularly in hepatocellular carcinoma, correlates with improved survival outcomes, thus highlighting the dual oncogenic and immunogenic roles of XPO1[9]. These findings suggest that combining XPO1 inhibition with NK cell-based therapies might offer a novel strategy for targeting solid tumors, particularly those with high XPO1 expression. The dual functionality of XPO1 as both a driver of tumor progression and a facilitator of immune activation positions it as a critical target for future cancer immunotherapies.

Biomarkers of XPO1 dependency

The combination of XPO1 inhibition and NK cell activation might enhance the sensitivity of tumors to treatment and improve patient outcomes. Key biomarkers of XPO1 dependency include expression levels of XPO1 as well as the subcellular localization of tumor suppressors such as FOXO3a. The cytoplasmic retention of FOXO3a is a hallmark of XPO1 overexpression and poor prognosis, whereas nuclear relocalization of FOXO3a after XPO1 inhibition is associated with enhanced sensitivity to therapy[5]. Additionally, the expression levels of HDAC7 and MYC play critical roles in determining XPO1

Table 1 Summary of XPO1-associated biomarkers

Biomarker	Type	Predictive/Prognostic	Validation Status	Evidence Source
HDAC7	Epigenetic regulator	Predictive	Preclinical	Qin et al., Adv Sci 2025[8]
MYC	Oncogene	Predictive	Preclinical	Qin et al., Adv Sci 2025[8] Deutzmann et al., Nat Commun 2024[13]
XPO1-derived peptides	Immune marker	Predictive	Preclinical	Blunt et al., Sci Adv 2024[9]
FOXO3a	Tumor suppressor localization	Predictive	Preclinical	Wang et al., Cancer Lett 2021[5]

HDAC7, histone deacetylase 7; FOXO3a, forkhead box O3a; XPO1, exportin 1.

dependency in molecular subsets of SCLC and other cancers. In preclinical models, tumors with elevated HDAC7/MYC expression exhibit markedly enhanced sensitivity to XPO1 inhibitors; therefore, these factors are important biomarkers for stratifying patients for XPO1-targeted therapy[8]. Beyond molecular biomarkers, immune-associated markers such as KIR2DS2 and NKp46/NCR1 offer valuable insights into the immune landscape of XPO1-expressing tumors. The presence of KIR2DS2$^+$ NK cells in tumors with high XPO1 expression correlates with improved long-term survival; consequently, coupling immune cell infiltration with XPO1 targeting might enhance therapeutic efficacy[9]. Furthermore, multi-omics approaches integrating genomic, proteomic, and immunophenotypic data will be crucial for identifying comprehensive biomarkers that predict responses to XPO1 inhibition and NK cell-based immunotherapies. In clinical settings, the combination of XPO1 inhibition with biomarker-driven patient stratification holds great promise for improving outcomes in patients with high XPO1 expression. These biomarkers might not only guide the selection of patients likely to benefit from XPO1-targeted therapies but also aid in assessing the effects of NK cell activation as part of combination treatment strategies (**Table 1**). Therefore, the identification and validation of biomarkers of XPO1 dependency will be essential for developing personalized cancer therapies that harness the dual functions of XPO1 in both oncogenesis and immune activation.

Clinical translation: challenges and innovations

Despite these promising insights, the clinical translation of XPO1 inhibitors faces several hurdles. Although XPO1 inhibition has demonstrated efficacy in preclinical models, particularly in HDAC7/MYC-driven SCLC[8], clinical validation in SCLC remains limited, and clinical responses have been variable in hematologic malignancies. These findings highlight the need for biomarker-driven patient stratification to identify patients most likely to benefit from XPO1-targeted therapies. For instance, tumors with high HDAC7/MYC expression and cytoplasmic retention of FOXO3a are particularly sensitive to XPO1 inhibition. Therefore, a robust biomarker panel including HDAC7, MYC, and FOXO3a localization might be used to guide patient selection and improve treatment outcomes.

Another challenge in clinical translation is the potential toxicity associated with XPO1 inhibitors. Although selinexor has remarkable efficacy in hematologic malignancies, its effects on hematopoietic stem cells in patients with solid tumors require careful evaluation. Data from a phase I clinical trial (NCT01607905) have revealed that the most common hematologic adverse events during selinexor treatment for advanced solid tumors are thrombocytopenia (16%), anemia (9%), and neutropenia (8%)[16]. Non-hematologic toxicities, predominantly fatigue, nausea, decreased appetite, and hyponatremia, are largely manageable with supportive care[17]. The occurrence of hyponatremia correlates closely with gastrointestinal reactions (e.g., nausea or vomiting) and preexisting comorbidities[17]. Compared with other XPO1 inhibitors (e.g., eltanexor), selinexor exhibits higher rates of gastrointestinal toxicity, because of its unique mechanism of action (e.g., irreversible XPO1 binding) and enhanced blood-brain barrier penetration[18,19]. Clinical strategies to manage hematologic toxicities include dose adjustments (e.g., treatment interruption or 50% dose decrease) or co-administration of thrombopoietin agonists[20]. Studies examining neoadjuvant therapy in locally advanced rectal cancer have shown that thrombopoietin agonists rapidly reverse selinexor-induced thrombocytopenia, and platelet recovery is achieved within days after treatment cessation[21]. The clinical translation of XPO1 inhibitors requires assessment of their complex toxicity profiles. However, innovative management strategies—such as dynamic dose optimization, targeted combination therapies, and biomarker-driven patient stratification—may markedly expand the

therapeutic window. The development of next-generation XPO1 inhibitors with improved pharmacokinetics, decreased toxicity, and enhanced blood-brain barrier penetration is a further key area for innovation. These new inhibitors might be particularly beneficial for treating cancers involving the brain or central nervous system, in which XPO1 plays a crucial role in tumor progression and immune evasion.

In addition, NK cell-based therapies, including chimeric antigen receptor natural killer (CAR-NK) cells and NK cell engagers, are emerging as promising therapeutic options in cancer immunotherapy. Combining these therapies with XPO1 inhibition might offer a "two-pronged" approach targeting both the tumor itself and the immune system's ability to recognize and eradicate cancer cells. This combination strategy might be particularly effective in cancers with high XPO1 expression, in which NK cells are recruited and activated through XPO1-derived peptides. Personalized application of NK cell therapies, on the basis of the presence of specific XPO1-derived antigens and individual patients' NK cell profiles, might enhance treatment efficacy.

As the field progresses, integrating multi-omics technologies will be critical for refining understanding of the XPO1-associated tumor microenvironment and improving patient stratification. Techniques such as single-cell sequencing, proteomics, and transcriptomics might help identify novel biomarkers of XPO1 dependency, and consequently open new avenues for personalized treatment and monitoring of therapeutic responses.

In conclusion, although the clinical translation of XPO1-targeted therapies faces substantial challenges, including toxicity management and patient stratification, the combination of XPO1 inhibitors with NK cell-based therapies has immense potential. Addressing these challenges through biomarker-guided clinical trials, next-generation inhibitors, and innovative combination strategies is expected to pave the way to the successful integration of XPO1-targeted therapies in clinical practice, particularly for cancers with high XPO1 expression.

Future directions

Emerging discoveries highlighting the dual roles of XPO1 in both cancer progression and immune surveillance have opened exciting new avenues for therapeutic innovation. Future clinical trials should focus on validating XPO1-derived peptides, such as NAPLVHATL, as biomarkers for NK cell-targeted therapies. The synergy between XPO1 inhibitors and NK cell-based therapies offers a promising combination strategy that might enhance the cytotoxic activity of NK cells against tumor cells overexpressing XPO1. Potential clinical applications might include the development of engineered NK cells or CAR-NK cells specifically targeting XPO1-derived peptides, thereby enhancing the precision targeting of solid tumors—a promising yet exploratory approach. Building on our previous findings, we are initiating a stratified umbrella clinical trial incorporating HDAC7/MYC expression to refine molecular subtyping of SCLC and enable personalized treatment across distinct subgroups.

Additionally, addressing resistance to XPO1 inhibition is essential. Mechanisms such as compensatory activation of alternative nuclear transport or immune checkpoint pathways could potentially undermine treatment efficacy. To overcome this effect, combining XPO1 inhibitors with immune checkpoint inhibitors might help counteract these resistance mechanisms. Moreover, research on next-generation XPO1 inhibitors with improved pharmacokinetics and decreased toxicity will be crucial to expanding the therapeutic window for treating solid tumors with high XPO1 expression.

Finally, integrating multi-omics approaches alongside real-time monitoring of immune responses in clinical settings will be crucial for optimizing treatment regimens and patient stratification, particularly in SCLC and other cancers. This integrated approach should help refine personalized treatment strategies, and ensure more effective and targeted therapies.

Conclusions

In summary, the emergence of XPO1 as a critical player in both tumor progression and immune surveillance positions this protein as a promising target for innovative dual-functional therapies. The identification of XPO1 inhibitors and their potential synergy with NK cell-based therapies provides a novel approach to enhancing SCLC treatment outcomes. Future studies focusing on the development of next-generation XPO1 inhibitors, biomarker-guided patient stratification, and combination therapies will be critical in translating these findings into clinical practice and ultimately improving survival rates for patients with SCLC.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Dingzhi Huang.
Wrote the paper: Tingting Qin, Jingya Wang.

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