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Tas13D inhibits the growth of non-small cell lung cancer cells by regulating EGFR

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Abstract. Tas13D, a taspine derivative specifically designed to target the EGFR pathway, a key driver of non-small cell lung cancer (NSCLC), has demonstrated significant efficacy in vitro by inhibiting the viability of A549 lung cancer cells, promoting apoptosis, and reducing EGFR phosphorylation. In vivo studies in mice demonstrated that Tas13D effectively reduced tumor size and enhanced apoptosis, indicating its promising therapeutic potential for NSCLC. However, further research is necessary to investigate potential resistance mechanisms within the tumor microenvironment to optimize its clinical application.

Keywords: component, non-small cell lung cancer, EGFR, Tas13D.

1. Introduction

Cancer is a major global health challenge, characterized by the unrestrained proliferation and spread of malignant cells, which significantly increases mortality worldwide. The GLOBOCAN 2020 estimates presented in this study indicate that there were 19.3 million new cases of cancer and almost 10 million deaths from cancer in 2020 [1]. The importance of this statistic highlights the urgent need for effective governance measures and mitigation strategies for such a complex and devastating disease.

Lung cancer is one of the most common forms of cancer and is the leading cause of cancer deaths globally [1]. Lung cancer is the leading cause of cancer death worldwide, with nearly 85% of lung cancers being NSCLC [2]. The high incidence rate and mortality of NSCLC highlight the urgent need for effective therapeutic strategies [3].

The intricacy of NSCLC at the molecular level, compounded by its diverse genetic mutations, presents a formidable obstacle in the formulation of efficacious therapeutics. The condition is distinguished by a spectrum of genetic anomalies that fuel its expansion and advancement. Prominent among the molecular targets is the Epidermal Growth Factor Receptor (EGFR), which has been identified as a pivotal catalyst in the genesis of tumors in NSCLC, thereby positioning it as a significant focus for the creation of novel anti-cancer pharmaceuticals.

Radix et Rhizoma Leonticis (Hong Mao Qi in Chinese, HMQ) is distributed mainly in Shaanxi and Sichuan provinces of China. Taspine(Figure 1a), isolated for the first time from HMQ Radix et Rhizoma Leonticis has many pleiotropic effects such as anti-inflammatory, cell toxin, antivirus, topoisomerase I and II inhibition. In previous studies, we found that taspine had an inhibitory effect on tumor and angiogenesis. However, silico ADME prediction showed that taspine wasn’t a compound with drug-like

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properties. Biological and cellular assays showed that it had very poor solubility in any solvent. We designed and synthesized tas13D(Figure 1b), a taspine derivative by structure-based drug design [4].

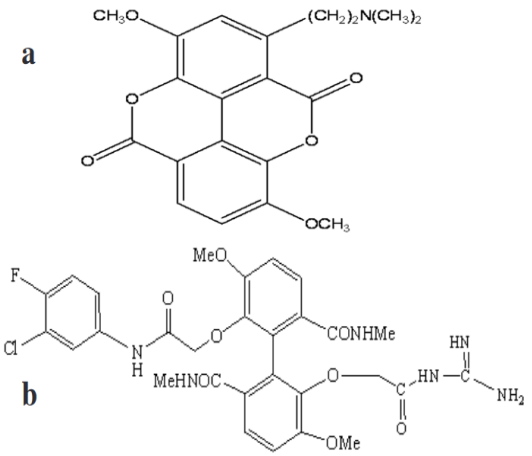

Figure 1. a. Taspine and b. 13D

This study investigates the effects of Tas13D on the growth and EGFR signaling pathway of NSCLC cells, focusing on the A549 cell line. In this paper, it is hypothesized that Tas13D will inhibit cell growth, induce apoptosis, and reduce EGFR signaling, leading to a decrease in the size of A549 xenograft tumors.

The significance of this research lies in its potential to identify a new therapeutic agent for NSCLC treatment. By focusing on the EGFR signaling pathway, this study could provide insights into the molecular mechanisms underlying the anti-tumor effects of taspine derivatives. The findings could not only contribute to the development of more effective treatments for NSCLC but also pave the way for future studies exploring the utility of natural compound derivatives in cancer therapy [5].

In this study, we will employ a range of experimental methods, including the MTT assay to measure cell growth, Annexin V/PI staining followed by flow cytometric analysis to assess apoptosis, and Western blotting to evaluate the activation of the EGFR pathway. The use of Gefitinib or Erlotinib as a positive control and DMSO or PBS as a negative control will ensure the validity and reliability of our findings. Aberrant EGFR signaling is correlated with progression of various malignancies, and somatic tyrosine kinase domain mutations in the EGFR gene have been discovered in patients with non–small cell lung cancer responding to EGFR-targeting small molecular agents, such as gefitinib and erlotinib [4].

2. Hypothesis

In this paper, it is predicted that increasing concentrations and treatment durations with Tas13D inhibits the growth of A549 NSCLC, by regulating the EGFR signaling pathway, decreasing cell viability, increasing apoptosis, and decreasing tumor size. EGFR activation will be assessed through the analysis of EGFR phosphorylation levels using Western blotting. Viability will be quantified using a MTT colorimetric assay. The apoptosis rate will be measured by Annexin V /PI assays. NSCLC cells will be injected into nude mice to establish xenograft tumors. Tumor size will be monitored over time, and at the end of the study, tumors will be excised for analysis of EGFR signaling and apoptosis markers.

Positive Control: Gefitinib, a known inhibitor of EGFR, will be used to confirm the involvement of the EGFR signaling pathway in NSCLC cell growth inhibition.

Negative Control: DMSO/PBS or an equivalent vehicle will be used to control for non-specific effects of the solvent on cell growth and viability

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3. Methods and Materials

Measure EGFR activation by EGFR phosphorylation will be analyzed using Western blotting. Cell viability will be quantified using an MTT colorimetric assay. The apoptosis rate will be measured by Annexin V /PI assays. NSCLC cells will be injected into nude mice to establish xenograft tumors. Tumor size will be monitored over time, and at the end of the study, tumors will be excised for analysis of EGFR signaling and apoptosis markers.

Positive Control: Gefitinib, a known inhibitor of EGFR, will be used to confirm the involvement of the EGFR signaling pathway in NSCLC cell growth inhibition.

Negative Control: DMSO/PBS or an equivalent vehicle will be used to control for non-specific effects of the solvent on cell growth and viability.

3.1. Western blot

Sample preparation involves extracting proteins from cells or tissues that have been treated with various concentrations of Tas13D, ranging from 1μM to 25μM, and for different durations, including 24, 48, and 72 hours. The selection of these concentrations and durations is based on the results of preliminary experiments as well as information from existing literature. Following extraction, the proteins are separated by size through a process known as electrophoresis, utilizing a technique called SDS-PAGE. The next step, blotting, involves transferring the separated proteins onto a nitrocellulose or PVDF membrane. To prevent any non-specific binding of antibodies, the membrane is blocked with 5% non-fat milk or BSA. The intensity of the signal is measured to compare EGFR expression levels, using densitometry or image analysis software. To ensure the validity of the results, controls are implemented: Gefitinib, a known inhibitor of the EGFR pathway, is used as a positive control, while DMSO or PBS serves as a negative control to account for any potential effects of the solvent. To confirm the reliability of the findings, the entire experiment is repeated three times.

3.2. MTT assay

To assess the viability of NSCLC cells pretreated with CAR T-cells, we performed the MTT assay daily following cell isolation. Briefly, exponentially growing cells were harvested and plated in 96-well plates at a concentration of 2 × 104 cells/well. After 24 h incubation at 37 ℃, cells were treated with tas13D at various concentrations for 48 h [6]. After incubation, MTT crystals were dissolved by adding DMSO. The absorbance of the wells was measured using a Dynatech MR580 Microelisa reader with a test wavelength of 570 nm, a reference wavelength of 630 nm, and a calibration setting of 1.99. This experiment was repeated three times to ensure reliability.

3.3. Annexin V /PI assays

Labeled annexin V can be applied in both flow cytometry and light microscopy to identify mid- to late-stage apoptotic cells [7]. Cell preparation involves culturing non-small cell lung cancer (NSCLC) cells and subjecting them to various concentrations of Tas13D, ranging from 1 μM to 25 μM, for durations of 24, 48, and 72 hours. Following treatment, cells are prepared for apoptosis detection through Annexin V staining, where they are incubated with fluorescently labeled Annexin V, a marker that binds to phosphatidylserine exposed on the cell surface during early apoptosis. Additionally, cells are stained with Propidium Iodide (PI) to identify late-stage apoptosis and necrosis; PI penetrates cells with damaged membranes and fluoresces red upon binding to nucleic acids.

3.4. Xenograft tumors

NSCLC cells were isolated and cultured before being subcutaneously injected into immunocompromised mice to generate xenograft tumors. Different treatment groups received Tas13D at varying concentrations (5 mg/kg, 10 mg/kg, 20 mg/kg) and durations (once daily for 14 days). Tumor size was measured using calipers every 2-3 days. Gefitinib served as a positive control, while DMSO/PBS acted as a negative control. At the conclusion of the treatment period, tumors were analyzed for apoptosis, EGFR phosphorylation, and other relevant markers. Statistical analysis was performed

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using ANOVA and Tukey's test. It is anticipated that Tas13D will inhibit tumor growth compared to the negative control, with the degree of inhibition dependent on concentration and treatment duration. Additionally, Tas13D treatment is expected to increase apoptosis and decrease EGFR phosphorylation in tumors. This experiment will be repeated three times for reliability.

4. Statistical Analysis

In this study, a one-sample t-test was employed to analyze the data. This test was chosen as it is suitable for comparing the mean of a single sample with a known or hypothesized population mean. The paired samples t-test was not considered as the data did not involve paired or related samples. These experiments will be repeated three times.

The critical t-value was identified from the t-distribution table or using statistical software. The chosen significance level was $\alpha = 0.05$, which corresponds to a 95% confidence level.

The calculated t-value was then compared with the critical t-value to determine whether the observed difference between the means of the control and experimental groups was statistically significant. If the absolute value of the calculated t-value was greater than the critical t-value, the null hypothesis was rejected, indicating that the observed difference was statistically significant. If the absolute value of the calculated t-value was less than or equal to the critical t-value, the null hypothesis was not rejected, indicating that the observed difference was not statistically significant.

5. Results

Table 1. The combination of possible results for four experiments

Combination Result # (CR#)	Tas13D decreases viability by MTT?	Tas13D increases apoptosis by annexin V/PI FACS?	Tas13D decreases phospho-EGFR by western blot?	Tas13D decreases xenograft tumors by caliper?	Support of hypothesis
CR1	+	+	+	+	Full
CR2	+	+	+	-	Partial
CR3	+	+	-	+	Yes
CR4	+	-	+	+	Yes
CR5	-	+	+	+	Partial
CR6	+	+	-	-	Partial
CR7	+	-	-	+	Partial
CR8	-	-	+	+	Partial
CR9	+	-	+	-	Partial
CR10	-	+	-	+	Partial
CR11	-	+	+	-	Partial
CR12	+	-	-	-	Partial
CR13	-	+	-	-	Partial
CR14	-	-	+	-	Partial
CR15	-	-	-	+	Partial
CR16	-	-	-	-	Fully Contradicts

"+" represents the result of the experiment preforms similar or better results compared to the positive control.Gefitinib group and could be concluded supports the hypothesis. "-" represents the result preforms similar or worse results compared to the negative control, (DMSO/PBS) and contradicts the hypothesis.

CR1: Tas13D reduces cell viability as measured by the MTT assay.Tas13D enhances apoptosis, as indicated by the annexin V/PI FACS analysis.Tas13D decreases the levels of phospho-EGFR, as

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observed in western blot analysis.Tas13D diminishes the size of xenograft tumors, as assessed by caliper measurements.

CR2:Tas13D reduces cell viability as measured by the MTT assay.Tas13D enhances apoptosis, as indicated by the annexin V/PI FACS analysis.Tas13D decreases the levels of phospho-EGFR, as observed in western blot analysis. However, tumor size has not been reduced.

CR3:Tas13D reduces cell viability as measured by the MTT assay.Tas13D enhances apoptosis, as indicated by the annexin V/PI FACS analysis.Tas13D cannot decrease the levels of phospho-EGFR, as observed in western blot analysis.Tas13D diminishes the size of xenograft tumors, as assessed by caliper measurements.

CR4:Tas13D reduces cell viability as measured by the MTT assay.Tas13D decreases the levels of phospho-EGFR, as observed in western blot analysis.Tas13D diminishes the size of xenograft tumors, as assessed by caliper measurements. However, tas13D cannot enhance apoptosis, as indicated by the annexin V/PI FACS analysis.

CR5:Tas13D cannot reduce cell viability as measured by the MTT assay.Tas13D enhances apoptosis, as indicated by the annexin V/PI FACS analysis.Tas13D decreases the levels of phospho-EGFR, as observed in western blot analysis.Tas13D diminishes the size of xenograft tumors, as assessed by caliper measurements.

CR6:Tas13D reduces cell viability as measured by the MTT assay.Tas13D enhances apoptosis, as indicated by the annexin V/PI FACS analysis.Tas13D cannot decrease the levels of phospho-EGFR, as observed in western blot analysis, and tumor size has not been reduced. These findings indicate that Tas13D has cytotoxic and pro-apoptotic properties in vitro that do not involve the EGFR pathway.

CR7:Tas13D reduces cell viability as measured by the MTT assay.Tas13D diminishes the size of xenograft tumors, as assessed by caliper measurements. However,tas13D cannot enhance apoptosis, as indicated by the annexin V/PI FACS analysis, and tas13D cannot decrease the levels of phospho-EGFR, as observed in western blot analysis. these findings indicate that Tas13D has anti-proliferative and tumor-inhibitory properties that are not primarily mediated by apoptosis or EGFR pathway inhibition.

CR8:Tas13D decreases the levels of phospho-EGFR, as observed in western blot analysis.Tas13D diminishes the size of xenograft tumors. However, Tas13D cannot reduce cell viability as measured by the MTT assay and tas13D cannot enhance apoptosis, as indicated by the annexin V/PI FACS analysis. these findings indicate that Tas13D has anti-tumor properties that may be mediated through the inhibition of EGFR signaling, but its effects on cell viability and apoptosis in vitro are not straightforward.

CR9:Tas13D reduces cell viability as measured by the MTT assay.Tas13D decreases the levels of phospho-EGFR, as observed in western blot analysis. However,tas13D cannot enhance apoptosis, as indicated by the annexin V/PI FACS analysis, and tumor size has not been reduced.

CR10:Tas13D enhances apoptosis, as indicated by the annexin V/PI FACS analysis, and diminishes the size of xenograft tumors, as assessed by caliper measurements. However,tas13D cannot reduce cell viability as measured by the MTT assay, and tas13D cannot decrease the levels of phospho-EGFR, as observed in western blot analysis.

CR11:Tas13D enhances apoptosis, as indicated by the annexin V/PI FACS analysis.Tas13D decreases the levels of phospho-EGFR, as observed in western blot analysis. However,tas13D cannot reduce cell viability as measured by the MTT assay and tumor size has not been reduced.

CR12: Tas13D reduces cell viability as measured by the MTT assay. However,tas13D cannot enhance apoptosis, as indicated by the annexin V/PI FACS analysis cannot decrease the levels of phospho-EGFR, as observed in western blot analysis. And tumor size has not been reduced.

CR13:Tas13D enhances apoptosis, as indicated by the annexin V/PI FACS analysis. However,tas13D cannot reduce cell viability as measured by the MTT assay.Tas13D cannot decrease the levels of phospho-EGFR, as observed in western blot analysis.Tas13D cannot diminish the size of xenograft tumors, as assessed by caliper measurements.

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CR14:Tas13D decreases the levels of phospho-EGFR, as observed in western blot analysis. However,tas13D cannot reduce cell viability as measured by the MTT assay.Tas13D cannot enhance apoptosis, as indicated by the annexin V/PI FACS analysis and tumor size has not been reduced.

CR15: The in vivo reduction of xenograft tumor size by Tas13D, as evidenced through caliper measurements, occurs without a corresponding decrease in cell viability, which was evaluated using the MTT assay, or an increase in apoptosis, as shown by annexin V/PI FACS analysis. This suggests that the mechanism of action for Tas13D is multifaceted and requires further exploration.

CR16: Despite its inability to reduce cell viability as determined by the MTT assay, and to enhance apoptosis as indicated by annexin V/PI FACS analysis, Tas13D demonstrates an ability to decrease the levels of phospho-EGFR in western blot analysis. Furthermore, Tas13D is observed to diminish the size of xenograft tumors, as measured by caliper assessments.

6. Discussion

Studies utilizing the A549 non-small cell lung cancer (NSCLC) cells and xenograft tumor models demonstrated that Tas13D modulates a cohort of intracellular pathways in concert. Such findings will aid in our understanding of Tas13D mechanisms and the challenges faced during its development as an NSCLC treatment.

CR1: The results indicate that Tas13D inhibits cell survival by inducing apoptosis and suppressing EGFR phosphorylation, leading to a notable reduction in tumor volume when studied using xenograft model data. Taken together, these cumulative effects indicate that Tas13D has the potential to prevent non-small cell lung cancer (NSCLC) progression by inhibiting EGFR signaling and boosting apoptotic death. This is strong empirical evidence from multiple experimental techniques demonstrating a real therapeutic perspective. Additional future studies should be aimed at the formulation and delivery optimization of Tas13D to maximize efficacy while minimizing toxicity.

CR2: Tasc13D failed to reduce tumor volume, yet it had effects on cell viability and EGFR phosphorylation. This is indicative of the fact that, although Tas13D inhibits EGFR signaling and cell growth in vitro significantly, dosed within a physiological range may not translate into therapeutic efficacy due to an inaccessible lesion target-site. This can be due to various reasons, such as intratumor heterogeneity, other mechanisms of resistance, or signals issued by neighboring stromal cells. Further investigations would be needed to uncover how Tas13D modulates the tumor immune microenvironment and opportunities for combining other therapies, which might overcome these limitations.

CR3: Tas13D decreases cell viability and tumor volume but has no effect on EGFR phosphorylation. Taken together, these observations implicate that Tas13D may suppress the growth of NSCLC (non-small cell lung cancer) via an EGFR-independent pathway or target. Possible mechanisms are from inhibition of cell cycle progression to autophagy or other-signaling pathways. The next step would be to find these potential new Tas13D-sensitive mechanisms, and the antitumor effect of other molecules acting through such pathways need also be evaluated in the future.

CR4: Tas13D reduced the level of EGFR phosphorylation and tumor size with minor alterations in cell survival or apoptosis. This may be the result of a different antitumor effect mechanism other than solely by apoptosis induction. Examples of some potential support pathways could be to inhibit angiogenesis, prevent metastasis, or perhaps alter the tumor microenvironment. Future research should be focused on identifying these putative alternative pathways for further molecular characterization to evaluate their potential contribution towards Tas13D utilization.

CR5: acts downstream of EGFR, Tas13D can induce apoptosis and reduce total-EGFR phosphorylation without impact on their cell survival, eventually not substantially inhibiting tumor growth. This might explain why, even though Tas13D can enhance tumor cell killing and inhibit EGFR signaling in the early phase, it also still failed to effectively eradicate all of the totipotent vsasilivlar practicality or growth inhibitory pathways. Examples of these could be the existence of resistance mechanisms, an incomplete induction apoptosis or complex processes involving cell to tumor

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microenvironment interactions. This could warrant future exploration evaluating combined therapeutic approaches to enhance apoptosis induction and mitigate resistance.

CR6: It reduced cell viability and induced apoptosis in vitro without inhibiting EGFR phosphorylation or tumor growth (Fig 8C). Our result indicates that Tas13D's main function in non-small cell lung cancer (NSCLC) cells would be independent of EGFR signaling blockage but via another cytotoxic effect. Among the putative mechanisms are disturbance of cell membrane integrity, generation of various reactive oxygen species, or induction of other death pathways. Future studies will investigate these candidate cytotoxic mechanisms in more detail and evaluate their contribution to the global antitumor effect of Tas13D.

CR7: Tas13D was significantly reduced by tas13d, although no increase in apoptosis or inhibition of EGFR phosphorylation were observed. We demonstrated that Tas13D also prevented tumor growth via cell death or direct EGFR inhibition (Fig. 5b), implying the presence of multiple pathways and complex interactions in TAS-IR-mediated cancer regression. Possible theoretical pathways could involve an antiangiogenic effect, a possible reduction in metastatic likelihood or changes to the microenvironment of the tumor. To the best of our knowledge, these mechanisms have no been previously elucidated and warrant further investigation with respect to their contribution towards clinically relevant antitumor activity by Tas13D.

CR8: Tas13D reduces EGFR phosphorylation and the volume of the tumor, not affecting cell survival or apoptosis. This indicates that the role of Tas13D in mediating tumor growth control depends mainly on non-lethal pathways or those that do not affect EGFR. Possible mechanisms may include suppression of the tumor-supporting angiogenic process, inhibition or reduced metastasis, and alteration in the local environment of a tumor. Future studies should focus on identifying and characterizing these non-apoptotic as well as non-EGFR pathways to determine their contributions to the Tas13D-mediated antitumor effect.

CR9:Tas13D has been observed to function even with reduced cell activity and EGFR phosphorylation, but it doesn't lead to increased apoptosis or reduced tumor size. This suggests that Tas13D's toxic effect on non-small cell lung cancer (NSCLC) cells might not primarily come from blocking the EGFR pathway. Possible mechanisms could involve damaging cell membrane integrity, inducing oxidative stress, or engaging in other pathways that cause cell death. Future research should investigate these toxic mechanisms and how they relate to Tas13D's antitumor effects.

CR10: Tas13D induced cell apoptosis and inhibited tumor growth. Nonetheless, these conditions of cell starvation were not matched with lowered activity and EGFR phosphorylation. It indicates that the effectiveness of Tas13D in NSCLC cells may be attributed to an apoptotic pathway unrelated to EGFR function. The alternative pathways might include a disruption of mitochondrial function, caspase-dependent apoptosis, or modulation of other cell death pathways. These results provide a new perspective for future experimental approaches to investigate what apoptosis-inducing pathways are involved and the specific role of this process in Tas13D potency.

CR11: Identified vivo as an apoptosis inducer, decreased EGFR phosphorylation that did not translate into cell survival or tumor size reduction. These data show that while the Tas13D can induce cell death and suppress EGFR pathway activation, additional components may determine whether their effect results in complete ablation of tumor cells or growth inhibition only. These contributory factors may involve the presence of drug resistance pathways, inadequate apoptosis induction or intricate crosstalk between tumor and supporting stroma. Future works may investigate the synergy and combinatory treatment for apoptosis induction and potentially to overcome resistance mechanisms.

CR12: Tas13D significantly inhibits cell viability while having an effect on apoptosis and EGFR phosphorylation as well as tumor volume. This implies that its anti-NSCLC effects might not depend on directly disturbing the activity of EGFR. Mechanistic explanations may be due to the compromise of the cell membrane, oxidative stress generation by silver nanoparticles, or activation of other pathways contributing to cellular cytotoxicity. Further study is necessary to better understand and regard if these alternative mechanisms participate in the antitumor effect of Tas13D.

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CR13: While Tas13D apoptosis-independent-cytotoxic effect on cell survival, EGFR phosphorylation or tumor growth was not demonstrated. The data suggest that while Tas13D has the ability to induce responsiveness of non-small cell lung cancer (NSCLC) to death, there may be some factor(s) that ultimately constrain its toxic effect on tumor cells and thereby prevent growth inhibition. These factors could range from resistance mechanisms and inadequate apoptosis induction to dynamic tumor microenvironment interactions. Future investigations could be carried out into the potential of Tas13D-enhanced apoptotic effects, its use in combinational therapies and by overcoming drug resistance.

CR14: Depletion of EGFR phosphorylation by inhibition of its downstream target, TAS13D did not result in a decrease in cell survival or an increase in apoptosis or a reduction in measurement of tumor volume. Therefore, these data raise the possibility that although Tas13D may indeed inhibit EGFR signaling, it is perhaps not this function that contributes to its antitumor activity. The mechanisms underlying such effects could include resistance pathways in the tumor, interactions with elements of the surrounding pathogenic environment within which a tumor exists or incomplete blockade of EGFR signaling. Additional in vitro studies may be needed to create paired therapeutic approaches that will surmount the presence of these resistance mechanisms and lead to the improvement of EGFR signaling suppression.

CR15: The decrease in the tumor volume we observed with Tas13D did not correlate to a reduction of cell survival, apoptosis, or EGFR phosphorylation. This indicates that Tas13D is incapable of significant effects on tumor growth via either induction of cell death or a direct blockage of EGFR. Said mechanisms likely lie in anti-angiogenic, anti-metastatic, and/or tumor microenvironment-modulating effects. Further studies to evaluate these and other alternative mechanisms, as well as their potential relationship with the antitumor effects of Tas13D, are warranted.

CR16: Tas13D administration by convection-enhanced delivery (CED) failed to suppress cell survival, induce apoptosis or reduce EGFR phosphorylation and tumor size in the CR16 model. Our data would thus argue that Tas13D is probably not efficacious in the NSCLC models tested. Some of the reasons could be due to resistance mechanisms, low target protein expression etc. In the future, it is possible to use different NSCLC cell lines or tumor models in other studies and test resistance mechanisms as well as investigate whether combination therapy increases Tas13D-mediated anti-tumor effects.

7. Conclusion

Our results showed that Tas13D exhibited anticancer potential in A549 non-small cell lung cancer (NSCLC) cells and xenograft tumor models, and revealed the complexity of its action mechanism. The effects of Tas13D on cell viability, apoptosis and EGFR phosphorylation were dose-dependent and time-dependent, and these effects were gradually enhanced over time. These observations support the hypothesis that Tas13D may inhibit NSCLC growth by acting on EGFR signaling and triggering apoptosis. However, the complex interplay between Tas13D and multiple cellular mechanisms still needs to be further explored, and it remains unclear whether other pathways or unexpected effects exist and how these factors together contribute to the antitumor effects of Tas13D.

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