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Original Article

Mutation-Specific Activation of YAP/TAZ in Hippo Pathway-Mediated Resistance to Sotorasib in KRAS G12C-Mutant Non-Small Cell Lung Cancer

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Abstract

Background: Drug resistance remains a critical challenge in the treatment of KRAS G12C-mutant non-small cell lung cancer (NSCLC) with sotorasib (AMG 510). Emerging evidence suggests that the activation of YAP/TAZ via Hippo signaling pathway disruption plays a pivotal role in adaptive resistance mechanisms, highlighting a potential therapeutic target.

Methods: This study investigated the role of Hippo pathway disruption in mediating resistance to sotorasib using KRAS G12C-mutant (NCI-H23) and KRAS wild-type (NCI-H1975) NSCLC cell lines. Dose-response assays were conducted to determine IC_{50} values, while Western blot analysis assessed the expression levels of YAP/TAZ, phosphorylated YAP (Phospho-YAP, Ser127), and upstream Hippo components (MST1, MST2, LATS, and MOB) following 72 hours of treatment.

Results: Sotorasib treatment in the NCI-H23 cell line led to a significant increase in YAP/TAZ protein expression, accompanied by a marked reduction in phosphorylated YAP and upstream Hippo components, indicating robust Hippo pathway disruption. Conversely, the NCI-H1975 cell line exhibited only a modest increase in YAP/TAZ levels, with no significant alterations in phosphorylated YAP or upstream components, suggesting a mutation-specific resistance mechanism in KRAS G12C-mutant cells.

Conclusion: This study provides compelling evidence that YAP/TAZ activation contributes to drug resistance in KRAS G12C-mutant NSCLC. Targeting both KRAS and the Hippo-YAP/TAZ axis could represent a promising therapeutic strategy to overcome resistance and enhance treatment efficacy. Further studies are urgently needed to validate these findings and explore innovative combination therapies to improve clinical outcomes in resistant NSCLC.

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1. INTRODUCTION

Non-small cell lung cancer (NSCLC) is the most prevalent type of lung cancer, accounting for approximately 85% of all cases worldwide. Among its various genetic drivers, oncogenic mutations in the KRAS gene play a pivotal role in tumorigenesis, with the KRAS G12C mutation emerging as a particularly significant target. This mutation is especially prevalent, contributing to approximately 13% of NSCLC cases in populations from Europe and North America, and is a key driver of cancer initiation and maintenance through the constitutive activation of the RAS/MAPK signaling pathway [1]. Given its critical role in cancer progression, KRAS G12C has become a prime therapeutic target, fueling the development of targeted inhibitors.

The introduction of KRAS G12C inhibitors, such as sotorasib (AMG 510), marks a major breakthrough in precision oncology. Sotorasib is the first-in-class KRAS G12C inhibitor that selectively and irreversibly binds to the mutant KRAS G12C protein, leading to its inactivation and demonstrating substantial clinical benefits in patients with advanced KRAS G12C-mutant NSCLC [2]. Despite these advancements, the clinical efficacy of sotorasib is significantly hindered by the emergence of primary and acquired drug resistance, which remains a formidable barrier to sustained therapeutic success. Resistance mechanisms include adaptive signaling through alternative pathways, such as EGFR, MET, and FGFR, as well as secondary mutations within the KRAS gene itself [3].

Emerging evidence suggests that the Hippo signaling pathway, particularly its downstream effectors YAP (Yes-associated protein) and TAZ (transcriptional coactivator with PDZ-binding motif), plays a crucial role in mediating resistance to KRAS G12C inhibitors [4]. The Hippo pathway is a fundamental regulator of tissue homeostasis and tumor suppression, primarily through a kinase cascade that inactivates YAP/TAZ by promoting their phosphorylation and subsequent cytoplasmic retention. However, in the context of drug-resistant NSCLC, RAS blockade by sotorasib paradoxically triggers YAP/TAZ activation, leading to enhanced tumor cell survival and proliferation [5]. Previous studies have demonstrated that activated YAP contributes to intrinsic, adaptive, and acquired resistance mechanisms in KRAS G12C-mutant cancers treated with KRAS G12C inhibitors [6].

The novelty of this study lies in its focused exploration of mutation-specific mechanisms by comparing KRAS G12C-mutant (NCI-H23) and KRAS wild-type (NCI-H1975) NSCLC cell lines, providing unique insights into how Hippo pathway disruption contributes to adaptive resistance. Building on the existing foundation of knowledge, this study delves deeper into the specific role of Hippo pathway disruption in sotorasib-treated NSCLC cell lines, offering novel perspectives on mutation-specific adaptive responses. By evaluating upstream Hippo components such as MST1, MST2, LATS, and MOB, this study aims to uncover mutation-specific disruptions that drive YAP/TAZ activation and resistance to sotorasib. These findings may pave the way for the development of innovative combination therapies that target both KRAS and the Hippo-YAP/TAZ axis, offering promising new strategies to enhance treatment efficacy and overcome drug resistance in KRAS G12C-mutant NSCLC.

2. MATERIAL AND METHODS

2.1. Cell Culture

In this study, non-small cell lung cancer (NSCLC) cell lines NCI-H23 (KRAS G12C mutant) and NCI-H1975 (KRAS wild-type) were procured from the American Type Culture Collection (ATCC). Both cell lines were cultured in RPMI 1640 medium (Cat. No. 52400-025, GIBCO) supplemented with 10% Fetal Bovine Serum (FBS, Cat. No. 10500064, GIBCO) and 0.5% Penicillin/Streptomycin. All cultures were maintained under standard conditions of 5% CO_2, 95% humidity, and 37°C, ensuring optimal growth and stability of the cell lines.

2.2. Cell Viability Assay

The efficacy of the KRAS G12C inhibitor sotorasib was evaluated in NCI-H23 (KRAS G12C mutant) and NCI-H1975 (KRAS wild-type) NSCLC cell lines. Cells were seeded at a density of 10^4 cells per well in 96-well plates. Sotorasib was administered at concentrations ranging from 0 to 0.01 µM for H23 cells and 0 to 20 µM for H1975 cells. Following 72 hours of treatment, cell viability was assessed using the Promega CellTiter96 assay, with absorbance measured at 570 nm to determine IC_{50} values.

2.3. Western Blot Analysis

Proteins were extracted from NCI-H23 and NCI-H1975 cell lines following 72-hour sotorasib treatment using RIPA buffer (Santa Cruz Biotechnology, Cat. No: sc-24948) containing protease and phosphatase inhibitors. Protein concentrations were measured using the Bradford assay with BSA standards (Thermo Scientific, Cat. No: 23208).

Samples (50 µg) were separated on SDS-PAGE gels and transferred to PVDF membranes (Merck Millipore, Cat. No: IPVH00010) under standard conditions. Membranes were blocked with 5% non-fat milk in TBS-T and incubated with

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primary antibodies (1:1000), followed by HRP-conjugated secondary antibodies (1:7500). Protein bands were visualized using ECL reagent (Millipore, Cat. No: WBLUF0500) and imaged with the Odyssey® Fc Imaging System (LI-COR Biosciences).

2.4. Statistical Analysis

IC_{50} values were calculated using R software, utilizing specialized packages such as the DRC (Dose-Response Curve) package for dose-response curve generation and nonlinear regression analysis. Western blot results were analyzed for band density using Image Studio Lite software, and statistical significance was determined using a paired t-test with the IBM SPSS 17 software package.

3. RESULTS

3.1. Data Acquisition and Analytical Framework

Comprehensive pathway analyses were conducted using Reactome [7], KEGG [8], and DrugBank [9] to elucidate the molecular interactions and pharmacological properties of sotorasib. Protein annotations and structural data for KRAS and Hippo pathway components were obtained from UniProt [10] and the Protein Data Bank [11]. Network interactions were meticulously visualized using Cytoscape [12] and STRING [13], while data on drug sensitivity and genetic variations were integrated from CCLE [14], PharmGKB [15], and TCGA [16]. This multi-dimensional analytical approach provided deep insights into the mechanisms of resistance and Hippo pathway activation associated with sotorasib treatment.

3.2. Determination of IC_{50} Values for Sotorasib in the Cell Lines

To assess the efficacy of sotorasib, IC_{50} values were determined in NCI-H23 (KRAS G12C-mutant) and NCI-H1975 (KRAS wild-type) NSCLC cell lines. Cells were seeded at 10^4 cells per well in 96-well plates, and sotorasib was administered at a range of concentrations in duplicate experiments.

Sotorasib exhibited potent inhibitory activity against KRAS G12C-mutant cells, with an IC_{50} value of 7.58×10^{-3} μM in the NCI-H23 cell line. In contrast, the KRAS wild-type NCI-H1975 cell line demonstrated a markedly higher IC_{50} value of 11.23 μM, indicating significantly reduced sensitivity to sotorasib (**Figure 1, Table 1, and Table 2**). These results underscore the specificity and efficacy of sotorasib in targeting KRAS G12C-mutant NSCLC cells, highlighting its therapeutic potential in precision oncology.

3.3. YAP/TAZ Protein Detection in in the Cell Lines

In the KRAS G12C-mutant NSCLC cell line NCI-H23 and the KRAS wild-type cell line NCI-H1975, baseline protein levels of YAP/TAZ, critical nuclear effectors of the Hippo signaling pathway, were evaluated prior to sotorasib treatment (**Figure 2**).

Western blot analysis revealed distinct YAP/TAZ protein expression patterns between the cell lines, with GAPDH used as a loading control to ensure normalization of protein expression levels. Quantitative analysis indicated that YAP/TAZ protein levels were significantly higher in the NCI-H1975 cell line compared to the NCI-H23 cell line, highlighting a mutation-specific difference in Hippo pathway activity that may influence sotorasib sensitivity.

3.4. YAP/TAZ Protein Detection in Sotorasib-Treated NCI-H23 Cell Line

To explore the interaction between KRAS signaling and the Hippo pathway in KRAS G12C-mutant NSCLC, the NCI-H23 cell line was treated with the KRAS G12C-specific inhibitor sotorasib for 72 hours, with untreated NCI-H23 cells serving as a control. Western blot analysis revealed that YAP/TAZ protein levels were significantly elevated following sotorasib treatment (**Figure 3**).

To further elucidate the functional status of YAP, the levels of phosphorylated YAP (Phospho-YAP, Ser127) were also assessed. Phospho-YAP is known to remain in the cytoplasm and undergo proteasomal degradation, thereby inhibiting its transcriptional activity [17]. The analysis demonstrated that 72 hours of sotorasib treatment resulted in a notable reduction in Phospho-YAP levels, while total YAP/TAZ protein levels were upregulated compared to control samples.

These findings suggest a potential shift in YAP/TAZ activity, indicative of Hippo pathway disruption and increased nuclear translocation of YAP/TAZ, which may contribute to adaptive resistance mechanisms (**Figure 4**).

3.5. YAP/TAZ Protein Detection in Sotorasib-Treated NCI-H1975 Cell Line

The KRAS wild-type NCI-H1975 cell line was treated with the KRAS G12C-specific inhibitor sotorasib for 72 hours to assess the impact of treatment on Hippo pathway activity. Western blot analysis was performed on protein samples from both sotorasib-treated and control NCI-H1975 cells, providing a quantitative comparison of YAP/TAZ protein levels (**Figure 5**).

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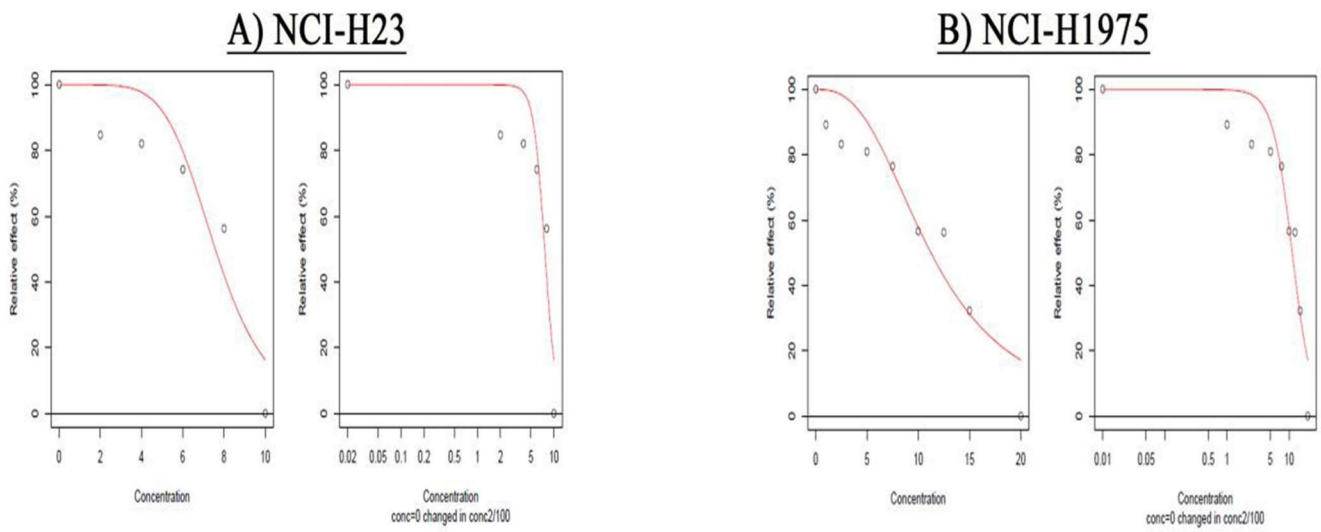


Figure 1. Dose-Response Curve and IC_{50} Determination of Sotorasib in KRAS G12C-Mutant NCI-H23 and KRAS Wild-Type NCI-H1975 Cell Lines

Table 1. Estimation of ICn Values and Confidence Intervals in the NCI-H23 Cell Line. This table presents the IC50, IC90, and IC99 values for the NCI-H23 cell line, along with their standard errors, 95% confidence intervals, and CI ratios. The parameter Gamma reflects the slope of the dose-response curve, indicating the steepness of the drug's inhibitory effect.

ICn in NCI-H23 cell line					
	Estimation	**Standard error**	**Lower CI95%**	**UpperCI95%**	**Ratio CI**
IC50	7.58	0.63	5.83	9.32	1.6
IC90	11.02	0.78	9	13.03	1.45
IC99	16.58	1	14.02	19.14	1.37
Gama	5.87	2.77	-1.81	13.56	-

Table 2. Estimation of ICn Values and Confidence Intervals in the NCI-H1975 Cell Line. This table presents the IC50, IC90, and IC99 values for the NCI-H23 cell line, along with their standard errors, 95% confidence intervals, and CI ratios. The parameter Gamma reflects the slope of the dose-response curve, indicating the steepness of the drug's inhibitory effect.

ICn in NCI-H1975 cell line					
	Estimation	**Standard error**	**Lower CI95%**	**UpperCI95%**	**Ratio CI**
IC50	11.23	0.98	8.91	13.54	1.52
IC90	25.16	1.22	22.34	27.97	1.25
IC99	60.68	1.56	57.1	64.26	1.13
Gama	2.72	0.74	0.98	4.47	-

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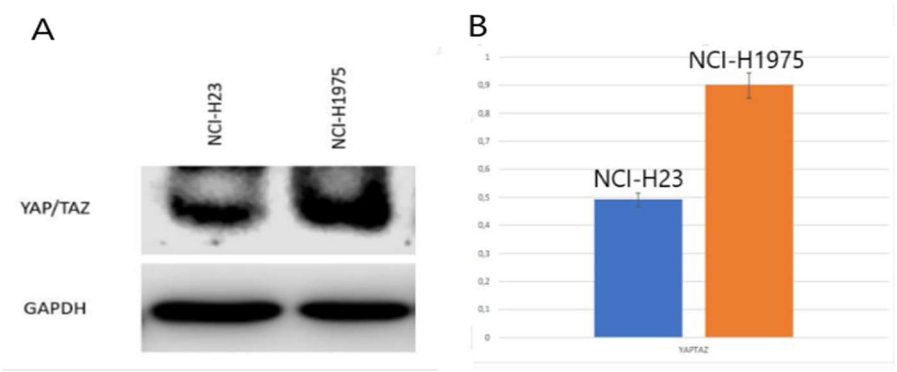


Figure 2. Relative YAP/TAZ Expression Levels in NCI-H23 and NCI-H1975 Cell Lines. A) YAP/TAZ Protein Levels in the Cell Lines Used in This Study. B) Comparison of Relative YAP/TAZ Expression Levels in NCI-H23 (Blue) and NCI-H1975 (Orange) Cell Lines.

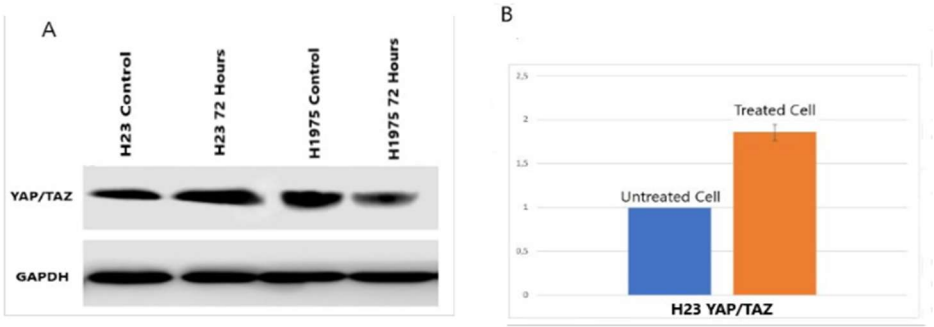


Figure 3. Relative YAP/TAZ Levels in NCI-H23 Cell Lines After Sotorasib Treatment. A) The protein levels of Phospho-YAP (Ser127), total YAP/TAZ, and GAPDH as a loading control in NCI-H23 and NCI-H1975 cell lines following sotorasib treatment B) Comparison of Relative YAP/TAZ Expression Levels in the Untreated NCI-H23 (Blue) and treated NCI-H23 (Orange) Cell Lines.

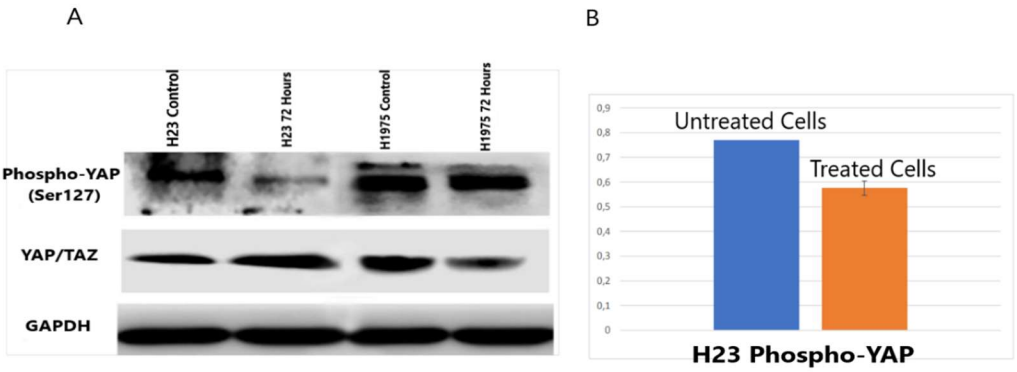


Figure 4. Relative Phospho-YAP Levels in NCI-H23 Cell Lines After Sotorasib Treatment. A) The protein levels of total YAP/TAZ, and GAPDH as a loading control in NCI-H23 and NCI-H1975 cell lines following sotorasib treatment. B) Comparison of relative Phospho-YAP (Ser127) expression levels in the untreated NCI-H23 (blue) and treated NCI-H23 (orange) cell lines.

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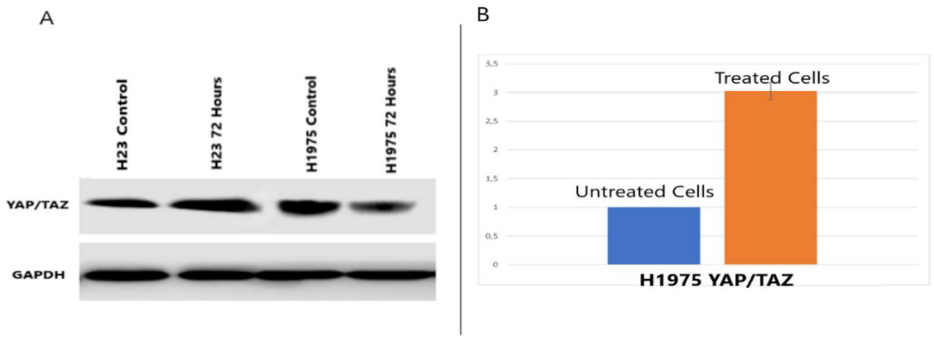


Figure 5. Relative YAP/TAZ Levels in NCI-H1975 Cell Lines After Sotorasib Treatment. A) The protein levels of total YAP/TAZ, and GAPDH as a loading control in NCI-H23 and NCI-H1975 cell lines following sotorasib treatment B) Comparison of relative YAP/TAZ expression levels in the untreated NCI-H1975 (Blue) and treated NCI-H1975 (Orange) cell lines.

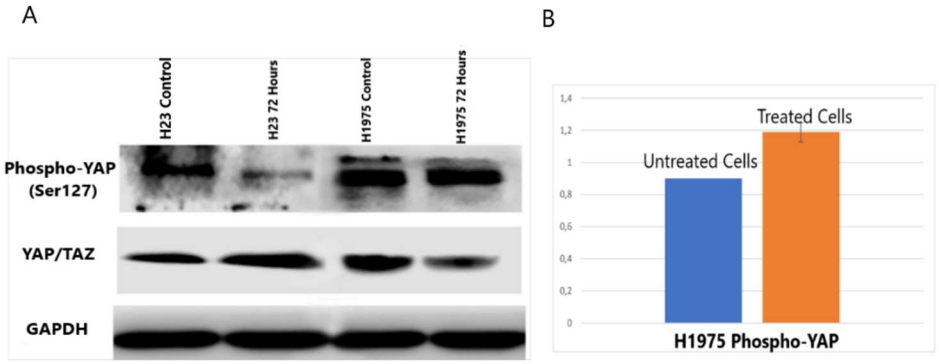


Figure 6. Relative Phospho-YAP Levels in NCI-H1975 Cell Lines After Sotorasib Treatment. A) The protein levels of total YAP/TAZ, and GAPDH as a loading control in NCI-H23 and NCI-H1975 cell lines following sotorasib treatment. B) Comparison of relative Phospho-YAP (Ser127) expression levels in the untreated NCI-1975 (blue) and treated NCI-H1975 (orange) cell lines.

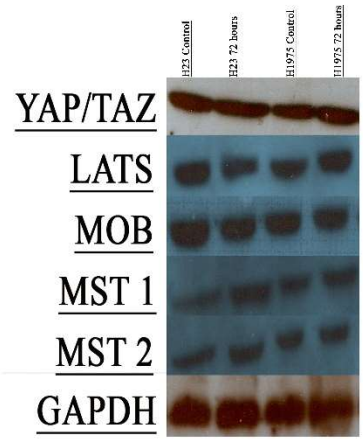


Figure 7. Western Blot Analysis of Key Hippo Pathway Components in Sotorasib-Treated KRAS G12C-Mutant NCI-H23 and KRAS Wild-Type NCI-H1975 Cell Lines

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The results indicated a statistically significant increase in YAP/TAZ protein expression in the sotorasib-treated samples compared to the control group, suggesting a potential compensatory activation of YAP/TAZ signaling in response to KRAS inhibition.

To further investigate the functional status of YAP, Western blot analysis was conducted to measure phosphorylated YAP (Phospho-YAP, Ser127) levels. Unlike the NCI-H23 cell line, the NCI-H1975 cells showed no statistically significant difference in Phospho-YAP levels between control and sotorasib-treated samples after 72 hours of treatment (**Figure 6**). This finding suggests that, while total YAP/TAZ expression increased, phosphorylation status remained unchanged, potentially indicating a limited nuclear activation of YAP/TAZ in the wild-type KRAS context.

3.6. Expression of Hippo Pathway Components in Sotorasib-Treated Cell Lines

Western blot analysis was performed to assess the expression levels of key Hippo pathway components, including LATS, MOB, MST1, and MST2, in both NCI-H23 (KRAS G12C-mutant) and NCI-H1975 (KRAS wild-type) NSCLC cell lines. GAPDH served as a loading control for protein normalization.

In the NCI-H23 cell line, sotorasib treatment not only led to the upregulation of YAP/TAZ but also resulted in a notable decrease in upstream Hippo components, including LATS and MOB, suggesting a disruption of the Hippo signaling cascade. Similarly, MST1 and MST2 levels were modestly reduced in sotorasib-treated samples, indicating a potential suppression of core kinase activity within the Hippo pathway.

In contrast, the NCI-H1975 cell line exhibited no significant changes in the expression levels of LATS, MOB, MST1, or MST2 following sotorasib treatment. These findings suggest that KRAS G12C inhibition may selectively disrupt the Hippo pathway in KRAS G12C-mutant cells, while its impact on KRAS wild-type cells remains minimal (**Figure 7**).

3. DISCUSSION

The development of drug resistance remains a major obstacle in the clinical management of KRAS G12C-mutant non-small cell lung cancer treated with KRAS G12C inhibitors, such as sotorasib [18]. The data presented here demonstrates that activation of the Hippo signaling pathway, specifically through YAP/TAZ upregulation, functions as a key mechanism of adaptive resistance in KRAS-mutant NSCLC cell lines.

This study offers novel insights by revealing that sotorasib treatment in the KRAS G12C-mutant NCI-H23 cell line led to a significant increase in YAP/TAZ protein levels, alongside a reduction in phosphorylated YAP (Phospho-YAP, Ser127). Since Phospho-YAP is functionally inactive and subject to cytoplasmic degradation, this shift suggests that KRAS G12C inhibition may initiate compensatory signaling through the Hippo pathway [21,22], leading to YAP/TAZ activation and nuclear translocation. Such changes are known to enhance cell survival and proliferation, aligning with previous studies linking Hippo pathway dysregulation to drug resistance and tumor progression [18], [5].

A distinctive finding of this study is the reduction in upstream Hippo components (MST1, MST2, LATS, MOB) following sotorasib treatment, suggesting a disruption of the canonical Hippo signaling cascade. This disruption potentially facilitates nuclear localization and transcriptional activation of YAP/TAZ, promoting cellular adaptation to KRAS inhibition [19]. The mutation-specific effects observed in the KRAS wild-type NCI-H1975 cell line, which exhibited only a modest increase in YAP/TAZ protein levels and no significant changes in Phospho-YAP or upstream Hippo components, emphasize the unique dependency of KRAS G12C-mutant cells on Hippo pathway dysregulation for drug resistance. These findings suggest that the impact of sotorasib on the Hippo pathway is predominantly KRAS G12C-dependent, highlighting the selective disruption of Hippo signaling in mutant cell lines.

The reduction in MST1 and MST2 levels observed in the NCI-H23 cell line indicates a suppression of Hippo core kinase activity, which is essential for maintaining YAP/TAZ phosphorylation and cytoplasmic retention. This suppression likely facilitates nuclear translocation and transcriptional activation of YAP/TAZ, thereby enhancing drug resistance. These observations align with the role of the Hippo signaling pathway as a critical regulator of organ size, tissue homeostasis, and tumorigenesis, primarily through its core effectors, YAP and TAZ [20]. Under normal conditions, YAP is phosphorylated, retained in the cytoplasm, and degraded, which limits its transcriptional activity. However, when the Hippo pathway is disrupted, YAP/TAZ translocate to the nucleus, driving the expression of genes associated with cell survival, proliferation, and drug resistance [19].

The evidence provided supports the notion that sotorasib treatment may activate YAP/TAZ as a compensatory survival mechanism, contributing to reduced drug efficacy in KRAS G12C-mutant NSCLC (23). The significant increase in YAP/TAZ protein levels and the decrease in

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phosphorylated YAP in the NCI-H23 cell line underscore the Hippo pathway's potential role as a mediator of resistance to sotorasib. Combining KRAS G12C inhibitors with targeted therapies against YAP/TAZ or upstream Hippo components may offer a novel strategy to overcome resistance and improve therapeutic outcomes. Recent research has demonstrated that dual inhibition of KRAS and YAP/TAZ can suppress tumor growth and enhance treatment sensitivity, supporting our findings [20,23].

5. CONCLUSION

In conclusion, this study reveals that Hippo pathway activation, particularly through YAP/TAZ upregulation, represents a mutation-specific mechanism of adaptive resistance to sotorasib in KRAS G12C-mutant NSCLC. The differential response between mutant and wild-type cell lines underscores the importance of mutation-specific therapeutic strategies. Further in vivo studies and clinical investigations are warranted to validate these findings and explore the potential of combination strategies targeting both KRAS and the Hippo-YAP/TAZ axis to advance precision oncology in lung cancer therapy.

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Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical statement

This study did not involve human participants or animal subjects, and therefore ethical approval was not required. All experiments were conducted using established cell lines (NCI-H23 and NCI-H1975), which do not fall under the scope of ethical considerations for human or animal research.

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