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Understanding the relationship between circulating platelets and epithelial to mesenchymal transition – a step towards in discovering new epithelial ovarian cancer targeted therapies

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ABSTRACT

In the last decades understanding the relationship between the circulating platelets and the biological aggressivity of ovarian cancer gave the opportunity to researchers to introduce new therapeutic lines in ovarian cancer patients with promising results. Therefore, this subject has become intensively studied and surprising correlation ships have been observed. One of the most recently investigated issues regards the influence of circulating platelets on epithelial ovarian cancer refers to the platelets' ability to induce the epithelial to mesenchymal transition. The current paper aims to discuss about this subject and about the clinical implications of the process.

Keywords: epithelial to mesenchymal transition, ovarian cancer, platelets

INTRODUCTION

Ovarian cancer is one of the most widely investigated malignancies due to the fact that it is still responsible for a significant number of deaths among women worldwide, being also known as a "silent killer" [1,2]. This name was given to ovarian carcinomas due to the fact that in most cases the disease remains asymptomatic for a long period of time, being therefore diagnosed in advanced stages of the disease [1]. In order to improve the long-term outcomes of ovarian cancer patients, attention was focused in understanding the pathogenic processes involved in this process [3-5]. In this respect, particular attention was given to epithelial to mesenchymal transition. This phenomenon is physiologically present during the embryogenic process and leads to organ development; however, in adults, the

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re apparition of this process is frequently related to carcinogenesis [6-8].

Epithelial to mesenchymal transition and ovarian cancer

Epithelial to mesenchymal transition represents a commonly discussed subject referring to the transformations to which the cells are submitted during the neoplastic generation and ovarian cancer genesis [8]. According to this hypothesis, epithelial cells which are fixed, polarized unites lose these characteristics and transform into motile, spindle cells, without polarity and with a high capacity of dissemination. Moreover, during this process the disruption of the epithelial cellular junctions occur and lead to an increased invasiveness of the resulting cells, increasing in this way their capacity of spread and metastasation [9,10]. This phenomenon has been widely described in ovarian cancer and therefore is considered to play a central role in the apparition of peritoneal spread. Therefore, the epithelial ovarian cells located at the level of the adnexal surface which are submitted to epithelial to mesenchymal transition will lose their polarization and will present an increased mobility; therefore they will spread into the liquid which is normally present at the level of the abdominal cavity and will be further submitted to the same circuit with the peritoneal fluid. Furthermore, they will seed in gravitational areas and will block the lymphatic flow at this level conduct in in this way to the development of peritoneal carcinomatosis nodules [11,12]. Moreover, the development of these structures will further inhibit the normal process of absorption of the peritoneal fluid leading to the apparition of ascites and leads to the development of therapy resistance [12]. This phenomenon has been widely demonstrated so far; however, in ovarian cancer patients it seems to be influenced by significant factors such as the number of circulating platelets.

Moreover, it seems that the presence of epithelial to mesenchymal transition is associated with low levels of E-cadherin, a protein which has an important role as a ligand between cells; once E cadherin expression diminishes, the cells become more mobile and have a higher capacity of spread. Moreover, cells presenting a higher expression of the epithelial to mesenchymal transition usually also associate a higher level of vimentin, and therefore, a higher risk to develop chemotherapy resistance. In this respect, studies published so far demonstrated that cases in which the epithelial to mesenchymal transition was present reported poorer long-term outcomes expressed through a lower cancer related survival [13-15].

The relationship between epithelial to mesenchymal transition and the circulating platelets

Another significant pathogenic aspect which is related to the biological aggressivity of ovarian cancer is related to the inflammatory and to the coagulation status of the host. As expected, the presence of a higher proinflammatory and procoagulant status is associated with a poor prognosis in most malignancies. Therefore, the presence of a higher number of circulating platelets is widely associated with advanced stages and more aggressive subtypes of ovarian carcinomas. This aspect is justified through the fact that platelets contain a higher amount of tumor growth factor beta (TGF β) at the level of their granules; once the degranulation process begins, a higher amount of TGF β will be available in the systemic circulation, stimulating in this way the tumoral proliferation. Moreover, this molecule also seems to induce the process of epithelial to mesenchymal transition [16-18].

Platelet derived TGF β as a new targeted therapy for ovarian cancer patients

The potential benefit of targeted therapies was demonstrated by blocking the TGF β type I receptors and observing that in such cases the first encountered result was the reversal of epithelial to mesenchymal transition [19]. An interesting study was conducted on this issue by Cai et al in 2019 and was published in Gynecologic Oncology Journal. According to this study, patients presenting advanced stages of epithelial ovarian cancer also reported a higher number of circulating platelets and a higher tumoral burden when compared to cases presenting normal levels of circulating platelets. Furthermore, the authors isolated two lines of ovarian cancer cells – SK-OV-3 and OVCAR-3 which were co-incubated for 48 hours with purified platelets and observed that their invasiveness increased for 3 folds when comparing them with untreated cells. Moreover, the level of E cadherin was significantly decreased in platelet treated ovarian cancer cells while the level of metalloproteinases was significantly increased in these lines demonstrating therefore that the presence of platelets significantly influence the epithelial to mesenchymal transition phenomenon. In the same study the authors also measured the serum levels of TGF β and observed higher values if the platelets count surpassed $350*10^9$ /l; meanwhile the same correlation was observed in the in vitro part of the study, on SK-OV-3 and OVCAR-3 cell lines. Therefore, cultures in which platelets coexisted exhibited a higher level of TGF β. Moreover, inhibiting the TGF β A83-01 receptor diminished the epithelial to mesenchymal transition and the invasiveness of ovarian cancer cells [19]. In this respect, attention has been focused on identifying new targeted therapies which might provide the TGF β A83-01 blockade. As expected, the first studied molecule was the

one of aspirin, which is widely known for it's antiaggregant effect; however, it seems that it was not able to block these receptors and to diminish the epithelial to mesenchymal transition process [20]. Interestingly, TGF β A83-01 blockade seem also to be efficient in treating other types of malignancies such as breast cancer; therefore, it's association with trastuzumab provided a significant benefit even in cases in which trastuzumab resistant cells had been documented [21].

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CONCLUSIONS

Better understanding the complex relation ship between the circulating platelets and epithelial to mesenchymal transition in ovarian cancer gives the opportunity to the researchers to explore new targeted therapies in ovarian cancer patients. This aspect is particularly important due to the fact that it seems that the presence of epithelial to mesenchymal transition is also corelated with chemotherapy resistance and therefore with poorer long-term outcomes if standard treatment is administrated.

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