Targeting Nrf2 may reverse the drug resistance in ovarian cancer

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Abstract

Background: Acquired resistance to therapeutic drugs has become an important issue in treating ovarian cancer. Studies have shown that the prevalent chemotherapy resistance (cisplatin, paclitaxel etc.) for ovarian cancer occurs partly because of decreased production of reactive oxygen species within the mitochondria of ovarian cancer cells.

Main Body: Nuclear erythroid-related factor-2 (Nrf2) mainly controls the regulation of transcription of genes through the Keap1-Nrf2-ARE signaling pathway and protects cells by fighting oxidative stress and defending against harmful substances. This protective effect is reflected in the promotion of tumor cell growth and their resistance to chemotherapy drugs. Therefore, inhibition of the Nrf2 pathway may reverse drug resistance. In this review, we describe the functions of Nrf2 in drug resistance based on Nrf2-associated signaling pathways determined in previous studies.

Conclusions: Further studies on the relevant mechanisms of Nrf2 may help improve the outcomes of ovarian cancer therapy.

Keywords: Nrf2, Drug resistance, Reactive oxidative stress, Ovarian cancer

Background

Malignant ovarian tumors are one of the most common malignant tumors of the female reproductive organ. Among them, ovarian epithelial cancer has the highest mortality rate, posing a serious threat to women’s life. Early stage ovarian tumors are usually located deep inside the pelvis, exhibit no typical symptoms and are thus discovered only at the advanced stage. The treatment options for advanced ovarian cancer are usually cytoreductive surgery and chemotherapy. However, the current chemoresistance in ovarian cancer (OC) has become a key cause of treatment failure and OC-related deaths [1]. Although extensive research has been carried out on complex factors, including increased drug efflux, drug inactivation, alteration in drug target, and increased DNA repair, the existing mechanisms fail to completely account for the drug resistance in OC [2, 3]. In recent years, the level of oxygen species (ROS) has also been reported to play a vital role in the development of drug resistance in OC, and thus targeting ROS levels may be a promising strategy to conquer cancer chemoresistance.

Oxidative stress refers to the process of oxidative damage caused by an imbalance between the production and scavenging of oxygen free radicals in the body or cells, resulting in the accumulation of ROS and RNS in the body or cells. Increased ROS levels activate relevant signaling pathways, inhibit the function of tumor suppressor genes, and induce oncogenic mutations, ultimately leading to tumorigenesis [4, 5]. Moreover, the significance of elevated ROS lies in facilitating genomic instability and DNA damage in tumors with drug resistance and recurrence [6, 7]. Consequently, more researches on ROS regulation would assist us to overcome drug resistance in OC.

Nrf2 exerts a modifying influence on cellular oxidative stress response. At the same time, by modulating the...
expression of antioxidant genes, Nrf2 can help prevent cell damage from ROS and electrophiles and keep the balance of intracellular redox homeostasis [8, 9]. Conversely, findings from previous studies suggest that continuous activation of antioxidant Nrf2 may be beneficial to the growth of cancer cells, and may become a way for cancer cells to escape the attack of chemotherapy drugs, providing conditions for cancer cells to develop drug resistance [7, 10–12]. Accordingly, the purpose of this review is to review recent research on Nrf2-related drug resistance and mechanisms in OC to provide reference for clinical treatment.

Nrf2 and ROS

ROS regulation in OC

Recently, several studies showed that the generation of ROS is associated with drug resistance [13–16]. On the one hand that ROS mediate cytotoxicity induced by drugs in tumor cells. On the other hand, cancer cells are surrounded by antioxidant molecules to keep ROS in the tumor microenvironment (TME), which contributes to the maintenance of drug resistance in OC [17]. This phenomenon may be caused by the different concentrations of ROS in cancer cells [18]. Usually, at low levels, ROS stimulate cell proliferation and survival in the form of mitogens [19, 20]. At medium levels, ROS may hinder the cell cycle process at varying degrees and induce cell differentiation [21]. At high levels, ROS might impair fundamental cellular substances such as proteins, DNAs, RNAs, and cause gene mutations—inhition of tumor suppressor genes (P53, PTEN) and activation of oncogenes (K-ras, ERK, AKT), resulting in tumorigenesis in normal cells or multidrug resistance in cancers [18]. Consistently, Meng et al. and Dharmaraja et al. have identified that platinum-resistant OC cells can maintain steady high levels of ROS, which results in DNA damage [13, 22, 23]. In addition, several studies have indicated that in the TME, hypoxia-induced ROS cause cisplatin resistance by downregulating p-Drp1 (Ser637) and Mfn1 in OC cells [15, 16]. Common radio- and chemotherapeutic agents affect tumor outcome by modulating ROS; therefore, the impact of ROS modulation is essential for cancer treatment.

Nrf2 regulation in OC

Nrf2 is a member of the Cap-n-Collar (CNC) regulatory protein family and is a transcription factor with a highly conserved basic leucine zipper structure. Nrf2 is a regulatory protein containing seven domains, Neh1–7, and has diverse features (Fig. 1). The Neh1 domain consists of the CNC-bZIP region, in which DNA binds to sMaf proteins as Nrf2 dimerization partners [24, 25]. The Neh2 domain contains two sites, namely DLG and ETGE, which combine with the cytoplasmic protein Keap1, a negative regulator of Nrf2 transcriptional activity [26]. Neh3–5 can bind to coactivating factors and are transactivating structural domains of Nrf2 [27, 28]. Neh6 is a serine-rich region associated with the negative regulation of Nrf2 stability, which relies on Keap1 [29]. Neh7 containing the retinoid X receptor inhibits the transcriptional activity of Nrf2 [30].

![Fig. 1 Structure of the human Nrf2 protein. The Neh1 domain consists of the CNC-bZIP region, in which DNA binds the sMaf proteins as Nrf2 dimerization partners. The Neh2 domain contains two sites, namely DLG and ETGE, which combine with the cytoplasmic protein Keap1, a negative regulator of Nrf2 transcriptional activity. Neh3–5 can bind to coactivating factors and are transactivating structural domains of Nrf2. Neh6 is a serine-rich region associated with the negative regulation of Nrf2 stability, which relies on Keap1. Neh7 containing the retinoid X receptor inhibits the transcriptional activity of Nrf2.](image)
Under physiological conditions, Nrf2 is anchored in the cytoplasm by Keap1 as a substrate for the cullin 3-dependent E3 ubiquitin ligase complex and can induce ubiquitination and promptly degrade Nrf2 via the proteasome. However, when ROS or electrophiles attack cells, Nrf2 detaches from Keap1 and is rapidly translocated into the nucleus, forming a heterodimer with the sMaf protein and then integrating with the ARE, thereby transcriptionally activating Nrf2-regulated antioxidant gene expression including HO-1, NQO1, GCL, PRDX, and SOD to exert anti-oxidative effects (Fig. 2). Nrf2 has a short half-life of around 10–30 min, and thus the high turnover of Nrf2 induced by Keap1 maintains ultra-low levels of Nrf2 [31, 32]. The protein products of these genes mediate detoxication through glutathione coupling and participate in ATP-dependent drug efflux, which may be involved with cisplatin resistance in OC [33]. High levels of Nrf2 provide a protective environment in both normal and cancer cells.

Excessive activation of Nrf2 is considered as an intermediate link in cell proliferation and causes drug resistance in cancer therapy as well [34–36]. To be specific, Nrf2 activation and Keap1 inactivation mutations are the precursors of permanent constitutive activation of the Nrf2-dependent AR pathway, which is frequently observed in cancer. Besides, anti-cancer radiation and chemotherapies, rely heavily on the production of ROS to induce cytotoxicity [37–39]. Hence, excessive activation of the Nrf2-dependent AR pathway will reduce the effectiveness of such treatments [40, 41].

A clinical study has indicated that high cytoplasmic Nrf2 expression (the inactivated form of Nrf2) in serous carcinoma subtypes is associated with longer survival (p < 0.05), which appears to correlate with high ERα expression (p < 0.05) [42]. The same team found that Nrf2 expression in the cytoplasm was positively correlated with PR expression (p < 0.05) [43]. Furthermore, a retrospective study of the relationship between Nrf2 expression and clinical prognosis in 108 patients with different subtypes of OC showed that a high expression of Nrf2 in OC indicates short DFS (HR: 2.084; 95% CI: 1.229–3.536) and OS (HR: 2.487; 95% CI: 1.443–4.286) [44]. Konstantinopoulos et al. found that among 64 advanced EOC patients, the upregulation of Nrf2 promoted cisplatin
resistance in OC patients and was associated with a short OS (P < 0.05) [45]. However, another study showed that chemoresistance is not significantly correlated with Nrf2 expression, although patients with low Nrf2 expression have higher recurrence rates and death rates than patients with high Nrf2 expression. [46] Hence, further studies on the relationships between clinical prognosis and Nrf2 expression, as well as relevant drug resistance mechanisms related to Nrf2, are needed.

**Effect of Nrf2 on treatments for OC**

Oncogenic mutations in OC may promote drug resistance by activating Nrf2

Disorder of Nrf2/Keap1 caused by mutation and activation of up-stream oncogenes is associated with nuclear transportation and constitutive activation of Nrf2. Gina et al. have confirmed that oncogenic mutations in primary murine cells, such as Kras, Braf and Myc, separately increased the constitutive transcription of Nrf2 to stabilize the basal Nrf2 level and hence reduce intracellular ROS, ultimately causing cells to escape from apoptosis and promoting tumorigenesis, metastasis and chemoresistance [9, 47]. In view of the relationship of ROS and Nrf2 with tumorigenesis, Nrf2 appears to be a significant target for cancer treatment.

**Role of Nrf2 in ROS-mediated therapy resistance in OC**

**Role of Nrf2 in ROS-mediated cisplatin resistance in OC**

As mentioned earlier, ROS play an indispensable role in the development of drug resistance. As the main antioxidant regulator, Nrf2, which is involved in ROS detoxification, tightly regulates drug resistance of tumors. It has been reported that during oxidative stress, as the transcription target of Nrf2, p62/SQSTM1 competes with Nrf2 for binding to Keap1 and forms a positive feedback loop between p62 and Nrf2 [48]. Xia et al. showed that overexpressed p62 may protect cells from vitamin K3-induced ROS generation by up-regulating antioxidant genes downstream of Nrf2, including HO-1 and NQO1, in OC [49]. Additionally, recent cases reported by Wu et al. also support the hypothesis that overexpression of CD99, a significant downstream gene of Nrf2, facilitates Nrf2-mediated cisplatin resistance in OC [50, 51]. Bao et al. suggested that low levels of Nrf2 suppressed the expression of ABCF2 and enhanced cisplatin sensitivity in OC cells by mediating the drug efflux pump mechanism [52]. Chen et al. argued that knockdown of Nrf2 in the SKVO3 cell line increased the production of ROS induced by cisplatin by increasing the phosphorylation level of p38-JNK. This subsequently led to elevation of ATF2 levels, followed by decreased expression of AKR1C1, which is involved in apoptosis, ultimately promoting the sensitivity of OC to cisplatin [53]. It was recently reported that activation of Nrf2 promotes activation of its downstream gene AKR1C1, which converts progesterone to an inactive form and promotes platinum resistance in ovarian cancer, while metformin reverses this process by increasing PR expression [54]. Mechanistically, Sun et al. found that SIRT5 contributes to the cisplatin resistance of OC by inhibiting cisplatin-mediated DNA damage via ROS through Nrf2 pathway modulation [55]. SLC40A1, as a novel iron metabolism-associated gene, serves as the only iron exporter gene with several putative Nrf2 binding sites. Wu et al. found that Nrf2 is highly expressed in cisplatin-resistant OC cells. Significantly increased gene expression of SLC40A1, a transferrin that inhibits Nrf2 translocation into the nucleus, reverses iron overload—induced cisplatin resistance in OC cells [56].

**Molecular factors involved in Nrf2 regulation contribute to paclitaxel resistance**

Paclitaxel is a first-line adjuvant drug for the treatment of OC, but only about half of OC patients respond to it [57, 58]. It is a new anti-microtubule drug that promotes tubulin polymerization to inhibit depolymerization, keeps tubulin stable, and inhibits cell mitosis. These different mechanisms cause a cascade of toxic effects in OC, such as the reduction of Δψm or elevation of ROS, which will eventually lead to cell death [59]. Enhancing the sensitivity of OC patients to paclitaxel is of great significance to improve prognosis. Stimulation of NADPH oxidase to accumulate ROS is an important part of paclitaxel cytotoxicity in cancer cells [60, 61]. Woo et al. held the view that inhibition of Nrf2 can enhance the chemosensitivity of cancer cells to paclitaxel [62]. We have reason to believe that targeting Nrf2 levels in OC cells may play an important role in overcoming paclitaxel resistance.

**Role of Nrf2 in ROS-mediated PARP inhibitor sensitivity in OC**

At present, under the condition of platinum resistance in OC, PARPi have shown encouraging effects in the first [63–65] and second-line [66, 67] maintenance therapy for patients with BRCA1/2 mutation and HRD [68]. Cells with HRD must depend on the replaceable mechanisms of NHEJ and BER, both of which require PARP enzymes [69]. BRCA1/2 mutant cancer cells may develop PARPi resistance by restoring HR repair and/or protecting replication forks [70].

Mitochondrial metabolism and ROS production cause DNA oxidative damage and genomic instability in cancers [71]. HRD OC cells require high levels of NAD+ and ATP to power PARP-dependent DNA repair [72]. Besides, some scholars have found that PARPi enhanced the effect of Nrf2 inhibitors in BRCA1-mutant OC cells without fear of side effects from the combination of Nrf2 inhibitors with chemotherapeutics [73]. From the above
findings, we can speculate that Nrf2 may play an irreplaceable role in PARPi repair of ROS-DNA oxidative damage.

Role of Nrf2 in ROS-mediated pertuzumab and trastuzumab resistance in OC
Several studies have proved that HER2/HER3, Nrf2, and ROS play a key role in promoting growth and drug resistance in cancer cells [74–79]. Specifically, as a key regulator of the Nrf2 pathway, ROS can regulate the HER2/HER3 complex and activate its function. When pertuzumab and trastuzumab, which target HER2/HER3 receptors, are used to treat with OC cell lines, Nrf2 inhibition suppress the Nrf2-dependent antioxidant response pathway, thereby allowing OC cells to overcome resistance to monoclonal antibodies. Khalil et al. proved that Nrf2 is a key factor driving the drug resistance in OC; this provides a new treatment idea in the sensitization of OC to immune targeted therapy [80].

Nrf2 inhibition increases the sensitivity of OC cells to adriamycin, one of the chemicals used in the treatment of OC [81]. Besides, Nrf2 modulates the sensitivity of OC cells to lapatinib and erlotinib by regulating the HER1 receptor [82].

Role of Nrf2 in ROS-mediated Mppa-PDT resistance in OC
PDT is a new type of tumor treatment method that has emerged in response to the development of medicine. It uses a photosensitizer that specifically accumulates in tumor tissues—currently, Mppa has a wide range of clinical application prospects due to its good absorption, high energy density, and strong permeability [83, 84]. It is activated under a specific wavelength of light, and a complex photochemical reaction occurs to generate ROS, which lead to irreversible tumor damage [85–87]. According to a previous research, Nrf2 silencing enhanced PDT sensitivity in breast, colon, renal, and glioblastoma cancer cells based on Mppa, which can increase the accumulation of photosensitizers by down-regulating ABCG2, thereby promoting the production of ROS [88]. Coincidentally, Tian et al. found that the inhibition of Nrf2-ABCG2 / HO-1 signaling increased ROS levels by attenuating antioxidants or pumping Mppa out of OC cells—suggesting that Nrf2-ABCG2 signaling might be involved in the intrinsic resistance to Mppa-PDT [89].

Role of Nrf2 in ROS-mediated ferroptosis resistance in OC
Ferroptosis is a novel mode of cell death first discovered by Dixon et al. in 2012 that is, associated with unique morphological structure, biochemical, and genetic manifestations; it is essentially oxidative damage caused by excessive accumulation of iron ion-dependent lipid peroxidation products, mainly mitochondrial alterations [90]. Under normal conditions, Nrf2 remains inactive; when induced by ROS stimulation or electrophile substances, Nrf2 changes its molecular conformation and activates downstream antioxidant enzymes to play the role of an antioxidant and inhibit cellular ferroptosis [91]. There are two pathways to synthesize glutathione, which plays an essential role in combating oxidative stress, reducing lipid peroxidation, and protecting tissue cells,—in tumor cells: (a) The classical XC-system: the key factor is SLC7A11; and (b) Reverse transsulfuration pathway, and the key enzyme in this pathway is CBS; The above pathways can be activated by the ability of GPx4 to specifically convert highly toxic lipid hydrogen peroxide to non-toxic lipid alcohols, breaking down hydrogen peroxide to water, and its inactivation can induce excessive production of lipid ROS, which can contribute to ferroptosis. It has been reported that GPx4 is an Nrf2 downstream gene and that Nrf2 upregulation or GPX4 overexpression may be significantly associated with ferroptosis resistance in head and neck cancer, but this has not been confirmed in OC [92, 93]. In addition, Liu et al. showed that in OC, Nrf2 also causes erastin-induced ferroptosis resistance by activating CBS [94].

Natural inhibitors of Nrf2
Given that Nrf2 has a protective effect on tumors and can cause chemotherapy resistance, in recent years, many chemical substances and plant extracts have been reported to inhibit Nrf2 to confront the problem of drug resistance [95–100].

Brusatol, a quassinoid compound derived from Brucea javanica, is considered as a general translation inhibitor that results in decreased levels of short-lived proteins including Nrf2 [95]. For this reason, brusatol’s ability to overcome chemoresistance is compromised. Recently, Chen et al. isolated a plCSA-binding peptide from the malaria protein VAR2CSA, which effectively promotes the binding of brustol to OC, thus overcoming the drawback mentioned above [96]. In addition, Cucci et al. showed that ailanthone from Ailanthus altissima could significantly inhibit the expression of Nrf2 and YAP protein and subsequently inhibit the growth and colony formation of cisplatin-sensitive and cisplatin-resistant OC cells, and exert greater inhibitory effects on the migration of targeted cisplatin-resistant cells [97].

There are also some compounds that have not been proven in OC. Ascorbic acid, an inhibitor of Nrf2, partially restored cell sensitivity to imatinib by down-regulating Nrf2 and reducing the expression of y-GCSL and the level of glutathione [98], and increased the sensitivity of HeLa cells to cisplatin and adriamycin [99]. Apigenin, a flavonoid extracted from various vegetables and fruits, inhibits the Nrf2 pathway, thereby making
doxorubicin-resistant liver cancer cells sensitive to doxorubicin and increasing intracellular doxorubicin [100].

**Conclusions**

The Keap1-Nrf2-ARE system is a critical defense mechanism to protect cells from oxidative stress and electrophilic stress. While temporary Nrf2 activation during stress is advantageous for cell proliferation [101], sustained Nrf2 activation in cancer cells confers chemoresistance and aggressive tumorigenic activity, which has deleterious effects on the cancer patients [102–105]. Since Nrf2 increases the antioxidant and detoxification capacity of cancer cells, sustained high levels of Nrf2 activity can enhance therapeutic resistance of cancer cells. Nrf2 also drives metabolic reprogramming and cooperates with other oncogenic pathways to establish cellular metabolic processes that favor cell proliferation.

Most patients with OC treated by chemotherapy, immunotherapy, and molecular targeted therapy eventually develop resistance and show poor outcomes. In fact, there are many proteins that regulate the process of drug resistance in OC;—for example, downregulation of 14-3-3ζ, a key protein involved in ovarian development and gamete function [106–108], by RNA interference in OC cells results in enhanced sensitivity to cisplatin-induced cell death [109]. Meanwhile, multiple isoforms of 14-3-3 protein strongly interact with the cell cycle protein CDC25B, which is inactivated in Nrf2−/− cells, to regulate cell cycle in oocyte [110, 111]. Why did we choose to review Nrf2 as a key pivot in the regulation of drug resistance in OC? As described above, Nrf2, as the main regulator of the antioxidant response pathway, has received increasing attention for its significant effect in drug-resistant OC and thus, may be targeted for treating advanced OC. So far, several Nrf2 inhibitors have been used for overcoming drug resistance in OC. In addition to Nrf2 inhibitors, new potential therapeutic targets related to Nrf2 for overcoming drug resistance in OC are being identified (Fig. 3; Table 1). However, the mechanisms of Nrf2-associated drug resistance in

![Fig. 3 Various drug resistance mechanisms associated with Nrf2. SIRT5, CD99, ABCG2/HO-1, HER1, HER2/HER3, ABCF2, GPX4, AKR1C1, and CBS have a positive relationship with Nrf2 as molecules regulated by Nrf2 or regulating Nrf2, while ATF and SLC40A1 have a negative relationship with Nrf2. As the transcription target of Nrf2, p62/SQSTM1 competes with Nrf2 for binding with Keap1 and form a positive feedback loop between p62 and Nrf2. (→ represents "activation" — — means "inhibition").](image-url)
OC cells remain unclear and should therefore be further investigated. There is also a need to develop appropriate animal models to evaluate the therapeutic efficacy of Nrf2-related therapeutic targets in drug-resistant OC.

Besides active exploration and mechanistic research on therapeutic targets associated with Nrf2, studies for discovering diagnostic biomarkers and surrogate markers for refractory OC are also needed. For progress in diagnosis and treatment, further researches and technical improvements are required. Consequently, a thorough elucidation of the function of Nrf2 will help to improve the clinical diagnosis and prognosis of OC.

 Abbreviations
OC: Ovarian cancer; Nrf2: Nuclear erythroid-related factor-2; Keap-1: Kelch-like ECH-associated protein-1; sMaf: Small musculoaponeurotic fibrosarcoma; ROS: Reactive oxygen species; bZIP: Basic leucine zipper; HO-1: Heme oxygenase 1; NQO1: NAD(P)H dehydrogenase (quinone) 1; ABCG2: ATP-binding cassette, subfamily G, member 2; Keap-1: Kelch-like ECH-associated protein-1; SIRT5: Sirtuin 5; SLC40A1: Solute carrier family 40 member 1; TME: Tumor microenvironment; Mppa-PDT: Methyl pyropheophorbide- mediated photodynamic therapy; ABC: ATP-binding cassette; P-gp: P-glycoprotein; PARPi: Poly-ADP Ribose Polymerase inhibitors; HRD: Homologous recombination deficiency; CBS: Cystathionine β-synthase.

Acknowledgements
We thank Amanda, Editage (www.editage.cn), for English editing a draft of this manuscript.

Authors’ contributions
SZ and XC: conceptualization; DL: writing—original draft preparation; DLXH and FZ: writing—review and editing; SZ and XC: permission to submit. All authors read and approved the final manuscript.

Funding
Not applicable.

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