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Drawing a link between the thromboxane A_2 pathway and the role of platelets and tumor cells in ovarian cancer

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ABSTRACT

Ovarian cancer is the most lethal gynecologic malignancy among women. Due to the heterogeneity and complexity of the disease, as well as the insidious onset of symptoms, timely diagnosis remains extremely challenging. Despite recent advances in chemotherapy regimens for ovarian cancer patients, many still suffer from recurrence and ultimately succumb to the disease; thus, there is an urgent need for the identification of novel therapeutic targets. Within this rapidly evolving field, the role of platelets in the ovarian cancer tumor microenvironment has garnered increased attention. It is well-established that platelets and tumor cells exhibit bi-directional communication in which platelets enhance tumor cell invasion, extravasation, and protection from host system defenses, while tumor cells serve as platelet agonists, increasing platelet adhesion, aggregation, and degranulation. This mini-review focuses on the platelet-tumor cell relationship in ovarian cancer, specifically highlighting the essential role of bioactive lipid mediators at this interface.

1. Introduction

Ovarian cancer is the most lethal gynecologic malignancy and ranks as the fifth leading cause of cancer-related deaths in women [1]. Because of the subtle, and in most cases, asymptomatic presentation of this occult disease, almost 70% of cases are diagnosed at an advanced stage with subsequently poor patient prognosis [2]. The unforgiving rapid onset of late-stage ovarian cancer yields a 5-year survival rate of approximately 29% among patients [3].

The current first-line treatment for ovarian cancer patients is cytoreductive surgery followed by platinum- and taxane-based chemotherapy; often times confirmation of the diagnosis and staging of the disease occurs during surgery [2]. Adding to the complexity of late-stage diagnosis, ovarian cancer is considered a highly heterogeneous disease with various histologic subtypes. To date, there are five main types of malignant ovarian cancer: high-grade serous, mucinous, clear cell carcinoma, endometriod, and low-grade serous [3]. These histologic subtypes differ both morphologically and genetically, making it very challenging to define precursory events of the disease [4]. Among these morphological differences, both the clear-cell carcinoma and serous subtypes are relatively chemo-resistant [2]. First-line chemotherapy regimens for treatment of ovarian cancer consist of a combination of platinum-based chemotherapy coupled with a taxane-agent; the most common therapy is a carboplatin-paclitaxel therapeutic regimen [5]. Although many patients may initially respond to first-line chemotherapy, most develop recurrence post-therapy. To date, there are two major forms of recurrence that ultimately lead to chemo-resistance. The first, platinum refractory, occurs when the tumor progresses during first-line treatment, and the second, platinum resistance, occurs when recurrence is observed within 6 months after completion of first-line treatment. Tumor sensitivity to platinum is considered a continuum and ultimately the type of recurrence dictates second-line therapy [2].

Given the complex biology of ovarian cancer, as well as the high-rate of recurrence and subsequently poor response to second-line treatment, there is an active on-going search for novel therapies and biological targets of the disease. Currently, the “hot-targets” for ovarian cancer treatment include angiogenesis inhibitors, specifically vascular endothelial growth factor (VEGF) inhibitors, such as bevacizumab [6]. Additionally, researchers have identified VEGF receptors as potential targets, such as the VEGF receptor inhibitor cediranib. In addition to angiogenesis factors, targeting the PARP1 and PARP2 enzymes, which play a critical role in DNA repair, with PARP inhibitors (poly(ADP-ribose) polymerase protein inhibitors), have been employed in ovarian cancer treatment [2]. Despite the many research groups dedicated to investigating these targets as alternative treatment options to second-

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line therapies, most patients exposed to such therapies eventually relapse and recurrence remains an almost terminal event [7]. Thus, the search for more efficacious therapeutic targets for women suffering from ovarian cancer is urgently needed. Recently in ovarian cancer, the significance of tumor cell interactions with the surrounding microenvironment and specifically with platelets, has gained attention as supported by emerging experimental and clinical studies [8]. This mini-review will hone in on several recent findings regarding platelet-tumor cell interactions in ovarian cancer and subsequently highlight the key role of lipid signaling in these interactions in the ovarian tumor microenvironment.

2. Platelets in the tumor microenvironment

Platelets are key players in wound healing processes, inflammation, and homeostasis. These anucleate megakaryocyte derivatives are integral first responders in the initial processes of blood clotting, vasoconstriction, inflammation, and wound healing, all of which help expedite tissue repair and resolution [9]. Platelets are surrounded by a phospholipid membrane with various glycoproteins and integrins that mediate platelet activation, adhesion, and aggregation [10]. Platelets were first identified as key players in the tumor microenvironment in 1872 by Riess et al., when a clear correlation between elevated platelet count and malignant tumors was established [11]. Although platelets are primarily known for their hemostatic role in inflammatory and wound healing processes, important studies have established the vital influence of platelets on metastasizing tumors. Platelets contribute to cancer metastasis *via* facilitating tumor cell migration, invasion, and arrest within the vasculature, and provide cancer cell protection from host-immune system defenses [9,11–13].

Platelets may also play a pro-tumorigenic role in cancer by increasing both the risk and prevalence of thrombotic events among cancer patients and *vice versa* [14]. This risk is highly relevant among ovarian cancer patients, in which paraneoplastic thrombocytosis as well as venous thromboembolism complicates the treatment course in up to 25% of patients [8]. The magnitude of circulating platelets can serve as a prognostic factor for both development of thrombotic events and an indicator of disease severity. Approximately one-third of newly diagnosed ovarian cancer patients have exceedingly high platelet counts, averaging 450,000/μL, and are associated with shortened survival [15]. Moreover, elevated platelet counts in ovarian cancer patients at the time of secondary cytoreductive surgery have recently been demonstrated to be associated with suboptimal resection and shortened overall survival [16]. Several groups have also identified that circulating platelet levels, in addition to several coagulation cascade factors (plasma D-dimer, tissue factor, and fibrinogen), in ovarian cancer patients serve as indicators of disease progression and surgery outcome [8,17–19]. Thus, growing experimental and clinical evidence show a correlation between platelet counts at time of initial diagnosis and subsequently at the time of cytoreductive surgery, suggesting that platelets may serve as a biomarker for disease recurrence and aggressiveness [7].

There is a crucial link connecting increased thrombotic events to the platelet activity in the tumor microenvironment in cancer patients. It is now well-established that the tumor microenvironment can both directly and indirectly activate platelets. This dynamic tumor cell – platelet relationship plays an integral role in the progression of ovarian cancer, along with other cancers such as gastrointestinal, lung, breast, and pancreatic cancer [8,9,12]. Tumor cells can directly induce platelet aggregation, a phenomenon called tumor cell-induced platelet aggregation (TCIPA) that was first identified in 1968 [12]. TCIPA primarily occurs through tumor cell release of platelet mediators such as ADP, thrombin, thromboxane A2, and tumor-associated proteinases. TCIPA not only increases platelet aggregation, but also promotes adhesive properties of both platelets and tumor cells; such changes intensify activation and release of secondary mediators involved in platelet activation [20].

3. Platelets and ovarian cancer

Recently, several groups have shown that the presence of platelets are important in ovarian cancer progression beyond their roles in the development of paraneoplastic thrombocytosis and thrombotic events. Specifically, it has been shown that ovarian cancer cells, such as the 59 M and SKOV3 cell lines, can induce platelet activation *in vitro*, as identified by flow cytometry analysis of P-selectin expression on platelets [21]. This study also showed that ovarian cancer cells potentiate thrombin receptor activating peptide, arachidonic acid, and PAR4 agonist-induced platelet activation, suggesting that ovarian cancer cells can penetrate the complex thrombosis process *in vivo* [21].

Additionally, platelets directly impact ovarian cancer cell growth and survival shown by *in vitro* and *in vivo* studies utilizing human ovarian cancer lines, OVCAR5 and SKOV3, and murine cell lines, ID8 and 2C6 [22]. In this study, Cho et al., showed that platelets stimulate proliferative activity of ovarian cancer cells when the cells were co-incubated *in vitro*. Interestingly, this effect was not dependent on direct contact between the cell types, but rather *via* secretion of transforming growth factor beta 1 (TGF-beta1) by platelets [22]. The group also showed that the proliferative activity of ovarian cancer cells was similar to platelet activity *in vivo*. Similar to Egan et al. [21], Cho et al. in 2017 investigated the role of ADP released by ovarian cancer cells in the presence of platelets. ADP is a known platelet agonist, inducing activation and degranulation of platelets and release of growth factors by alpha-granules [23]. Platelets have two ADP receptors, P2Y1 and P2Y12. Presently, P2Y12 inhibitors are utilized in the clinic for management of cardiovascular diseases. Cho et al. investigated the role of P2Y1 and P2Y12 along with the clinically used P2Y12 inhibitor, ticagrelor, in ovarian tumor cell-platelet interactions [23]. They demonstrated that ADP secreted by ovarian cancer cell lines directly activates platelets circulating in the tumor microenvironment *via* P2Y1 and P2Y12 receptors. Additionally, Cho et al., showed that use of ticagrelor reduced ovarian tumor growth by 60% compared to aspirin treatment and by 75% as compared to placebo *in vivo* [23]. The importance of platelet P2Y12 was confirmed by showing re-established ovarian tumor growth in *P2Y12*$^{-/-}$ mice. Moreover, in the absence of platelets, exposure of ovarian cancer cells to ticagrelor or ADP, and knockdown of P2Y12 or ecto-apyrase genes (*i.e.* CD39), did not affect cancer cell proliferation *in vitro* or tumor growth *in vivo*. This further confirmed the P2Y12-dependent role in the interaction between platelets and ovarian cancer cells [23].

Additionally, a study performed by Bottsford-Miller et al., showed that ovarian cancer cells co-incubated with platelets were protected against taxane-based chemotherapy-induced apoptosis *in vitro* [24]. The group went on to investigate the significance of platelets in the tumor microenvironment in an orthotropic ovarian cancer model. To simulate effects of excess platelet volume, allogeneic platelet transfusions were performed; these platelet transfusions resulted in a 1.9-fold increase in aggregate mean tumor weight compared to control ($p = 0.01$) [24]. *Ex vivo* immunohistochemistry of the resected tumor specimens showed that platelet transfusion resulted in a 37% lower rate of tumor cell apoptosis compared to control ($p = 0.009$) [24]. Additionally, *in vivo* studies assessing the effects of platelets in response to taxane-based chemotherapy showed that the widely used chemotherapy drug, docetaxel, showed an additional 62% reduction in aggregate tumor weight when coupled with the use of an anti-platelet antibody agent [24].

In addition, a key player in the platelet-tumor cell cross-talk is the role of platelet secreted TGF-beta1 [25]. Most plasma TGF-beta1 is secreted by platelets and is known to have an essential role in cancer. Specifically, Hu et al., showed that platelet-derived TGF-beta1 stimulated primary tumor growth in murine ovarian cancer models and that inhibition of TGF-beta1 receptors is highly effective in suppressing ovarian cancer growth in said models [26]. Platelet-derived TFG-beta1