doi.org/10.36721/PJPS.2026.39.6.178.1

Low-dose dihydroartemisinin resensitizes lung cancer cells to cisplatin by suppressing interleukin-6 release by macrophages

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Abstract: **Background**: The clinical application of dihydroartemisinin (DHA) is limited by its pharmacokinetic profile, making high *in vitro* concentrations clinically unattainable. Its effects at physiologically relevant low doses, especially in the complex tumor microenvironment (TME), are poorly understood. **Objectives**: This study investigated how clinically attainable low-dose DHA affects the efficacy of cisplatin in lung cancer in both monoculture and macrophage co-culture conditions, thereby uncovering a novel TME-dependent mechanism. **Methods**: Using human lung cancer cells and THP-1-derived macrophages, we conducted viability and invasion assays and measured IL-6 levels in both monoculture and co-culture systems. The effects of DHA on cisplatin sensitivity and invasion were evaluated, and rescue experiments using recombinant IL-6 and neutralizing antibodies were performed. **Results**: Low-dose DHA antagonized cisplatin cytotoxicity in monoculture but potently enhanced cisplatin-induced cell death after co-culturing with macrophages. Mechanistically, this sensitization was mediated via DHA-mediated inhibition of IL-6 secretion by macrophages. Adding exogenous IL-6 partly reversed this effect, while an IL-6 neutralizing antibody mimicked this effect. Furthermore, cisplatin paradoxically promoted cancer cell invasion by inducing IL-6 release from macrophages, which was efficiently blocked by low-dose DHA via the same pathway. **Conclusion**: At clinically relevant concentrations, the principal antitumor property of DHA lies in TME modulation rather than direct cytotoxicity. By inhibiting macrophage-derived IL-6, DHA simultaneously mitigated chemoresistance and invasion, resensitizing lung cancer cells to cisplatin. These findings provide a mechanistic rationale for combining DHA with platinum-based chemotherapy.

Keywords: Cisplatin; Dihydroartemisinin (DHA); Interleukin-6 (IL-6); Lung cancer; Macrophage

Submitted on 14-08-2025 – Revised on 25-10-2025 – Accepted on 07-11-2025

INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality worldwide (Smolarz *et al*., 2025; Sung *et al*., 2021), with cisplatin-based chemotherapy serving as a cornerstone of treatment for many patients (Rottenberg *et al*., 2021; Umar *et al*., 2024). However, the efficacy of cisplatin is severely limited by intrinsic and acquired resistance (Umar *et al*., 2024; Yu *et al*., 2025). The tumor microenvironment (TME) is now considered a critical driver of treatment resistance (Dallavalasa *et al*., 2021; Xiao *et al*., 2025). Within the TME, tumor-associated macrophages (TAMs) are key players in chemoresistance (Hao *et al*., 2025; Luo *et al*., 2022; Xia *et al*., 2025), secreting many cytokines, chemokines and growth factors that shield cancer cells from therapeutic agents (Mantovani *et al*., 2008; Rani *et al*., 2019).

Interleukin-6 (IL-6), a pleiotropic cytokine predominantly secreted by TAMs in the TME (Thuya *et al*., 2025), has been identified as a principal mediator of cisplatin resistance in non-small cell lung cancer (NSCLC) (Duan *et al*., 2015; Yan *et al*., 2014). IL-6 signaling, primarily through the signal transducer and activator of transcription 3 (STAT3) pathway, promotes the survival, proliferation and invasion of cancer cells, thereby undermining the efficacy of chemotherapy (Huang *et al*., 2022; Song *et al*., 2023; Thuya *et al*., 2025). Notably, some studies have shown that chemotherapeutic agents, like cisplatin, can promote the invasion and metastasis of surviving cells (Akhlaghipour and Moghbeli, 2024), with IL-6 regarded as a key driver of "chemotherapy-induced invasion" (Su *et al*., 2023). Therefore, targeting the IL-6 axis represents a promising strategy to overcome resistance and inhibit metastasis.

Dihydroartemisinin (DHA), a derivative of artemisinin, has shown broad-spectrum anticancer potential in numerous preclinical studies (Dai *et al*., 2021; Rani *et al*., 2025). However, a significant translational gap exists, as most *in vitro* studies employed DHA concentrations (e.g., >10 μM) far greater than the transient peak plasma concentrations (Cmax ≈ 1-2 μM) observed in humans (Kiang *et al*., 2014; Morris *et al*., 2011; Navaratnam *et al*., 2000). This pharmacokinetic (PK) and pharmacodynamic (PD) dissociation raises a critical question: what is the true biological effect of DHA at clinically achievable concentrations?

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We hypothesized that at these physiologically relevant low doses, DHA may not function as a direct cytotoxic agent but rather as a modulator of the TME. This study investigated the effects of low-dose DHA on cisplatin sensitivity in lung cancer. We found that low-dose DHA antagonized the effects of cisplatin in monoculture, whereas it potently enhanced the effects of cisplatin in the presence of macrophages by specifically suppressing IL-6 secretion by macrophages, while simultaneously inhibiting cisplatin-induced tumor cell invasion. This work uncovered a novel, environment-dependent mechanism of DHA and provided a new paradigm for its clinical application.

MATERIALS AND METHODS

Cell lines and reagents

Human lung adenocarcinoma cell lines A549 and H1299 and the human monocytic cell line THP-1 were purchased from the American Type Culture Collection (ATCC). The cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) containing 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin. DHA and cisplatin were purchased from Selleck Chemicals. Recombinant human IL-6 and the IL-6-neutralizing antibody were purchased from R&D Systems.

Cell viability assay

Cell viability was determined using 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay as previously described (Wang *et al*., 2024). The cells were seeded in 96-well plates. For co-culture experiments, THP-1 macrophages were seeded into Transwell inserts (0.4 μm pore), which were then placed into wells containing lung cancer cells. After 48 hours of treatment, the inserts were removed and MTT solution was added to cancer cells. Absorbance was measured at 490 nm.

Enzyme-linked immunosorbent assay (ELISA)

IL-6 levels in cell culture supernatants were measured using a human IL-6 ELISA kit according to the manufacturer's instructions and our previous descriptions (Wang *et al*., 2024). The intensity of the color was recorded at 450 nm and the IL-6 levels were obtained from 5 biological replicates.

Transwell invasion assay

Invasion assays were conducted using Transwell chambers coated with Matrigel as previously described (Wang *et al*., 2020). Lung cancer cells were seeded into the upper chambers in serum-free medium. Conditioned medium (CM) from various treatment groups was placed in the lower chamber as a chemoattractant. After 24 hours, invaded cells on the lower membrane were stained with crystal violet and counted. The Transwell membranes were incubated with 2% deoxycholic acid for 35 mins and the absorbance of each well was read at 595 nm. Deoxycholic acid was used as a detergent to solubilize the crystal violet dye, allowing for the quantitative spectrophotometric measurement of the invaded cells (Li *et al*., 2025; Lucio-Eterovic *et al*., 2009).

Statistical analysis

All data are presented as mean ± standard deviation (SD) from at least three independent experiments. Statistical analyses were conducted using one-way *ANOVA* followed by Tukey's post hoc test. A P-value < 0.05 was considered statistically significant.

RESULTS

DHA exhibited environment-dependent, biphasic effects on cisplatin sensitivity

To investigate the effect of low-dose DHA on cisplatin sensitivity, we first treated lung cancer cells in standard monoculture systems. As shown in Fig. 1A (A549 cells, monoculture panel) and Fig. 1B (H1299 cells, monoculture panel), 5 μM cisplatin alone significantly decreased the viability of A549 and H1299 cells. Intriguingly, in monoculture, co-treatment with increasing concentrations of DHA (0.25-2 μM) significantly increased cell viability compared to cisplatin alone, suggesting the antagonistic effects of DHA on cisplatin cytotoxicity in both cell lines. However, these cells exhibited increased resistance to 5 μM cisplatin after being co-cultured with human monocytic THP-1 macrophages (Fig. 1A, A549 cells, Co-culture panel; Fig. 1B, H1299 cells, Co-culture panel). Cell viability remained relatively high compared to monoculture. Strikingly, in this co-culture setting, the addition of low-dose DHA reversed the observed antagonistic effect. Compared to cisplatin alone in co-culture, DHA (0.25-2 μM) potently enhanced cisplatin-induced cell death, significantly reducing cell viability in A549 and H1299 cells. These results unequivocally demonstrate that the effect of low-dose DHA on cisplatin sensitivity fundamentally relies on the presence of macrophages, reversing its action from antagonism in monoculture to potent sensitization in the TME mimicking co-culture setting for both A549 and H1299 lung cancer cells.

Low-dose DHA resensitized cancer cells by modulating the macrophage secretome

We prepared CM from co-cultures (lung cancer cells with THP-1 macrophages) to determine if the observed sensitization effect was mediated by soluble factors. CM collected from control co-cultures effectively conferred resistance to 5 μM cisplatin in freshly plated A549 and H1299 lung cancer cells, as treatment with cisplatin in the presence of control CM did not significantly reduce cell viability compared to untreated cells (Fig. 2A). In contrast, CM from co-cultures treated with low-dose DHA (1 and 2 μM) significantly sensitized A549 and H1299 cells to cisplatin, dose-dependently reducing cell viability compared to cells treated with control CM and cisplatin (Fig. 2A).

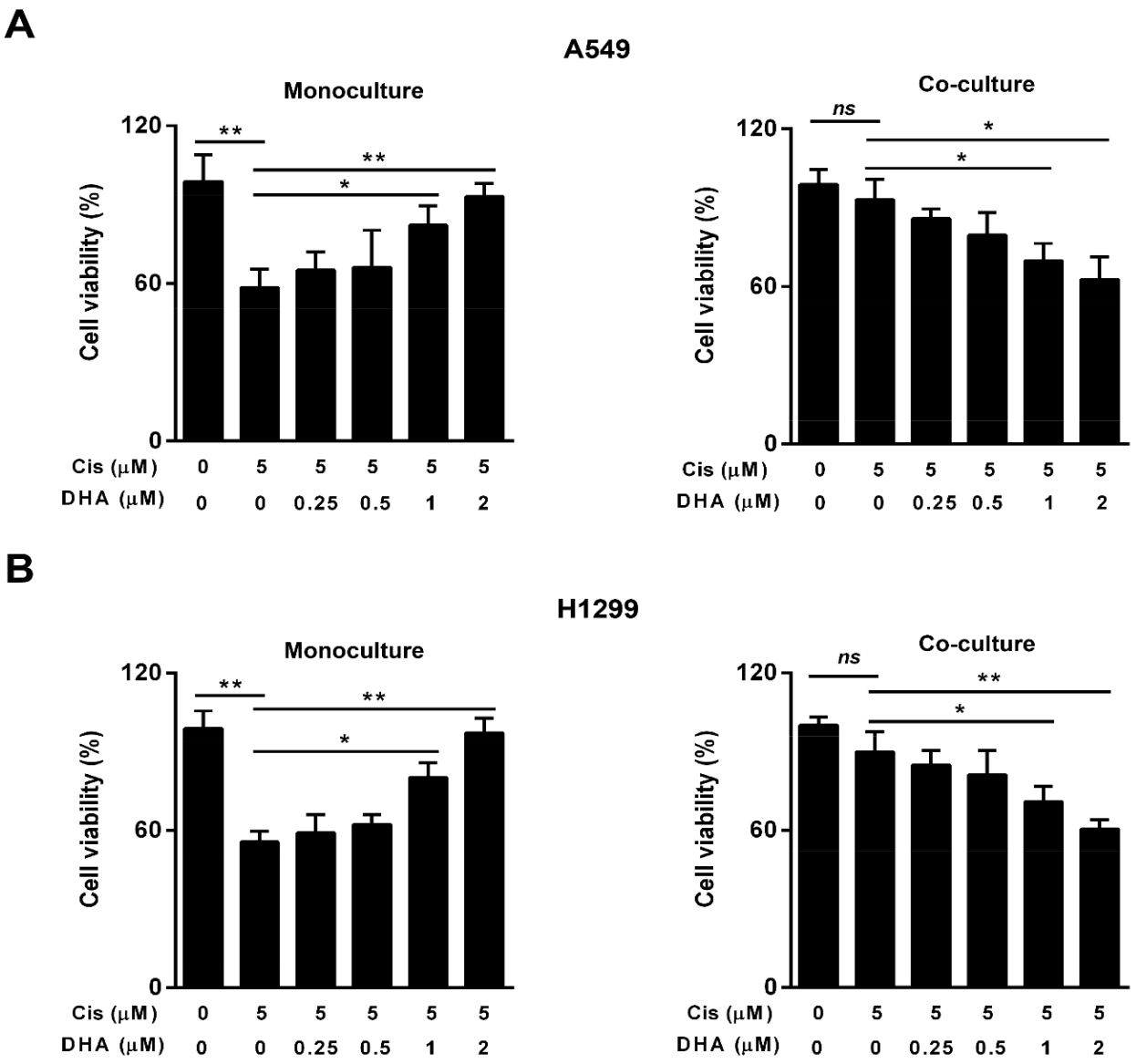

Fig. 1: Environment-dependent, biphasic effects of low-dose DHA on cisplatin sensitivity. (A) In monoculture, low-dose DHA (0.25-2 μM) antagonizes cisplatin (5 μM) cytotoxicity in A549 cells. In co-culture with THP-1 macrophages, low-dose DHA (0.25-2 μM) significantly enhances cisplatin cytotoxicity in A549 cells. (B) In monoculture, low-dose DHA (0.25-2 μM) antagonizes cisplatin (5 μM) cytotoxicity in H1299 cells. In co-culture with THP-1 macrophages, low-dose DHA (0.25-2 μM) significantly enhances cisplatin cytotoxicity in H1299 cells. Data are presented as mean ± SD. $^{*}P < 0.05$, $^{**}P < 0.01$, ns indicates not significant.

This finding indicates that DHA modulates the secretome of the co-culture system to promote the efficacy of cisplatin. To investigate whether this sensitizing effect was mediated by proteinaceous factors, we subjected the conditioned media to repeated freeze-thaw (FT) cycles to denature proteins.

The sensitizing effect of DHA-treated CM was completely abrogated after freeze-thaw in A549 and H1299 cells (Fig. 2B). Furthermore, the resistance conferred by control CM also disappeared after treatment with FT, with 5 μM cisplatin significantly reducing cell viability. These findings strongly suggest that DHA acts by modulating the macrophage secretome, specifically by modulating soluble protein factors. Given the established role of IL-6 in cisplatin resistance, we next measured its concentration in the conditioned medium. Co-culturing lung cancer cells with THP-1 macrophages increased IL-6 secretion (Fig. 2C). Notably, low-dose DHA (1 and 2 μM) dramatically and dose-dependently reduced IL-6 secretion in conditioned medium from both A549 and H1299 co-culture systems. These results strongly suggest that low-dose DHA resensitizes cancer cells by specifically inhibiting IL-6 release from macrophages.

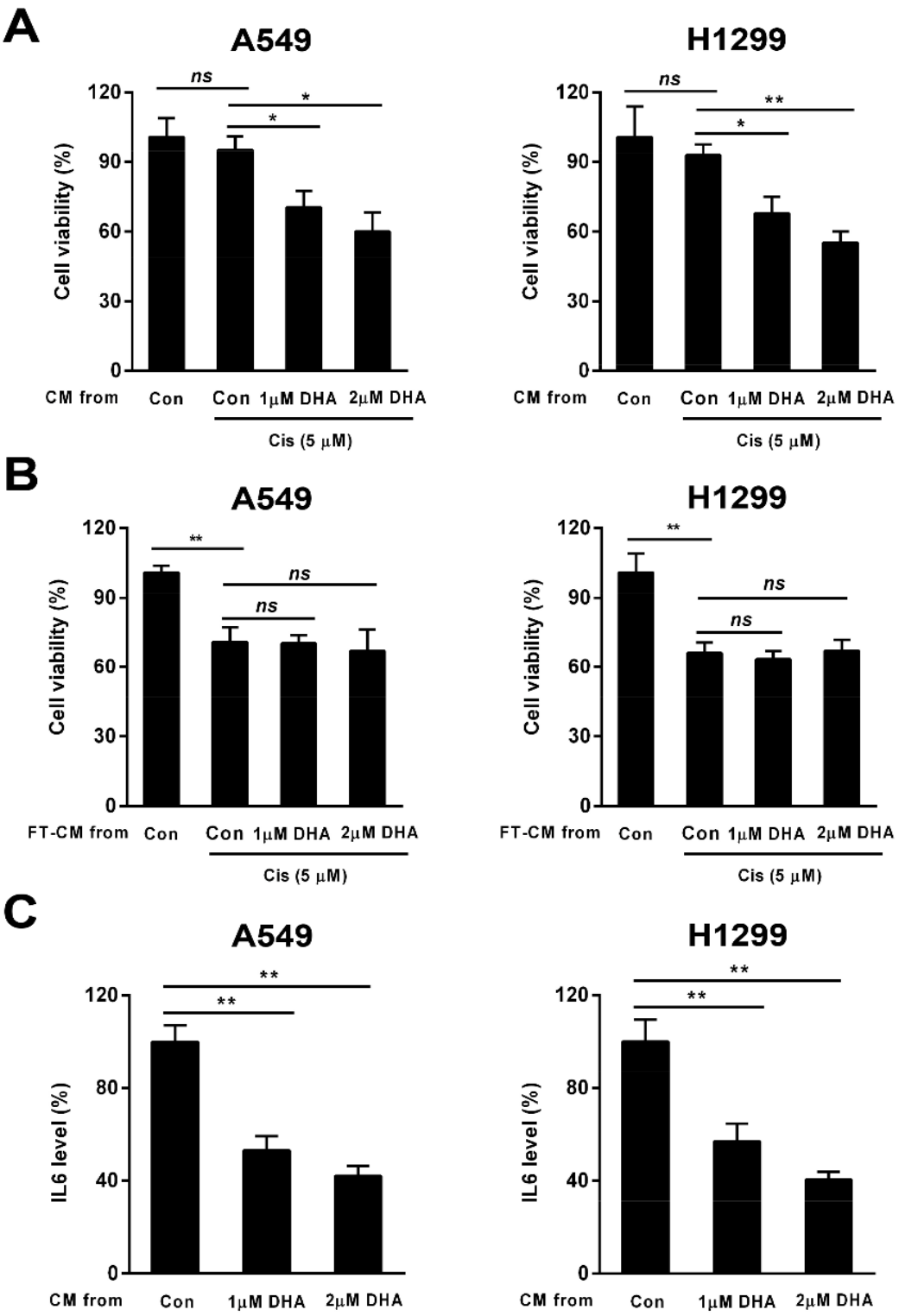

Fig. 2: Low-dose DHA modulates the macrophage secretome to sensitize lung cancer cells to cisplatin. (A) Conditioned medium (CM) from control co-cultures confers cisplatin resistance, while CM from low-dose DHA (1 and 2 μM)-treated co-cultures sensitizes both A549 and H1299 cells to 5 μM cisplatin. (B) The sensitizing effect of DHA-treated CM and the resistance conferred by control CM are abrogated by repeated freeze-thaw (FT) cycles in both A549 and H1299 cells. (C) Low-dose DHA (1 and 2 μM) dramatically and dose-dependently reduces IL-6 secretion in conditioned medium from co-culture systems for both A549 and H1299. Data are presented as mean ± SD. $^{*}P < 0.05$, $^{**}P < 0.01$, ns indicates not significant.

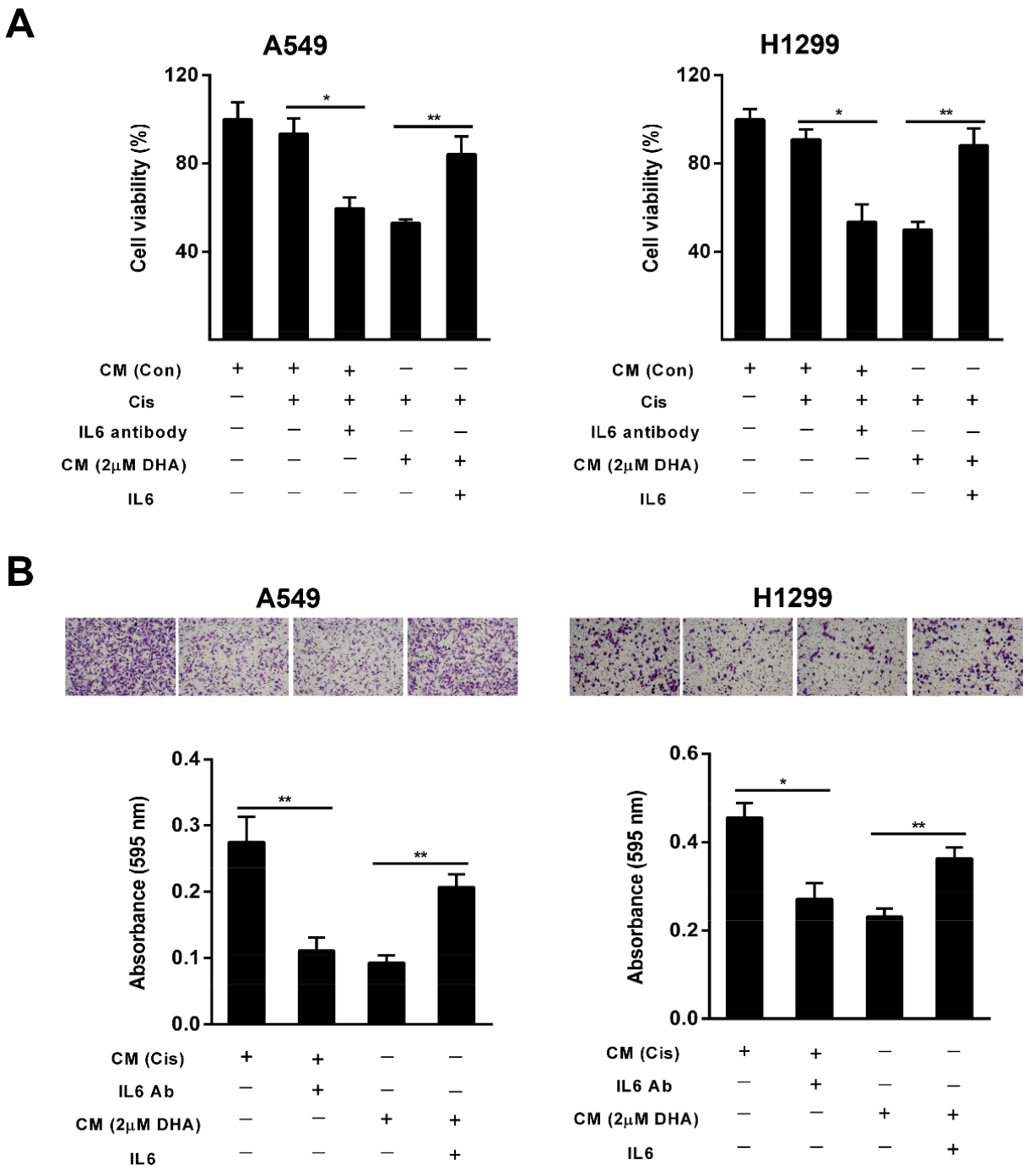

Fig. 3: IL-6 is the key functional mediator of low-dose DHA's effects on chemosensitization and invasion. (A) The sensitizing effect of DHA is reversed by exogenous recombinant human IL-6 (IL6) and mimicked by an IL-6 neutralizing antibody (IL6 Ab) in A549 and H1299 cells. (B) Conditioned medium from cisplatin-treated co-cultures [CM (Cis)] promotes lung cancer cell invasion. This pro-invasive effect is inhibited by an IL-6 neutralizing antibody and by CM from DHA-treated co-cultures [CM (2μM DHA)]. The anti-invasive effect of DHA is reversed by exogenous IL-6, shown for A549 and H1299 cells. Data are presented as mean ± SD. $^{*}P < 0.05$, $^{**}P < 0.01$.

IL-6 was identified as the key functional mediator involved in the effects of DHA on chemosensitization and invasion

We conducted rescue and mimicry experiments for both chemosensitization and invasion to functionally validate the critical role of IL-6 in the effects of DHA. For chemosensitization, in the control conditioned medium setting, adding an IL-6-neutralizing antibody (IL6 Ab) significantly reduced the viability of both A549 and H1299 cells in the presence of cisplatin (Fig. 3A), mimicking the

sensitizing effect of DHA. Conversely, when recombinant human IL-6 (IL6) was added to the conditioned medium derived from DHA-treated co-cultures, it significantly increased the viability of both A549 and H1299 cells, thereby reversing the sensitizing effects of DHA. We also investigated the role of IL-6 in cell invasion. The conditioned medium collected from cisplatin-treated co-cultures significantly promoted the invasive capacity of both A549 and H1299 cells (Fig. 3B). This pro-invasive effect on both cell lines was significantly attenuated after adding IL6 Ab. Furthermore, conditioned medium from co-cultures treated with 2 μM DHA also significantly inhibited cell invasion compared to CM (Cis), highlighting the anti-invasive role of DHA. Functional validation confirmed that the anti-invasive effect of DHA also relied on IL-6. Adding recombinant human IL-6 significantly restored the pro-invasive capacity in both A549 and H1299 cells, thus reversing the anti-invasive effect of DHA.

DISCUSSION

This study resolved a critical paradox surrounding the therapeutic application of DHA. By employing a physiologically relevant low dose and a TME-mimicking, all-human co-culture model, we indicated that the anticancer activity of DHA is highly context-dependent. Most strikingly, DHA revealed antagonistic effects on cisplatin efficacy in monoculture, while potent synergistic effects in the presence of macrophages. This discovery explains why previous *in-vitro* studies, often performed in sterile monoculture conditions, may have underestimated or misinterpreted the true clinical potential of low-dose DHA. The low-dose concentrations of DHA (0.25-2 μM) used in this study were carefully chosen to reflect the reported transient peak plasma concentrations (Cmax ≈ 1-2 μM) observed in humans (Kiang *et al*., 2014; Morris *et al*., 2011; Navaratnam *et al*., 2000), thereby ensuring physiological relevance compared to the supra-pharmacological doses employed in many *in-vitro* studies.

This study identified decreased release of macrophage-derived IL-6 as the definitive mechanism involved in this sensitization effect. TAMs form a pro-survival niche for cancer cells (Shah *et al*., 2025; Wang *et al*., 2024), wherein IL-6 activates anti-apoptotic pathways, like STAT3 (Huang *et al*., 2022; Song *et al*., 2023; Thuya *et al*., 2025), thereby conferring robust resistance to DNA-damaging agents, like platinum-based drugs (Duan *et al*., 2015; Yan *et al*., 2014). Our data indicated that low-dose DHA acts not only on cancer cells but also as a "TME modulator" that specifically targets and "re-educates" macrophages to halt the production of this key resistance and pro-invasive factor.

Cisplatin, as the primary "infantry", faces not only the fortified "enemy" (the cancer cell) but also the risk of triggering "enemy reinforcements" (pro-invasive signals). DHA acts as a dual-function "special forces" unit: on one hand, it neutralizes the enemy's "command center" (by inhibiting IL-6 secretion), dismantles the cancer cell's resistance shield and allows a more effective attack by the infantry. On the other hand, it severs the enemy's "reinforcement lines" (by blocking cisplatin-induced invasion), preventing the spread of the conflict. This coordinated strike against both "resistance" and "invasion" is the core strength of this combination strategy.

This work repositions DHA from a conventional cytotoxic drug to an agent meticulously modulating the TME. This finding has profound implications for clinical development. It suggests that future clinical trials should consider combining low-dose DHA with standard chemotherapy and incorporate TME-related biomarkers, such as serum IL-6, for patient stratification and response monitoring. Furthermore, our findings underscore the critical need for more complex and physiologically relevant preclinical models that include TME components to accurately predict drug efficacy.

While our study provided mechanistic evidence for the role of DHA in modulating macrophage-tumor interactions, the current work was limited to *in vitro* systems. Given the heterogeneity of lung tumors and the diverse functional states of TAMs *in-vivo* (Dallavalasa *et al*., 2021; Xiao *et al*., 2025), reliance on two lung cancer cell lines (A549, H1299) and a single THP-1-derived macrophage model constrains generalizability. To strengthen translational relevance, future studies should validate these findings across a broader panel of lung cancer models, including patient-derived organoids (PDOs) (Wang *et al*., 2022), primary human TAMs from multiple donors and *in-vivo* systems, such as humanized patient-derived xenografts (PDX) and syngeneic mouse models (Park *et al*., 2024). These approaches will better capture complex drug interactions and immune dynamics and enable the assessment of the potential therapeutic window, efficacy and tolerability of the combination strategy.

Our data identified IL-6 as a key soluble mediator. To refine the mechanism, future studies should delineate the effects of DHA on downstream signaling, including STAT3 phosphorylation and target gene programs, in both macrophages and cancer cells and link these molecular events to functional outcomes, such as survival, invasion and EMT.

Given the complexity of the TME (Dallavalasa *et al*., 2021; Xiao *et al*., 2025), broader cytokine and chemokine profiling, such as multiplex assays and secretome analyses of conditioned media, can help identify additional macrophage-derived factors modulated by DHA and define their contribution to tumor progression and therapeutic response. We also recognized that relying on conditioned medium in the invasion assay primarily addresses the role

of soluble factors and may not fully capture the intricate effects of direct macrophage-cancer cell interaction, which may also affect cancer cell invasion. Future studies incorporating direct co-culture into 3D invasion models can provide further insights (Micalet *et al*., 2023).

We also noted that low-dose DHA may attenuate cisplatin activity in monoculture. Although not the primary focus here, this paradox warrants investigation. Studies should investigate whether, in the absence of macrophage-mediated IL-6 suppression, low-dose DHA affects stress response or pro-survival pathways in cancer cells that temporarily attenuate cisplatin cytotoxicity. Furthermore, whether these effects are schedule-, dose-, or context-dependent deserves more studies. Evaluating combination timing, dose ranges consistent with clinically achievable exposures and interaction metrics, alongside PK/PD considerations, can help resolve these dynamics and guide rational combinations.

CONCLUSION

This study demonstrated that clinically achievable, low-dose DHA resensitizes lung cancer cells to cisplatin and inhibits their invasion by suppressing IL-6 secretion from human-derived macrophages. This environment-dependent mechanism challenges the conventional view regarding the mode of action of DHA and provides a novel rationale for its use as a TME-modulating agent to overcome chemoresistance and metastasis in lung cancer.

Acknowledgments
Not applicable.

Author's contribution
Zhiyong Wang and Fagang Liu designed the study and wrote the paper. Jie Ruan and Jinbao Yin generated the data. Xuan Zeng analyzed the data. All authors read and approved the final manuscript.

Funding
This project was supported by grants from the Scientific Research Project of Guangdong Bureau of Traditional Chinese Medicine (No. 20232096), the Guangdong Medical Research Fund Project (No. A2023169), and the Guizhou Provincial Special Research Grant on Traditional Chinese Medicine and Ethnic Minority Medicine Science and Technology (No. QZYY-2025-088).

Ethical approval
This study was conducted *in vitro* using established human cell lines. All cell lines used in this study were commercially available and purchased from the American Type Culture Collection (ATCC). The study did not involve any direct experiments on human participants or animals. Therefore, ethical approval was not required for this work.

Data availability statement
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest
There is no conflict of interest.

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