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Review

The hemostatic system. 2nd Part

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Abstract

The hemostatic system (HS) is crucial for human survival, both by preventing excessive bleeding and also through close links to the immune system. Both systems cooperate to defend us from attacks by microorganisms and viruses. However, the behavior of the HS changes radically in the presence of cancer, becoming its powerful ally. Excessive individual responses of the HS to sepsis or virus attacks also require further investigation. The current review aims to explain the main pathophysiological mechanisms responsible for the behaviors of the HS in inflammation and cancer. We address the three main components of the HS, i.e., platelets, blood coagulation, and fibrinolysis, separately, and provide detailed information on their different activities in relation to inflammation and cancer. A better understanding of the mechanisms underlying the HS may help to improve daily clinical practice. This review also considers the possible roles of anticoagulant and antifibrinolytic drugs in counteracting the abnormal reactions of the HS during the course of infectious diseases and cancer. Further *ad hoc* studies are needed to assess if these drugs can reverse or at least reduce the adverse impacts of the HS in infections and cancer.

Keywords

Platelets, blood coagulation, fibrinolysis, cancer, sepsis, COVID-19.

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Introduction

The hemostatic system (HS) is crucial for our survival, by both protecting against excessive bleeding and also via close links to the immune system [1]. Both systems cooperate to defend us from attacks by microorganisms and viruses. However, the behavior of the HS changes radically in the presence of cancer, becoming its powerful ally. The current review aims to explain the main pathophysiological mechanisms responsible for the behavior of the HS in inflammation and cancer. We consider the three main components of the HS, i.e., platelets, blood coagulation, and fibrinolysis, separately, to provide more precise information on their different activities regarding the two main topics of this narrative review, i.e., inflammation and cancer. Furthering our understanding of the mechanisms underlying the HS may help to improve daily clinical practice, as well as guiding studies into the possible use of anticoagulant and antifibrinolytic drugs to counteract the abnormal reactions of the HS in infectious diseases and cancer.

Materials and methods

We scanned the MEDLINE database up to December 2021 with the following keywords: "platelets" OR "blood coagulation" OR "fibrinolysis" AND "venous thromboembolism", OR "haemorrhage" OR "infectious diseases" OR "pulmonary embolism" OR "arterial thrombosis" OR "cancer". We limited our search to articles published in English. Articles were defined as eligible if they were related to the review topics and were published in peer-reviewed journals. We first screened articles retrieved from the electronic database by examining the titles and abstracts. Further critical review of full-text eligible articles was based on an evaluation of the described pathophysiology, methodology, and possible impact on the review topics. Articles were excluded if they were not closely related to the topics of the review or were not published in peer-reviewed journals.

Platelets

Platelets play a role in the hemostatic process by helping to prevent mucocutaneous bleeding [2], as well as being involved in the pathogenesis of atherosclerosis and arterial thrombotic events [3]. Platelets can thus act as both friends and enemies, depending on the settings of their actions.

Importantly, platelets also mediate the relationship among hemostasis, the immune system, and inflammation [4]. During their circulation in the vasculature, platelets are extremely sensitive to foreign invaders, such as viruses, bacteria, and parasites. They cooperate in host defense by helping to kill pathogens, either directly or by facilitating their clearance by activating macrophages and inducing neutrophil extracellular traps (NETs) [5, 6] (**Fig. 1**). Thrombocytopenia is a common clinical feature of early sepsis, possibly because platelets are consumed during these functions, although other causes have also been considered [7]. Platelets become activated following antigen recognition, depending on the individual response. However, this may also be dangerous, by enhancing inflammation and provoking endothelial damage and thrombosis [8]. Platelets are hyperactivated following infection with the SARS-CoV-2 virus (COVID-19), thus contributing to the thrombo-inflammatory features of the disease. SARS-CoV-2 RNA was shown to be associated with platelets in 114 patients with mild or severe COVID-19 infections. Moreover, platelets can enhance the plasma cytokine load [9] and disrupt the balance between von Willebrand factor and ADAMTS13 [10].

Platelets may also be activated by thrombin, the final protease of blood coagulation, during disseminated intravascular coagulation (DIC) [11]. A platelet count less than 50×10^9/L is one criterion of the International Society on Thrombosis and Haemostasis (ISTH) score for the laboratory diagnosis of DIC [12]. In sepsis with DIC, platelets are activated by both thrombin and inflammatory molecules, such as platelet-activating factor [13]. P-selectin is then expressed on the platelet surface, inducing them to adhere

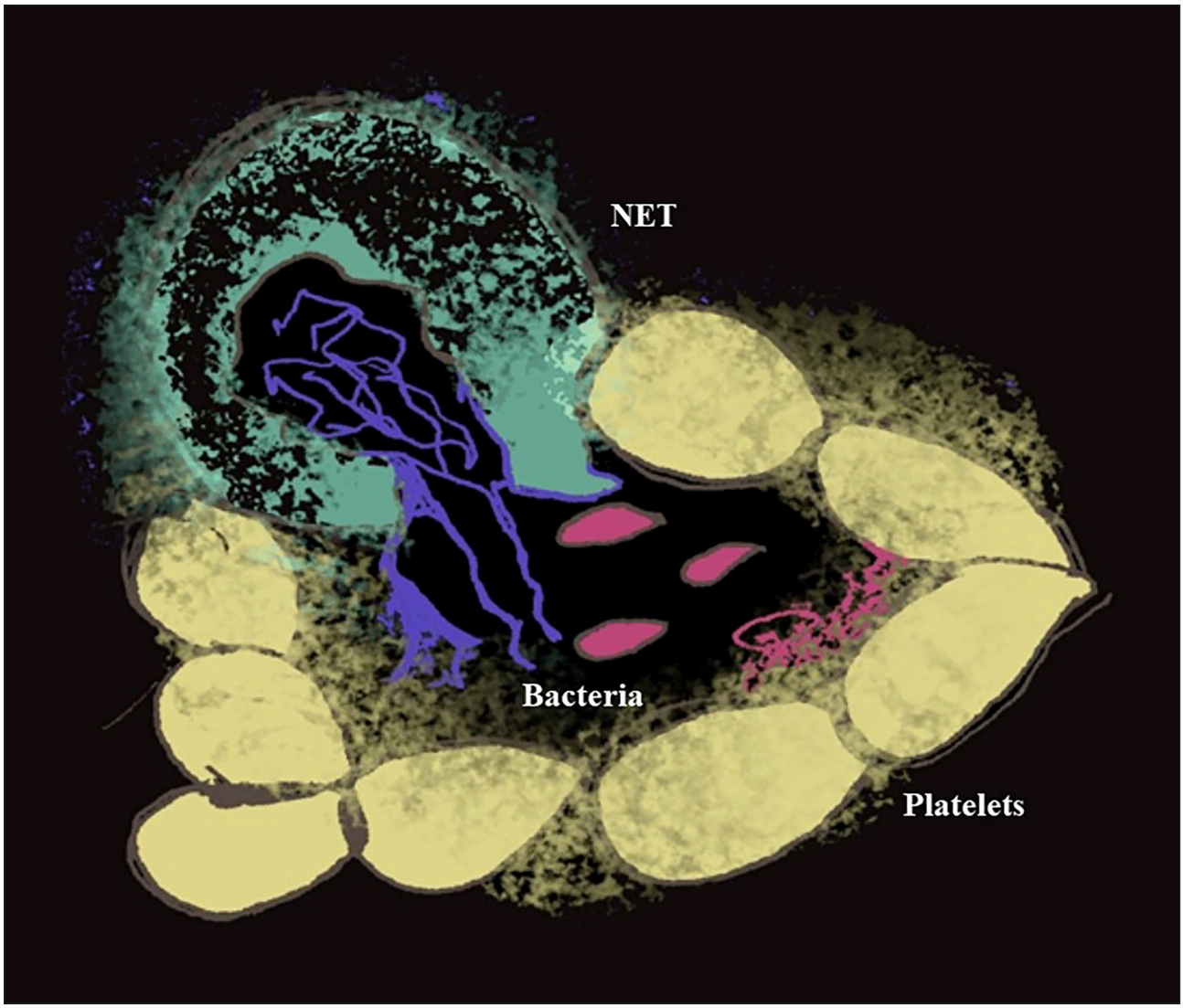

Figure 1. Platelets, bacterial and neutrophil extracellular trap (NET).
Platelets cooperate with neutrophils with the aim to trap bacteria and virus. They can activate an important defensive system: the NET.

to leukocytes and endothelial cells [14]. Platelets thus comprise part of the HS, which functions to defend the host from bleeding and from foreign invaders; however, their behavior changes when the host develops a malignant neoplastic disease. Although platelets have antineoplastic properties, their pro-neoplastic properties become much more pronounced, and even though platelets recognize neoplastic cells as foreign invaders, they may change from "allies" to "enemies" [15]. Platelets try to exert the defensive actions that they employ against bacteria and viruses against the cancer cells, but the latter exploit their capabilities, including their array of enzymatic functions and adhesive proteins [16]. Cancer cells thus utilize the platelets' functions to help them to proliferate and spread, becoming part of the cancer's invasion strategy [17]. The defensive role of the platelets in cooperating with the innate immune system against foreign invaders is eventually overcome by cancer. Cancer cells can activate platelets via many mechanisms [18]. They stimulate platelet aggregation by expressing ADP, which activates platelets via the P2Y1 and P2Y2 receptors, which induce platelets to release ADP, so causing further aggregation [19]. Cancer cells can also bind the FcγRIIa receptor on the platelet surface to provoke dense-granule secretion [20]. Other mechanisms also favor cancer cell cross-talk with platelets. Aggregated platelets surround cancer cells, thus protecting them from immune elimination (**Fig. 2**), while another mechanism promotes the adhesion of tumor cells to the endothelium, thus facilitating their extravasation and metastasis [21, 22]. Angiogenesis is also facilitated by platelets via microparticles, microRNAs, and several

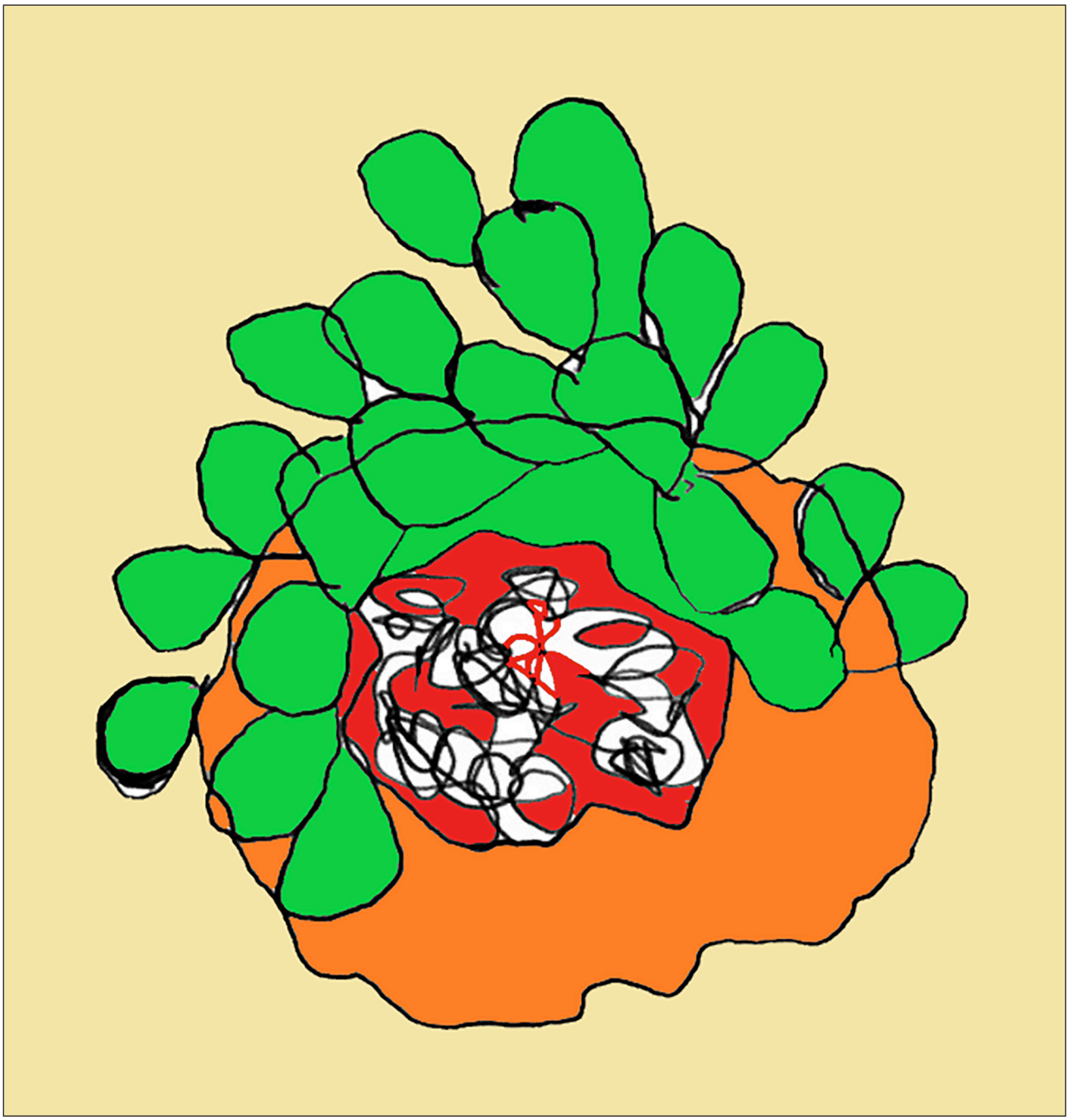

Figure 2. Platelets and cancer.
Cancer cells can activate platelet aggregation, so escaping the immune system.

surface receptors [23]. Moreover, platelets protect cancer cells from shear stress [24], help them to avoid natural killer cells, and induce the cancer cells' capacity to cross the endothelium and spread to distant organs [25]. Finally, platelets favor the malignant transition from an epithelial to an invasive mesenchymal phenotype, thus enhancing metastatic invasion [26]. However, platelets may also be helpful, via the analysis of so-called tumor-educated platelets (TEP) by means of liquid biopsy obtained by blood sampling, in which spliced TEP mRNA can be detected as an important tool for reaching a cancer diagnosis [27].

Reducing platelet involvement in the neoplastic progression by inhibition of cyclooxygenase-1 using low-dose aspirin has been proposed as an antineoplastic and antimetastatic strategy [28], with favorable results [29]. However, large clinical studies are needed to recommend aspirin both for the primary prophylaxis of cancer and in association with chemosurgical management of the disease.

Blood coagulation

Blood coagulation acts synergistically with the immune system to counteract foreign attacks by microorganisms and viruses. The HS and immune systems have early origins and have co-evolved to defend the host [30]. Platelets are the natural support for blood coagulation activation [31], which can be triggered by several factors. First, monocytes release cytokines when stimulated by endotoxins or viruses, damaging the endothelial cells, which in turn express tissue factor, which triggers blood coagulation [32], while the monocytes themselves also express tissue factor, resulting in blood coagulation activation [33] (**Fig. 3**). Neutrophils stimulated by platelets form NETs, which can also directly activate blood coagulation [34]. Although these phenomena have evolved as a defensive host response against invaders, they may also have undesired effects. An excessive host response may be harmful to the host itself. For example, during sepsis or viral invasion, high levels of cytokines may attack the host [35], resulting in a severe inflammatory state and leading to diffuse fibrin formation and deposition [36]. Secondary fibrinolysis activation thus occurs, ultimately leading to DIC with a prothrombotic phenotype due to a fibrinolytic shutdown [37]. The consequence of this dysregulated massive blood coagulation activation is hampered by an endothelial prothrombotic reaction [38]. Notably, the ISTH criteria for a diagnosis of DIC only consider the laboratory parameters, without taking account of the clinical hemorrhagic features of the syndrome [39, 40]. COVID-19 infection provides a practical example. Tang et al. showed that the ISTH criteria for DIC were present in most of their COVID-19 patients [41], but no clinical signs of overt DIC were reported. We challenged the conclusion of this study, stating that DIC was common during COVID-19 infection, and proposed that DIC could be a local phenomenon in the lungs, with pulmonary thrombosis resulting from the host's response to the virus attack [42]. This possible event was subsequently confirmed by histologic findings, which demonstrated diffuse intravascular fibrin deposition in the lungs [43]. On the other hand, we previously proposed the concept of pulmonary thrombosis in 2019, prior to the COVID-19 pandemic. Indeed, the deposition of fibrin in the pulmonary vasculature has been recognized in chronic obstructive pulmonary disease, asthma, pneumonitis, drepanocytosis, Gaucher disease, and assisted reproductive procedures [44]. The classic definitions of pulmonary embolism should thus be revised to improve our understanding of the involvement of the lungs in inflammatory conditions. During SARS-CoV-2 infection, viral

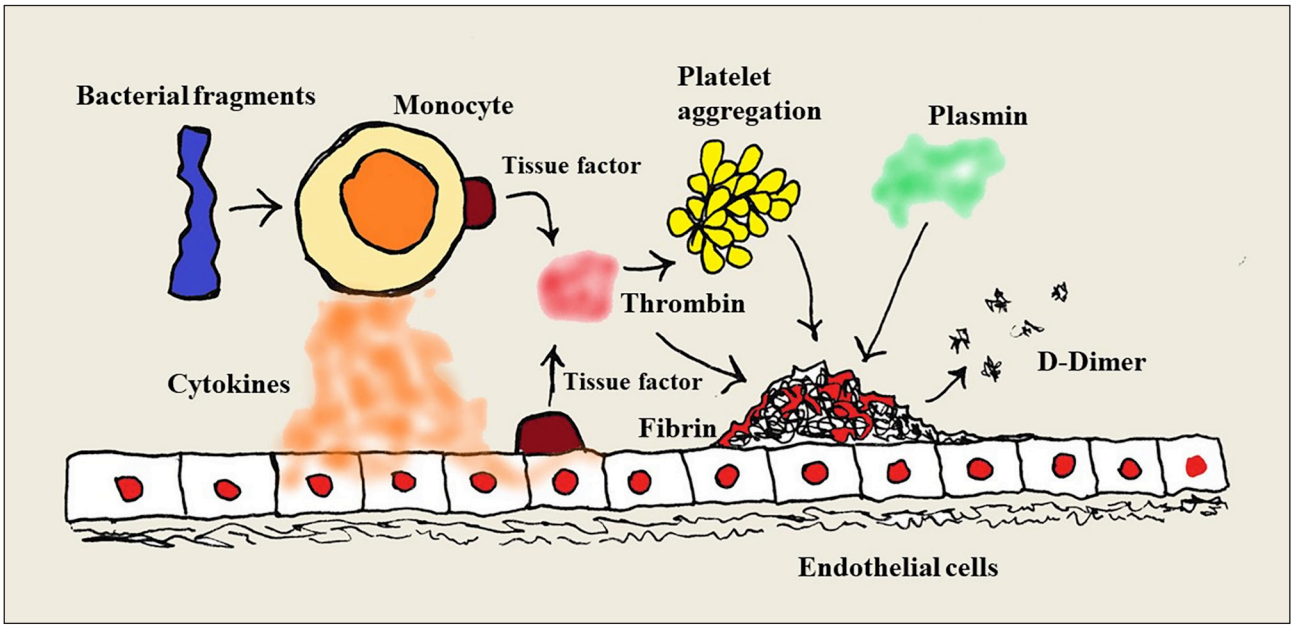

Figure 3. Blood coagulation and disseminated intravascular coagulation (DIC).
Bacterial fragments activate monocytes, which release cytokines and expose tissue factor, the trigger of blood coagulation. The final outcomes are endothelial damage with secondary tissue factor exposition and production of thrombin, which provokes platelet aggregation and fibrin intravascular deposition. Fibrinolysis subsequently attacks fibrin, causing the release of D-dimer.

attachment to the endothelial cells via ACE2 receptors is a crucial step in the development of the thrombotic features of the disease [45]. In this setting, monocytes play a crucial role, as described above. Overactivation of blood coagulation may again be fatal as a result of widespread occlusion of the vasculature. A therapeutic dose of heparin may be helpful in this setting, and has been shown to reduce mortality in non-critically ill patients with COVID-19 [46, 47].

Blood coagulation also plays an important role in cancer. Cancer cells *per se* have pro-coagulative properties [48], which help cancer cells to survive by producing an excess of thrombin, which in turn has a proangiogenic effect [49]. In contrast, there is an imbalance between thrombin formation and inhibition, in which the former is greatly enhanced. The reaction of the host may exacerbate this phenomenon, given that monocytes became activated after contact with cancer cells [50], thus producing more tissue factor, which in turn triggers blood coagulation [51]. These pathways imply significantly increased risks of both arterial and particularly venous thromboembolism (**Fig. 4**). The association between cancer and thrombosis is called "Trousseau syndrome", named after the French doctor who first described it in 1865 [52,

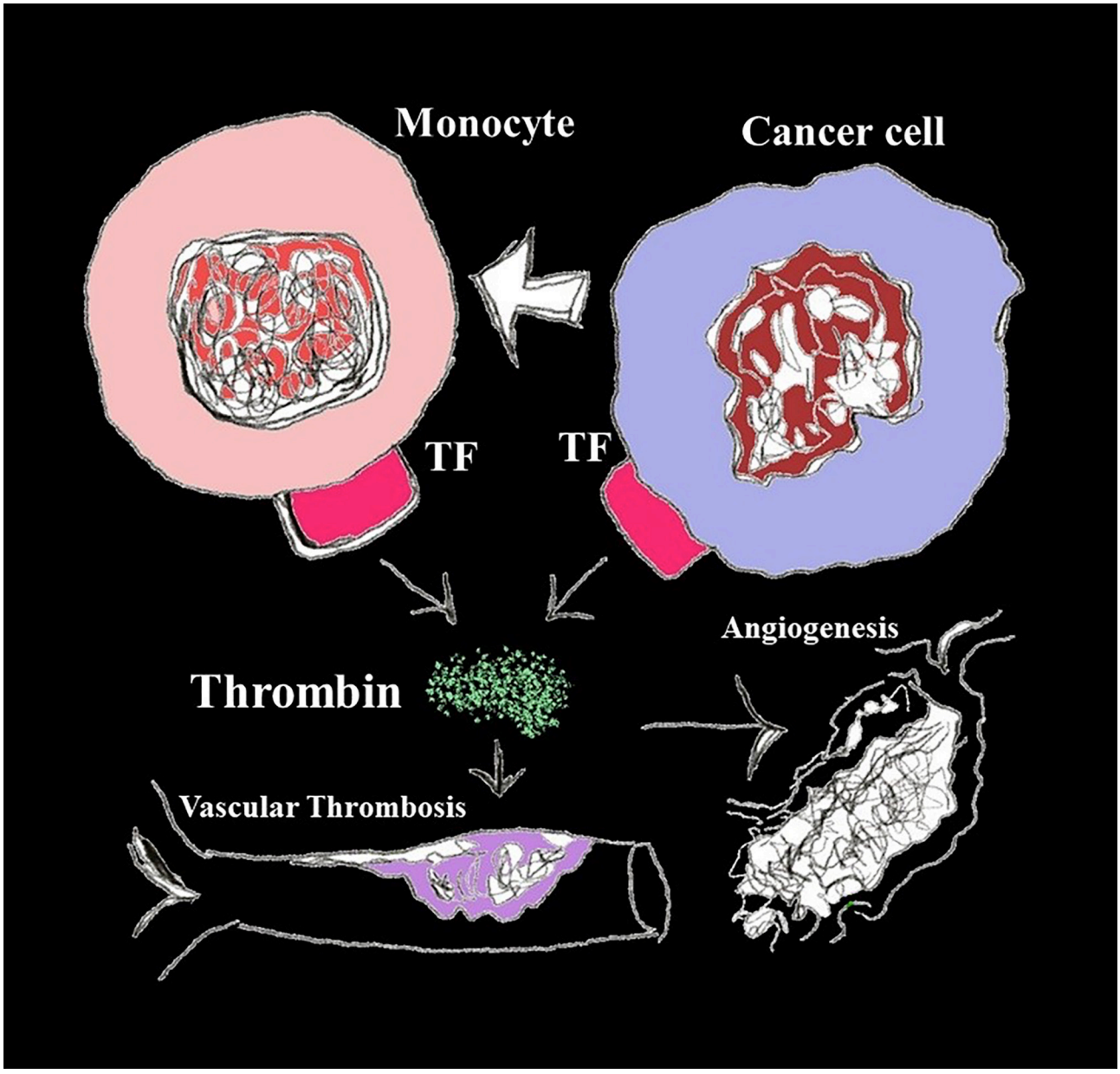

Figure 4. Cancer cells activate monocytes.
Both expose tissue factor (TF), which induces a hypercoagulable state, so leading to vascular thrombosis (the "Trouseau syndrome").

53]. Given the important role of blood coagulation in cancer, extensive research has focused on the possible use of anticoagulants, such as warfarin and low-molecular-weight heparins (LMWHs), for increasing cancer survival independently of their role in treating and preventing venous thromboembolism [54, 55]. However, although both warfarin and LMWHs have demonstrated antineoplastic effects [56], many of the studies were small, addressed different types of cancer, and the results were often inconsistent [57]. Further well-planned and high-powered studies are therefore needed to determine if antithrombotic drugs, especially LMWHs and direct oral anticoagulants, could have therapeutic or prophylactic roles in improving cancer survival, as well as to investigate the types and stages of cancer that are most likely to be sensitive to this kind of drugs.

Fibrinolysis

The fibrinolytic system was first described by Dastre at the end of the 19th century [58]. Its main function is to limit the growth of blood clots and promote their dissolution. It thus plays an essential role in the HS by modulating fibrin formation. Plasminogen cleaves fibrin via its activated form, plasmin [59]. Plasminogen is activated to plasmin by tissue-type plasminogen activator (t-PA), which is released by endothelial cells [60], and by urokinase-type plasminogen activator (u-PA) [61]. t-PA activity is strongly dependent on fibrin, because both t-PA and plasminogen bind to its lysine residues, thus using it as a cofactor for plasmin generation. However, plasmin formation by plasminogen activators is controlled by plasminogen activator inhibitors (PAI)-1 and PAI-2 [62], which are in turn controlled by α2-antiplasmin (α2-AP) after fibrin dissolution. Covalent binding to fibrin induced by factor XIII is important because it reduces the degradation of this glycoprotein [63]. The physiological importance of α2-AP has been highlighted in families with α2-AP deficiency, which, although rare, can cause severe bleeding, especially in early life [64, 65]. Fibrin formation is also controlled by thrombin-activatable fibrinolysis inhibitor (TAFI), which is activated by thrombin. TAFI cleaves fibrin lysine residues, thus reducing the binding of both plasminogen and t-PA to fibrin and increasing the stability of the clot [66]. However, plasmin also exerts non-hemostatic actions, such as neutrophil and monocyte recruitment, smooth muscle cell proliferation, enhanced foam cell formation, and the release of cytokines, and has a negative effect on angiogenesis [67]. Fibrinolysis and inflammation are thus clearly closely linked. This association is not surprising, given that the HS, including fibrinolysis, acts together with inflammation in host defense, but chronic poor control of both systems can have pathologic consequences, such as atherosclerosis and lung diseases [68, 69]. Hyperfibrinolysis is a typical feature of DIC, as reported above, and is secondary to the widespread development of thrombi in the microcirculation. However, fibrinolysis may be inhibited during DIC secondary to endotoxemia or sepsis, by increased PAI formation (the so-called fibrinolysis shutdown), leading to multiple organ failure [70, 71]. On the other hand, an exaggerated fibrinolytic response may occur during DIC because the excess plasmin formation overcomes its major inhibitor, α2-AP, so inducing breakdown of fibrinogen and clotting factors after fibrin dissolution. This results in severe bleeding, because the enhanced fibrinolytic activity is added to the consumption coagulopathy typical of DIC [72]. Thus, although the fibrinolytic system is a defensive mechanism, its activity can also be exploited by foreign invaders, such as bacteria and viruses, as described previously [73].

The fibrinolytic system is also involved in cancer [74], notably involving u-PA and PAI-1. u-PA induces the activation of metalloproteinases after the activation of plasminogen to plasmin, leading to lysis of the extracellular matrix and, thus, allowing cell migration [75] (**Fig. 5**). Plasmin can also favor tumor cell growth by stimulating growth factors, such as platelet-derived growth factor and fibroblast growth factor [76].

PAI-1 plays an intriguing role in cancer. It has been shown to counteract the pro-carcinogenesis action of u-PA and its receptor (u-PAR), but has also been involved in cancer progression [74]. Indeed, PAI-1 has several pro-carcinogenesis properties: it induces angiogenesis [77] and inhibits apoptosis, thus favoring neoplastic cell survival [78], tumor growth, and metastasis in an independent way. After complexing with u-PA/u-PAR, PAI-1 is internalized. Its role thus changes from that of an ally to an enemy of the host (the u-PA/uPAR-PAI-1 paradox) [79], further indicating the capacity of cancer cells to enslave the host's defensive systems.

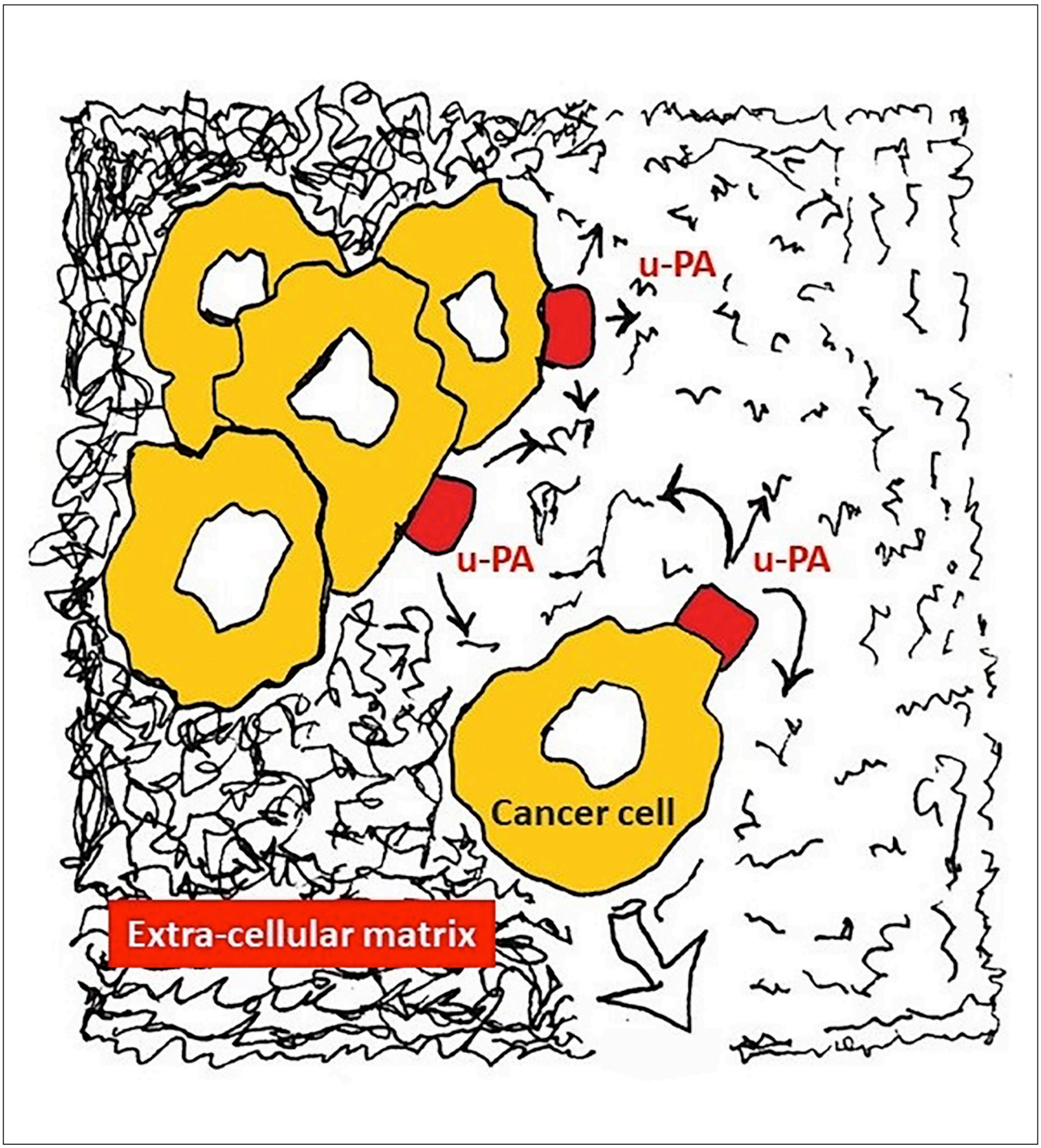

Figure 5. Urokinase-type plasminogen activator (u-PA), released by cancer cells, activates the degradation of the extracellular matrix, so leading to cellular metastasis.

Finally, the role of D-dimer deserves attention. On the one hand, D-dimer is a recognized marker of fibrinolytic activity, and levels below a certain threshold are thus used to exclude venous thromboembolism. However, its interpretation is difficult, because D-dimer testing has high sensitivity but poor specificity [80], and high D-dimer levels do not necessarily indicate a thrombotic event. Indeed, many conditions result in abnormal D-dimer levels, including DIC, inflammation, pregnancy, aging, and cancer [81]. D-dimer levels have been correlated with cancer progression, and high levels were found in patients with metastatic cancer, and in patients with early relapse [82]. Finally, D-dimer comes from fibrin deposited in the vascular and alveolar structures in patients with COVID-19, further indicating its different possible sources [83] (**Fig. 6**).

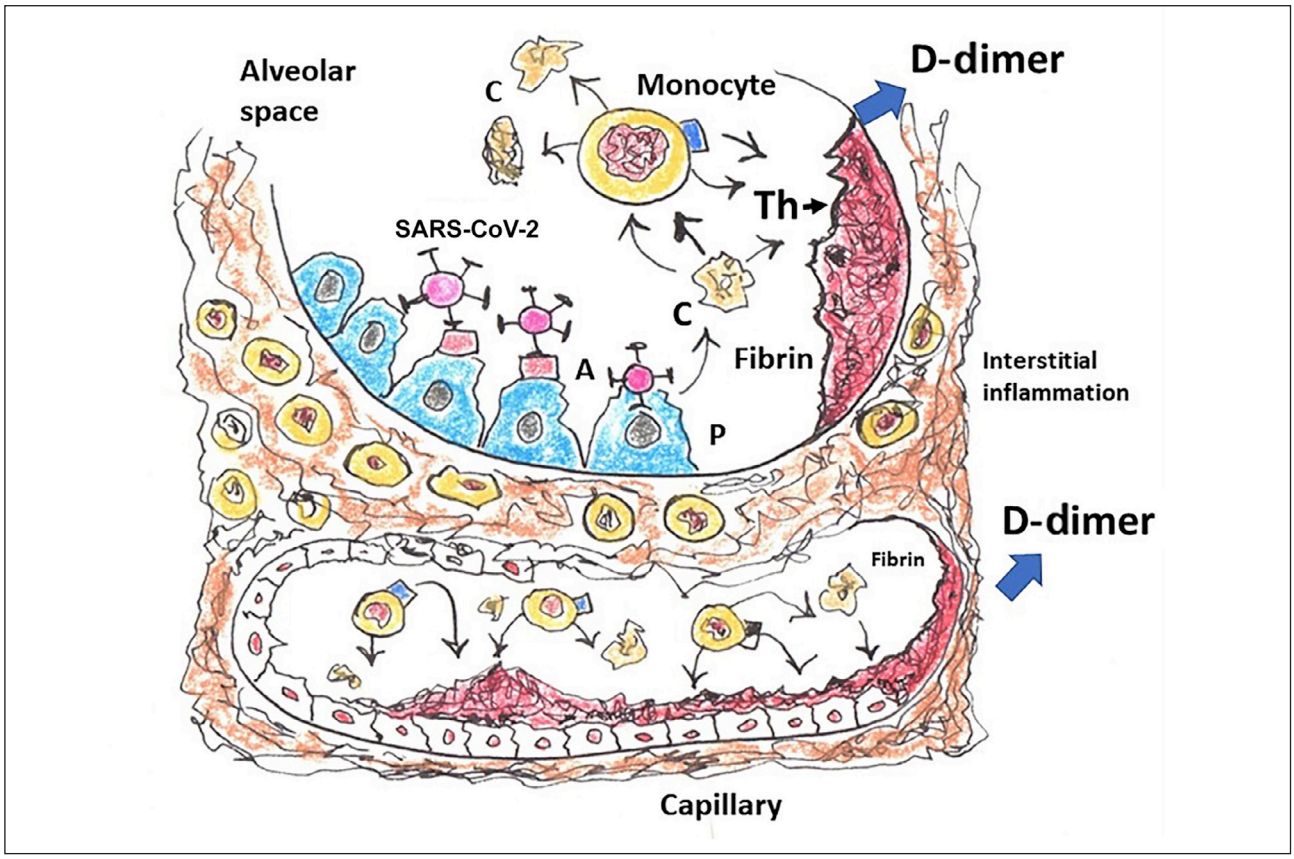

Figure 6. In SARS-CoV-2 infection, D-dimer comes from fibrin formed inside both the alveolar and capillary spaces.
A: ACE receptor; C: cytokines; p: pneumocytes; Th: thrombin.

Conclusions

The purpose of this review was to explore the pathophysiological mechanisms underlying the HS by considering the roles of platelets, blood coagulation, and fibrinolysis, focusing on their roles in inflammation, COVID-19 infection and cancer (**Fig. 7**). The complex nature of the pathophysiological mechanisms involved meant that this review was unable to consider all the processes in detail. Nevertheless, on the one hand, we considered the crucial role of the HS and its cooperation with the immune system in countering bacterial and viral invasion, and on the other hand, we assessed its harmful role in patients with cancer. In addition, we discussed the importance of excessive individual responses to sepsis or virus attacks, as in COVID-19. This review also presented the possible antineoplastic roles of anticoagulant and antifibrinolytic drugs. Further studies are needed to assess the abilities of these drugs to reverse or reduce the adverse impacts of the HS in patients with bacterial or viral infections and cancer.

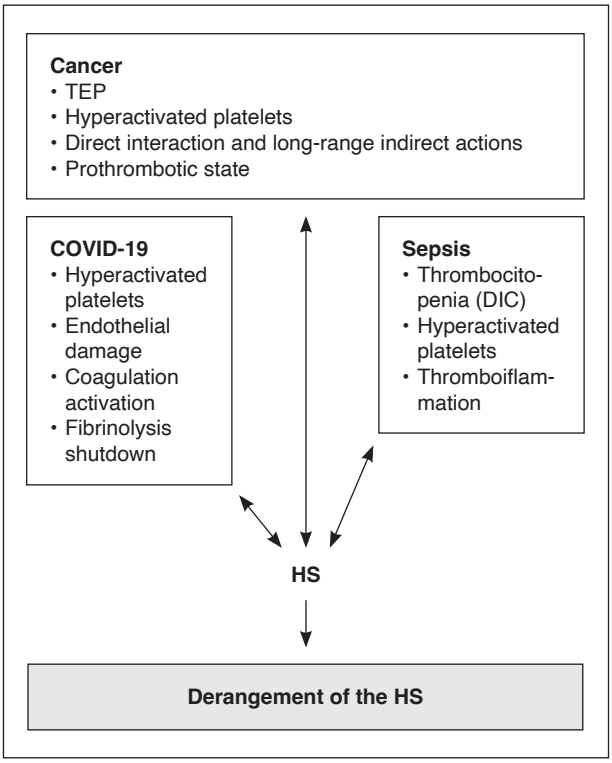

Figure 7. Reciprocal cross-talking among the hemostatic system (HS), cancer, sepsis and COVID-19.
DIC: disseminated intravascular coagulation; HS: hemostatic system; TEP: tumor-educated platelets.

Declaration of interest

The Authors declare that there is no conflict of interest.

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