MECHANISMS INVOLVED IN CHEMORESISTANCE IN OVARIAN CANCER

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SUMMARY

Chemotherapy is a major treatment modality for ovarian cancer, but chemoresistance is a clinical problem that compromises the efficiency of treatment and finally results in treatment failure. The development of resistance to chemotherapeutic agents might be related to multiple mechanisms such as alterations in drug transport, changes in cellular proteins involved in detoxification, altered drug target, changes in DNA repair mechanisms, and increased tolerance to drug-induced DNA damage. This article is a summary of the various mechanisms that are involved in chemoresistance in ovarian cancer. [Taiwanese J Obstet Gynecol 2005;44(3): 209–217]

Key Words: chemoresistance, chemotherapy, ovarian cancer

Introduction

Ovarian cancer is the leading cause of death from gynecologic malignancies since most ovarian cancers are diagnosed at an advanced stage [1]. Despite combinations of chemotherapy agents yielding complete responses in 60–80% of patients with advanced disease, most patients with ovarian cancer eventually relapse and become refractory to additional treatment [2]. Therefore, the long-term survival of patients with advanced disease rarely exceeds 30%.

The review of el-Deiry showed that failure of chemotherapy may be caused by development of drug resistance that is related to multiple mechanisms such as alterations in drug transport, changes in cellular proteins involved in detoxification, altered drug target, changes in DNA repair mechanisms, and increased tolerance to drug damage [3]. In this review, we summarize the possible mechanisms of the development of resistance to the chemotherapeutic agents used in ovarian cancer.

Alterations in Drug Transport

Multiple drug resistance (MDR) is a phenomenon whereby tumor cells acquire cross-resistance to a variety of structurally and functionally unrelated compounds. It is commonly known that some forms of MDR arise from the overexpression of ATP-binding cassette transporters such as P-glycoprotein (P-gp), MDR-associated protein 1, and/or breast cancer resistance protein (BCRP) [4].

P-gp, a 170,000-Da transport protein, functions as an energy-dependent efflux pump for a number of drugs and is responsible for decreased drug accumulation within cells, thereby causing MDR [5]. Amplification or overexpression of the P-gp family of membrane transport proteins such as multidrug resistance protein (MRP), which act as efflux pumps for anticancer agents, will contribute to physiologic alterations, i.e. intracellular pH and plasma membrane potentials [3,6].

The human MRP1 gene is located on chromosome 16 at p13.1, spans about 194 kb, and is composed of 31 exons [7]. The originally published MRP1 cDNA encodes...
1,531 amino acids and is predicted to form three membrane-spanning domains and two nucleotide-binding domains [8–10]. To date, six splice variant sequences of \( \text{MRP1} \) besides the one mentioned above have been deposited in the National Center for Biotechnology Information RefSeq database [8]. In these splice variants, exons 5, 13, 17, 18, 17 and 18, and 30 are skipped, respectively.

\( \text{MRP1} \), originally identified from a drug-resistant lung cancer cell line, is a prototypical member of the ATP-binding cassette transporter subfamily that has been associated with MDR [8–10]. Some studies have demonstrated that overexpression of \( \text{MRP1} \) in tumor cell lines can confer resistance to many natural product chemotherapeutic agents such as anthracyclines (e.g. doxorubicin), vinca alkaloids (e.g. vincristine), and epipodophyllotoxins (e.g. etoposide) by reducing their cellular accumulation [11–13].

He et al reported that the \( \text{MRP1} \) gene undergoes alternative splicing at a higher frequency in ovarian tumors than in matched normal tissues. Some of these splice variants, in which expression of splicing factors PTB and SRp20 is strongly associated with the alternative splicing of the \( \text{MRP1} \) gene, confer resistance to doxorubicin [14].

Current strategies to prevent or reverse MDR have focused primarily on the development of agents that are competitive inhibitors of P-gp. Development of these agents for clinical use has been hindered by toxicity and limited efficacy [15]. In addition, some studies have indicated that these and related P-gp inhibitors stimulate \( \text{MRP1} \) expression [16]. Alternative strategies involving the inhibition of transporter expression may offer superior mechanisms for reversing the MDR phenotype.

Small interfering RNAs (siRNAs) are double-stranded RNA molecules that induce sequence-specific degradation of homologous single-stranded RNA. In plants and insects, siRNA activity plays a role in host cell protection against viruses and transposons [17,18]. From a biological research perspective, siRNA is a very powerful technique to “knockdown” specific genes, thereby enabling the evaluation of their physiologic roles in Caenorhabditis elegans, Drosophila melanogaster, and human cells. siRNA technology has several major advantages over other post-transcriptional gene silencing techniques (e.g. antisense or gene knockout technology), in that it is easier to deliver, requires only small doses of siRNA to produce its silencing effect, and can inactivate a gene at almost any stage in development.

Duan et al evaluated the utility of siRNA in reversing paclitaxel resistance in human ovarian cancer cells selected for resistance by treatment with paclitaxel. These cells had been characterized previously and exhibit the classic MDR phenotype accompanied by increased expression of \( \text{MRP1} \) [19]. The study indicated that siRNA targeted to \( \text{MRP1} \) can sensitize paclitaxel-resistant ovarian cancer cells in vitro, suggesting that siRNA treatment may represent a new approach to the treatment of \( \text{MRP1} \)-mediated drug resistance. Another study by Wu et al confirmed the effectiveness of siRNA in inhibiting \( \text{MRP1} \) expression and the subsequent reversal of resistance to paclitaxel [20].

Changes in Cellular Proteins Involved in Detoxification

el-Deiry showed that the detoxification procedure involves the glutathione S transferase enzymes (GSTs), the major antioxidant glutathione (GSH), metallothioneins, the human homologue of the \( \mu \text{T} \) gene of Escherichia coli, bleomycin hydrolase, and dihydrofolate reductase [3]. Among these, the GSTs, GSH, and metallothioneins have been studied most extensively and they are described below.

Glutathione and glutathione S transferases

GSH, a nonprotein sulfhydryl, and its associated enzymes, GSTs, detoxify some chemotherapeutic drugs such as alkylating agents and platinum-based drugs [5], and glutathione peroxidase (GPx) removes toxic oxygen intermediates.

Six families of enzymes, \( \alpha, \mu, \pi, \theta, \zeta, \) and \( \Omega \), have been identified [21], of which \( \text{GST} \alpha_1, \text{GST} \pi_1, \) and \( \text{GST} \Omega_1 \) have been studied most. The \( \text{GST} \mu_1 \) gene is located on chromosome 1p13.3, the \( \text{GST} \pi_1 \) gene is located on chromosome 11q13, and the \( \text{GST} \Omega_1 \) gene is located on chromosome 22q11.2. \( \text{GST} \alpha_1 \) and \( \text{GST} \pi_2 \), the two major \( \text{GST} \alpha \) genes, are mentioned less frequently in the literature and are located on chromosome 6p12 [21]. The \( \text{GST} \pi_1 \) gene has been mapped to chromosome 14q24.3 [22] and the \( \text{GST} \Omega_1 \) gene has recently been characterized [23].

\( \text{GST} \alpha \) has a particular role in cellular resistance to the alkylating agents melphalan and chlorambucil [24], while nitrosourea detoxification may be carried out by \( \text{GST} \mu_1 \) [25]. \( \text{GST} \pi_1 \) is the most prevalent in human tumors, and transfection experiments in yeast have demonstrated that it confers resistance to doxorubicin and chlorambucil [26].

Coughlin and Hall found that the results of some studies carried out to date do not confirm associations between \( \text{GST} \mu_1, \text{GST} \pi_1, \) and \( \text{GST} \Omega_1 \) and epithelial ovarian cancer [27]. However, the associations are biologically plausible because GSTs metabolize exogenous and endogenous substances that may have a
role in ovarian cancer carcinogenesis [28–30]. Studies that examine associations within specific histologic types of ovarian cancer are a promising area for further research.

**Metallothioneins**

Metallothioneins are a group of low-molecular weight and cysteine-rich intracellular proteins. The expression and induction of these proteins are associated with protection against DNA damage, oxidative stress and apoptosis [31]. Although metallothionein is a cytosolic protein in resting cells, it can be translocated transiently to the cell nucleus during cell proliferation and differentiation. Cherian et al reviewed a number of studies that showed increasing expression of metallothioneins in various human tumors of the breast, colon, kidney, liver, lung, nasopharynx, ovary, prostate, salivary gland, testes, thyroid and urinary bladder [31]. However, metallothionein is downregulated in certain tumors such as hepatocellular carcinoma and liver adenocarcinoma.

*In vitro* studies using human cancer cells demonstrate a possible role for p53 and estrogen receptor in the expression and induction of metallothioneins in epithelial neoplastic cells [31]. However, chemoresistance in human tumors is a multifactorial phenomenon, and it is difficult to conclude that metallothionein is a more crucial factor than others.

**Altered Drug Target**

**Changes in β-tubulin structure**

Taxanes represent the most important class of anticancer agents obtained from plants and have been available in clinics from the 1990s. Taxanes bind to β-tubulin subunits and inhibit microtubule dynamics, thereby blocking cell cycle progression during mitosis at the metaphase/anaphase transition and activating cell death [32].

Despite the contribution of taxanes to improving the quality of life and overall survival of cancer patients, drug resistance to these compounds represents the most important clinical problem. Many patients, even those who respond initially to therapy, fail to respond further when disease relapses, and a small number do not even respond at the first cycle of therapy. A variety of mechanisms have been proposed to explain taxane resistance, but one of the most prominent mechanisms seems to be the overexpression of specific β-tubulin isotypes, as reported by Kavallaris et al [33].

Point mutations in the paclitaxel binding site of β-tubulin were first described by Giannakakou et al in cancer cell lines [34], and were later reported to be associated with drug resistance in lung cancer patients [35]. However, more recent studies did not find tubulin mutations in ovarian and lung cancer patients exhibiting paclitaxel resistance [36,37]. Therefore, the contribution of tubulin point mutations to inducing the paclitaxel-resistant phenotype remains debated, and additional clinical studies are needed to ascertain the frequency of tubulin mutations in paclitaxel-resistant tumors. Among the possible mechanisms of paclitaxel resistance, the most prominent in *in vitro* systems seems to be the overexpression of the class III β-tubulin isotype [38].

**Mutation of topoisomerase genes**

Topoisomerases are nuclear enzymes and members of the gyrase family, which transiently break and unwind DNA during DNA replication and transcription. They are also involved in many cellular activities including chromosome condensation, DNA recombination, DNA segregation during mitosis, and DNA repair. Mammalian topoisomerases are classified into two types (I and II) based on the number of strands of DNA on which they act (single versus double) [39]. Topoisomerase I (TopoI), coded by a single-copy gene on chromosome 20 and involved in DNA transcription, catalyzes a transient single-strand DNA break, allows passage of another single DNA strand through the break, and then reseals the break. Topoisomerase II (TopoII), coded by a single-copy gene on chromosome 17 and involved in the separation of chromosomes for DNA replication, catalyzes a transient double-strand DNA break allowing for the passage of another DNA duplex through the break and then reseals the break. TopoII is expressed in specific phases of the cell cycle, G2, S, and M, in both normal and neoplastic cells [39].

TopoI and TopoII play a crucial role in the cell cycle, and their expression is increased in malignant ovarian neoplasm compared with borderline tumors. They are also the target of several chemotherapeutic agents, such as camptothecin, etoposide, teniposide, novobiocin, anthracyclines, and mitoxantrone [40–43].

Although TopoI and TopoII inhibitors are effective in malignant ovarian neoplasm, Pommier described that DNA TopoII rather than TopoI is involved in drug resistance and sensitivity in human tumors [44]. Two isoforms have been described, Topo-Ilt and Topo-IIl. These DNA conformation-controlling nuclear enzymes are the targets for several widely used anticancer drugs, including anthracyclines (e.g. doxorubicin) and epipodophyllotoxins (e.g. etoposide). These drugs exert their action by stabilizing a reaction intermediate formed during the catalytic cycle of TopoII. The presence of this stabilized protein–DNA complex, which is
called the cleavable complex, interferes with several processes that take place at the DNA level (transcription and replication), causing DNA damage and, ultimately, cell death. Topoll-related drug resistance is caused by a decrease in cleavable complex formation in the nucleus, which will lead to less DNA damage and less cell death [44]. Since topotecan is an inhibitor of Topol and is less involved in drug resistance, it may be suitable for use in drug-resistant ovarian cancer.

Increased DNA Repair Activity

A human ovarian cancer cell line resistant to cis-diamminedichloroplatinum(II) (DDP) (2780CP) was compared with its DDP-sensitive parental cell line (A2780) to determine whether differences in the removal rate of DNA-bound platinum were related to resistance [45]. This study indicated that the mechanism of DDP resistance in the 2780CP cell line is related to an increased ability to remove platinum-DNA adducts, and not to a difference in initial DDP binding to DNA.

Parker et al investigated acquired resistance to cisplatin in human ovarian cancer cells [46]. The same cell lines, A2780 and A2780/CP70, were studied to assess their respective characteristics of drug accumulation and efflux, cytosolic inactivation of drug, and DNA repair. The authors concluded that in these paired cell lines, alterations in drug uptake/efflux and DNA repair are the major contributing factors to acquired resistance to cisplatin.

Zhen et al reported that acquired cellular resistance to cisplatin may be associated with increased genespecific DNA repair efficiency of a specific lesion, the interstrand cross-link [47]. The study of Johnson et al also supports a role for DNA repair and alterations in interstrand cross-link formation in cisplatin resistance and provides evidence for heterogeneous interstrand cross-link formation in the genome [48].

The repair of platinum-DNA lesions is believed to occur primarily by the process of nucleotide excision repair (NER). NER removes DNA damage as part of an oligonucleotide 24–32 residues long. DNA damage is thought to be recognized by the zinc-finger protein XPA in association with the heterotrimeric replication protein RPA. The XPA–RPA complex is then believed to recruit the basal transcription factor TFIIH, a multisubunit protein that also plays a role in transcription, to the site of damage [49]. Two subunits of TFIIH, called XPB and XPD, have helicase activities that are believed to open up the DNA around the adduct, thus allowing structure-specific nucleases to incise the DNA. The ERCC1-XPF heterodimer, a structure-specific endonuclease, is responsible for cutting the strand on the 5' side of the damage, and the XPG protein incises on the 3' side. DNA polymerase δ or ε and accessory proteins, replication factor C, and proliferating cell nuclear antigen fill in the gap, and the DNA is joined by the action of DNA ligase. In addition to the proteins described above, the incision stage of the reaction requires XPC, a protein that may be involved in DNA damage recognition and/or stabilizing an incision reaction intermediate [50]. The study of Ferry et al supports a role for ERCC1-XPF endonuclease as a determinant of increased NER in this platinum resistance model in ovarian cancer [49]. However, knowledge is currently limited as to which of these NER proteins may be critical or rate-limiting in the enhanced DNA repair in platinum-resistant cell lines.

Increased Drug Damage Tolerance

Apoptosis is a distinct mode of genetically-controlled programmed cell death that is a complement to cell proliferation in normal tissues. The ability of a cancer cell to respond to a chemotherapeutic agent is believed to be due, in part, to its apoptotic capacity. Increased chemotherapy damage tolerance is associated with decreased susceptibility to apoptosis. Moreover, it is accepted that the process of drug-induced apoptosis is governed not only by the upregulation of pro-apoptotic factors or tumor suppressors, but also by modulation of cell survival factors [51]. A number of genes involved in either the induction or inhibition of apoptosis, namely the p53, Akt, and phosphoinositol-3-OH-kinase (PI3K) gene families, are aberrantly regulated in ovarian cancer [52,53]. Because of their wide-ranging biologic effects, deregulation of one or more of these factors may result in a failure of drug-induced apoptosis.

Aberrent regulation of the apoptotic regulators, including p53, the inhibitor of apoptosis (IAP) family, the Akt family, and the death-receptor family, plays a significant role in the induction and maintenance of chemoresistance [51]. Cisplatin has been shown to upregulate the pro-apoptotic factors p53, fas (also known as CD95), and bax in a number of cell types [54–56]. However, it also downregulates specific cell survival factors such as X-linked IAP (Xiap) and the Akt family [57]. Recent evidence suggests that chemoresistance may represent an overall imbalance between these two phenomena. Mansouri et al showed that the expression of Xiap and downregulation of fas ligand are linked to chemoresistance in ovarian carcinoma cells and may represent one of the potential anti-apoptotic mechanisms involved during this process [58].
Caspases are a family of cysteine-dependent aspartate-directed proteases that play critical roles in the initiation and execution of apoptosis. Following activation of the caspase cascade, downstream molecules are activated, including caspase activated DNase and acinus (apoptotic chromatin condensation inducer in the nucleus), leading to chromatin condensation and 180-basepair DNA laddering, a hallmark of apoptotic cell death [59]. One of the proteins responsible for caspase-independent chromatin condensation is apoptosis-inducing factor (AIF). The AIF gene is localized within the mouse X chromosome region A6, which is syntenic to the human X chromosome region Xq25–26 [60]. Ahn et al demonstrated that AIF is involved in paclitaxel-induced apoptosis in the human ovarian carcinoma cell line SKOV3 [61].

IAP was first identified in baculovirus [62]. The human IAP family includes Xiap, human IAP (Hiap)-1 and -2, neuronal apoptosis inhibitor protein (Naip), survivin, and livin [63]. Xiap is a 55-kDa protein that directly inhibits the initiator caspase-9 and execution caspase-3 and -7, attenuating both mitochondria/cytosol and death receptor-mediated apoptosis [64]. Cisplatin downregulates Xiap in chemosensitive, but not chemoresistant, ovarian cancer cells. Moreover, Xiap is a determinant of chemoresistance, since downregulation of Xiap in chemoresistant cells renders the cells sensitive to the cytotoxic actions of cisplatin, while overexpression of Xiap in chemosensitive cells causes reversion to the chemoresistant phenotype [57, 65].

Death receptors are cell-surface proteins belonging to the tumor necrosis factor (TNF) superfamily. These receptors or their downstream effectors play an important role in regulating apoptosis, cellular growth, and proliferation. The most widely studied death receptors are fas, TNF receptor-1 (TNFR1), TNFR2, and the TNF-related apoptosis inducing ligand (TRAIL) receptors, all of which are characterized by an intracellular region of about 80 amino acids termed the death domain (DD) [51]. The DD motif is essential for the induction of apoptotic cell death via recruitment of adapter proteins containing a DD motif (e.g. fas-associated death domain, FADD, and TNFR-associated death domain, TRADD) and formation of a receptor signaling complex, fas ligand, resulting in intracellular clustering of DDs and the recruitment of FADD to the receptor via homologous DD interactions [66]. Alterations in the expression of fas have been demonstrated in various cancers as a mechanism for tumor cells to escape from immune surveillance. Lysophosphatidic acid induces translocation of fas from the cell membrane to the cytosol, which may provide a mechanism by which ovarian cancer cells evade fas ligand-bearing immune cells [67].

Initiator caspses implicated in the death receptor-mediated apoptotic pathways (e.g. caspase-8) are activated through interaction with the caspase-recruitment domain motif of the death receptor-associating proteins [68]. Downstream execution caspses (e.g. caspase-3 and -7) are subsequently activated by initiator caspses. Two of the death receptor pathways, TNFα–TNFR1 and fas ligand–fas, have been suggested to play an important role in chemoresistance in ovarian cancer cells. In human ovarian cancer cells, DNA-damaging agents such as cisplatin can upregulate fas and fas ligand, resulting in activation of caspase-8 and -3 and induction of apoptosis. In a chemoresistant variant, cisplatin failed to upregulate fas ligand or induce apoptosis [69]. Fraser et al also supported the notion that dysregulation of the fas/fas ligand system may be an important determinant in cisplatin resistance in ovarian cancer cells [51].

fas-associated death domain-like interleukin-1β-converting enzyme (FLICE)-like inhibitory protein (FLIP) is recruited to the death-inducing signaling complex through FADD, thereby preventing caspase-8 recruitment and activation and downstream apoptotic events [70, 71]. Binding of TNFα to TNFR2 induces IκB phosphorylation and degradation and activates nuclear factor κB (NFκB), which in turn regulates TNFα-induced apoptosis by inducing the expression of genes that modulate apoptotic pathways (e.g. IAPs and FLIP). TNFα is believed to play an important role in ovarian cancer biology and tumorigenesis, with concentrations significantly increased in ovarian cancer patients [72] and levels of TNFα expression positively correlated with tumor grade [73]. Xiao et al demonstrated that TNFα induces NFκB-mediated FLIP expression, which protects ovarian cancer cells from the cytotoxic action of the cytokine [74]. The resistance of ovarian cancer cells to the cytotoxic action of TNFα may be associated with the induction of FLIPs in response to the cytokine. In addition, since activation of the fas/fas ligand system is an important mechanism of cisplatin-induced apoptosis in human ovarian cancer cells [56], the possibility that FLIP is differentially regulated in chemoresistant ovarian cancer cells cannot be excluded. Mezzanzanica et al revealed that the inhibitory protein c-FLIP(L) is involved in resistance to fas-mediated apoptosis in ovarian carcinoma cells with wild-type p53 [75].

Many cancers have constitutively activated NFκB, the elevation of which contributes to cancer cell resistance to chemotherapeutic agent-induced apoptosis. Although mitogen-activated protein kinase/ extracellular-regulated kinase kinase-3 (MEKK3) has
been shown to participate in the activation of NFκB, its relationship to apoptosis and cancer are unclear. Samanta et al established that elevated expression of MEKK3 appears to be a frequent occurrence in breast and ovarian cancers and that overexpression of MEKK3 leads to increased NFκB activity and increased expression of cell survival factors and ultimately contributes to cell resistance to apoptosis [76]. As such, MEKK3 may serve as a therapeutic target to control cancer cell resistance to cytokine- or drug-induced apoptosis.

PI3Ks are a family of lipid kinases that play a crucial role in a wide range of important cellular processes associated with malignant behavior including cell growth, migration, and survival. They are heterodimers with separate regulatory (p85) and catalytic (p110) subunits. AKT (a subfamily of the serine/threonine protein kinases) is the only downstream target of PI3K that has been associated with malignant transformation, and its activation mediates a variety of cellular responses including cell growth, transformation, differentiation, motility, and cell survival. The intermediates of the PI3K/AKT survival pathway are often altered in human ovarian cancer, and high levels of PI3K and AKTs have been linked to poor prognosis and chemoresistance [77]. Amplification of AKT2 (a candidate oncogene at 19q13) has been demonstrated in breast, ovarian, and pancreatic cancer. Moreover, the gene that encodes the p110 subunit of PI3K is amplified in some cases of ovarian cancer, and the p85 subunit of PI3K is also targeted for mutation in human cancer [78]. Fraser et al have demonstrated a role for the PI3K/AKT pathway in resistance to a number of anti-tumor agents [79]. Yuan et al have also demonstrated that cells expressing a constitutively active AKT2 are resistant to cisplatin [80]. The study of Asselin et al indicates that Xiap prevents apoptosis through PI3K-dependent inhibition of the caspase cascade, demonstrating a novel mechanism by which Xiap regulates apoptosis and the possible involvement of the PI3K/AKT survival pathway in Xiap-mediated chemoresistance of ovarian cancer cells [81].

The cellular apoptosis susceptibility (CAS) gene is the human homologue of the yeast chromosome segregation gene CSE and is located at 20q13.1. It is related to TNFα-mediated apoptosis, probably because of its involvement in nuclear transport of apoptosis-associated proteins [82]. CAS is frequently upregulated in serous ovarian carcinomas, correlated with apoptosis and mitotic activity, and is prognostically relevant [83].

The bcl family is a group of apoptosis-regulating genes that prevent or trigger apoptosis. bcl-2 is a physiologic inhibitor of programmed cell death and considered a “generalized cell death suppressor” gene that directly regulates apoptosis [84]. Through alternate splicing mechanisms, the bcl-x gene, another member of the bcl family, encodes two proteins that exert different functions: bcl-xL, the longer form, inhibits apoptosis, while the shorter form, bcl-xS, is a dominant inhibitor of bcl-2, promoting apoptosis [85]. Overexpression of bcl-2 occurs frequently in human cancers and is associated with tumor cell resistance to chemotherapeutic agents by preventing the apoptotic response normally induced by those agents [86]. Yang et al showed that overexpression of anti-apoptotic proteins bcl-2 and bcl-xL and downregulation of caspase-3 activity may be associated with cisplatin resistance in human ovarian cancer [87].

p53 inhibits progression of stressed cells through the cell cycle and even induces apoptosis in a desperate attempt to contain the damage and protect the organism. The pro-apoptotic activity of p53 is mediated through the mitochondrial pathway by activation of bcl family members such as bax. Thus, the p53 protein provides a critical brake on tumor development [88]. Sasaki et al demonstrated that Xiap downregulation following adenoviral antisense expression induces apoptosis in cells with wild-type p53, but not in mutated or null cells [65]. Xiap downregulation results in caspase-3 activation, caspase-mediated MDM2 processing, and p53 accumulation. Restoration of wild-type p53 in p53-mutated or -null cells significantly enhances the pro-apoptotic effect of Xiap antisense expression. Down-regulation of Xiap induces apoptosis in chemoresistant ovarian cancer cells, a process dependent on p53 status.

Conclusion

Drug resistance of tumor cells is recognized as the primary cause of failure of chemotherapeutic treatment of ovarian tumors. Drug resistance is a multifactorial phenomenon involving multiple interrelated or independent mechanisms. The relevant mechanisms that can contribute to drug resistance include: alterations in drug transport, changes in cellular proteins involved in detoxification, altered drug target, changes in DNA repair mechanisms, and increased tolerance to drug-induced DNA damage. Alterations in specific genes (oncogenes, tumor suppressor genes, metastasis suppressor genes) appear to be associated directly with the loss of chemosensitivity.

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