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The impact of P-glycoprotein and Midkine on Paclitaxel/ Cisplatin Chemoresistance in Ovarian Cancer

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Abstract

Chemoresistance is one of the most important factors leading to high mortality in ovarian cancer (OC). Overexpression of P-glycoprotein (P-gp) in OC cells may results in resistance to paclitaxel treatment by pumping the drug out of the cells, which in turn decreases the intracellular drug concentration. Additionaly overproduction of midkine (MK) can also affect the development of chemoresistance in OC. Although, the mechanisms of action of P-gp and MK are not the same, overexpression of both proteins in OC may intensify chemoresistance to paclitaxel treatment. Therefore, simultaneously inhibition of P-gp and MK in overcoming chemoresistance to drugs may improve treatment results in OC.

Introduction

Ovarian cancer (OC) is the fourth most common type of gynecological cancers worldwide and has the highest mortality rates among female genital tract malignancies [1–3]. Even patients with same clinical characteristics, such as cancer stage, histological type and grade display different disease progression and treatment results [3–5]. Due to absence of specific symptoms in the early stage, OCs are diagnosed at the advanced stages in two thirds of the patients [6]. The overall 5 year survival rate is still less than 40% despite some advances in the treatment of OC, including the combination of surgery, radiation and chemotherapy. This may be attributed to the late stage diagnosis, poor prognosis and resistance to chemotherapy, which is one of the major problems to controlling malignant tumors [3, 7, 8]. The first-line treatment of OC is cytoreductive surgery followed by adjuvant chemotherapy, including paclitaxel and cisplatin [3, 9–11]. Paclitaxel, administered as monotherapy or in combination with cisplatin, is potentially effective therapeutic regimen in OC. Paclitaxel may be regarded as a mitotic poison and affects the cellular microtubule network. It inhibits chromosome alignment and segregation and then trigger the apoptosis pathway [10, 11].

Initial response rates to chemotherapy vary between 40 and 80% in OCs. However, majority of these patients who respond to chemotherapy at first, eventually have recurrence following the development of chemoresistance. Thus, acquired resistance is the main cause of unsuccessful treatment in OC. The molecular mechanisms behind chemoresistance is multifactorial and involves multiple processes, including drug transport and metabolism, DNA repair and apoptosis. Currently, the factors that affect the development of chemoresistance in OC has not been completely understood [6, 12]. Chemoresistance is usually attributed to the overproduction of P-gp. It has been reported that overexpression of P-gp is the major factor for reduced chemo-sensitivity in a lot of malignancies, including OC [6, 12–14]. It has been demonstrated that the overexpression of P-gp in aggressive OC cells results in the development of resistance to paclitaxel treatment [10, 11, 15]. Although the mechanism of P-gp-induced chemoresistance is not fully known, it is considered to acts essentially as an efflux pump and plays an important role in the exclusion of drugs from tumor cells, resulting in decreased accumulation of chemotherapy drugs within cancer cells [8, 10, 11, 15].

Another important protein, MK, is overexpressed in many cancers, including OC and induces the growth and survival of tumors. On the other hand, overproduction of MK can also affect the development of chemoresistance. The chemoresistance caused by MK is mainly due to its inhibitory action on the apoptosis process.

Our proposal is that both proteins, namely P-gp and MK, may protect tumor cells against chemotherapeutic drugs more effectively by a synergistically way than they do one by one and they could increase chemoresistance [3, 16–19]. Therefore, it can be speculated that inhibition of both proteins may enhance the effectiveness of paclitaxel chemosensitivity in OC.

The role of P- glycoprotein in chemoresistance to paclitaxel /cisplatin in ovarian cancer

ATP-binding cassette transporter B1 (ABCB1), also known as P-gp or multidrug resistance protein 1 (MDR1) is an adenosine

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triphosphate (ATP)-dependent efflux transporter located in the plasma membrane of many different cell types [20]. It is a 170 kD transmembrane glycoprotein and has unusually broad polyspecificity for structurally different substances, including anticancer drugs such as paclitaxel and cisplatin. Most of these substances are hydrophobic, thus, P-gp acts like a ''hydrophobic vacuum cleaner" [20].

P-gp leads to chemoresistance by pumping drugs out of the cells and decreases the intracellular drug concentration [9]. P-gp is also associated with a more progressed malignant phenotype in carcinogenesis. The function of P-gp in relation to cellular differentiation may be pleiotropic, depending on the origins from which the cancer arises [8]. P-gp is localized in the membrane of epithelial cells in the intestine, liver, proximal tubule of the kidney and in the capillary endothelial cells. It functions as a blood–brain barrier, blood–placenta barrier and blood-testis barrier and protects them from toxic xenobiotics [20]. This transporter may affect the pharmacological treatment of numerous diseases by changing drug pharmacokinetics and inhibiting accumulation of anticancer drugs in cancer cells. Cancer cells of some tissues also produce very large amount of P-gp, which lead to chemoresistance by transfering chemotherapeutic agents out of cancer cells. Additionally, increased intestinal expression of P-gp can inhibit the absorption of orally administered drugs, promotes their biliary and renal elimination and as a result, decreases plasma concentrations of these drugs, which causes unsuccesful treatment [6, 19, 20].

Fojo *et al*. have reported that the *MDR1* gene is overexpressed in many cancers arising from some tissues in which the *MDR1* gene is expressed at high levels. Most of these cancers are resistant to chemotherapy, and the *MDR1* gene plays an important role in intrinsic and acquired chemoresistance [8, 21]. Approximately 40% of OCs after chemotherapy produce P-gp at high level, suggesting chemoresistance in OCs may be most likely acquired [8, 22]. However, some OC cases before chemotherapy are intrinsically multidrug resistant, which can be determined by *MDR1* gene expression, and this phenotype should be taken into account for effective chemotherapy of ovarian epithelial carcinomas [8]. It has been revealed that the overexpression of P-gp in aggressive OC cells is associated with the development of resistance to paclitaxel treatment [10, 11, 15]. In contrast, downregulation of P-gp increases the effectiveness of certain chemotherapeutic agents. For example, myricetin (a dietary-flavonoid) enhances the chemotherapeutic potential of paclitaxel in OC cells by downregulating P-gp and inhibits the migratory properties of OC cells [10]. Alike, microRNAs (miRNA), which are endogenous, noncoding RNAs may regulate the *ABCB1* gene. Recently, Sun *et al*. have demonstrated that miR-186 overexpression may sensitize OC cells to paclitaxel and cisplatin by downregulating P-gp in the OC cell lines [9]. Another study has demonstrated that miR-21 may regulate the production of MDR1/P-gp, by targeting hypoxia-inducible factor-1α (HIF-1α,) which influences the development of drug resistance in paclitaxel-resistant OC A2780/taxol cell lines. Furthermore, the inhibition of miR-21 may sensitize A2780/taxol cells to paclitaxel [12]. Aditionally, upregulation of miR-27a expression results in inhibition of P-gp expression and decreases paclitaxel-resistance in OC cell line [15].

As the expression of P-gp in cancer cells usually results in multidrug resistance (MDR) to chemotherapeutic drugs, which is the main cause of chemotherapy failure in cancer treatment, it is important to develop new treatment strategies, which target P-gp [11]. Some MDR reversal agents that inhibit the drug efflux activity of P-gp could increase the intracellular drug levels [11]. It has been demonstrated that MDR1 expression levels after promethazine (an antihistaminic agent) administration is significantly reduced and verapamil (a calcium channel antagonist) leads to a significant decrease in MDR1 mRNA levels and downregulates P-gp activity [23].

The role of midkine in chemoresistance to paclitaxel / cisplatin in ovarian cancer

Midkine (MK), a heparin-binding growth factor, was firstly found to be the product of a retinoic acid-responsive gene during embryogenesis [24, 25]. Despite its high expression during embryogenesis, MK is downregulated to neglible levels in healthy adults and only re-expressed in some pathological processes [16, 25, 26]. MK promotes many cellular functions including survival, growth, migration, reproduction and repair, and gene expression while inhibiting apoptosis [27]. Due to its multiple functions, MK has significant impact on the pathogenesis of neurological, cardiovascular and inflammatory diseases and malignancies [19, 25]. It induces several signal transduction pathways including phosphoinositide 3-kinase (PI3K) and extracellular signal-regulated kinase (ERK), therefore participates in the regulation of diverse biological processes. Recent studies showed that MK expression is influenced by hypoxia, growth factors, and cytokines through a nuclear factor-κB (NF-κB) dependent pathway. The precise regulatory mechanisms behind MK expression is not fully understood [25, 28, 29]. MK plays significant roles as a growth factor during carcinogenesis, such as transformation, fibrinolysis, cell invasiveness, cell survival, anti-apoptosis, and angiogenesis processes [24, 27, 29–33].

It has been shown that MK is overexpressed in various human malignancies, including oral, lung, thyroid, bladder, prostate, cervical and OCs [18, 25, 35–37]. MK is also a plasma-secreted protein, and its levels in blood may increase in patients with malignant diseases [25]. Nakanish *et al*. have demonstrated that the expression of MK in germ cell ovarian tumors is significantly lower than in epithelial ovarian tumors, and expression in malignant epithelial tumors is significantly higher than in benign ones [18]. MK not only induces carcinogenesis but also contributes to chemoresistance [34]. It is considered that MK-induced chemoresistance is mainly due to inhibitory impact on apoptosis mediated by the Janus-activated kinases (JAKs) and STAT1 by activating the Akt-mediated survival pathway and senescence of tumor cells [19, 31]. On the other hand, it appears that some of the mechanisms of its chemoresistance actions are partially similar to those of P-gp [19].

MK, has been verified overexpressed in many cancers, including OC. It has been shown that MK is increased in the serum of patients with epithelial OC. MK may also be an indicator of the response to paclitaxel and/or cisplatin in the clinical treatment of OC [3, 16–18]. Zhang *et al*. have demonstrated that cancer-associated fibroblasts (CAFs) in the tumour microenvironment (TME) may lead to the

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high level of MK in tumours and that CAF-derived MK can induce cisplatin resistance via inhibition of the cell apoptosis in the TME by increasing production of lncRNA ANRIL. CAF-derived MK increases lncRNA ANRIL expression in tumour cells and thus promoting the up-regulation of ABC family proteins, multidrug resistance-associated protein 1 (MRP1) and ABCC2, which ultimately cause resistance to cisplatin. These findings related to the source of MK in tumour tissues, may serve as a novel therapeutic approach for cancer [34]. Further evidence is that a novel midkine inhibitor (iMK) has antitumor effect against oral squamous cell carcinoma and it has been demonstrated that iMK inhibits the expression of MK and suggested that iMK can be effectively used for the treatment of oral squamous cell carcinoma [19, 25, 38].

On the contrary, Wu *et al*. have suggested that the MK expression has a positive correlation with the predicted survival time and chemosensitivity of OC to paclitaxel/cisplatin. This study proposed that MK could down-regulate the expression of multidrug resistance-associated protein 3 (MRP3), and in turn increases the cytotoxicity of paclitaxel and/or cisplatin [3]. Despite this contrary opinion, it is generally considered that MK increases chemoresistance and decreases effective treatment during chemotherapy. On the other hand, due to its biological significance in carcinogenesis, it is suggested that MK can be regarded as a candidate molecular target for therapy against human carcinomas [25].

Conclusion

Chemoresistance is one of the important factors leading to high mortality in OC. At present paclitaxel and cisplatin are the most used drugs to treat OC. However, numerous patients with OC frequently relapse following the development of chemoresistance to chemotherapeutic agents, including paclitaxel and cisplatin. Overexpression of P-gp and MK have important impacts on chemoresistance in many cancer types, including OCs. Therefore, inhibition of both P-gp and MK may overcome chemoresistance in OCs. However, whether they act synergistically or in contrary remains unclear and further investigations are needed to clarify the interplay of these proteins in cancer cells and in the treatment of malignancies.

References

1. Konstantinopoulos PA, Matulonis UA. Current status and evolution of preclinical drug development models of epithelial ovarian cancer. Front Oncol.2013;3: 296.
2. Rajanbabu A, Kuriakose S, Ahmad SZ, Khadakban T, Khadakban D, Venkatesan R, Vijaykumar DK. Evolution of surgery in advanced epithelial ovarian cancer in a dedicated gynaecologic oncology unit-seven year audit from a tertiary care centre in a developing country. Ecancermedicalscience. 2014;8: 422.
3. Wu X, Zhi X, Ji M, Wang Q, Li Y, Xie J, Zhao S. Midkine as a potential diagnostic marker in epithelial ovarian cancer for cisplatin/paclitaxel combination clinical therapy. Am J Cancer Res. 2015;5(2): 629–38
4. Romero-Laorden N, Olmos D, Fehm T, Garcia-Donas J, Diaz-Padilla I. Circulating and disseminated tumor cells in ovarian cancer: a systematic review. Gynecol Oncol. 2014;133(3): 632–9.
5. Musrap N, Diamandis EP. Revisiting the complexity of the ovarian cancer microenvironment-clinical implications for treatment strategies. Mol Cancer Res. 2012;10(10): 1254–64.
6. Norouzi-Barough L, Sarookhani M, Salehi R, Sharifi M, Moghbelinejad S.CRISPR/Cas9, a new approach to successful knockdown of ABCB1/P-glycoprotein and reversal of chemosensitivity in human epithelial ovarian cancer cell line. Iran J Basic Med Sci. 2018;21(2): 181- 187.
7. Bast RC Jr. Early detection of ovarian cancer: new technologies in pursuit of a disease that is neither common nor rare. Trans Am Clin Climatol Assoc.2004;115: 233–47.
8. Arao S, Suwa H, Mandai M, Tashiro H, Miyazaki K, Okamura H, Nomura H, Hiai H, Fukumoto M. Expression of multidrug resistance gene and localization of P-glycoprotein in human primary ovarian cancer. Cancer Res. 1994; 54(5): 1355–9.
9. Sun KX, Jiao JW, Chen S, Liu BL, Zhao Y (2015) MicroRNA-186 induces sensitivity of ovarian cancer cells to paclitaxel and cisplatin by targeting ABCB1. *J Ovarian Res* 8: 80. [crossref]
10. Zheng AW, Chen YQ, Zhao LQ, Feng JG. Myricetin induces apoptosis and enhances chemosensitivity in ovarian cancer cells. Oncol Lett. 2017; 13(6): 4974–78.
11. Wang B, Li S, Meng X, Shang H and Guan Y: Inhibition of mdr1 by G-quadruplexoligonucleotides and reversal of paclitaxel resistance in human ovarian cancer cells. Tumour Biol. 2015; 36: 6433–6443.
12. Xie Z, Cao L, Zhang J. miR-21 modulates paclitaxel sensitivity and hypoxia-inducible factor-1a expression in human ovarian cancer cells. Oncol Lett. 2013; 6(3): 795–800.
13. Gottesman MM, Ling V. The molecular basis of multidrug resistance in cancer: the early years of P-glycoprotein research. FEBS Lett. 2006; 580(4): 998–1009.
14. Binkhathlan Z, Lavasanifar A. P-glycoprotein inhibition as a therapeutic approach for overcoming multidrug resistance in cancer: current status and future perspectives. Curr Cancer Drug Targets. 2013; 13(3): 326–46.
15. Zhang H, Wang J, Cai K, Jiang L, Zhou D, Yang C, Chen J, Chen D, Dou J. Downregulation of gene MDR1 by shRNA to reverse multidrug-resistance of Ovarian cancer A2780 cells. J Cancer Res Ther. 2012; 8(2): 226–31.
16. Jones DR (2014) Measuring midkine: the utility of midkine as a biomarker in cancer and other diseases. *Br J Pharmacol* 171: 2925–2939. [crossref]
17. Rice GE, Edgell TA, Autelitano DJ (2010) Evaluation of midkine and anterior gradient 2 in a multimarker panel for the detection of ovarian cancer. *J Exp Clin Cancer Res* 29: 62. [crossref]
18. Nakanishi T, Kadomatsu K, Okamoto T, Tomoda Y, Muramatsu T (1997) Expression of midkine and pleiotropin in ovarian tumors. *Obstet Gynecol* 90: 285–290. [crossref]
19. Aynacioglu AS, Bilir A, Kadomatsu K. Dual inhibition of P-glycoprotein and midkine may increase therapeutic effects of anticancer drugs. Med Hypotheses. 2017; 107: 26–28.
20. Wolking S, Schaeffeler E, Lerche H, Schwab M, Nies AT. Impact of Genetic Polymorphisms of ABCB1 (MDR1, P-Glycoprotein) on Drug Disposition and Potential Clinical Implications: Update of the Literature. Clin Pharmacokinet. 2015; 54(7): 709–35.
21. Fojo AT, Ueda K, Slamon DJ, Poplack DG, Gottesman MM, et al. (1987) Expression of a multidrug-resistance gene in human tumors and tissues. *Proc Natl Acad Sci U S A* 84: 265–269. [crossref]
22. Bell DR, Gerlach JH, Kartner N, Buick RN, Ling V. Detection of P-glycoprotein in ovarian cancer: a molecular marker associated with multidrug resistance. Clin Oncol. 1985; 3(3): 311–5.
23. Dönmez Y, Akhmetova L, Iseri ÖD, Kars MD, Gündüz U. Effect of MDR modulators verapamil and promethazine on gene expression levels of MDR1 and MRP1 in doxorubicin-resistant MCF-7 cells. Cancer Chemother Pharmacol. 2011; 67(4): 823–8.
24. Kadomatsu K, Huang RP, Suganuma T, Murata F, Muramatsu T. A retinoic acid responsive gene MK found in the teratocarcinoma system is expressed in spatially and temporally controlled manner during mouse embryogenesis. J Cell Biol. 1990; 110(3): 607–16.
25. Jono H, Ando Y (2010) Midkine: a novel prognostic biomarker for cancer. *Cancers (Basel)* 2: 624–641. [crossref]
26. Matsubara S, Tomomura M, Kadomatsu K, Muramatsu T. Structure of a retinoic acid-responsive gene, MK, which is transiently activated during the differentiation of embryonal carcinoma cells and the mid-gestation period of mouse embryogenesis. J Biol Chem. 1990; 265(16): 9441–3.
27. Muramatsu T (2014) Structure and function of midkine as the basis of its pharmacological effects. *Br J Pharmacol* 171: 814–826. [crossref]
28. Owada K, Sanjo N, Kobayashi T, Mizusawa H, Muramatsu H, Muramatsu T, Michikawa M. Midkine inhibits caspase-dependent apoptosis via the activation of mitogen-activated protein kinase and phosphatidylinositol 3-kinase in cultured neurons.J Neurochem. 1999; 73(5): 2084–92.
29. You Z, Dong Y, Kong X, Beckett LA, Gandour-Edwards R, et al. (2008) Midkine is a NF-kappaB-inducible gene that supports prostate cancer cell survival. *BMC Med Genomics* 1: 6. [crossref]
30. Kojima S, Muramatsu H, Amanuma H, Muramatsu T. Midkine enhances fibrinolytic activity of bovine endothelial cells. J Biol Chem. 1995; 270(16): 9590–6.
31. Ratovitski EA, Kotzbauer PT, Milbrandt J, Lowenstein CJ, Burrow CR. Midkine induces tumor cell proliferation and binds to a high affinity signaling receptor associated with JAK tyrosine kinases. J Biol Chem. 1998; 273(6): 3654–60.

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32. Huang Y, Hoque MO, Wu F, Trink B, Sidransky D, Ratovitski EA. Midkine induces epithelial-mesenchymal transition through Notch2/Jak2-Stat3 signaling in human keratinocytes. Cell Cycle. 2008; 7(11): 1613–22.
33. Huang Y, Sook-Kim M, Ratovitski E. Midkine promotes tetraspanin-integrin interaction and induces FAK-Stat1alpha pathway contributing to migration/ invasiveness of human head and neck squamous cell carcinoma cells. Biochem Biophys Res Commun. 2008; 377(2): 474–478.
34. Zhang D, Ding L, Li Y, Ren J, Shi G, Wang Y, Zhao S, Ni Y, Hou Y. Midkine derived from cancer-associated fibroblasts promotes cisplatin-resistance via up-regulation of the expression of lncRNA ANRIL in tumour cells. Sci Rep. 2017; 7(1): 16231
35. Ruan M, Ji T, Wu Z, Zhou J, Zhang C (2007) Evaluation of expression of midkine in oral squamous cell carcinoma and its correlation with tumour angiogenesis. *Int J Oral Maxillofac Surg* 36: 159–164.
36. Aridome K, Tsutsui J, Takao S, Kadomatsu K, Ozawa M, Aikou T, Muramatsu T. Increased midkine gene expression in human gastrointestinal cancers. Jpn J Cancer Res. 1995; 86(7): 655–61. [crossref]
37. Kato M, Shinozawa T, Kato S, Endo K, Terada T. Increased midkine expression in intrahepatic cholangiocarcinoma: immunohistochemical and in situ hybridization analyses. Liver. 2000; 20(3): 216–21.
38. Masui M, Okui T, Shimo T, Takabatake K, Fukazawa T, Matsumoto K, Kurio N, Ibaragi S, Naomoto Y, Nagatsuka H, Sasaki A. Novel Midkine Inhibitor iMDK Inhibits Tumor Growth and Angiogenesis in Oral Squamous Cell Carcinoma. Anticancer Res. 2016; 36(6): 2775–81.
39. Shen Y, Zhang XY, Chen X, Fan LL, Ren ML, Wu YP, Chanda K, Jiang SW. Synthetic paclitaxel- octreotide conjugate reverses the resistance of paclitaxel in A2780/Taxol ovarian cancer cell line. Oncol Rep. 2017; 37(1): 219–226.
40. Gillet JP, Gottesman MM (2010) Mechanisms of multidrug resistance in cancer. *Methods Mol Biol* 596: 47–76. [crossref]
41. Pan ST, Li ZL, He ZX, Qiu JX, et al. (2016) Molecular mechanisms for tumour resistance to chemotherapy. *Clin Exp Pharmacol Physiol* 43: 723–737. [crossref]

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