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Review Article

Systemic review on paclitaxel resistance in ovarian cancer

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ABSTRACT

The multi drug-resistant [MDR] gene product p-glycoprotein confers simultaneous resistance of tumor cells to a great variety of drugs and cytotoxic agents. This phenomenon is the main obstacle to successful chemotherapeutic treatment of cancer resistance to paclitaxel has been associated with either over expression of the p-glycoprotein [a drug efflux pump that induces the MDR phenotype alterations in the bindings of the drug to microtubules or a decrease in the levels of polymerized tubulin. When tumor cells acquire resistance to mitomycin C [MMC] they generally develop simultaneous cross-resistance or collateral sensitivity to various other structurally and functionally distinct anticancer agents. Our review mainly focused on [MDR] of pacilitaxel resistance in ovarian cancer. We developed a search strategy to find any publications about the pacilitaxel resistance in ovarian cancer. These to search the medline [2000 to current update] CINAHL, DOAJ, PUBMED databases using the key phrases P-glycoprotein, Drug resistance, and ovarian cancer. We identified supporting evidence and generated recommendations and /or directions for future research. This article suggests that adjustment of dosage is needed in the case of patients those who developed paclitaxel resistance and therapeutic drug monitoring is advisable in order to minimize the adverse effect of the drug and dose related problem. In future, further studies are needed to overcome the resistance thereby, increasing the sensitivity of pacilitaxel to tumor cells.

Keywords : Pacilitaxel, Resistance, Kallikreins, P-glycoprotein, multidrug resistance.

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INTRODUCTION

Every year, more than 6 million cancer deaths were reported in the world. Of the 10 million new cases each year, more than half occur in developing countries. WHO predictions shows that, out of 15 million cases 66% will occur in developing countries by 2015 [1].Ovarian cancer is a common gynecologic cancer and is the leading cause of death from gynecologic cancer worldwide. Despite significant initial response rates for advanced ovarian carcinoma using paclitaxel in combination with carboplatin as first-line chemotherapy, clinical drug resistance posses a major impediment to the successful use of such an effective agent. The development of resistance to paclitaxel may occur through mechanisms that involve the expression of P-glycoprotein, but there must be some as yet unknown genes involved in the drug resistance. The high mortality associated with ovarian cancer is largely due to advanced disease at the time of diagnosis. The overall 5- year survival rate for ovarian cancer is about 45% and that for stage III disease is 11% to 40% [2]. Because both systemic (lymphovascular) and local spreads happened with the progression of disease, systemic and loco regional therapy is necessasary to control advance ovarian cancer.

Paclitaxel is an antimitotic agent which stabilizes the assembly of microtubules by preventing depolymerization, thus arresting cells prior to or during mitosis. Several types of paclitaxel resistance in cultured cells have been reported. Multi drug résistance cells which over produce P-glycoprotein or resistance to paclitaxel as well as to drugs such as vincristine, doxorubicin and etoposide. Resistance has been associated with altered α or β tubulin subunits, thus altering the kinetics of depolymerization in the presence of paclitaxel. Paclitaxel resistance may also occur when cells following treatment, enter another round of DNA replication without dividing (polyploidisation). Reduction of cellular glutathione levels by exposure of cultured cells to butathion sulphoxime also induces resistance to paclitaxel, suggesting a role for glutathione in resistance [3].

BASIC MECHANISM OF PACLITAXEL RESISTANCE IN OVARIAN CANCER

Theoretically some resistance mechanisms of taxanes such as increased multidrug resistance (MDR) or tubulin alterations, could represent a limitation to the drug using weekly [at lower than standard doses]. However much experimental evidences does not support this hypothesis.

P-glycoprotein induced multidrug resistance (MDR)

P-glycoprotein is the first multidrug resistance protein to be characterized and is relevant to the failure of chemotherapy in many cancers. Because multidrug resistance reversal trials have already been initiated for many cancers including ovarian cancer, it is highly pertinent to ask if increased P-glycoprotein causes chemotherapy to fail in patients with ovarian cancers. Modulating the functions of the Pglycoprotein with cyclosporine or verapamil has been reported to be associated with enhanced chemotoxicity [4]. The multidrug resistance gene

product P-glycoprotein confers drug resistance to tumor cells by acting as a transporter that blocks the entry into the cells of a great variety of drugs and hydrophobic peptides.

Multidrug resistance (MDR) is one of the main obstacles in the chemotherapy of cancer. MDR is associated with the over expression of P-glycoprotein, resulting in increased efflux of chemotherapy from cancer cells. Multidrug resistance is a phenomenon whereby tumor cells exposed to one cytotoxic agent develop cross-resistance to a range of structurally and functionally unrelated compounds. The drug resistance that develops in cancer cells often results from elevated expression of particular proteins, such as cell membrane transporters, which can result in an increased efflux of the cytotoxic drugs from the cancer cells, thus lowering their intra cellular concentrations. Resistance to the drugs may be primary where the tumor does not respond to drugs from the start or secondary in which case the tumor initially responds but slowly acquires resistance. The cytotoxic drugs that are most frequently associated with MDR are hydrophobic, amphipathic natural products, such as the taxanes (paclitaxel & docetaxel), vinca alkaloids and anthracycline, antimetabolites apipodophyllotoxins.

Development of resistance to a wide spectrum of drugs occurred through a variety of mechanisms which are propose to explain the development of multi drug resistance (MDR). These include modulation of genes alterations in DNA repair capacity, altered target enzyme levels, detoxification involving glutathione conjugation and MDR through efflux pumps such as P-glycoprotein [1].

Over expression of the multidrug resistant (MDR) gene product P-glycoprotein confers simultaneous resistance of tumor cells to a great variety of drugs and cytotoxic agents. This phenomenon is the main obstacle to successful chemotherapeutic treatment of cancer. The mechanism of P-glycoprotein mediated multi drug resistance is not completely understood. The difficulty stems from an apparent lack of substrate specificity manifested by the ability to transport a great variety of drugs and compounds dissimilar in their molecular structure, size, or biological action. Since the initial demonstration that P-glycoprotein interacts with its substrates within the hydrophobic phase of the membrane, the information emerging from structural and functional studies is consistent with the view that substrates first partition into the lipid phase of the membrane before they access putative binding sites on the molecule it self . An important feature of p-glycoprotein over expressing multidrug resistant cells is their ability to block the entry of a great variety of hydrophobic peptides like gramicidin D and valinomycin. Other members of the ATP binding cassette [ABC] family of transporters function as transporters of peptides across membranes [5].

Many different taxanes mechanism of resistance have been described. The resistant to numerous natural alkaloids, which enter the cell by passive diffusion, is related to the presence of cellular membrane proteins, such as P-glycoprotein, capable of intracellular drug withdrawl [19]. Although this phenomenon may be fundamental in some conditions, the relative MDR phenol type frequency is not assessed, when compared to other resistance mechanisms, and its role has lossed relevance in many recent studies [20]. For example, paclitaxel is effective even

in those clinical conditions showing an increased P-glycoprotein activity, such as in anthracycline resistance patients. Moreover, an increased MDR1 expression has never been found in paclitaxel-resistance ovarian endometrial cancers. Tubulin encoding gene mutations may produce protein with less drug affinity or less polymerization capability. Although a possible taxane resistance mechanism may be related to mutations in genes encoding for tubulin in the taxanes binding domain, the frequency with which genes that control its synthesis occur make the mechanism improbable. Moreover the presence of 5-10% tubulin bound paclitaxel is enough for the complete polymerization blockade. Paclitaxel therapeutic efficacy is guaranteed, in the presence of a single gene mutation, by the intra cellular levels of normal tubulin subunits that are sufficient for paclitaxel binding. Some tubulin mutations determining different levels of polymerization have been described; higher polymerization ability is associated with higher vinca alkaloid resistance, lower polymerization ability correlates with taxanes resistance. From a clinical view point, it is interesting to note that, in the presence of such tubulin alterations, vinca alkaloid resistance clones are hypersensitive to paclitaxel, while paclitaxel resistant cells show sensitivity to tubulin polymerization inhibiting drugs [4].

MAP is necessary for correct tubulin subunit assembly. Moreover, because of the *in vivo* MAP function redundancy, no clear evidence exists concerning the relationship between their synthesis alterations and paclitaxel resistance. A different taxanes resistance mechanism may be related to tubulin synthesis alterations, deriving from mutations in encoding genes or in their expressions. In mammals, seven different beta tubulin genes encoding for six isotype classes exist. These different isotypes express different polymerization and drugs associations. A different tubulin isotype expression has been described in paclitaxel resistant ovarian cancer cell line.

As with other anticancer drugs, different paclitaxel resistant mechanism are possible such as alterations in drug distributions or metabolism, or apoptosis control machinery changes. Moreover in paclitaxel resistant cells, the drug induces an abnormal progression through prophase via specific caspases activity, leading to the development of a multi nucleated phenotype, consequent polyploidy and pharmacological resistance.

Independently of taxane resistance mechanism weekly administration of paclitaxel dose does not seem to be less effective than higher doses in a three weekly schedules. In fact, the p-glycoprotein role is not substantial, a low paclitaxel tubulin [5-10%] association rate can assure a maximal response rate and the possible tubulin expression are MAP alterations do not determined different effects in the case of weekly administration [4].

The mechanisms of resistance to paclitaxel have been described. One mechanism of acquired resistance is characterized by the multi drug resistance (MDR) phenotype related to over production of P-glycoprotein. This membrane glycoprotein act as an energy-dependent drug efflux pumps to maintain intracellular drug concentrations below cytotoxic levels [6]. A highly resistant cell line (J77 4.2/taxol) selected with paclitaxel from the maurine tumor J77 4.2 cells displays the MDR phenotype with the amplification of P-glycoproteins. Using this cell line,

docetaxel was at least five fold more potent than paclitaxel in inhibiting the replication of J77 4.2/taxol. The correlation between MDR1 expression and resistance to paclitaxel was suggested in human ovarian tumors in agar culture. *In vitro* studies have suggested that continuous exposure to paclitaxel may partly over come P-glycoprotein drug resistance [7].

Another mechanism of acquired paclitaxel resistance has been observed by Cabral et al. in Chinese hamster ovary cell lines having altered alpha and beta tubulin. These altered tubulin subunits, identified by aberrant migration during polyacrylamide gel electrophoresis, have impaired ability to polymerize tubulin diamers into microtubules. When grown in the absence of paclitaxel, these cells lack normal microtubules in interpolar mitotic spindles.Paclitaxel must be present continuously to allow normal micro tubule assembly in this cell line, which is unusually sensitive to the vinca alkaloids. Other investigators have demonstrated a paclitaxel resistant human small lung cancer cell line that is partially dependent on paclitaxel for its growth. Multidrug resistant RNA was not detected in this cell line [8].

Lehnert and associates examined reversal of resistance to paclitaxel and docetaxel in human myeloma cell line. In that study, the effects of eight chemosensitizers on P170-associated paclitaxel/ docetaxel resistance were evaluated in clonogenic assays using myeloma cells. The results suggest that oral quinidine could prove useful for clinical reversal of P170-associated resistance to paclitaxel or docetaxel. Jachez and co-workers examined the chemo sensitizers agents SDZ PSC833 (a cyclosporine derivative) and SDZ 280-446[a semi synthetic cyclo peptolide] and noted that they can restore normal paclitaxel sensitivity to highly, resistant cell lines, the multidrug resistant Chinese hamster ovary cells and the murine monocytic leukemia P388 [9].

The sensitivity of leukemia cell lines to paclitaxel may be related to the formation of irreversible microtubule bundles. Microtubule bundling is reversible in cells resistant to paclitaxel, and sensitive cells retain their microtubule bundling even in the subsequent absence of paclitaxel. Cells sensitive to paclitaxel are effected during inter phase. Most resistant leukemia cells accumulate in the G2/M phase, form multiple abnormal asters, and contain polyploidy DNA after prolonged paclitaxel administration [10].

ALTERATIONS OF TUBULIN DYNAMICS

BIII-Tubulin Induces Paclitaxel Resistance

Microtubules are dynamic polymers composed of tubulin hetero dimers that, both *in vitro* and in living cells, can continuously grow and shorten through tubulin dimer addition and loss at the microtubule end. Dynamic microtubules are required for many processes in cells including cell migration, cell signaling, and mitosis. Mitosis is particularly sensitive to changes in microtubule dynamics, and mitotic progression depends upon the maintenance of microtubule dynamics and microtubule polymer levels within a narrow range [11-15]. Paclitaxel is an extremely effective microtubule targeted anticancer drug used to treat a wide range of tumor

types. The binding of paclitaxel to tubulin in microtubules arrest cells in mitosis, leading to cell death. Acquired resistance to paclitaxel is one of the most significant reasons for its failure in chemotherapy. Determining the molecular mechanisms of paclitaxel resistance is of great clinical value both in the design of chemotherapeutic treatment strategies and in the development of drugs to avoid or overcome resistance. The antimitotic and anti proliferate effects of paclitaxel are attributed to its ability to suppress microtubule dynamics and to induce microtubule polymerization and bundling , driving dynamics and polymer levels outside of an acceptable range. Because the lowest concentrations of paclitaxel that effectively inhibit cell proliferation and block mitosis suppress microtubule dynamics without significantly increasing microtubule polymer levels, suppression of microtubule dynamics appears to be its most potent mechanism of mitotic arrest [16]. Paclitaxel binds to the subunit of tubulin, of which at least seven isotypes exist at the protein level in humans: I, II, III, IVa, IVb, V, and VI. The isotypes differ primarily within the C-terminal amino acids, a region of the protein that lies on the exterior of the microtubule and is the putative binding site for several microtubule associated proteins (MAPs) I [17]. Expression of some tubulin isotypes is restricted to specific tissues, whereas other isotypes are constitutively expressed, resulting in a unique pattern of expression for each tissue. In non-neuronal cells, I is often the predominant tubulin isotype, where as III-tubulin is generally expressed at very low levels. Tumor cells often express a different complement of tubulin isotypes than their normal counterparts. The functional significance of variations in tubulin isotype expression in both normal and tumor cells is not known.Overexpression of III-tubulin has been associated with paclitaxel resistance in cell lines and in tumors. Kavallaris *et al.* showed that paclitaxel-resistant A549 cells over expressed III-tubulin compared with their sensitive counterparts and that partial sensitivity to paclitaxel was regained by down regulation of III-tubulin in these cells. Hari *et al.* [16] reported that over expression of III-tubulin conferred 1.5–2-fold resistance to paclitaxel in CHO cells; however, the mechanism of resistance remains unclear.

Over expression of I Tubulin -Increase in Dynamic Instability

One mechanism by which III-tubulin has been proposed to mediate resistance to paclitaxel is to constitutively increase microtubule dynamics, such that in the presence of paclitaxel microtubules would remain sufficiently dynamic to complete mitosis. In living interphase CHO cells in the absence of paclitaxel, over expression of III-tubulin did not significantly alter any parameters of microtubule dynamic instability. Thus, in these cells a high level of III-tubulin over expression does not cause an inherent increase in dynamic instability, indicating that this is not the mechanism of III tubulin-induced resistance. Hari *et al.* [18] showed previously that in the III-tubulin-over expressing CHO cells polymer mass was decreased by 30%. Taken together, these results suggest that a reduction in polymer mass does not necessitate a change in cellular microtubule dynamics. This result also suggests that in previous study of paclitaxel-resistant and dependent A549 cells , the increased microtubule dynamics resulted not from the increased levels of III-tubulin but rather from other changes associated with resistance [a mutation in the putative stathmin and MAP4 binding site in conjunction with increased levels of unphosphorylated (active) stathmin and phosphorylated

(inactive) MAP4) .The lack of a difference in microtubule dynamic parameters in the absence of paclitaxel observed in the previous study in cells over expressing either I or III-tubulin is perhaps surprising .In two previous *in vitro* studies, the microtubules assembled from III-tubulin were significantly more dynamic than microtubules assembled from IV-tubulin. For example, comparison of their dynamic it is indicated that III-microtubules were 2.2-fold more dynamic than IV-microtubules in one study and 1.7-fold more dynamic in a second study [19, 20]. The sequence of IV resembles that of I; thus one might expect that microtubules in cells over expressing III-tubulin might be more dynamic than those in cells over expressing I-tubulin. In cells, tubulin undergoes post-translational modifications and interacts with a large number of microtubule regulatory proteins [ranging from proteins that induce catastrophe to those that stabilize microtubule dynamics]; thus the dynamics of individual isotopes may be significantly altered in cells.

III Tubulin overexpression-Weaker Effect on Dynamic Instability

Microtubules in cells over expression tubulin were significantly less susceptible to the suppressive effects of paclitaxel than in control cells. In controls [I-over expressing cells or un induced III-tubulin transfected cells], paclitaxel significantly reduced the mean growth and shortening rates and lengths and dynamicity. In III-over expressing cells, only the mean shortening rate and length were reduced, and these parameters were affected to a microtubule dynamics correlates with inhibition of proliferation and sensitivity to paclitaxel [21]; thus, the lack of suppression of microtubule dynamics is the most likely explanation for the resistance phenotype.

NOVEL MECHANISMS OF RESISTANCE

Down-Regulation OF Bcl-2 genes

In earlier studies, the microtubule network appeared as the main target of paclitaxel (Schiff et al., 1979; Manfredi et al., 1982). In fact, taxanes bind to tubulin subunits, there by disrupting normal turnover of the microtubules. The final consequence is the arrest of the cell cycle in M phase with formation of aberrant mitosis and the activation of cell death pathways (Jordan et al., 1993). Along with arrest in M phase of the cell cycle, taxanes have also been reported to induce post-translational serine phosphorylation of the Bcl-2 protein (Haldar et al., 1995). The *BCL2* gene is the homologous of the nematode CED-9 gene product (Hengartner and Horvitz, 1994) and is capable of prolonging cell survival by inhibiting apoptotic cell death. Over expression of Bcl-2 has been observed in follicular lymphoma, where this protein is deregulated by chromosomal translocation, and in a large number of human tumors, including breast, ovarian, lung, and prostate cancer [22].

Disagreement exists on the levels of Bcl-2 and resistance to taxanes. A strong suggestion for a direct role of Bcl-2 in mediating paclitaxel sensitivity comes from the observation that a cell line not expressing Bcl-2 is resistant to paclitaxel induced apoptosis (Haldar et al., 1996).

Further support for this view stems from the observation that paclitaxel is able to entrap, from a random peptide library, a panel of peptides showing a high degree of structural homology with the disordered loop of Bcl-2, thereby indicating the latter as a motif for direct paclitaxel binding (Rodi et al., 1999) . In apparent contrast with this view, over expression of exogenous Bcl-2 or Bcl-xL protected HL-60 leukemic cells from paclitaxel-induced apoptosis (Tang et al., 1994; Ibrado et al., 1997), so the role of Bcl-2 as modulator of paclitaxel sensitivity remains controversial. In addition, in clinical studies, Bcl-2 up regulations sometimes related to a better clinical outcome; in other cases, however, it is a marker of poor prognosis (Blagosklonny, 2001). Such a paradox can be explained by taking into consideration Bcl-2 levels along with the functional status of the death machinery. In fact, Bcl-2 up-regulation can be a marker of still functional death machinery is consequent.

Maintained sensitivity to chemotherapy-induced apoptosis (Blagosklonny, 2001).Several authors have pointed out the possibility that taxanes dependent antitumor activity could originate not only from its effects on microtubule assembly (Danesi et al., 1995; Moos and Fitzpatrick, 1998; Pae et al., 1998) but also thought the interaction with intracellular targets other than microtubules, although conflicting data have been reported (Blagosklonnyand Fojo, 1999). Nevertheless, this hypothesis still remains very attractive because natural products have a marked pleiotropism; during thousands of years of evolution, plants have performed "combinatorial chemistry" by modification of molecules with pre-existing biological activities to overcome the environmental selective pressure. Therefore, a new molecule originates from the framework of a compound with previous biological activities. In previous study reported that, the approach of the assumption and studied mitochondria as a possible target for taxanes [23].
Several reports have indicated that taxanes can interact with isolated mitochondria (Evtodienko et al., 1996; Andre et al., 2000; Varbiroet al., 2001; Kidd et al., 2002), but the mitochondrial target of taxanes remains elusive at the molecular level. Carre et al. [2002] very recently discovered that tubulin is an inherent component of mitochondrial membranes with a still unknown function, thereby providing a potential ligand for taxanes in mitochondria. The previous study report that paclitaxel binds to isolated mitochondria, and we found that these bindings can be increased in condition of activation of the mitochondrial respiratory state. Bcl-2 participates in this binding, and its role as intracellular target for taxanes is supported by the fact that Bcl-2 down-regulation is observed in a panel of paclitaxel-resistant A2780 cells and that paclitaxel sensitivity is partially restored by Bcl-2 over expression. Finally, previous study noticed that Bcl-2 down-regulation in a small series of ovarian cancer patients resistant to paclitaxel containing chemotherapy [24].

The taxanes interact with Bcl-2 in mitochondria at clinically achievable doses; and Bcl-2 down regulation seems to be associated, at least in ovarian cancer, with taxane-resistance. Clinical studies are now needed to ascertain whether Bcl-2 expression can be regarded as a potential factor of chemo sensitivity for taxanes, and it is essential to correlate Bcl-2 expression and taxanes sensitivity in other solid malignancies. Finally, the insight into taxane/Bcl-2 interaction could contribute to the development of a new generation of taxanes able to interact with Bcl-2 in a more efficient manner [22]

Low expression of S100P

The human protein S100P belongs to the S100 sub family of Calcium-binding proteins that share a common Ca2+ binding structural motif, the EF-hand. Twenty members of the subfamily have been identified to date [25]. S100P is one of the least studied members, a 95-aminoacid protein first purified from placenta with a restricted cellular distribution. The molecular structure of S100P has been well described. Altered expression of S100P proteins is documented for many human diseases and tumors. Over expression of S100P might be a marker for chemotherapy resistance and poor prognosis of the patients with pancreatic carcinoma. In a previous study, found that low expression of S100P is associated with acquired oxaliplatin resistance in a colon cancer cell line 8307[26]. And suspected that S100P may be affect chemotherapy resistance differently depending on the cell type. Whether S100P expression plays a role in resistance to chemotherapy in ovarian cancer is unknown. To characterize the effect of S100P to drug resistance in ovarian cancer cell lines, transfected cells to either under or over expressS100P. The drug selected was paclitaxel, a first line chemotherapeutic agent for ovarian cancer. Taken together, the results suggest an essential role for S100P expression in maintaining paclitaxel sensitivity of cancer cells. Currently, standard primary therapy for advanced ovarian cancer involves a combination of maximally cytoreductive surgery and chemotherapy with paclitaxel plus carboplatin or with carboplatin alone.

However, effective management of ovarian cancer is often limited by the relative lack of response to these drugs. To find the genes related with drug resistance is the best way to understand the mechanism underlying this drug resistance. Over expression or mutation of β tubulin and over expression of P-glycoprotein, have been linked to the acquisition of taxol resistance. In the previous, analysis gene expression profiles of anoxaliplatin-resistant colon cancer cell line THC8307/L-OHP by micro assay, and confirmed the down regulation of S100P in these cells. Previously hypothesized that S100P might serve as a marker for acquired resistance to chemotherapeutic drugs. Tanino T et al 2007 reported that the role of S100P in ovarian cancer cell lines for paclitaxel resistance [27].

The most common form of cancer of the ovary is epithelial ovarian cancer (EOC). Ovarian carcinoma cell lines, such as, SKOV3, OVCAR3, which were derived from clinically drug resistant patients with EOC, are useful for *in vitro* anticancer drug screening and for the identification of valuable, novel treatment regimens. First, determined basic S100P expression levels in SKOV3 and OVCAR3 cells. Then, evaluated the response of the two kinds of cells to paclitaxel. The sensitivity of the cells to paclitaxel *in vitro* was significantly different. In OVCAR3 cells, the IC50 for paclitaxel was more than 30 fold higher than in SKOV3 cells. Interestingly, the expression level of S100P in OVCAR3 was lower than in SKOV3 cells. To determine whether the S100P level is a factor in paclitaxel sensitivity, an RNA interference technique was used to silence its cellular expression effectively. The cytotoxic MTT assay subsequently suggested that a lower intracellular S100P concentration was responsible for the resistance to the microtubule

polymerizing drug paclitaxel. The increase in survival in OVCAR3 cells was as great as the increase in SKOV3 cells when the S100P silencing effect was similar. Based on previous study, hypothesized that S100P might act as a marker of drug sensitivity for ovarian cancers. To confirm our hypothesis, transfected OVCAR3 cells with S100P/pCDNA3flu, and obtained S100P/3, a G418 selected S100P high expression clone. Higher expression of S100P in OVCAR3 cells was associated with decreased resistance to paclitaxel. This finding was consistent with the RNAi result above. Taken together and conclude that the expressions of S100P can maintain paclitaxel sensitivity in ovarian cancer cells. This finding should help us identify ovarian cancer patients who will benefit most from paclitaxel based chemotherapy. Still, the role of S100P in resistance to chemotherapeutic drugs remains controversial. The previous data were supported by Kang et al ;[28] they found that S100P was down regulated in 5-FU resistant gastric cells. But differences were seen for colon cancer, where S100P expression was elevated in doxorubicin resistant cells; in pancreatic cells, S100Pexpression was correlated with increased survival after 5-fluorouracil exposure. 8S100P has recently become a topic of major interest owing to its differential expression in a variety of tumors and its putative involvement in metastasis [29]. The ability of decreasing S100P expression to improve cell survival induced by paclitaxel suggests that S100P may enhance the performance of chemotherapeutic agents by reducing drug resistance. In view of that, the expression of S100P in many cancers seemed to be an unfavorable prognostic factor. Paclitaxel based adjuvant chemotherapy should be considered in those patients with high S100P expression, although its effect in clinical drug resistance still needs further research. Although the foregoing research sheds some light on S100P involvement in resistance to paclitaxel in ovarian cancer cells, what is not known at present is the mechanism whereby lower expression of S100P leads to the development of resistance to paclitaxel. It was observed that S100P can interact with the cytoskeleton proteinezrin in a Ca2+ dependent manner and influence its ability to bind β-actin.21 S100P has also been reported to be able to interact with CacyBP/SIP, a component of a novel ubiquitinylation pathway, leading to catenindegradation [30]. The function of S100P in drug sensitivity may correlate with drug uptake by regulating the dynamic state of the plasma membrane cytoskeleton through the mechanisms described above.

Kallikrein 4 – expression

Kallikreins [KLKs], a family of the serine proteases, have recently attracted significant attention by their potential roles as tumor markers in ovarian cancer. Several members of the KLK family, including KLKs 5–11, have been reported to be expressed in ovarian cancer and related to disease prognosis [31]. KLK4 is a novel member of the KLK family, which was cloned recently by several groups. The function of KLK4 in normal or cancer cells is not known at present. Over expression of KLK4 mRNA in ovarian cancer, recently reported by two groups, may indicate poor prognosis of the patients [32]. However, the possible mechanisms of poor prognosis that may be linked to KLK4 expression in ovarian cancer are still not known.

Many previous studies have aimed to identify and implicated potential diagnostic or prognostic markers for ovarian cancer. These include trypsin, hepsin [33], and members of the

KLK family. The previous study had shown that hK4 expression is significantly increased among high-grade ovarian cancer lesions. This finding is consistent with KLK4 mRNA expression analysis in ovarian cancer that was previously reported. Since the function of hK4 is still unknown, and do not yet know the target of hK4 in ovarian carcinoma cells. As hK4 is a distinct member of the KLK family, and in particular, since it is intracellular [34], as opposed to secreted forms for other family members, it may serve a unique physiological function in ovarian carcinogenesis that is different than other KLKs that have been shown to be expressed in ovarian cancer to date. It is possible, for example, that hK4 is involved in nuclear organization and may influence gene expression and cellular proliferation.

The central finding is that the expression of hK4 is significantly associated with paclitaxel resistance. Two classic paclitaxel resistance mechanisms have been characterized to date based on *in vitro* experiments. First, some cancer cells have the alpha and beta-tubulin with impaired ability of polymerization of microtubules, which could hinder the assembly of microtubules induced by taxanes. A second mechanism reported is the action of the drug-efflux pump, such as P-glycoprotein (MDR-1). Interestingly, an increasing expression of MDR-1 has never been found in the paclitaxel-resistant ovarian [35], endometrial, or breast cancer specimens, which related to the overall survival. More attention has therefore been focused on the relationship between elements of the apoptotic pathway and paclitaxel action, such as Bax, Bcl2 [36], and P53 [37].

The steroid hormones, such as androgen, estrogen, and progesterone, all regulate KLK4 expression in the prostate cancer cell line LNCaP [38]. It has been shown that hK4 is upregulated by estrogen in the ovarian cancer cell line OVCAR-3 [39]. It is also known that estrogen inhibits taxol-induced apoptosis of human breast cancer MCF-7 cells [40]. It is possible that similarly, hK4 may be involved in the estrogen- induced ‘‘anti-paclitaxel’’ effect in ovarian cancer.

CONCLUSION

Our review suggests that even though there is some basic mechanism explaining paclitaxel resistance in ovarian cancer, there are some novel biochemical parameters like Bcl-2 regulation, low expression of S100P, and Kallikreins-4, other parameters are elevated during the development of paclitaxel resistance in ovarian cancer. Measuring p-glycoprotein prospectively may identify those patients likely not respond well to chemotherapy, in whom early intervention with these toxic experimental modalities, including the use of p-glycoprotein inhibitors similar to verapamil or cyclosporine that accentuate chemotoxicity. And finally the adjustment of dosage is needed in the case of patients those who developed paclitaxel resistance and therapeutic drug monitoring is advisable in order to minimize the adverse effects of the drug and dose related problems. The resistance of the paclitaxel may influence the therapeutic outcome of the patients, so further studies are needed to overcome the resistance, thereby increasing the sensitivity of paclitaxel to tumor cells.

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