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TROP2 as a Candidate Upstream Inhibitor of Ferroptosis in Ovarian Cancer: A Hypothesis-Driven Review Based on YAP1/HMOX1 Signaling and Lipid Metabolic Reprogramming

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Abstract: Ovarian cancer ranks as the gynecologic malignancy with the highest mortality rate, and platinum resistance represents a core bottleneck limiting long-term patient survival. Ferroptosis, an iron-dependent form of regulated cell death driven by lipid peroxidation, opens new avenues to reverse chemoresistance in ovarian cancer. TROP2 is frequently overexpressed in ovarian cancer. Cumulative evidence indicates that beyond serving as a cell-surface antigen, TROP2 acts as a central signaling hub sustaining malignant tumor phenotypes. A previous study conducted in non-small-cell lung cancer first demonstrated that TROP2 sequesters YAP1 in the cytoplasm and represses *HMOX1* transcription, thereby conferring tumor-cell resistance to ferroptosis. Nevertheless, no systematic review has addressed whether this signaling axis is conserved in ovarian cancer. In this hypothesis-driven review, we compile independent evidence describing the involvement of YAP1 and HMOX1 in ferroptosis regulation in ovarian cancer, and propose that TROP2 functions as a candidate upstream suppressor of ferroptosis in this disease. Together with preliminary, as-yet-unpublished data from our r group showing that *TROP2* knockout down-regulates *GPX4* and *SLC7A11*, up-regulates *ACSL4*, markedly alters lipid-metabolism pathways (per Gene Ontology enrichment of transcriptomic data), and substantially reduces *ELOVL7* expression, we extend our hypothesis to lipid-metabolism regulation. ELOVL7, an elongase facilitating incorporation of long-chain polyunsaturated fatty acids into phospholipids, may serve as a key node governing substrate availability for membrane lipid peroxidation under TROP2 regulation. This article also explores the therapeutic potential of combining TROP2-targeted antibody-drug conjugates (ADCs) with ferroptosis inducers and outlines validation workflows spanning cellular models, patient-derived xenograft (PDX) models and clinical specimens.

1. Introduction

Ovarian cancer exhibits the highest mortality among gynecologic malignancies. Most patients are diagnosed at advanced stages due to inconspicuous because early-stage symptoms are

nonspecific. Although platinum-based chemotherapy followed by PARP-inhibitor maintenance therapy yields high initial response rates, relapse and acquired resistance are nearly inevitable for advanced-stage patients, and only modest gains in 5-year survival have been achieved over the past two decades[1]. Conventional chemotherapies exert anti-tumor effects predominantly by triggering apoptosis, yet ovarian cancer cells frequently evade cell death via down-regulation of pro-apoptotic proteins or up-regulation of anti-apoptotic signals such as Bcl-2[2]. This observation has motivated research interest in non-apoptotic regulated cell-death pathways.

Ferroptosis denotes an iron-dependent form of regulated cell death driven by lipid peroxidation[2,3]. Multiple pre-clinical studies have shown that ovarian cancer cells are relatively susceptible to ferroptosis and that pharmacological activation of ferroptosis signaling overcomes platinum resistance in pre-clinical models[1]. Tumor cells, however, develop ferroptosis resistance through metabolic reprogramming[1,2]. The precise molecular mechanisms sustaining such resistance remain incompletely characterized in ovarian cancer.

TROP2 (trophoblast cell-surface antigen 2) is a type-I transmembrane glycoprotein encoded by the *TACSTD2* gene. It is expressed at low levels in normal epithelia but overexpressed in many epithelial-origin malignancies including ovarian cancer, and high TROP2 expression correlates with advanced tumor stage, metastasis and poor clinical outcomes[4]. Beyond its function as a surface marker, TROP2 triggers intracellular signaling cascades including calcium signaling, ERK/MAPK and PI3K/AKT, promoting tumor-cell proliferation, survival and epithelial-mesenchymal transition[5]. A recent investigation by Wu and colleagues uncovered a novel biological role for TROP2: in non-small-cell lung cancer (NSCLC), TROP2 prevents YAP1 nuclear translocation and inhibits transcription of *HMOX1* (encoding heme oxygenase-1), consequently suppressing ferroptosis. HMOX1 activity mobilizes labile iron and accelerates lipid peroxidation[6].

Notably, TROP2-targeted antibody-drug conjugates (ADCs) are undergoing rapid clinical development for breast and gynecologic malignancies[7]. TROP2 therefore represents not only a basic-science signaling hub but also a therapeutically actionable clinical target. This review adopts a hypothesis-driven framework. We first summarize core ferroptosis mechanisms and multi-layered ferroptosis-defense systems in ovarian cancer, followed by an overview of TROP2-mediated signaling, alongside independent evidence supporting YAP1- and HMOX1-dependent ferroptosis modulation. On this basis, we formulate the hypothesis that TROP2 acts as an upstream ferroptosis suppressor in ovarian cancer. Integrating our unpublished preliminary findings regarding ELOVL7, we further expand this mechanistic model to encompass lipid metabolism. Finally, we discuss therapeutic implications for combining TROP2-targeted ADCs with ferroptosis inducers and delineate experimental designs required for hypothesis validation.

2. Ferroptosis and Its Regulatory Mechanisms in Ovarian Cancer

2.1 Core mechanisms of ferroptosis

Ferroptosis is characterized by intracellular reactive oxygen species (ROS) accumulation and iron-dependent peroxidation of polyunsaturated fatty acid (PUFA)-containing phospholipids in cell membranes[2,3]. In this process, labile ferrous iron (Fe^{2+}) catalyzes the Fenton-type decomposition of lipid hydroperoxides, generatinghighly reactive lipid radicals, initiating chain- propagating lipid peroxidation that disrupts membrane integrity[3]. Malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), reactive aldehyde by-products of lipid peroxidation, are routinely measured as readouts for lipid-peroxidation-driven events such as ferroptosis[3]. Overall, three major determinants govern whether ferroptosis proceeds within a cell: bioavailability of labile iron, abundance of membrane phospholipids containing PUFAs, and capacity of antioxidant systems to eliminate lipid peroxides.

2.2 Ferroptosis-defense systems in ovarian cancer

Ovarian cancer cells deploy multiple molecular systems to counteract ferroptosis. The GPX4/GSH axis constitutes the primary enzymatic defensive cascade: glutathione peroxidase 4 (GPX4) reduces phospholipid hydroperoxides using glutathione (GSH) and halts ferroptotic progression[1,2]. A second GPX4-independent defensive system centers on ferroptosis suppressor protein 1 (FSP1), which regenerates ubiquinol (reduced coenzyme Q10) to trap lipid radicals and thereby preserves membrane integrity[1,2]. Apart from enzymatic defenses, lipid remodeling represents another critical regulatory layer. Acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) together dictate cellular abundance of peroxidation-prone PUFA-containing phospholipids[1]. Ovarian cancer cells can export ACSL4 in exosomes, thereby reducing intracellular ACSL4 abundance and diminishing ferroptotic susceptibility[8].

Given functional redundancy among these defensive modules, therapeutic interventions targeting single downstream effector molecules often produce limited efficacy. Identification of upstream master regulators coordinating multiple ferroptosis-resistance pathways would therefore carry greater therapeutic relevance, which renders TROP2 a compelling candidate.

2.3 HMOX1: a double-edged sword

While the aforementioned defensive machineries serve as the “shield” against ferroptosis in ovarian-cancer cells, HMOX1 functions conversely as a potential “spear”. HMOX1catalyzes heme degradation into biliverdin, carbon monoxide and free ferrous iron, amplifying Fenton-reaction activity and lipid peroxidation[6]. In ovarian-cancer research, natural compounds have been reported to trigger ferroptosis by elevating HMOX1 and increasing intracellular labile-iron pools[9].

Nevertheless, HMOX1 exerts context-dependent effects and does not universally promote ferroptosis. Within the ovarian-cancer microenvironment, macrophage-derived HMOX1 fosters an immunosuppressive tumor milieu[10]. Systemic HMOX1 activation may thus introduce immunological risks. Such cell-type-dependent bioactivity argues against direct pharmacological HMOX1 activation as a viable therapeutic approach. A more rational strategy is to target upstream regulators that selectively modulate *HMOX1* within tumor cells. Enrichment of TROP2 in malignant tumor cells satisfies this requirement.

3. TROP2-Mediated Signaling and Targeted Therapies in Ovarian Cancer

3.1 Structural features and signaling outputs

The extracellular domain of TROP2 undergoes dynamic conformational shifts and oligomerization[5]. These properties influence ligand binding and epitope accessibility for therapeutic antibody recognition. In ovarian-cancer cells, TROP2 overexpression activates PI3K/AKT and ERK/MAPK signaling cascades. TROP2 knockdown reduces levels of p-AKT2, Bcl-2, vimentin and β-catenin, while increasing cleaved caspase-3 and E-cadherin[5]. These observations indicate that TROP2 sustains proliferative and mesenchymal phenotypes through AKT/β-catenin-dependent mechanisms. TROP2 also participates in tumor-microenvironment crosstalk: extracellular vesicles originating from malignant ascites deliver TROP2 to peritoneal mesothelial cells, activating the TNF-α/NF-κB axis and driving mesothelial-to-mesenchymal transition[1].

3.2 Prognostic significance and ADC development

High TROP2 expression represents an independent adverse prognostic marker in serous ovarian carcinoma. In one observational cohort of 73 patients, TROP2 overexpression was detected in 67.1% of specimens and correlated with shortened overall survival (OS) and progression-free survival (PFS)[4]. These clinical features make TROP2an attractive ADC target. Pre-clinical proof of concept has been obtained: sacituzumab govitecan (SG) demonstrated anti-tumor activity and survival benefits in TROP2-positive low-grade serous ovarian-cancer PDX models[11].

Several novel TROP2-targeted ADC agents -such as DB-1305(BNT325) have exhibited preliminary anti-tumor activity in ongoing translational investigations[7]. Such clinical-development progress validates TROP2 as a therapeutically tractable target. Importantly, TROP2 is more than merely a delivery moiety for cytotoxic payloads. If TROP2 actively suppresses ferroptosis, therapeutic TROP2 blockade would not only deliver cytotoxic payloads but also intrinsically lower the cellular threshold for ferroptosis induction. This putative dual-mode therapeutic effect constitutes the core rationale for this review and forms the central hypothesis tested in Section 4.

4. Central Hypothesis: TROP2 Inhibits Ferroptosis in Ovarian Cancer via YAP1/HMOX1 Signaling

4.1 Evidence derived from lung cancer: the TROP2-YAP1-HMOX1 axis suppresses ferroptosis

To validate this hypothesis, direct molecular evidence describing TROP2-dependent ferroptosis regulation must be established. Mechanistic insights originate from lung-cancer studies. Knockdown of *TROP2* sensitizes NSCLC cells to RSL3-induced ferroptosis, accompanied by elevated lipid peroxidation, ROS and MDA, as well as reduced glutathione concentrations. Mechanistically, *TROP2* deletion promotes YAP1 nuclear translocation, driving *HMOX1* transcriptional activation, expanding labile-iron pools and enhancing ferroptosis[6]. This regulatory axis has been validated in xenograft animal models[6].

More importantly, these lung-cancer findings are not isolated observations: HMOX1 likewise functions as a key ferroptosis regulator in ovarian cancer, and its pharmacological upregulation can induce ferroptosis[9]. Accordingly, we hypothesize that this TROP2-dependent regulatory cascade is likely conserved in ovarian cancer.

4.2 Independent evidence linking YAP1 and HMOX1 to ferroptosis in ovarian cancer

Multiple reports have directly associated YAP1 with ferroptosis in ovarian cancer. In ovarian clear-cell carcinoma, YAP1 activation augments erastin-triggered ferroptosis, whereas tumors exhibiting low nuclear YAP1 abundance correlate with inferior patient outcomes. ZDHHC7 confers ferroptosis resistance by suppressing YAP1 activity[12]. In high-grade serous ovarian cancer, FAK inhibition promotes YAP1 cytoplasmic retention and mitigates platinum resistance[13]. Pharmacological studies further indicate that honokiol induces ferroptosis in ovarian-cancer cells by modulating OTUB2 and dampening YAP-dependent signaling. These results position YAP1 as an upstream determinant of ferroptotic susceptibility in ovarian cancer, consistent with the model whereby cytoplasmic YAP1 sequestration (mediated by TROP2 in lung cancer) suppresses ferroptosis.

HMOX1 also bears functional relevance in ovarian-cancer biology. As described above, natural compounds induce ferroptosis by up-regulating HMOX1 and facilitating labile-iron

accumulation[9]. Reported crosstalk between HMOX1 and PI3K/AKT signaling in the ovarian-cancer microenvironment further situates HMOX1 within the broader TROP2-activated signaling network[10].

Collectively, these independent lines of evidence, interpreted alongside mechanistic data from lung cancer, support our primary hypothesis: in TROP2-overexpressing ovarian-cancer cells, TROP2 restricts YAP1 nuclear localization, represses *HMOX1* transcription, shrinks labile-iron pools and blunts ferroptosis. TROP2 inhibition achieved through RNA interference, antibody-based therapy or ADC treatment would relieve this inhibitory brake and restore cellular sensitivity to ferroptosis.

4.3 Extended hypothesis covering lipid metabolism: ELOVL7 as a putative downstream node

Iron bioavailability represents only one determinant of ferroptotic sensitivity. A second key factor is the cellular pool of peroxidation-susceptible PUFA-containing phospholipids. Our unpublished preliminary data suggest that TROP2 also modulates this second regulatory dimension.

Gene Ontology (GO) enrichment analysis of transcriptomic data from *TROP2*-knockout ovarian-cancer cells revealed widespread remodeling of lipid-metabolic pathways. At the transcript level, *GPX4* and *SLC7A11* were down-regulated, *ACSL4* was up-regulated, and *ELOVL7* expression decreased substantially. ELOVL7 is a key elongase in very-long-chain fatty-acid biosynthesis that preferentially elongates C18 polyunsaturated fatty acids. Recent research demonstrates that ELOVL7 drives accumulation of long-chain-PUFA-containing phospholipids and sensitizes cells to ferroptosis; conversely, *ELOVL7* knockdown diminishes lipid peroxidation and ferroptotic susceptibility[14].

Under physiological conditions with intact TROP2 function, TROP2 maintains ELOVL7 expression. *TROP2* loss-of-function-mediated *ELOVL7* suppression would reduce PUFA-phospholipid substrate availability and mitigate ferroptosis. This effect operates in opposition to the pro-ferroptotic output of *HMOX1* up-regulation. These two opposing influences are not mutually exclusive: overall ferroptosis exacerbation is primarily governed by *HMOX1* de-repression together with alterations in the GPX4/SLC7A11/ACSL4 axis. ELOVL7-dependent substrate reduction cannot override this dominant pro-ferroptotic signal, underscoring the dominance of this branch. The net biological outcome in individual cells depends on the relative dominance of each signaling branch.

This conceptual framework aligns with previous findings demonstrating that lipid-droplet-mediated PUFA sequestration within the ovarian-cancer ascites microenvironment mediates ferroptosis resistance[15]. Accordingly, we formulate our secondary extended hypothesis: TROP2 sustains a lipid-metabolic landscape permissive for ferroptosis evasion, partially through ELOVL7-dependent PUFA elongation and phospholipid remodeling. *TROP2* ablation lowers ELOVL7 levels and reduces PUFA-phospholipid abundance. Despite counter-balancing effects against HMOX1-driven signaling, the combined outputs of both pathways ultimately set the cellular threshold for ferroptosis activation.

Our primary and secondary hypotheses together constitute a dual-branch mechanistic model: TROP2 coordinates two major tiers of ferroptosis defense. It modulates labile-iron availability via YAP1/HMOX1 signaling while regulating peroxidation-substrate supply through ELOVL7-dependent lipid remodeling. When TROP2 remains functional, these two arms synergistically reinforce ferroptosis resistance. Following TROP2 disruption, the dominant pro-ferroptotic signal predominates and shifts the cellular state toward ferroptosis execution.

5. Interpretation of Preliminary Observations

These preliminary observations derive from a single experimental system and should be interpreted cautiously without over-extrapolation. Several important limitations must be acknowledged.

First, although the direction of *ELOVL7* expression change aligns with its known pro-ferroptotic function, reduced PUFA-phospholipid incorporation and attenuated lipid peroxidation following *TROP2* knockout have not been directly validated in our cellular model. Lipidomic profiling and quantitative measurement of discrete PUFA-phospholipid species are required for confirmation. Second, the regulatory relationship between the HMOX1 and ELOVL7 branches remains undefined. If *TROP2* loss concurrently triggers *HMOX1* de-repression and *ELOVL7* down-regulation, net ferroptotic susceptibility may not represent simple additive effects, and the balance between these two pathways varies across histologic ovarian-cancer subtypes. Third, it remains unresolved whether *ELOVL7* constitutes a direct transcriptional target of YAP1, a downstream effector of TROP2-driven PI3K/AKT signaling, or is governed by alternative TROP2-coupled cascades. Concurrent expression changes of *HMOX1* and *ELOVL7* upon *TROP2* knockout are suggestive but insufficient to prove shared upstream control. These caveats do not invalidate our hypotheses; instead, they define key experimental endpoints for future mechanistic validation.

6. Therapeutic Implications: Combining TROP2 Blockade with Ferroptosis Inducers

If TROP2 suppresses ferroptosis through iron- and lipid-dependent mechanisms, TROP2-targeted therapies may function as ferroptosis-sensitizing agents beyond simple cytotoxic payload delivery. This possibility bears tangible clinical relevance.

TROP2-targeted ADCs such as SG exhibit anti-tumor activity in platinum-resistant ovarian-cancer models and TROP2-positive PDX systems[11]. Their cytotoxic payloads preferentially eliminate dividing tumor cells, yet therapeutic efficacy is constrained by the fraction of tumor cells capable of sufficient ADC internalization. Given that *TROP2* deficiency intrinsically elevates ferroptotic susceptibility, combining TROP2-ADC therapy with ferroptosis inducers (RSL3, erastin or sorafenib) can lower the death threshold for residual surviving tumor cells and represents a promising combinatorial strategy to reverse ovarian-cancer chemoresistance. This regimen compensates for incomplete ADC internalization and synergizes with the ferroptosis-prone cellular state induced by *TROP2* disruption. Pre-clinical NSCLC data have already shown that combined *TROP2* knockdown and RSL3 treatment amplifies lipid peroxidation and tumor-cell death[6]. Additional pre-clinical reports demonstrate that metabolic interventions sensitize ovarian-cancer models to ferroptosis inducers[16].

Considering the cell-context-dependent and bidirectional activities of HMOX1, direct HMOX1-targeted therapeutics carry substantial risk of undesirable off-target effects[10]. Targeting upstream tumor-enriched TROP2 may therefore afford a wider therapeutic index.

7. Proposed Experimental Validation Strategies

To translate these hypotheses toward clinical application, future investigations should adopt the following multi-layered validation workflow.

In vitro mechanistic validation: Perform *TROP2* knockdown or ADC treatment across ovarian-cancer cell lines representing high-grade serous ovarian cancer (HGSOC) and ovarian clear-cell carcinoma (OCCC) subtypes. Conduct lipidomic profiling to quantify shifts in PUFA/MUFA ratios. Use nuclear-cytoplasmic fractionation assays to assess YAP1 subcellular localization and measure *HMOX1* expression.

Ferroptosis-susceptibility assessment: Evaluate cellular responsiveness to RSL3 or erastin after *TROP2* perturbation. Quantify lipid-peroxidation products (MDA, 4-HNE) and labile-iron levels.

In vivo studies and clinical translation: Assess the anti-tumor efficacy of TROP2-ADC plus ferroptosis-inducer combination regimens in ovarian-cancer PDX models. Analyze clinical tumor specimens via immunohistochemistry to correlate *TROP2* expression with YAP1 nuclear abundance, HMOX1 levels and lipid-peroxidation markers such as 4-HNE, to identify predictive biomarkers for patient selection for this combinatorial therapeutic approach.

8. Limitations and Open Research Questions

Several unresolved aspects constrain this proposed mechanistic model. First, ovarian cancer exhibits pronounced inter-tumoral heterogeneity. HGSOC and OCCC differ fundamentally in baseline iron handling, lipid metabolism and intrinsic ferroptotic sensitivity. The relative contributions of the YAP1/HMOX1 axis and lipid-remodeling branch may diverge between these histologic subtypes. Second, non-malignant cells within the tumor microenvironment also express *TROP2*. The impacts of ADC exposure on macrophage HMOX1 activity and immunosuppressive microenvironment formation remain incompletely characterized. Third, clinically available ferroptosis-inducing agents remain limited, and systemic toxicities constitute a critical practical concern. Finally, the present hypotheses are extrapolated from studies performed in other tumor types, and direct in vivo evidence specific to ovarian cancer remains sparse. Our preliminary unpublished observations require independent experimental replication.

9. Conclusions

TROP2 overexpression is well-established in ovarian cancer and represents a validated therapeutic target. If mechanistic paradigms derived from lung cancer extend to ovarian disease, TROP2 additionally functions as an upstream suppressor of ferroptosis. We put forward testable hypotheses stating that TROP2 constrains YAP1 nuclear entry to limit HMOX1-mediated iron release, while concurrently sustaining ELOVL7-dependent PUFA-phospholipid remodeling to maintain pools of lipid-peroxidation substrates. Our preliminary unpublished data lend directional support to this model, although definitive conclusions await formal experimentation. Successful experimental validation would reconceptualize TROP2 biology: beyond serving merely as a targeting moiety for ADC payload delivery, TROP2 orchestrates a druggable ferroptosis-resistance program in ovarian-cancer cells.

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Declarations

Author contributions: D.Y. conceived the hypothesis, reviewed the literature, and wrote the manuscript.

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