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Semaphorin 3A (SEMA3A), protocadherin 9 (PCDH9), and S100 calcium binding protein A3 (S100A3) as potential biomarkers of carcinogenesis and chemoresistance of different neoplasms, including ovarian cancer — review of literature

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ABSTRACT

Ovarian cancer is the fifth leading cause of cancer-related deaths in women. Its high mortality rate results from lack of adequate and sensitive methods allowing for the detection of the early stages of the disease, as well as low efficiency of the treatment, caused by the cytotoxic drug resistance of cancer cells. Unfortunately, tumours are able to develop new pathways and protective mechanisms that allow them to survive toxic conditions of chemotherapy. Therefore, intensive search for new genes and proteins involved in resistance to cytotoxic drugs is still needed, especially from a clinical point of view. The article presents an overview of the available literature on the role of semaphorin 3A (SEMA3A), protocadherin 9 (PCDH9), and S100 calcium binding protein A3 (S100A3) in carcinogenesis and chemoresistance of various tumors including ovarian cancer. As it turns out, the role of described genes/proteins is not limited only to their native biological activity but they function also as an oncogenic or suppressor factors in the tumor development. Moreover, they can also play an important role in development of drug resistance, as it was shown in ovarian cancer cell lines.

Key words: ovarian cancer; carcinogenesis; chemotherapy; drug resistance; semaphorin 3A (SEMA3A); protocadherin 9 (PCDH9); S100 calcium binding protein A3 (S100A3)

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INTRODUCTION

Despite its relatively low incidence, ovarian cancer (OC) is the fifth leading cause of cancer-related deaths in women [1]. Most patients are diagnosed at late stages of the disease with overall survival rate of 30%. At the time of diagnosis, ovarian cancer is usually sensitive to most cytotoxix drugs, whereas during therapy, the cancer cells may develop drug resistance, which may cause ineffectiveness of further treatment lines, and hence is considered as one of the main reasons of such poor clinical outcomes of OC treatment. A standard first-line strategy for ovarian cancer is aggressive surgery accompanied by first- line chemotherapy with platinum and taxane agents. The most common cytotoxic drugs used in the second-line treatment of OC are doxorubicin and topotecan. However, despite all of the recent research on surgical techniques and chemotherapy, the improvement in the outcomes of the disease is not satisfactory and approximately 80% of the patients will present with recurrence within 12 to 18 months after initial diagnosis and eventually succumb to OC [2].

The choice of cytotoxic drugs for treatment of OC relapse depends on patient's reaction to first-line therapeutics. Traditionally, OC is divided in terms of response to initial platinum-based treatment into platinum-sensitive, platinum-refractory and platinum-resistant. Patients that are platinum sensitive respond well to the first-line therapy, with platinum-free interval (PFI) of minimum 6 months. Platinum-refractory patients develop progression during the treatment with the use of platinum compounds. In platinum resistant cases, the initial response to treatment is good, but eventually the relapse within 6 months since the end

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of the treatment is observed [3]. In cases of platinum-resistant recurrence, second line treatment options consist of liposomal doxorubicin, topotecan, gemcitabine, or oral etoposide [4]. Unfortunately, the effectiveness of second-line chemotherapy is usually low, at around 15 to 35% [5]

Despite all of described treatment options, the prognosis of advanced or recurrent disease remains poor. Late diagnosis at late clinical stage, tumoral heterogeneity and inherent or acquired during treatment drug resistance of cancer cells are considered to be the main reasons of the poor clinical outcomes.

There is a number of known and well described cellular mechanisms of drug resistance. The most important one is the active removal of the drug outside the cell involving the transporters of the ABC family [6]. Other mechanisms responsible for cytotoxic-drug resistance are: breaking the apoptotic signaling pathways, inactivating the drugs by binding to metallothionein or glutathione or using the detoxification enzymes, increase in the activity of pro-survival and anti-apoptotic pathways, reconstruction of damaged DNA, and forming mutations in the genes encoding proteins that bind cytotoxic drugs [7]. Unfortunately, tumors are able to develop a range of different mechanisms that lead to gain of resistance to the abovementioned agents, both on the cellular and tissue levels. Currently, there are no specific markers allowing for prediction or detection of ovarian cancer drug resistance. Therefore, intensive search for new genes and proteins involved in resistance to cytotoxic drugs is still needed, especially from a clinical point of view.

Although many drug resistance models have been described so far, cancer cells are still able to develop new pathways and protective mechanisms that allow them to survive toxic conditions. This indicates that drug resistance is a complex phenomenon with a variety of new and still undiscovered genes and processes to be involved in. Microarray- based studies of chemoresistance in OC proved this hypothesis and revealed a wide range of genes that were shown to be under- or overexpressed in drug resistant cancer cell lines. The results of the analyses indicate that new genes, previously unrelated and non-associated not only with drug-resistance but even with cancer development, may be involved in chemoresistance [8–10]. *Semaphorin 3A* (SEMA3A), *protocadherin 9* (PCDH9), and *S100 calcium binding protein A3* (S100A3) were discovered among the genes that exhibited changed expression and have not been previously associated with the development of drug resistance. The expression of all of these genes was shown to be altered in microarray- based studies conducted on ovarian cancer cell lines resistant to most commonly used cytotoxic drugs [11–13].

SEMAPHORIN 3A (SEMA3A)

SEMA3A belongs to a large family of membrane- bound and secreted proteins-semaphorins, which were initially known to play an important role in axonal guidance [14]. They can be classified into 8 classes (SEMA 1–7 and viral semaphorins). Class 3 semaphorins is the only type secreted in vertebrates, and consists of seven proteins (SEMA3A–G), which are secreted by several types of cells including neurons, epithelial cells, endocrine cells or cardiac muscle cells. They are expressed in the nucleus and cytoplasm of normal ovarian epithelium [15] and play a role in organogenesis and angiogenesis. Lately however, their wide expression and potential role in the tumor growth has been investigated. Recent studies had shown that SEMA3A, besides its anti- angiogenic role, might also serve as either tumor-inhibitory or tumor-promoting factor, depending on the microenvironment. Its antitumoral effect might be achieved by inhibiting cell migration and proliferation, reducing the adhesion or migration of tumor cells and promoting apoptosis [16]. SEMA3A being a candidate gene of tumor suppression was shown to be downregulated in several types of cancer, for example oral cancer, gastric cancer, breast cancer, prostate cancer as well as glioblastoma and OC. Moreover, the expression of SEMA3A protein usually significantly correlated with clinicopathological features of these neoplasms, such as: stage and grade of the disease, depth of invasion, presence of metastases and the survival [15, 17–22].

In gastric carcinoma, the underexpression of SEMA3A correlated with poor differentiation, depth of invasion, presence of metastases and vascular invasion as well as the advanced TNM stage. It also seemed to be an independent prognostic factor of poor survival. Furthermore, in in vitro studies on gastric cancer the overexpression of SEMA3A was shown to inhibit cell proliferation and migration [18]. In prostate cancer, positive expression of SEMA3A in tumor cells was associated with predictors of good prognosis such as lower pathological stage and lower preoperative PSA level [20]. On the other hand, decreased expression of SEMA3A in prostatic cancer cells was also found to be a predictor of resistance to hormonal treatment [23]. In OC, the underexpression of SEMA3A significantly correlated with FIGO stage, grade and presence of metastatic disease. However, no correlation between SEMA3A expression and histological type or size of the tumor was found in ovarian carcinoma [15].

On the contrary, in some neoplasms, like lung cancer, SEMA3 family was found to promote carcinogenesis. SEMA3A was investigated as a potential therapeutic target in eradication of lung cancer stem cells as the knockdown of SEMA3A expression resulted in total suppression of tumorigenicity of lung cancer [24].

In conclusion, SEMA3A expression seems to be an independent prognostic factor of overall survival of various types of neoplasms. It was proved that for gastric and OC the overall survival of the underexpressed SEMA3A group of patients was significantly shorter comparing to the group with

positive SEMA3A expression. It may suggest that SEMA3A may be an inhibitor of tumors of epithelial origin [15, 17, 18, 21, 22, 24–26]. It is of general knowledge that metastatic and poorly differentiated tumor cells are usually more resistant to cytotoxic drugs. It would be of great interest to specify the role of SEMA3A in development of drug resistance, especially from clinical point of view. Some preliminary studies with the use of microarray based gene expression have already demonstrated that SEMA3A was one of the underexpresed genes in drug resistant ovarian cancer cell lines [11]. In paclitaxel resistant ovarian cancer cell lines, very high downregulation of the SEMA3A transcript level was observed [12].

As described before, there is an increasing evidence of the role of SEMA3A in carcinogenesis. However, little is known about its potential role in development of drug resistance. Since it is a serious tumor suppressor candidate, not only in OC but also in other tumors, it seems to be of great importance to examine its role in drug resistance development.

PROTOCADHERIN 9 (PCDH9)

Another gene with noticeably altered expression revealed in microarray studies of drug resistant ovarian cancer cell lines, was PCDH9. PCDH9 (protocadherin 9) belongs to cadherin superfamily and is a calcium-dependent cell-cell adhesion molecule. It is expressed predominantly in the nervous system, however it was also observed in healthy tissues of the human body. Protocadherins have also been shown to play an important role in tumorigenesis, cell migration, survival and growth of different cancer tissues. Recently, various PCDHs including PCDH9 (and PCDH8, PCDH10, PCDH17, PCDH20) have been reported as candidate tumor suppressor genes in variety of cancers (e.g. prostate, gastric, hepatocellular cancer) [27–29]. The expression of PCDH9 in cancerous tissues of prostatic, gastric, hepatocellular cancers as well as non-nodal mantle cell lymphoma (MCL) and glioma was substantially lower in comparison to tissues of healthy organs [27–30]. Moreover, the expression of PCDH9 significantly inversely correlated with histological grade of those, and the findings on the protein and RNA levels are consistent. This might suggest that down-regulation of PCDH9 may be a factor in the carcinogenesis of these neoplasms, however the association between PCDH9 and the pathogenesis of these and other cancers remains elusive. What is more, significantly lower expression of PCDH9 was observed more frequently in high grade and worse histological type of tumors and was also associated with worse mean survival rate of glioma, gastric and prostatic cancer patients [27, 28, 30]. In prostatic cancer, significant downregulation of PCDH9 was shown during progression to the advanced or metastatic stage. Furthermore, lower PCDH9 expression correlated with shorter time to biochemical relapse and higher levels of PSA and the recurrence itself, as well as worse histological type and decreased overall survival [27]. Chen et al. observed that PCDH9 expression has been markedly reduced or completely lost in lymph node and hepatic metastases of gastric cancer. In this case, it also inversely correlated with tumor size, clinical stage and differentiation of the disease, and finally, patient survival. Interestingly, forced expression of PCDH9 gene in gastric cancer cell lines inhibited cancer cell growth and migration. The results of statistical analysis correlating PCDH9 expression with clinico-pathological data revealed that it might be considered as an independent prognostic factor for gastric cancer [28].

Another type of tumor where the relation of PCDH9 with the process of carcinogenesis was described is hepatocellular carcinoma. Zhu and colleagues had shown that PCDH9 plays a critical role in establishment of metastases by inhibiting the epithelial-mesenchymal transition of hepatocellular carcinoma cells, suggesting that it might serve as a key regulator of detachment and spreading cancer cells. They also proved that downregulation of PCDH9 expression correlated with increased malignant invasion and metastasis formation [29].

As outlined above, it is known that the expression of PCHD9 is downregulated in many tumor types and the loss of its expression may be related to more invasive phenotype [11]. However, the role of this phenomenon in the field of multidrug resistance development is scarce and insufficient. All of abovementioned research results strongly imply a tumor suppressor role of PCDH9 in the development and progression of human cancers like glioma, prostatic and gastric cancer, together with hepatocellular carcinoma. Thus, loss of its expression might be related to a more invasive and hence more resistant phenotype. Januchowski and colleagues, in their microarray- based studies had examined the PCDH9 gene expression in ovarian cancer cell lines resistant to cytotoxic drugs used in standard treatment of OC: paclitaxel, topotecan, doxorubicin and cisplatin [12, 13]. The studies revealed the statistically significant decrease in PCDH9 transcript levels in paclitaxel-resistant cell lines [12]. These results can serve as the starting point for more advanced research on the role of PCDH9 in the development of chemotherapy resistance.

All of the results clearly indicate that PCDH9 might play a crucial role in carcinogenesis and forming of metastases followed by its potential role in chemoresistance development and suggest that the re-expression of PCDH9 might serve as a potential therapeutic strategy for cancer treatment.

S100 CALCIUM BINDING PROTEIN A3 (S100A3)

In humans, the S100 genes are known to encode 25 proteins of calcium-binding protein family. The S100 proteins

are located in cytoplasm and/or nucleus of different cells and they are involved in a large number of important cellular processes including cell cycle regulation, cell proliferation, differentiation, apoptosis, calcium homeostasis, inflammation, energy metabolism and migration/invasion [31]. Latest studies revealed that the S100 proteins also play crucial role in tumorigenesis. More importantly, they are involved in regulation of epithelial-mesenchymal transition and tumor microenvironment reorganization and hence they promote cancer progression and metastasis. The role of these proteins in tumorigenesis is mostly cell type specific and may include oncogenic or tumor-suppresive functions, depending on the type of cell and tumor. Their functional characteristics differ, depending on their extracellular environment. Many studies had shown higher expression of S100 protein in different types of cancers like gastric, hepatocellular or colorectal cancer and the overexpression of these proteins usually shows great clinical implications for the diagnosis, staging and prognosis of these tumors.

Within the wide range of S100 proteins the matricellular S100A3 is described lately as directly involved in tumorigenesis. The protein is expressed in various tissues and cell types and was found in different cell structures like cell membrane or the cytoplasm. It is encoded by the S100A3 gene and contains two EF-hand calcium binding motifs in humans. The results of some studies indicate that dysregulation of S100A3 expression and function contributes to pathological conditions such as cancer progression or/and metastases. The oncogenic role of S100A3 is still under investigation, however it has been shown that the inhibition of S100A3 expression in prostate cancer cell lines reduced cell viability and invasiveness. A positive correlation between S100A3 expression and tumor type and grade in neoplasms like astrocytoma, prostate and gastric cancer was found [31]. In gastric cancer, S100A3 upregulation correlates positively with the TNM stage and tumor differentiation, where higher levels of the protein were noticed for stages III and IV of the disease and in poorly differentiated tumors. Similarly, in colorectal cancer tissues, a notable increase in expression of this protein was detected, with the highest expression levels in the tumor cells and tumor interstitial regions and the significant reduction was observed after the cytotoxic treatment [32]. The S100A3 gene activation was also proven to be involved in tumorigenesis and tumor aggresiveness of hepatocellular carcinoma and prostate cancer [33, 34]. In the prostate cancer the positive correlation of S100A3 expression with tumor size was found. Moreover, silencing of the S100A3 gene led to marked reduction of tumor growth and final tumor size and mass [34]. Also, studies conducted on ovarian cancer cells revealed that elevated levels of S100A3 expression was found, especially in cells resistant to cisplatin, topotecan and paclitaxel [11, 12]. This shows that S100A3 inhibition may effectively induce tumor growth suppression and remain a promising option for molecular-targeted anti-cancer therapies [34] and might also serve as a potential target for OC drug resistance reduction. [11].

SUMMARY

The article presents a overview of the available literature on the role of semaphorin 3A (SEMA3A), protocadherin 9 (PCDH9), and S 100 calcium binding protein A3 (S100A3) in carcinogenesis and chemoresistance of various tumors. Until now, there is only few studies investigating the role of presented genes and proteins in OC and only one of them was performed on the human neoplastic lesions. Other studies were usually conducted with the use of ovarian cancer cell lines. Spreading the investigation to the human cancerous tissues and then analyzing the results and comparing with the clinical data would offer significant information about the actual role of the these genes and proteins in OC tumor growth, development of metastases and drug resistance. In addition, the proteins could become potential biomarkers of tumorigenesis and response to standard cytotoxic drugs and thus become an integral part of tailored treatment of OC. This could serve as an important tool in establishing personalized anti-cancer therapies.

Conflict of interest

None declared.

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