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Review Article

Updates of the role of oxidative stress in the pathogenesis of ovarian cancer

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HIGHLIGHTS

- Oxidative stress plays an essential role in the pathogenesis of ovarian cancer.
- Modulating the redox balance may have therapeutic value.
- Chemoresistant ovarian cancer cells have an even further elevated oxidative stress.
- Chemotherapy-induced mutations in redox enzymes may contribute to chemoresistance.

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ABSTRACT

Clinical and epidemiological investigations have provided evidence supporting the role of reactive oxygen species (ROS) and reactive nitrogen species (RNS), collectively known as oxidative stress, in the etiology of cancer. Exogenous factors such as chronic inflammation, infection and hypoxia are major sources of cellular oxidative stress. Specifically, oxidative stress plays an important role in the pathogenesis, neoangiogenesis, and dissemination of local or distant ovarian cancer, as it is known to induce phenotypic modifications of tumor cells by cross talk between tumor cells and the surrounding stroma. Subsequently, the biological significance of the relationship between oxidative stress markers and various stages of epithelial ovarian cancer highlights potential therapeutic interventions as well as provides urgently needed early detection biomarkers. In the light of our scientific research and the most recent experimental and clinical observations, this review provides the reader with up to date most relevant findings on the role of oxidative stress in the pathogenesis of ovarian cancer and the possible therapeutic implications.

Contents

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1. Ovarian cancer

Ovarian cancer is the fifth leading cause of cancer death; the leading cause of death from gynecologic malignancies, and the second most commonly diagnosed gynecologic malignancy; yet the underlying pathophysiology continues to be delineated [1]. The majority of advanced-stage tumors are of epithelial cell origin and can arise from serous, mucinous, or endometrioid cells on the surface epithelium of the ovary or the fallopian tube [1]. Surgical cytoreduction followed by platinum/taxane chemotherapy results in complete clinical response in 50–80% of patients with stage III and IV disease, but most will relapse within 18 months with chemoresistant disease [1]. Mortality rates for this type of malignancy are high because of a lack of an early-stage screening method, as well as the development of drug resistance [1].

Many cases of ovarian cancer continue to be described as de novo although several theories regarding its origination have been proposed. Some of these theories include 1) the incessant ovulation hypothesis, where ovarian surface epithelial cells are injured due to repeated ovulation leading to eventual transformation and malignancy, 2) the gonadotropin hypothesis describes overstimulation of ovarian surface epithelium through hormone receptors leading to malignant transformation, and 3) the cell of origin for most epithelial ovarian cancer is not originating in the ovary but rather coming from the fallopian tube and spreading to the ovary, and beyond [1–3]. Thus, the exact origin(s) and pathogenesis of ovarian cancer still remains under debate.

Recently, a revised model of epithelial ovarian carcinogenesis has been proposed that distinguishes more clearly between type I and type II tumors based on both molecular genetic findings and histopathologic studies [3]. Kurman and Shih describe a dualistic model of ovarian carcinogenesis where type I tumors develop from benign extraovarian precursor lesions that implant on the ovary are classified into three groups described as; endometriosis-related tumors (endometrioid, clear cell, and seromucinous), low-grade serous carcinomas, and then mucinous carcinomas and malignant Brenner tumors [3]. On the other hand, type II tumors develop from intraepithelial carcinomas in the fallopian tube, and involve both the ovary and extraovarian sites and are classified as high-grade serous carcinomas that can be further subdivided into morphologic and molecular subtypes [3].

The overwhelming majority of ovarian cancers are derived from ovarian surface epithelium. Metastasis is achieved through detachment of single cells or clusters of cells from the primary tumor followed by implantation on peritoneal mesothelial lining [4]. Unlike many other type of cancer, ovarian carcinomas rarely metastasize outside of the peritoneal cavity [5]. Additionally, the presence of spheroids in ascites is a contributing factor to not only metastasis but also to chemoresistance. Spheroid cells are also known as ovarian cancer stem cells that have numerous characteristics of cancer stem cells including self-renewal, the ability to produce differentiated progeny, increased expression of genes associated with cancer stem cells, higher invasiveness, migration potential, altered metabolism, and enhanced chemoresistance [4,6].

Ovarian cancer has also been characterized to manifest loss of function of the p53 gene due to mutations as well as other oncogenic pathways including retinoblastoma protein, the phosphatidylinositol 3 kinase (PI3K)/rat sarcoma viral oncogene pathways, and Notch signaling [1]. Moreover, ovarian cancer is associated with germline mutations in the *BRCA1* or *BRCA2* genes, affecting only 20–40% of patients, suggesting the possibility of the presence of unknown mutations in other genes [1]. Additional genetic variations, many of which have been identified in recent genome-wide association studies, have been hypothesized to act as low to moderate penetrant alleles, which contribute to ovarian cancer risk, as well as other diseases [7]. Several studies have been done to identify differentially expressed genes in ovarian carcinoma for diagnosis of early-stage ovarian cancer as well as the use of such markers as targets for improved therapy and treatment, although to date these have not yielded reproducible prognostic indicators for identification and clinical outcomes [1,8–10].

2. Oxidative stress

The imbalance between production and elimination of free radicals and reactive metabolites leads to a state of oxidative stress and subsequent damage of important biomolecules and cells, with potential impact on the whole organism [11]. Reactive oxygen species (ROS) are oxygen-derived small molecules, including oxygen radicals, such as superoxide ($O_2^{\bullet -}$), hydroxyl (HO•), peroxyl (RO_2•), and alkoxyl (RO•), as well as various non-radicals that can be converted to radicals or serve as oxidizing agents and include hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), ozone (O_3), and singlet oxygen ($^1O_2$) [11,12]. Reactive nitrogen species (RNS) are nitrogen-containing oxidants and are formed from nitric oxide (NO) that is generated from the mitochondrial respiratory chain under hypoxic conditions [11]. The persistent generation of cellular ROS and RNS is a consequence of many factors including exposure to carcinogens, infection, inflammation, environmental toxicants, nutrients, and mitochondrial respiration [11–14]. Various enzyme systems produce ROS and RNS including cytochrome P450, lipoxygenase, cyclooxygenase, nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase complex, xanthine oxidase (XO), and peroxisomes [11,13,15] (Fig. 1).

Various enzyme systems that neutralize toxic ROS and RNS are vital in maintaining the redox balance, and are summarized in Fig. 1. Superoxide dismutase (SOD) catalyzes the conversion of $O_2^{\bullet -}$ to H_2O_2, which then can be converted to water by catalase (CAT) or glutathione peroxidase (GPX) coupled with glutathione reductase (GSR) [12] (Fig. 1). Other important scavengers include thioredoxin coupled with thioredoxin reductase, and glutaredoxin, which utilizes glutathione (GSH) as a substrate. Additionally, glutathione S-transferase (GST) is involved in detoxification of varieties of environmental carcinogens and xenobiotics by catalyzing their conjugation to GSH, and subsequent removal from the cell [12] (Fig. 1). Glutathione plays a central role in maintaining redox homeostasis, and the GSH-to-oxidized-GSH (GSH/GSSG) ratio provides an estimate of cellular redox buffering capacity [16,17]. Moreover, evidence suggests that increased oxidative stress mediated by the GSH/GSSG complex results in enhanced activity of the GS-X-MRP1 efflux pump [17]. This pump is known to decrease the intracellular effective chemotherapeutic drug concentration; therefore it is considered one of the mechanisms of multiple drug resistance [16,17].

3. Oxidative stress and cancer

Oxidative stress has been reported to affect all phases of the oncogenic process including initiation, promotion, and progression [11,12]. Oxidative stress is known to activate several transcription factors including nuclear factor (NF)-κB, activator protein (AP)-1, p53, hypoxia inducible factor (HIF)-1α, peroxisome proliferator-activated receptor (PPAR)-γ, β-catenin/Wnt, and Nuclear factor erythroid 2-related factor 2 (Nrf2), which modulate the expression of numerous genes involved in immune and inflammatory responses, tissue remodeling and fibrosis, carcinogenesis, and metastasis [11]. The expression of some antioxidant enzymes is known to be controlled by the master transcription factor regulator Nrf2 [11,18]. The activation of Nrf2 involves a suppressor protein known as Kelch Like ECH Associated Protein 1 (Keap1) that binds Nrf2 in the cytoplasm, preventing its translocation into the nucleus for binding specific promoters [11,18].

Reactive oxygen species are known to alter the expression of several genes through induction of genetic mutations, resulting in alteration of the balance between cell proliferation and apoptosis [1,11,19]. Damage to DNA by ROS is now accepted as a major cause of cancer, and has been demonstrated in both breast and hepatocellular carcinoma [20]. Oxidation of DNA bases, such as thymidine glycol, 5-hydroxymethyl-2′-

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