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Editorial Open Access

Mechanisms of Chemoresistance in Human Ovarian Cancer at a Glance

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Abstract

Ovarian cancer is one of the most deadly malignancies in women because of its poor prognosis and that a majority of patients are diagnosed at advanced stage. Therefore, chemotherapy becomes the most important treatment option in most ovarian cancer cases. However, chemoresistance in relapsed cases is the major obstacle for the clinical management of this disease. Mounting evidences have suggested the de novo (intrinsic) and acquired (extrinsic) chemoresistance are two major underlying mechanisms occurring in human cancers. The de novo chemoresistance is attributed to the existence of cancer stem cells, while the genetic and/or epigenetic alterations in dysregulation of oncogenes or tumor suppressor genes contribute to the acquired chemoresistance. In this review, we will summarize and discuss the recent findings of the above mechanisms in chemoresistance and particularly, we will focus on the significance of putative miRNAs expressions and their associated signaling regulations in the development of acquired chemoresistance in ovarian cancer.

Keywords: De novo and acquired chemoresistance; Genetic and epigenetic alterations; MicroRNA; Signaling pathways; Ovarian cancer

Editorial

Ovarian cancer is one of the most leading fetal gynaecological malignance in women worldwide [1,2]. The high mortality rate of this disease is because of its poor prognosis and that approximately 75% of the patients are diagnosed at advanced stages (FIGO stages III and IV). Therefore, adjuvant chemotherapy is necessary for the clinical management of patients with advanced tumors [3]. Platinum-based combination chemotherapy is the standard first-line strategy for ovarian cancer patients. Although initial treatment achieves high percentage in responses, most of the patients will eventually develop resistance to anti-cancer drugs [4,5]. Therefore, chemoresistance is the major clinical obstacle for the treatment of ovarian cancer patients nowadays. Mounting evidences have documented that de novo (intrinsic) and acquired (extrinsic) chemoresistance are two major most likely mechanisms in various human cancers. However, the precise mechanism for chemoresistance in ovarian cancer remains unclear.

The de novo chemoresistance, also called as intrinsic chemoresistance, refers to cancer cells that are resistant to chemotherapeutic drugs from the very beginning of anti-cancer drug treatment. This type of chemoresistance originates from cells which have already had capacities of drug-resistance such as limiting drugs uptake, enhancing efflux, or activating detoxification of drugs [6]. Previous studies reported that the aberrant expressions of certain crucial proteins could lead to intrinsic chemoresistance. For instance, the reduced expression of BNIP3 (Bcl2/adenovirus E1B 19 kDa protein interacting protein) and increased expression of ISG15 (Interferon-Stimulated Gene 15) were associated with intrinsic gemcitabine resistance in pancreatic cancer patients [7,8]. Up to date, researchers have summarized that this subset of tumor cells with resistant properties against anti-cancer drugs is Cancer Stem Cells (CSC), which are also known as tumor initiating cells. This type of cells shows high cell survival rate under chemotherapeutic challenge, faster proliferation and high spreading capacity. Researchers believe such CSCs are responsible for the abilities of tumorigenesis, self-renewal, differentiation and chemo/radio-resistance [9,10]. A very recent report showed that MYC-driven murine tumors contained a subset of cells that refluxed Hoechst 33342. Such onco-genotype of the hepatic tumor could promote a specific mechanism of chemoresistance that contributed to the survival of hepatic CSCs [11]. This evidence suggests that CSCs contribute to intrinsic chemoresistance in human cancer. However, the characteristics of CSCs and their functions in chemoresistance of a wide range cancer types need more evidences to prove and elucidate [12-14].

On the other hand, the mechanism of acquired chemoresistance, which is also called extrinsic chemoresistance, includes genetic and epigenetic alternations of crucial genes in cancer cells during the repetitive treatment of chemotherapy. The genetic and epigenetic changes in cells may gradually induce cancer cells to adapt the apoptotic stresses of anti-cancer drugs [15]. In ovarian cancer, the first-line chemotherapy with a combination of platinum-paclitaxel yields response rates of more than 80%; with 40–60% cases have complete response in advanced ovarian cancer. However, the median progression-free survival is only 18 months as most of these patients relapse ultimately [16]. Re-treating these patients with the same drugs (carboplatin and paclitaxel) always confers response rates of around 50% in tumors that relapse more than 12 months after initial treatment. But this falls to 10–20% when the treatment-free interval is less than 6 months [17]. This indicates that the chemoresistance of ovarian cancer is likely due to the existence of acquired chemoresistance.

Although the underlying mechanism leading to acquired chemoresistance is still unclear, numerous studies have documented that genetic or epigenetic alterations are frequently occurred and are the cause of chemorsistance development in cancers. The reasons are attributed to the mechanisms of most anti-cancer drugs for inhibiting cancer cell growth through impairing DNA synthesis, damaging the DNA in the nucleus or breaking down the mitotic spindles of the cells. These effects could cause genetic and epigenetic changes in gene expressions. Genetic changes refer to the changes in DNA sequence, including mutation, deletion, amplification, translocation, and so on. When these changes happen to genes, such as TP53, RB1 and KRAS, which are significant for controlling cell cycle, proliferation,

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survival and apoptosis etc, they make cancer cells aggressive and chemoresistant [18-20]. Recently, abundant evidences have showed that the genetic alternations could be one of the causes of the acquired resistance in human ovarian cancer. For example, Shim et al. [21] reported that an elevation of a transcription factor NF-E2-Related Factor-2 (NRF2) activity might be a determining factor for resistance to doxorubicin in ovarian carcinoma cell lines and the adaptive activation of the NRF2 system could participate in the development of acquired resistance to anthracycline therapy. Fu et al. [22] found that the enhanced expression of Glycogen Synthase Kinase-3α (GSK-3α) was associated with acquired resistance to paclitaxel in ovarian carcinoma cells. Moreover, Ong et al. [23] using microarray analysis in a newly established arsenic-resistant ovarian cancer cell line OVCAR-3/AsR revealed that there was a dysregulation of multiple genes associated with the development of acquired chemoresistance to As(2)O(3) and increased tumor aggressiveness.

In the past few decades, emerging evidences have documented that the epigenetic alterations could be the novel mechanism leading to the acquired chemoresistance. Epigenetic changes, including DNA methylation, histone modifications and microRNA regulation, regulate crucial gene expressions critically in the development of drug-resistance [24-26]. Initially, researchers have focused on DNA methylation and histone modifications for gene expression regulation. This is because DNA hypermethylation, together with histone methylation and/or histone deacetylation, in the promoter region cause chromosome remodeling and further inhibit the binding of transcription factors to the promoter region. This induces gene silence in the transcriptional level [27,28]. For instance, hypermethylation in the transcription factor AP2E downregulated its expression, induced overexpression of DKK4 and further made colorectal cancer patients suffer to ineffectiveness to fluorouracil-based chemotherapy [29]. In ovarian cancer cells, MutL Hhomolog 1 (MLH1) and TAp73 are two well-known examples silenced by methylation and such gene silencing confers ovarian cancer cells to be acquired drug resistance [30,31]. Indeed, the recent comprehensive studies in methylation have been conducted and several drugs, such as 5-azacitidine (Aza) and hydralazine, have been used in clinical trials for tackling chemoresistance in human cancers [32,33], suggesting the DNA methylation is one of the major causes in chemoresistance.

Recently, researchers have found another type of epigenetic changes, microRNA (miRNA) playing a crucial role in gene regulation and chemoresistance. MiRNAs refer to a group of small, non-coding RNAs that bind to the 3'UTR of their target mRNAs under base complementarity via the miRNAs seed sequence. This induces the target mRNA degradation or translational repression, depending on the complementary level of the binding between miRNA and its target mRNAs [34,35]. Indeed, it's well known that the regulation of miRNA plays an important role in the cell development and differentiation during embryonic development. In contrast, deregulation of miRNAs usually contributes to various diseases including cancers [36,37]. Emerging evidences have suggested that the deregulation of miRNAs is closely associated with the acquired chemoresistance in various human cancers including ovarian cancer. For example, up-regulation of miR-21 enforced its function in $HER2^+$ BT474, SKBR3, and MDA-MB-453 breast cancer cells that were induced to the acquired trastuzumab resistance by long-term exposure to trastuzumab antibody [38]. In addition, loss of MiR-181a and miR-630 expressions might inhibit cisplatin-induced cancer cell death in Non Small Cell Lung Cancer (NSLC) [39]. Moreover, a recent study reported that the upregulation of miR-214 and miR-376c induced cell proliferation, cell survival and cisplatin resistance in ovarian cancer [40,41]. Therefore, further investigation of miRNA deregulation is a need to unveil the mechanism of chemoresistance in human cancers including ovarian cancer.

As the base complementarity between miRNA and its binding to the 3'UTR of mRNAs is not necessary to be 100%, one miRNA may regulate numerous target mRNAs. Hence, one miRNA may be involved in governing a network of signaling pathways such as the TGF-β, WNT and EGF signaling cascades. Considering these pathways act as very important roles in regulating cell proliferation, apoptosis, DNA repair etc., the deregulation of miRNAs expressions could cause dysfunction of these pathways in regulating cellular physiology and properties including increased resistance to anti-cancer drugs induced cell apoptosis [42-44]. There are several well-known pathways regulated by miRNAs found in ovarian cancer chemoresistance, such as PI3K/AKT/mTOR and Phosphatase and Tensin Homolog (PTEN) signaling cascades [45,46]. For example, Nagaraja et al. [47] found that miR-22 and miR-100 repressed AKT/mTOR signaling and enhanced sensitivity to the rapamycin analog RAD001 (everolimus) in clear cell ovarian cancer. In addition, Fu et al. [48] also found that miR-93 was inversely correlated with PTEN expression in CDDP-sensitive and induced resistant human ovarian cancer cells by activation of AKT signaling pathway. Apart from the above pathways, NOTCH signaling is one of the most famous pathways for the development of chemoresistance in various human cancers including ovarian cancer. The conserved ligand-receptor NOTCH, governing its signaling factors such as the HES family and the HEY family, plays critical roles in cell proliferation, survival, apoptosis as well as resistance to anti-cancer drugs [49-51]. Numerous reports found that miR-34 participated in the Notch pathway regulation and involved in the acquired drug resistance in prostate cancer and breast cancer, suggesting that miRNA mediated NOTCH signaling activity was involved in chemoresistance of cancers [52,53]. NOTCH pathway contains abundant signaling factors for regulating its gene expression and cross-talking with Wnt and Hedgehog pathways, indicating miRNAs modulate not only NOTCH but also other signaling pathways [54,55]. Apart from NOTCH pathway, recent findings also raise the importance of FOXM1 transcription factor network in human cancers including ovarian cancer [49]. Our laboratory have previously revealed that the aberrant activation of FOXM1 signaling cascade triggered cell migration in ovarian cancer cells, suggesting that FOXM1 was associated with aggressive chemoresistant ovarian cancer [56]. Therefore, further investigations in miRNAs regulating of NOTCH and FOXM1 pathways may provide new insights in the mechanism of chemoresistance and assist in exploring molecular therapeutic strategies in ovarian cancer.

In conclusion, although recent studies have suggested that the acquired resistant mechanism is the major chemoresistance in ovarian cancer, further investigations to support this notion is needed. Moreover, the understanding of miRNA regulated signaling pathways controlling cell proliferation, apoptosis, DNA repair etc. such as NOTCH and FOXM1 pathways may provide valuable insights in the molecular mechanisms of the development of acquired chemoresistance.

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