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THE POTENTIAL AND LIMITATIONS OF MIR-150-3P AS A CISPLATIN SENSITIZER IN NSCLC: A COMMENT *ON MIR-150-3P ENHANCES THE SENSITIVITY OF NON-SMALL CELL LUNG CANCER TO CISPLATIN BY DOWN-REGULATING THE EXPRESSION OF AKT2*

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ABSTRACT – Lung cancer, particularly non-small cell lung cancer (NSCLC), remains a major therapeutic challenge, with cisplatin resistance limiting clinical efficacy. The study under discussion identifies miR-150-3p as a tumor suppressor and cisplatin sensitizer that acts through direct downregulation of AKT2, thereby enhancing chemotherapy responsiveness. Using TCGA data and functional assays in A549 and H358 cells, the authors demonstrate antiproliferative and antimigratory effects of miR-150-3p, together with potentiation of cisplatin cytotoxicity. These findings highlight the PI3K/AKT pathway as a central mediator of drug resistance and underscore the potential of miRNA-based therapeutic strategies. Nonetheless, important limitations restrict translational applicability: reliance on only two cell lines fails to capture NSCLC heterogeneity, while tumor-microenvironment and systemic factors remain unexplored. Emerging evidence indicates that host-microbiota interactions, microbial metabolites, and iatrogenic factors such as antibiotics or proton pump inhibitors may critically modulate PI3K/AKT signaling and thereby influence cisplatin response. Moreover, challenges related to miRNA delivery and functional redundancy among AKT isoforms raise further concerns for clinical translation. Taken together, while the study provides strong evidence that miR-150-3p can sensitize NSCLC cells to cisplatin via AKT2 targeting, future research integrating *in vivo* models, microbiome profiling, and mechanistic dissection of AKT isoforms is required to fully assess its therapeutic potential.

KEYWORDS: Non-small cell lung cancer (NSCLC), Cisplatin resistance, MiR-150-3p, AKT2, PI3K/AKT pathway, Microbiota, Chemotherapy sensitization, Translational oncology.

INTRODUCTION

Lung cancer, particularly non-small cell lung cancer (NSCLC), remains a major global health burden[1]. Cisplatin continues to be a mainstay of treatment, but its clinical utility is limited by resistance[2]. The study under discussion identifies miR-150-3p as a tumor suppressor and cisplatin sensitizer, acting through downregulation of AKT2, and thereby proposes a novel strategy to enhance chemotherapy efficacy[3].

The authors combine TCGA data with functional assays in A549 and H358 cells to demonstrate that miR-150-3p exerts antiproliferative and antimigratory effects, and that its enforced expression potentiates cisplatin's cytotoxicity. The identification of AKT2 as a direct target provides mechanistic plausibility, as the PI3K/AKT pathway is central to cancer cell survival and drug resistance.

CRITICAL ANALYSIS

Despite its strengths, some limitations reduce the translational impact of the findings.

The use of only two cell lines does not capture NSCLC heterogeneity or tumor-microenvironment interactions. Tumor response to cisplatin is not solely determined by intrinsic cancer cell factors, but is profoundly shaped by the broader biological context[2]. Elements such as systemic inflammation, metabolic reprogramming, and, increasingly, host-microbiota interactions can influence the activation of signaling cascades, including PI3K/AKT[4]. These external modulators, which remain unexplored in the present study, may significantly impact AKT2 activity and ultimately modulate chemotherapy sensitivity. An emerging but underexplored dimension concerns the role of the microbiota. Increasing evidence indicates that microbial metabolites (e.g., short-chain fatty acids, bile acid derivatives) and microbial products (e.g., LPS) can modulate the PI3K/AKT pathway, influencing proliferation, apoptosis, and chemotherapy response[5]. Preclinical studies suggest that microbiota perturbation alters sensitivity to platinum drugs, with PI3K/AKT frequently implicated as a potential downstream effector[6]. However, a direct and specific regulation of AKT2 by the microbiota in NSCLC has not yet been demonstrated. This represents both a limitation and an opportunity: patient heterogeneity in microbiota composition may partly explain differential cisplatin responses, potentially through effects on AKT signaling. Integrating microbiome profiling with molecular analysis of AKT2 activation in NSCLC patients could uncover new predictive biomarkers or therapeutic strategies (e.g., microbiota modulation to enhance cisplatin efficacy). It is also important to consider iatrogenic factors that shape the microbiota and may indirectly affect PI3K/AKT signaling and cisplatin efficacy. Antibiotic exposure has been shown to disrupt gut microbial composition, leading to impaired chemotherapy response in preclinical cancer models[7]. Similarly, proton pump inhibitors (PPIs), widely used in oncology patients, alter gastric pH and microbial ecology, potentially influencing metabolite availability and downstream signaling pathways[8]. In addition, other factors should be considered. The therapeutic feasibility of miRNA mimics continues to pose significant challenges, as issues related to delivery, stability, and safety must be addressed before clinical application. Finally, although the focus on the AKT2 isoform is important, redundancy among AKT isoforms and compensatory signaling pathways may limit the overall therapeutic benefit.

CONCLUSIONS

The study convincingly positions miR-150-3p as a tumor suppressor and cisplatin sensitizer in NSCLC by targeting AKT2. Yet broader contextual factors, such as tumor heterogeneity and microbiota-driven modulation of signaling pathways, remain largely unaddressed. Future research should combine *in vivo* models, microbiome analysis, and mechanistic dissection of AKT isoforms to fully evaluate the clinical potential of miR-150-3p and related therapeutic strategies.

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Conflicts of Interest:

The authors declare no conflicts of interest.

REFERENCES

1. Garg P, Singhal S, Kulkarni P, Horne D, Malhotra J, Salgia R, Singhal SS. Advances in non-small cell lung cancer: current insights and future directions. J Clin Med 2024; 13: 4189.
2. Chen SH, Chang JY. New insights into mechanisms of cisplatin resistance: from tumor cell to microenvironment. Int J Mol Sci 2019; 20: 4136.
3. Liu SL, Tan K, Zhou Y, Lu X, Fu F, Dai P, Chen J. miR-150-3p enhances the sensitivity of non-small cell lung cancer to cisplatin by down-regulating the expression of AKT2. World Cancer Res J 2025; 12: e2911
4. Yu J, Li L, Tao X, Chen Y, Dong D. Metabolic interactions of host-gut microbiota: new possibilities for the precise diagnosis and therapeutic discovery of gastrointestinal cancer in the future—a review. Crit Rev Oncol Hematol 2024; 203: 104480.
5. Consolo P, Giorgi C, Crisafulli C, Fiorica F, Pinton P, Maurea N, Missiroli S, Quagliariello V, Mantoan B, Ottaiano A, Pellicano GF, Orru G, Scano A, Cacciola I, Pollicino T, Di Mauro G, Berretta S, Bignucolo A, Toscano E, Ciappina G, Berretta M. Investigating the impact of Fusobacterium nucleatum on oxidative stress, chemoresistance, and inflammation in inflammatory bowel disease and colorectal cancer: rationale and design of a clinical trial. Int J Mol Sci 2025; 26: 7823.
6. Chambers LM, Esakov Rhoades EL, Bharti R, Braley C, Tewari S, Trestan L, Alali Z, Bayik D, Lathia JD, Sangwan N, Bazeley P, Joehlin-Price AS, Wang Z, Dutta S, Dwidar M, Hajjar A, Ahern PP, Claesen J, Rose P, Vargas R, Brown JM, Michener CM, Reizes O. Disruption of the gut microbiota confers cisplatin resistance in epithelial ovarian cancer. Cancer Res 2022; 82: 4654-4669.
7. Martins Lopes MS, Machado LM, Amaral Silva PAI, Uchiyama AAT, Yen CT, Ricardo ED, Mutao TS, Pimento JR, Shimba DS, Hanriot RM, Peixoto RD. Antibiotics, cancer risk and oncologic treatment efficacy: a practical review of the literature. Ecancermedicalscience 2020; 17: 1106.
8. Ciappina G, Ottaiano A, Santorsola M, Esposito E, De Luca F, Giorgi C, Zito C, Capra AP, Carroccio P, Maurea N, Quagliariello V, Campo I, Passalacqua MI, Incognito D, Cacciola I, Consolo P, Berretta M. Impact of proton pump inhibitor use on progression-free and overall survival in cancer patients undergoing immune checkpoint inhibitor therapy: a systematic review and meta-analysis of recent studies. Cancers (Basel) 2025; 17: 2228.