NARRATIVE REVIEW

The role of reactive oxygen species metabolism-related genes in mediating cisplatin resistance in ovarian clear cell carcinoma

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Abstract

Cisplatin resistance in ovarian cancer, particularly in ovarian clear cell carcinoma, involves intricate mechanisms related to oxidative stress, deoxyribonucleic acid repair, and cell cycle. Resistance in ovarian clear cell carcinoma is associated with genes, such as pyruvate dehydrogenase kinase-2 and hepatocyte nuclear factor 1 beta, which enhance glycolysis and reduce reactive oxygen species that would normally facilitate cisplatin-induced deoxyribonucleic acid damage. Additionally, nuclear factor erythroid 2-related factor-2 and superoxide dismutase-2 play pivotal roles in regulating reactive oxygen species levels, thereby safeguarding ovarian clear cell carcinoma cells from oxidative damage. The postsynaptic density protein 95/discs large/zona occludens-1 (PDZ)-binding motif-angiopoietin-like 4-nicotinamide adenine dinucleotide phosphate oxidase-2 axis plays a crucial role in modulating ferroptosis, presenting potential therapeutic targets. A deeper understanding of these mechanisms offers promising strategies to overcome cisplatin resistance, particularly in ovarian clear cell carcinoma. These insights could pave the way for targetted therapies aimed at improving ovarian cancer outcomes, especially for ovarian clear cell carcinoma subtypes.

Key Words: Reactive oxygen species, Ovarian neoplasms, Drug resistance, Neoplasm.

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Introduction

Ovarian cancer (OC) is the seventh leading cause of cancer-related mortality among women.[1] Ovarian clear cell carcinoma (OCCC) accounts for approximately 5-10% of epithelial OC (EOC) cases, distinguished by its unique clinical and molecular pathological features.[2]

Epidemiological evidence indicates that women with endometriosis are at a 2.29-fold increased risk of developing OCCC compared to healthy individuals.[3] The infiltration of endometriosis into the ovary triggers cyclic shedding and haemorrhaging during menstruation, leading to the accumulation of aged blood within cysts. This process results in elevated iron ion levels, which catalyse the generation of reactive oxygen species (ROS) through the Fenton reaction, thereby inducing sustained oxidative stress in ovarian epithelial cells.[4] This oxidative stress promotes somatic mutations and facilitates tumorigenesis.[5] ROS, at varying concentrations, regulate tumorigenesis through mechanisms including deoxyribonucleic acid (DNA) damage, mutations, and alterations in key signalling pathways, such as nuclear factor-kappaB (NF-κB), activator protein-1 (AP1), extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) and phosphoinositide 3-kinase/protein kinase B (PI3K/Akt).[6] Comparative multi-omics analyses indicate that OCCC is characterised by a redox-metabolic-coagulopathic triad —enriched oxidative-stress adaptation (e.g., hepatocyte nuclear factor-1 beta (HNF1β)/nuclear factor erythroid 2-related factor-2 (NRF2)-linked programmes), glycogen-centric glucose metabolism (e.g., a tumour protein p53–glycogen synthase 1 (p53-GYS1) feedback circuit), and pro-coagulant/inflammatory signalling (e.g., tissue factor coagulation factor III/tissue factor (F3) and interleukin-6 [IL-6]). These are molecular themes that distinguish OCCC from other EOC subtypes.[7-10] Notably, genes such as hypoxia-inducible factor-1 alpha (HIF1α), IL-6, and superoxide dismutase-2 (SOD2), highlight the central role of oxidative stress in the phenotypic manifestation of OCCC.[11]

Among the subtypes of OC, OCCC is associated with the poorest prognosis, characterised by a particularly low five-year survival rate, especially in advanced-stage disease (20-30%).[12,13] A key factor contributing to this poor prognosis is OCCC's limited responsiveness to platinum-based chemotherapy.[14] In OCCC, constitutive antioxidant circuitry — including NRF2/Kelch-like ECH-associated protein 1 (KEAP1) activation and solute carrier

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family 7 member 11 (SLC7A11)–glutathione (GSH)–glutathione peroxidase 4 (GPX4) buffering, together with glycogen-supported metabolic plasticity — dampens therapy-induced ROS and reduces cisplatin cytotoxicity. Recent studies show that inhibiting NRF2 can resensitise KEAP1-mutant tumours to cisplatin, and ferroptosis-based strategies targeting GPX4/SLC7A11 are under active exploration in OC.[8,15-18] This highlights the urgent need for a comprehensive exploration of OCCC's molecular landscape in order to identify novel therapeutic strategies.[19]

The current narrative review was planned to elucidate the complex interplay between oxidative stress and cisplatin resistance, with a particular focus on the influence of OCCC's unique gene expression profile on ROS dynamics. The target was to critically appraise ROS quantification in OCCC models — chemical probes ((2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA), Amplex Red, mitochondria-targetted hydroethidine (MitoSOX)), genetically encoded sensors ((a genetically encoded hydrogen peroxide, H_2O_2, sensor); redox-sensitive green fluorescent protein 2-yeast oxidant receptor peroxidase 1 (roGFP2-Orp1), including two-photon readouts), and electron paramagnetic resonance (EPR) spin trapping — following the Nature Metabolism best-practice consensus and 2024-25 updates on calibration, specificity and compartmental targetting, to de-risk artifacts and prioritise redox-targettable vulnerabilities.[20]

Materials and Methods

The narrative review comprised an extensive literature search across multiple databases, with particular emphasis on PubMed, using key words such as "reactive oxygen species (ROS)", "ovarian clear cell carcinoma", "ovarian neoplasms", "drug resistance, neoplasm", and "gene".

The retrieved articles were screened, with their titles and abstracts carefully assessed against predefined inclusion

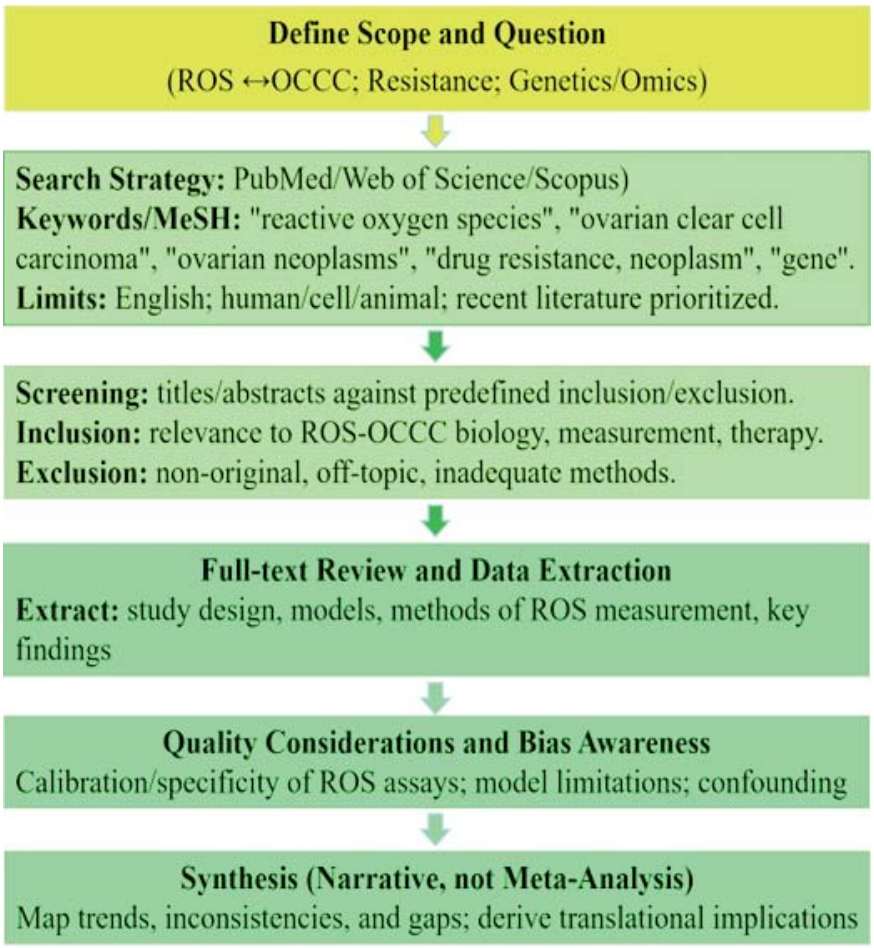

Figure-1: Workflow related t literature search for the review.

and exclusion criteria. Articles were included if they were relevant to the biology, measurement, or therapeutic targetting of ROS in OCCC. Articles were excluded if they were non-original, off-topic, or based on inadequate methods.

Subsequently, the selected studies were subjected to a comprehensive review. Key findings, methodologies and conclusions were extracted from each study, with particular attention given to identifying any discrepancies or inconsistencies among the studies.

The results and conclusions from the most recent and relevant studies were synthesised, highlighting trends, gaps and controversies within the field (Figure 1). This synthesis facilitated the development of insights and recommendations for future research directions, with- a particular focus on the role of ROS and genetic factors in ovarian clear cell carcinoma.

Results and Discussion

Relationship between oxidative stress and cisplatin resistance: The complex mechanisms underlying cisplatin resistance in ovarian cancer cells encompass DNA damage repair, cellular metabolism, oxidative stress response, cell cycle regulation, and tumorigenesis.[21]

Cisplatin, a platinum-based chemotherapeutic agent, exerts cytotoxic effects by forming DNA-protein and DNA-DNA interstrand and intrastrand crosslinks through interaction with the N7 atom of purine bases (particularly guanine) in DNA (Figure 2A).[22] This mode of action impedes DNA synthesis and replication, leading to cell cycle arrest and eventual apoptosis. However, in rapidly proliferating cancer cells, crosslink formation exacerbates DNA damage. While repair mechanisms may resolve minor lesions, extensive damage can result in irreversible harm and cell death (Figure 2B). The inherent inertness of cisplatin requires activation through hydration reactions to produce highly reactive mono-aqueous and diaqueous forms.[13] These reactive forms bind strongly to endogenous nucleophilic moieties, such as reduced glutathione (GSH), methionine and metallothioneins, resulting in elevated levels of ROS and inducing oxidative stress, while simultaneously limiting the bioavailability of active cisplatin (Figure 2A).[23] Beyond forming nuclear

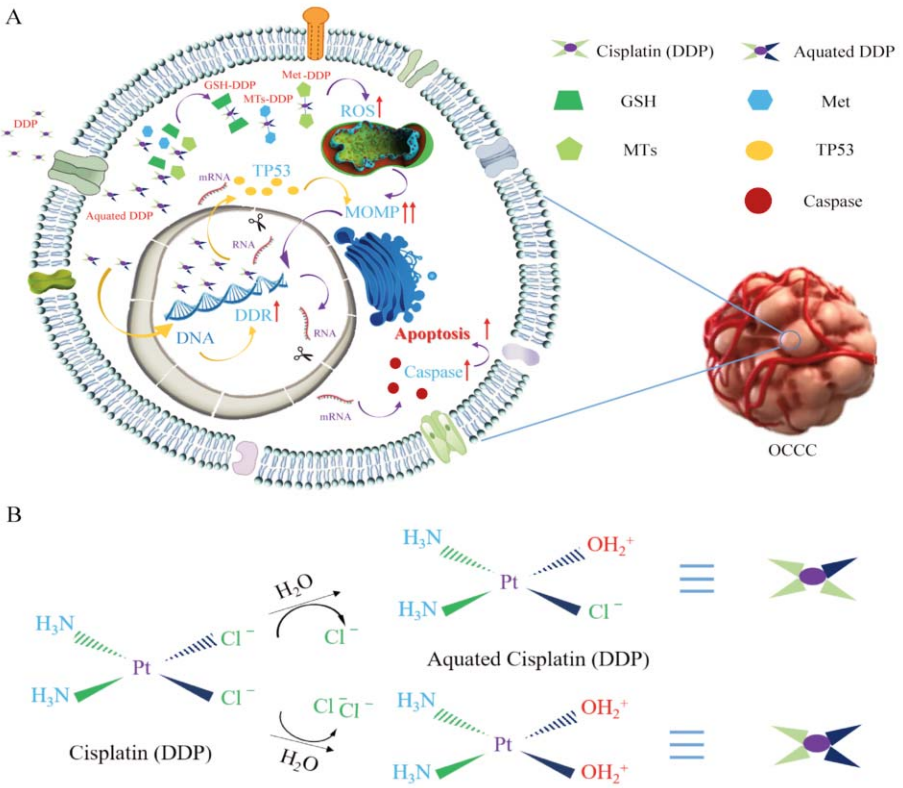

Figure-2: The therapeutic mechanisms of cisplatin in OCCC.
(A) The process by which cisplatin activates ROS in OCCC. (B) The intracellular hydrolysis process of cisplatin under low chloride ion conditions.
GSH: Glutathione, Met: Methionine, MTs: Metallothioneins, TP53: Tumour protein 53, Caspase: Cysteine-aspartate specific protease, which plays an essential role in programmed cell death (apoptosis) and inflammation, OCCC: Ovarian clear cell carcinoma.

DNA adducts, cisplatin directly perturbs mitochondria: it elevates mitochondrial superoxide/hydrogen peroxide, collapses the mitochondrial membrane potential (Δψm), promotes Bcl-2–associated X protein (BAX) / Bcl-2 homologous antagonist/killer (BAK)-dependent outer-membrane permeabilisation, and releases cytochrome c to activate the caspase-9/-3 cascade — hallmarks of the intrinsic apoptotic pathway. Recent ovarian-cancer studies report cisplatin-triggered mitochondrial ROS and caspase-9 cleavage, and show that agents which intensify mitochondrial dysfunction further sensitise platinum-resistant epithelial ovarian cancer to apoptosis.[24,25]

Effects of OCCC unique gene expression on ROS: Multiple contemporary datasets indicate that OCCC rewires ROS-handling programmes. Clinically oriented reviews highlight constitutive activation of antioxidant/phase-II detoxification modules (e.g., NRF2-dependent NAD(P)H:quinone oxidoreductase 1 (NQO1)/heme oxygenase-1 (HO-1)/glutathione S-transferase (GST) axes), enrichment of metabolic states that favour GSH sufficiency, and co-occurrence of AT-rich interaction domain 1A (ARID1A) loss with PI3K pathway activation that together remodel redox metabolism and therapy response.[7,26,27] Notably, therapeutically 'targeting hepatocyte nuclear factor-1β (HNF1B)' — a lineage transcription factor highly expressed in OCCC — has resurfaced in 2024-25 reviews as a strategy precisely because of its links to GSH-centred anti-oxidant programmes and platinum tolerance.[7,26] The pathogenesis of OCCC commonly involves dysregulation of genes related to ROS metabolism, with recent studies highlighting OCCC's ability to confer resistance to ROS through various mechanisms (Figure 3).[28-36] This resistance promotes tolerance to oxidative stress, thereby facilitating tumour cell proliferation and enhancing resistance to cisplatin chemotherapy.

Pyruvate dehydrogenase kinase-2 (PDK2): In mitochondria, pyruvate-derived acetyl-coenzyme A (CoA)

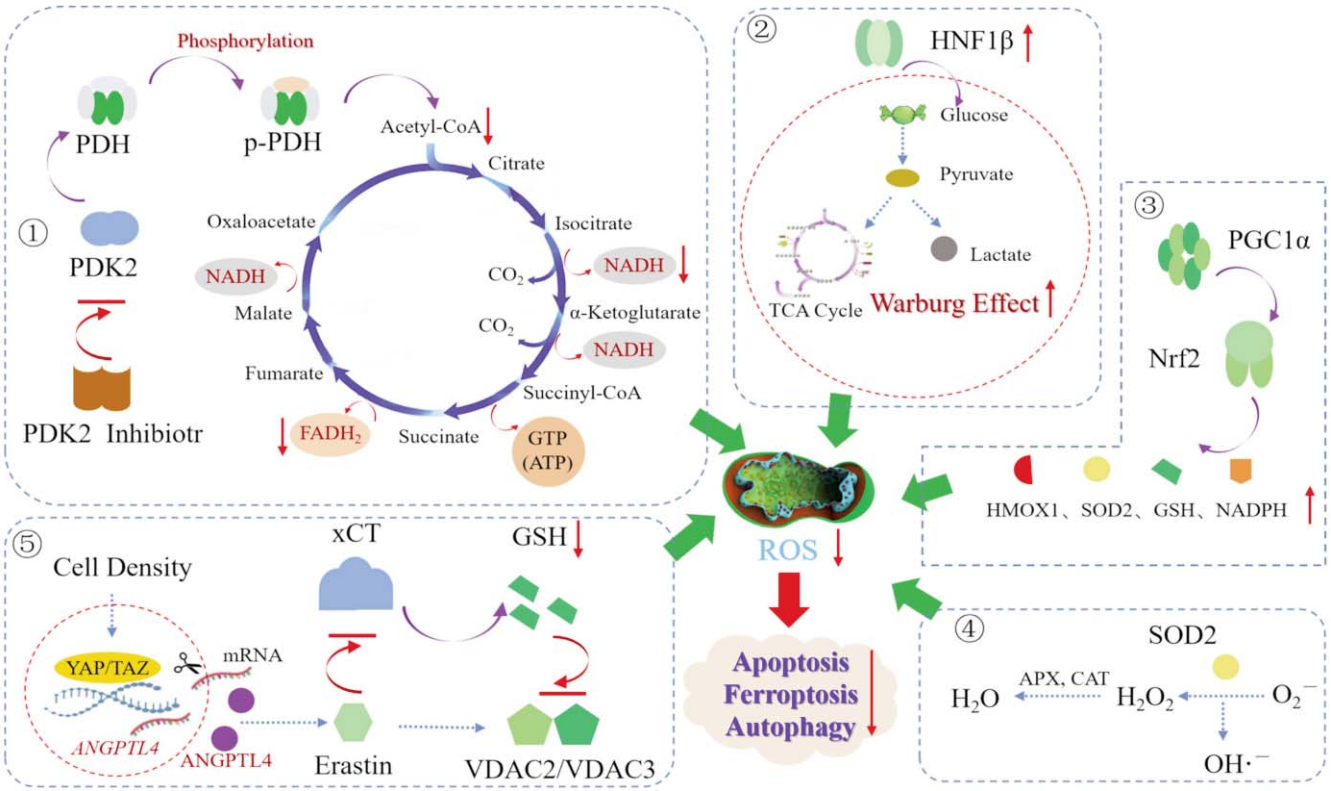

Figure-3: The impact of multifactorial gene expression on ROS resistance in OCCC.

PDK2: Pyruvate dehydrogenase kinase-2, PDH: Pyruvate dehydrogenase, p-PDH: Phosphorylated pyruvate dehydrogenase, NADH: Nicotinamide adenine dinucleotide, FADH2: Flavin adenine dinucleotide, HNF1β: Hepatocyte nuclear factor 1 beta, TCA: Tricarboxylic acid, PGC1α: Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha, Nrf2: Nuclear factor erythroid-2-related factor-2, HMOX1: Heme oxygenase 1, SOD2: Superoxide dismutase-2, GSH: Glutathione, NADPH: Nicotinamide adenine dinucleotide phosphate, APX: Ascorbate peroxidase, CAT: Catalase, YAP/TAZ: Yes-associated protein/transcriptional coactivator with postsynaptic density protein 95/discs large/zona occludens-1 (PDZ)-binding motif, ANGPTL4: Angiopoietin-like-4, Erastin: A ferroptosis inducer, xCT: Cystine/glutamate transporter, also known as solute carrier family 7 member 11 (SLC7A11), VDAC2/3: Voltage-dependent anion channel-2/3, ROS: Reactive oxygen species.

fuels the tricarboxylic-acid (TCA) cycle to generate reduced nicotinamide adenine dinucleotide (NADH) and reduced flavin adenine dinucleotide (FADH2) that donate electrons to the respiratory chain; electron leak at defined electron transport chain (ETC) sites produces superoxide/hydrogen peroxide, primarily at complexes I and III under physiologic and stress conditions. Recent work quantifies context-dependent ETC-ROS, including high-flux ROS from reverse electron transfer (RET) at complex I's Q-site and sustained output from complex III.[37-39] This data provides a mechanistic basis for how shifts in mitochondrial electron flow — such as those induced by cisplatin or by metabolic rewiring — translate into measurable ROS burdens. These reducing equivalents transfer electrons along the electron transport chain, leading to the reduction of molecular oxygen (O_2). During this process, a portion of O2 is converted into superoxide anion (O_2–) or hydrogen peroxide (H_2O_2), with O_2– being the primary precursor of ROS. Regulation of carbon flux through the TCA cycle and electron flux through the mitochondrial respiratory chain can modulate mitochondrial ROS production.[40]

The enzyme PDK2 plays a crucial role in regulating metabolic flux within the TCA cycle. By phosphorylating serine 293 (Ser293) on the E1 alpha (E1α) subunit of pyruvate dehydrogenase, PDK2 inhibits the conversion of pyruvate to acetyl-CoA, reducing the production of NADH and FADH2 and subsequently decreasing ROS production in the TCA cycle.[28] In OCCC and broader epithelial ovarian cancer models, activation of the pyruvate-dehydrogenase kinase (PDK) axis inhibits dehydrogenase (PDH) (E1α-Ser293 phosphorylation), diverts pyruvate away from oxidative metabolism, lowers mitochondrial electron flux and ROS formation, and thereby blunts cisplatin-elicited mitochondrial apoptosis. Functionally, phospho-PDH is elevated in cisplatin-resistant cells, and pharmacologic PDK inhibition with dichloroacetate (DCA) restores oxidative metabolism, increases mitochondrial ROS, and re-sensitises cells to cisplatin.[41,42] These observations support a model in which co-targetting PDK with platinum augments apoptotic commitment in resistant ovarian cancer. Moreover, combination therapy involving PDK2 inhibitors and cisplatin has been shown to decrease mitochondrial membrane potential, thus increasing mitochondrial ROS production and promoting apoptosis. PDK2 is also closely associated with hypoxia-inducible factor 1 alpha (HIF-1α), a molecule overexpressed in OCCC.29 A study suggests that mutations in mitochondrial NADH dehydrogenase subunit 2 (ND2) enhance pyruvate generation, thereby elevating ROS levels, upregulating PDK2, and promoting HIF-1α accumulation.[43] Furthermore, fibroblast growth factor-11 (FGF11) has been implicated in promoting platinum resistance in OCCC through modulation of HIF-1α.[44]

Hepatocyte nuclear factor 1 beta (HNF1β): HNF1B/ transcription factor 2 (TCF2)) is a lineage-defining transcription factor for OCCC. Recent disease overviews reaffirm its diagnostic utility and its role in transcriptional programmes that reshape metabolism and stress responses; in OCCC, HNF1B cooperates with related hepatocyte-nuclear-factor family members to regulate target genes implicated in redox buffering and drug tolerance.[7,45] Its pronounced overexpression in most OCCC cases, contrasted with its low or negligible expression in other EOC subtypes, positions HNF1β as a sensitive and specific marker for OCCC.[30] Previous studies have demonstrated elevated mitochondrial respiration rates in OCCC-derived OC cell lines compared to other tissue types, with HNF1β playing a key role in this metabolic phenotype.[46] Under hypoxic conditions, OCCC cells with high HNF1β expression exhibit enhanced survival and resistance to cisplatin. Notably, the survival advantage of HNF1β-overexpressing OCCC cells is significantly reduced under hypoglycaemic conditions, highlighting their dependence on glucose uptake for survival. HNF1β reduces oxidative phosphorylation by promoting glycolysis independently, thus limiting ROS production and conferring resistance to oxidative stress in OCCC cells.[46]

In most cancers, glucose transport and metabolism are robustly upregulated, irrespective of oxygen availability, a phenomenon known as the Warburg effect. Cancer cells frequently express the M2 isoform of pyruvate kinase (PKM2), which catalyses the conversion of phosphoenolpyruvate to pyruvate. Regulation of PKM2 activity can promote the accumulation and diversion of upstream glycolytic intermediates into biosynthetic pathways, including the pentose phosphate pathway. These intermediates are then channelled into biosynthetic pathways like the pentose phosphate pathway, promoting NADPH production and facilitating an optimal reduction-oxidation (REDOX) state crucial for cancer cell survival.[32] Moreover, HNF1β reduces ROS levels via mechanisms beyond the Warburg effect, including enhancing GSH activity, regulating the cystine transporter solute carrier family-3 member-1 (SLC3A1) in GSH synthesis, and promoting glucose uptake through glucose transporter-1 (GLUT1) in OCCC cell lines.[31] Hence, targetting HNF1β in future therapeutic strategies may hold significant promise for OCCC treatment.

Nuclear factor erythroid-2-related factor-2 (NRF2): The ubiquitin-proteasome system (UPS) is crucial for maintaining cellular homeostasis by modulating proteins

involved in signal transduction and cell cycle regulation.[47] Inhibition of the proteasome can lead to the accumulation of pro-apoptotic proteins, triggering apoptosis in tumour cells. A study has emphasised the importance of proteasome function in drug resistance, suggesting that enhancing proteasome activity is vital for tumour cell survival.[48] Maintaining mitochondrial REDOX homeostasis is essential for optimal proteasome function, as excessive ROS production compromises UPS activity. The transcription factor NRF2 governs the expression of mature proteasome proteins, thereby conferring resistance to proteasome inhibitors and promoting tumour cell survival.[49] NRF2 plays a central role in the antioxidant response element transcription complex, regulating the expression of various protective genes.

Research has shown that NRF2 is overexpressed in OCCC, where it reduces mitochondrial ROS production by upregulating heme oxygenase and the primary mitochondrial antioxidant enzyme SOD2, enhancing proteasome activity and fostering tumour resistance.[32] Additionally, NRF2 expression correlates with the activity of peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC1α), which synergistically participates in antioxidant responses. PGC1α expression is significantly higher in OCCC compared to other cell lines.[50] Therefore, investigating the regulatory roles of PGC1α and NRF2 in proteasome function and mitochondrial homeostasis may provide valuable insights into overcoming drug resistance in OC.

Superoxide dismutase-2 (SOD2): The enzyme SOD2, which is dependent on manganese, is significantly upregulated in OCCC compared to other histological subtypes of EOC, and it plays a pivotal role in the pathogenesis of OCCC. SOD2 functions in a dual capacity within the OCCC biology: firstly, by facilitating cell proliferation, clonogenicity and tumour growth through the mitigation of ROS-induced cellular damage; and, secondly, by modulating OCCC migration and metastasis through regulation of H_2O_2 homeostasis.[33] SOD2 serves as a crucial endogenous antioxidant by converting O_2- into H_2O_2 and O_2, maintaining cellular REDOX balance. An elevation in H_2O_2 levels is closely correlated with increased SOD2 expression. Previous studies have highlighted the role of H_2O_2 in cellular migration.[51] Paradoxically, cells with elevated SOD2 expression and increased H_2O_2 levels exhibit greater susceptibility to exogenous REDOX stressors, potentially reaching cytotoxic thresholds upon exposure to external ROS. This phenomenon triggers tumour cell death via multiple pathways, including apoptosis, DNA damage, and mitochondrial dysfunction.[52] Based on this premise, high-dose ascorbic acid has been proposed as a promising strategy to enhance chemotherapy sensitivity in OC, by generating localised H_2O_2 and mitigating chemotherapy-associated toxicity.[53] Although the study did not exclusively focus on OCCC, the high SOD2 expression characteristic of this subtype suggested the potential efficacy of such therapies. Future investigations should explore the utility of high-dose ascorbate in managing OCCC.

The postsynaptic density protein 95/discs large/zona occludens-1 (PDZ)-binding motif-angiopoietin-like 4-nicotinamide adenine dinucleotide phosphate oxidase-2 (TAZ-ANGPTL4-NOX2) Axis: Iron-dependent cell death, known as ferroptosis, has gained significant attention due to its association with lipid peroxidation induced by ROS. The small molecule Erastin has emerged as a potent inducer of ferroptosis by depleting intracellular GSH, disrupting cystine influx, and inducing REDOX imbalances.[54] Notably, OCCC cells are particularly sensitive to ferroptotic cell death, with sensitivity being modulated by cell density. Low-density OCCC cells exhibit heightened susceptibility to Erastin-induced ferroptosis.[34] The density-dependent behaviour of cancer cells is regulated by the Hippo signalling pathway, with Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) serving as key effectors. Elevated TAZ expression reduces cell density and enhances susceptibility to ferroptotic death. Mechanistically, TAZ regulates ferroptosis through activation of angiopoietin-like-4 (ANGPTL4), which stimulates ROS generation by inducing NADPH oxidase-2 (NOX2), culminating in ferroptotic cell death.[34,36] These findings suggest that TAZ activation could serve as a predictive biomarker for OCCC, and targetting the TAZ-ANGPTL4-NOX2 axis may offer novel therapeutic strategies. Furthermore, leveraging TAZ activation for diagnostic assays holds potential for advancing OCCC screening in the future.

While the current narrative has elucidated the role of ROS metabolism-related genes in mediating cisplatin resistance, there are several limitations that must be acknowledged. The molecular heterogeneity of OCCC may lead to variations in resistance mechanisms, necessitating further characterisation of molecular subtypes. The lack of clinical trials targetting ROS metabolism-related pathways underscores the need for translational research to evaluate the efficacy of targetting therapies. The complex interplay between oxidative stress, DNA repair, and cell cycle regulation requires further investigation using systems biology approaches. Additionally, the clinical utility of potential

biomarkers, such as HNF1β and PDK2, needs further validation. Lastly, the efficacy of high-dose ascorbate in clinical settings remains to be determined.

Future research should prioritise the development of targetted therapies and biomarkers to improve clinical outcomes for OCCC patients. Addressing these limitations will be crucial for advancing the management and prognosis of this aggressive OC subtype.

Conclusion

Characterised by its inherent resistance to oxidative stress, OCCC diminishes the efficacy of traditional chemotherapy. The review elucidated the role of ROS metabolism-related genes in mediating cisplatin resistance, highlighting the influence of OCCC's unique gene expression profile on ROS dynamics. It examined current methodologies for ROS detection and discussed potential insights that may facilitate the identification of novel therapeutic targets.

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