Platelets Extracellular Vesicles

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Extracellular vesicles (EVs) are a membrane-bound structures secreted both in physiological and pathological conditions by prokaryotic and eukaryotic cells. Their role in cell-to-cell communications has been discussed for more than two decades. Numerous papers showed EVs as tumor growth regulators, by transferring their cargo (e.g.: miRNA, proteins, receptors, cytokines) into cancer cells and cells in the tumor microenvironment. Platelet extracellular vesicles (PEVs) are formed during platelet apoptosis as well as their activation. PEVs are highly heterogeneous and the most abundant EVs population in the blood. The reason for the PEVs heterogeneity are their maternal activators, which is reflected on PEVs size and cargo. As PEVs are the most numerous EVs in circulation, their feasible impact on cancer growth isstrongly discussed. PEVs crosstalk could promote cancer cells proliferation, change tumor microenvironment and favor metastasis formation. In many cases these functions were linked to the transfer into recipient cells specific cargo molecules from PEVs.

exosomes ectosomes neoplasia

1. History and Development

The number of research work and scientific papers that discuss the involvement of cell-derived extracellular vesicles (EVs) in multiple physiological and pathological processes has increased rapidly during the last two decades. EVs might have an influence on target cells by delivering ligands and signaling complexes, and transferring mRNA and transcription factors that cause the epigenetic reprograming of recipient cells. EVs are submicron spherical membrane bound structures, that are generated by different prokaryotic (termed as membrane vesicles) and eukaryotic cells [1][2][3]. EVs nomenclature take into account their cellular origin and size. Their size ranges between 10 nm to 5 µm and comprises three heterogeneous populations of vesicles—exosomes (EXSMs), ectosomes (ECTSMs) also named microparticles (MPs), and apoptotic bodies (ABs) [4][5]. EVs actively secreted form parental cells with a diameter of 10 to 100 nm are named EXSMs, and those with a diameter ranging between 100 nm to 1 µm are ECTSMs. Lipid bilayer membrane protects their cargo from enzymes like proteases and ribonucleases [6]. The largest of EVs are ABs (with diameter 1–5 µm) represented by clumps of material generated during the late stage of cell apoptosis [5][6][7].

During activation, maturation, proliferation, stress, aging, or apoptosis, cells shed EVs into the extracellular space [8]. Their presence in a number of body fluids including—urine, synovial fluid, bronchoalveolar lavage fluid, saliva, and bile was confirmed [7][9][10][11]. In the bloodstream, EVs are released by—erythrocytes, leukocytes, platelets

(PEVs), megakaryocytes, and endothelial cells [10][12]. In addition, EVs are also secreted by cancer cells known as tumor-derived extracellular vesicles (TEVs) [4][12]. In both healthy subjects and those with a variety of pathologies, peripheral blood is a rich source of EVs, where the most abundant population are PEVs. Their percentage ranges between 70 to 90% of all EVs in the plasma of healthy individuals [13][14][15].

In 1967, Peter Wolf described “platelet dust”—a subcellular material derived from thrombocytes in the plasma and serum of healthy individuals [16][17]. This was a milestone in medicine research, allowing further examinations evaluating PEVs involvement in physiological and pathological processes. PEVs share many functional features with PLTs. These tiny fragments smaller than platelets (PLTs) were secreted during PLT activation and were known to be crucial in coagulation and clot formation [16][18]. Despite the fact that PLTs play a crucial role in hemostasis, PEVs coagulation capacity is several dozen higher than PLTs [19]. Platelets microparticles (PMPs) are enriched in tissue factor (TF), coagulation factors, and dozens of them expose about 3-fold higher phosphatidylserine (PS) concentration on the outer membrane than PLTs [20]. The coagulation process initiated by TF connection with coagulation factor VII, activates coagulation cascade. Activated PLTs, PMPs PS + offer a catalytic surface for the coagulation and binding of consecutive clotting factors. Moreover, in healthy individuals, the presence of integrin αIIbβ3 (CD41/CD61) on PMPs supports fibrin clot formation [21]. In various bleeding disorders, abnormalities in PMPs functions and their reduced number in blood were reported [22]. On the other hand, their increased amount was presented in thrombotic state and other pathologies [23]. PLTs of patients described by Castaman are unable to shed PMPs, conversely to patients with Scott syndrome in which the PMPs number is adequate, but the incorrect translocation of PS impairs prothrombinase activity, and causes hemorrhagic diathesis [22]. Patients with immune thrombocytopenia have higher PEVs level than healthy individuals, which might be an evolutionary way to prevent blood loss and maintain tissue integrity [24]. Additionally, contemporary papers showed that PEVs might be a potential biomarker or prognostic factor in other pathologies—inflammatory, cardiovascular, and autoimmune diseases, solid tumors and hematological malignancies [14][25].

2. The Potential of PEVs as Diagnostics Cancer Biomarkers

PEVs number in blood was raised about twice in myeloproliferative neoplasms, compared to healthy controls, up to four times in oral cancer and colorectal subjects and more than ten times in breast cancer patients [26][27]. The highest concentration of PEVs, more than 30-fold, was noticed in patients with IV stage of gastric cancer. In each group, the highest PEVs concertation were demonstrated in advanced cancer stages and in patients with distal metastases [26][27][28][29].

Investigation in patients with non-small cell lung cancer (NSCLC) categorized based on disease progression, showed the significantly higher number of circulating EVs from activated or apoptotic PLTs and from endothelial apoptotic cells, compared to healthy subjects. Changes in EVs levels in different stages of NSCLC showed that serial measurements of circulating PEVs are valuable prognostic biomarkers, mainly in the advanced stages of NSCLC [30].

PEVs as source of anionic phospholipids and TF on their surface are one of the important factors of procoagulant activity. Data demonstrated by Ren et al. showed the significantly increased number of EVs and PEVs in patients with oral squamous cell carcinoma (OSCC) in peripheral blood. PEVs level was also positively correlated with clinical stage and with fibrinogen concentration and patients hypercoagulable state [28]. Mege and colleagues showed correlations between increased PEVs number and the stage of the disease in patients with pancreatic cancer and colorectal cancer. They suggested that PEVs concentration in blood could be a useful marker for evaluation of the disease progression in these types of neoplasia [31].

Yenigürbüz et al. described another aspect of increased PEVs number in patients with neoplasia. Thromboembolism is one of the complications during induction of therapy in pediatric acute lymphoblastic leukemia (ALL) patients [32]. Children with ALL have increased levels of ABs, PEVs, endothelial-derived, and tissue factor-positive microvesicles during induction therapy. Further studies are needed to confirm the PEVs contribution in thromboembolism during the induction therapy period in children with ALL [32]. Similar observations were made in adult patients with myeloproliferative neoplasia, where the number of TF positive PMPs and endothelial derived EVs was significantly increased, which might also play a role in thrombotic complications in that group of subjects [33]. Tjon-Kon-Fat et al. demonstrated that tumor educated PLTs are a source of prostate cancer biomarkers [34][35]. In this context it seems to be interesting to evaluate the presence and role of EVs generated from tumor-educated PLTs.

3. The Potential of PEVs in Cancer Therapy

The paradigm of using nanoparticulate pharmaceutics as delivery vectors was established over the past decade [36]. To use EVs as drug transporters, their pharmacokinetics should be analyzed. Mice models of EXSMs distribution showed that the route of administration, EXSMs origin, and concentration critically influenced their biodistribution [37]. In the mice model, after intraperitoneal and subcutaneous administration of EXSMs, they preferentially localized in the pancreas and gastrointestinal tract. Whereas, intravenous administrated EXSMs were detected in the spleen and the liver [38]. In addition, EXSMs loaded with therapeutic anti-miRNA could be transferred locally into tumor or systemically. Other therapeutic strategies in cancer therapy were elimination of EXSMs from blood or prevention of EXSMs fusion with target cell [39][40]. Various strategies of using EXSMs in anticancer therapy are characterized in the literature, but more research is still needed.

In an elegant study, Kailashiya et al. documented that doxorubicin-loaded PEVs (doxo-PEVs) were taken by HL60, K562 cells (leukemia cell lines), and blast cells, in whole blood harvested from patients with newly diagnosed leukemia. Doxo-PEVs were uptaken by cells via P-selectin ligands and integrins. Moreover, doxo-PEVs transfer into leukemia cells was higher, compared to free doxorubicin, which could be used to increase the effectiveness of the therapy and minimize the side effects of drugs [36]. Gasperi et al. showed that PEVs with miR-126 and with miR-223 increased sensitivity of BT549 cells to the cisplatin chemotherapy [41].

PEVs drug-loaded could be a natural vectors-targeted medications. Engineering them from autologous platelets in large quantity and storing for several days, seems to be a new biocompatible and non-immunogenic new-

generation medicine. However, to make PEVs applicable and efficacious in clinical treatments, some of their underlying functions still need to be better researched and understood.

4. Summary

PEVs biogenesis depends on different signals that control their formation from PLTs. The role of PEVs in various physiological conditions, like hemostasis, or pathological like inflammation or atherosclerosis was confirmed. This review focused on the PEVs participation in cancerogenesis. A better understanding of the biology of PEVs and the mechanisms that allow them to function as mediators in cell-to-cell communication in cancer growth, could become a contribution to the development of new therapeutic strategies, which could also be applicable in cancer. Moreover, determining the number of PEVs and their cargo becomes a useful diagnostic marker or prognostic factor for the different clinical stages in a variety of neoplasia. Knowledge about the formation of distinct PEVs types dependent on PLTs activators could lead to the development of specific techniques for PEVs-mediated drug delivery to cancer cells, or to TME, to modulate their immune response or angiogenesis.

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