Thrombosis Research 150 (2017) 8–18

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Reciprocal links between venous thromboembolism, coagulation factors and ovarian cancer progression

Nathalie Swier, Henri H Versteeg *

Department of Internal Medicine, Thrombosis and Hemostasis Division, Leiden University Medical Center, Albinusdreef 2, 2333, ZA, Leiden, The Netherlands

ARTICLE INFO

Article history:
Received 29 August 2016
Received in revised form 23 November 2016
Accepted 3 December 2016
Available online 14 December 2016

Keywords:
Blood coagulation
Tissue factor
Thrombin
Platelets
Protease-activated receptors
Metastasis

ABSTRACT

Ovarian cancer is the most lethal gynecological malignancy, which is due to late presentation. Treating advanced stage ovarian cancer is difficult, and tumor recurrence and chemoresistance frequently occur. In addition, early detection remains a major challenge as there are no early warning signs and no appropriate biomarkers. To reduce mortality rates of ovarian cancer patients, novel drug targets and biomarkers are needed. We postulate that hemostatic keyplayers are of importance when combatting ovarian cancer. The majority of ovarian cancer patients have abnormal hemostatic blood serum marker levels, which indicate an activated coagulation system. This makes patients more prone to experiencing venous thromboembolism (VTE), and the occurrence of VTE in ovarian cancer patients adversely affects survival. Coagulation activation also promotes tumor progression as it influences tumor biology at several stages and the decreased survival rates associated with ovarian cancer-associated thrombosis are more likely due to cancer metastasis rather than to fatal thromboembolic events. In this review, we will discuss; (1) Population studies that address the bidirectional relationship between VTE and ovarian cancer, and the most important risk factors involved; (2) The mechanisms of coagulation factors and platelets that are critically involved in the development of VTE, and the progression of ovarian cancer; (3) Roles and future directions of coagulation factors in ovarian cancer therapy, and in diagnosis and prognosis of ovarian cancer as biomarkers.

Contents

Abbreviations: AT, antithrombin; BMI, body mass index; CA-125, cancer antigen 125; CCC, clear cell carcinoma; CD, cluster of differentiation; CG, control group; DVT, deep venous thrombosis; DOACs, direct-acting oral anticoagulants; EMT, epithelial mesenchymal transition; EOC, epithelial ovarian cancer; FVII, blood coagulation factor VII; FVIIa, activated FVII; FX, blood coagulation factor X; FXa, activated FX; HGS, high grade serous carcinoma; HIF, hypoxia inducible factor; IHC, immunohistochemistry; IIa, thrombin; IL, interleukin; LMWH, low molecular weight heparin; MMP, matrix metalloproteases; MPs, microparticles; NET, neutrophil extracellular trap; PAR, protease activated receptor; PE, pulmonary embolism; RCT, randomized controlled trial; SG, study group; TAM, tumor associated macrophage; TF, coagulation factor tissue factor; TF + MPs, tissue factor positive microparticles; TF-FVIIa, activated TF-FVII complex; TF-FVIIa + MPs, activated TF-FVII complex positive microparticles; TME, tumor microenvironment; TFPI, tissue factor pathway inhibitor; VTE, venous thromboembolism.

* Corresponding author.
E-mail address: h.h.versteeg@lumc.nl (H.H. Versteeg).

http://dx.doi.org/10.1016/j.thromres.2016.12.002
0049-3848/

1. Introduction

Worldwide, over 230,000 women develop ovarian cancer and ~ 150,000 ovarian cancer patients die each year [1]. As these statistics suggest, ovarian cancer is one of the most frequent causes of female cancer death. The high death rate in ovarian cancer is due to late presentation. More than 70% of the ovarian cancer patients are diagnosed at an advanced stage, at which tumors have widely metastasized into the abdomen [2]. Notably, the five year survival rate of patients diagnosed with ovarian cancer at an early stage is over ~90%, but it drops to ~45% in patients with advanced stages [3]. Early detection remains a major problem due to the lack of appropriate biomarkers and absence of early warning signs [2]. The first specific symptoms of ovarian cancer typically present in postmenopausal women [2], including pelvic pain and bloating [4]. These symptoms are mainly related to the presence of large tumors or massive ascites and indicate advanced stage disease [5]. Currently, blood serum levels of tumor marker cancer antigen 125 (CA-125), and abdominal and transvaginal measurements are used as diagnostic tools, but are not sufficiently sensitive or specific enough to detect early stage ovarian cancer [2].

Ovarian cancer comprises a heterogeneous group of malignancies. Virtually all ovarian cancer patients are diagnosed with epithelial ovarian cancer (EOC), however, ovarian cancer also includes rare sarcomas, and sex-cord and germ cell tumors. EOC is derived from the surface epithelium or inclusion cysts and is generally divided into five histological subtypes: high-grade serous (HGS)- (the most frequently diagnosed EOC subtype), low-grade serous-, endometrioid-, mucinous-, and clear cell carcinoma (CCC). HGS is most frequently diagnosed (~50%), whereas only ~5% of EOC patients are diagnosed with the CCC subtype. However, the relative frequencies of EOC subtypes diagnosed differ largely across countries and may reflect ethnical and cultural differences [6]. The different EOC subtypes have specific characteristics and respond differently to cancer therapy [2]. To date the standard treatment for ovarian cancer is tumor debulking surgery followed by platinum-based chemotherapy. Cancer treatment and surgery has improved over the previous three decades, and has resulted in an increase in median survival time for women with advanced ovarian cancer by 1.6 years [7]. Despite this improvement, most patients with high-stage ovarian cancer will typically develop recurrent malignancy within 18 months. With respect to the different EOC subtypes, low-grade serous carcinoma and CCC respond poorly to chemotherapy. In addition, a characteristic of HGS is the development of chemoresistance after many episodes of recurrent malignancies. These recurrent and chemoresistant ovarian malignancies are not curable by second line cancer treatment, and will eventually be terminal [2].

To reduce high death rates of ovarian cancer patients, more insight into potential drug targets to prevent or treat recurrent and aggressive tumors are needed. Personal medicine might be one of the future directions in ovarian cancer therapy, as EOC subtype-specific mutations have been recently identified [2]. Moreover, the inhibition of activated signaling cascades in cancer cells, such as PI3K- and RAS pathways, showed promising results in a trial with ovarian cancer patients [8]. The current review focusses on the blood clotting system. This system is a potentially important target in drug development and/or the identification of appropriate biomarkers in ovarian cancer progression.

Blood clotting strongly depends on the activation of the coagulation cascade (Fig. 1). This cascade is initiated by tissue factor (TF), expressed on sub-endothelial cells. Upon disruption of the endothelium, TF is exposed to the bloodstream and able to bind its ligand blood coagulation factor VII (FVII). The activated TF-FVII (TF-FVIIa) complex converts factor X (FX) into its activated form (FXa). FXa then cleaves prothrombin to thrombin. Thrombin affects other coagulation factors and platelets, and activation of positive feedback loops upon which more thrombin is activated. Eventually, large amounts of fibrin aggregate to from a network to close off the damaged vessel [9].

Investigation of the coagulation cascade will potentially lead to the identification of novel targets in ovarian cancer, due to multiple reasons. Firstly, the incidence of venous thrombosis (the obstructive clotting

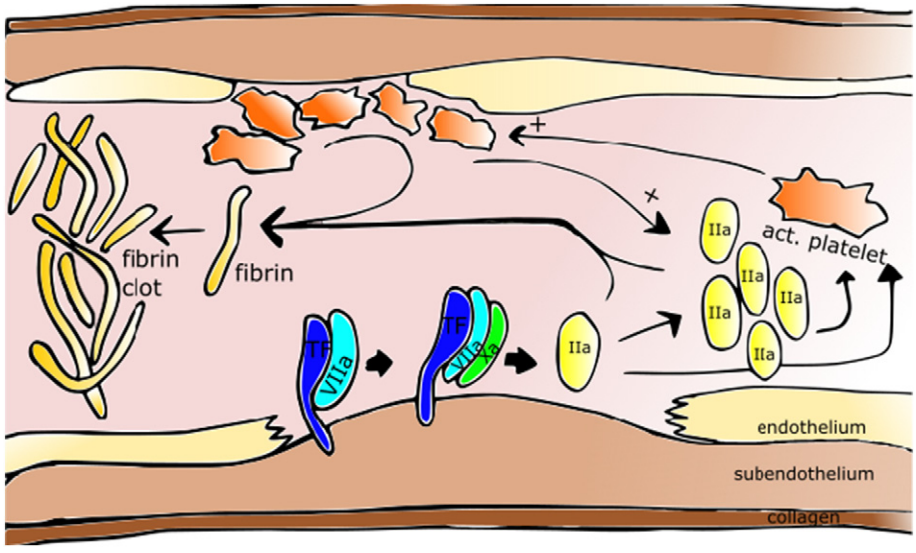

Fig. 1. Graphical display of the coagulation cascade. Upon disruption of the endothelium, tissue factor (TF) is able to bind and activate its ligand blood coagulation factor VII (VIIa). This activated complex then activates factor X (Xa), which then cleaves prothrombin to thrombin (IIa). The activation of thrombin then affects other coagulation factors and platelets, and activates positive feedback loops upon which more thrombin is activated. Eventually, large amounts of fibrin aggregate to from a network to close off the damaged vessel. (Adapted from Versteeg et al. [9])