Roles and molecular mechanisms of platelet-derived extracellular vesicles in regenerative medicine and disease treatment

**Title page**

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**Abstract：**

Extracellular vesicles (EVs), which contain rich growth factors, enzymes, RNA and other substances, are released by different types of cells and participate in physiological and pathophysiological processes. EVs can be divided into peripheral bodies, microcapsules and apoptotic bodies according to their diameters. Among them, platelet-derived extracellular vesicles (PEVs) are characterized by low immunogenicities, stable structure, simple extraction operation, targeted therapy, and potential drug carriers. They can be used in clinical applications such as inflammation suppression, tissue repair, and drug carriers. In this paper, the role and molecular mechanism of PEV in treatment were reviewed, and the future development of PEV was prospected.

**Keywords**: Platelet; Extracellular vesicles; Exosome; Regenerative medicine; Drug carrier

**1 Introduction**

Extracellular vesicles (EVs), such as exosomes and microvesicles (microparticles), are released by different cell types and engage in physiological and pathophysiological processes. Exosomes and microparticles comprise EVs' most prominently described classes [1] (Fig.1). They are encased in a phospholipid membrane and contain cell-type-specific combinations of proteins, including enzymes, growth factors, receptors, and cytokines, as well as lipids, coding, and non-coding RNAs and metabolites[2, 3].

The term platelet dust was firstly proposed by Peter Wolf in 1967 when he observed the procoagulant properties in blood platelet samples, and now these tiny vesicles are considered to be platelet-derived EVs (PEVs) [4]. In human blood, PEVs are evidenced to be the most abundant EV, despite the fact that the number of red blood cells is approximately 30 times that of platelets[5]. And it is estimated 70-90% of EVs in circulation come from platelets, 10% from granulocytes, and only 5% from endothelial cells, red blood cells, and monocytes[6]. PEVs contain a variety of growth factors and can be transferred to recipient cells and uptaken directly through autocrine and paracrine process[7]. They can be absorbed into the cells, or combined with the ligands of the target cells, cell communication signal and related substances with their integrity maintained then will be feasible for PEVs to transmit between, further regulating molecular pathways and gene expression[7-10]. So it is proposed that PEVs can be key role in signal transduction, cell communication, multitudes of functions regulation in the target cells, and tissue repair in the human body, thus conceivably displaying different roles in regenerative medicine and the treatment of disease.

Microparticles (MPs), the subtype of EV, are submicron vesicles shed from various cell types upon activation, stimulation, and death[11]. Platelet microparticles (PMPs) are the majority of EVs in blood[6]. Platelet-rich plasma (PRP) is defined as an autologous aggregation of platelets obtained from fresh whole blood with higher concentrations[12]. Extracellular vesicles produced by platelet-rich plasma (PRP-EVs) are confirmed to include internal platelet-related components insides[2], and PLT-EVs contribute to the main content profiles of serum EVs after coagulation activation from plasma, thus contribute to the major content of PRP-EVs[13]. So, it is considered that the PRP-EVs are mainly PLT-EVs, and thus PMPs, PLT-EVs and PRP-EVs are all considered as PEVs in this review and to be discussed (Fig.1).

**2 PEVs in regenerative medicine**

EVs, as cell-derived extracellular signaling organelles, facilitate intercellular communication by transmitting specific information from their cell of origin to their target cells. These characteristics make EVs of defined cell types may serve as novel tools for a range of therapeutic approaches, such as anti-tumor therapy, immune-modulatory, regenerative therapies, injury regeneration treatment, and drug delivery[14, 15].

In recent years, EVs have emerged as body damage repair in the regenerative biomedical field. EVs have different subpopulations, which differ in morphology, size, composition, and cellular origin. Compared with EVs from other sources especially stem cells, PEVs exhibit advantages in several aspects. First, owing to the direct extraction from platelet concentrates, the isolation of PEVs lowers the requirements of upstream expansion and avoids the crucial procedural or quality control difficulties associated with cell amplification, which is indispensable for EVs from other cells[16]. Additionally, the platelet concentrate is a kind of essential medicine authorized by the World Health Organization[17]. Blood donation is legal and encouraged in the majority of countries, which implies a rich allogeneic platelet source for the isolation of PRP-EVs[18]. Finally, the anucleated property of platelets further lessens safety concerns about potential tumorigenic risks.

In the current research, the application of extracellular vesicles for regeneration medicine is the current mainstream[19]. As an information transfer factor between cells, it can realize the communication between cells, and this mechanism can be effectively employed in the treatment of diseases (Fig.2). This review collects and sorts out the current application of platelet-secreted extracellular vesicles in repair in various systems of the body, including injuries, neurogenesis, muscle regeneration, angiogenesis, biomaterials, bone regeneration, and osteoarthritis.

**2.1 PEVs in nerve regeneration**

PEVs contain many growth factors, such as vascular endothelial growth factor (VEGF), and platelet derived growth factor (PDGF), fibroblast growth factor (FGF), and brain-derived neurotrophic factor (BDNF), which can promote neurotrophic effects and neurogenesis[20-22].

In terms of inducing nerve regeneration, current studies have shown that PEVs can promote the differentiation, proliferation, and survival of neural stem cells. These effects are mediated by the combination of fibroblast growth factor-2 (FGF2), VEGF, PDGF, and potentially other growth factors, since blocking the individual effects of these cytokines (but not those of platelet factor 4) led to partial reversal of the proliferative effects of PEVs. According to further research we show that PEVs may promote cell driven angiogenesis and neurogenesis with a significant functional gain in a rat model of cerebral ischemia.

Yael Hayon *et al.*[23] studied the effects of PEVs on neural stem cell (NSC). PEVs treatment, which was comparable with the effect of acceptable single growth factors such as FGF, VEGF and PDGF, led to larger neurospheres with increased cell survival and also increased the differentiation potential of NSC to glia and neurons. PEVs contain various growth factors, which play important roles in augmenting endogenous neural progenitor and stem cells angiogenesis and neurogenesis and might be utilized for treatment following brain injury. They (Yael Hayon *et al.*[24]) further delivered PEVs via a biodegradable polymer to the brain surface after permanent middle cerebral artery occlusion in rats to examine the effects of PEVs therapy *in-vivo,* which shows that PEVs led to a dose dependent increase in cell proliferation, neurogenesis and angiogenesis at the infarct boundary zone and significantly improved behavioral deficits. PEVs, which contained a range of neurotrophins, stimulated the wound closure in the scratch assay and induced SH-SY5Y differentiation as revealed by the increased length of neurites as well as β3-tubulin and neurofilament staining, which confirm the therapeutic potential of PEVs in the treatment of disorders of the central nervous system[24]. Interestingly, Ariunjargal Nyam-Erdene and colleagues purified EVs from the four Human platelet lysates and these PEVs exhibited a differential capacity to promote cell growth and migration in a wound-healing assay using SH-SY5Y neuronal cells, and one EV preparation stimulated network formation in primary neuronal cultures[25].

These data above suggest that PEVs have the ability to promote nerve regeneration, and some PEVs preparations may be used as alternative therapies for nerve regeneration medicine, opening up a new therapeutic model for nerve regeneration medicine.

**2.2 PEVs in revascularization**

The EVs derived from platelets have been proven to encapsulate principal growth factors from platelets, which also play a unique role in revascularization. The following researches prove this point: PEVs protein components, specifically, VEGF, BFGF, and PDGF, enhanced revascularization *in vivo* following chronic ischemia. Alexander Brill *et al.* [26]constructed a rat aortic ring model and a dose-dependent pro-angiogenic effect of PEVs was observed in this model. Furthermore, when agarose beads containing PEVs were transplanted subcutaneously into mice, PEVs induced angiogenesis in an *in vivo* model. This proves that PEVs can induce angiogenesis both *in vitro* and *in vivo*. And the process of revascularization after chronic ischemia might be improved by the injection of PEVs into the ischemic myocardium[26]. Chinedu Anene *et al*.[27] pointed out that the formation of robust capillary like structure was induced by co-culturing PEVs with human umbilical vein endothelial cells (HUVEC) on extracellular matrix gel, and the promoting effect of HUVEC migration and structure formation was also observed by PMVs of medium size in particular[28, 29]. *In vitro,* Wolf, P *et al*. conducted that PEVs proteins are functionally active and can induce robust angiogenesis in an endothelial cell/interstitial cell co-culture[11]. The adhesive proteins and natural targeting ability to injure the vasculature of platelets and the proangiogenic potential of EVs were both retained in PEVs. In the myocardial ischemia reperfusion model, PEVs preferentially accumulated in the injured endothelium of the ischemic hearts and enhanced the angiogenesis potency of EVs[30]. Vascular remodeling and revascularization may also be clarified by vascular smooth muscle cells (VSMCs). PMVs are reported to promote VSMC proliferation, dedifferentiation, and migration after vascular intimal injury[31-33], resulting in accelerating revascularization physiologically but intimal hyperplasia pathologically.

The possible mechanisms of PEVs promoting revascularization are as follows: The enriched growth factors can be encapsulated into PEVs and activate protein kinase B (Akt) and Extracellular signal kinase (Erk) pathways to promote angiogenesis[34]. Shang-Chun Guo *et al*.[35] also indicated that EVs released by platelets may promote cell proliferation and angiogenesis and contribute to PRP-induced angiogenesis through the activation of Erk and Akt signaling pathways. Shang-Chun Guo *et al*.[35] proved that PEVs can effectively induce proliferation and migration of endothelial cells and fibroblasts through Yes-associated protein (YAP) activation to improve angiogenesis in chronic wounds, which is the first to show that PEVs may exert the function of platelets. Angiogenic early outgrowth cells (EOCs) are conducive to endothelial regeneration and to limit neointima formation after vascular injury. PEVs can boost the potential of EOCs to restore endothelial integrity after vascular injury by enhancing EOC recruitment, migration, differentiation, and release of proangiogenic factors[36]. Additionally, endothelial progenitor cells (EPCs) are a subset of circulating bone marrow mononuclear cells (BMCs) and can attach to injured endothelium, differentiate into endothelial cells in vivo, playing a significant role in endothelial repair following vascular injury[37]. PEVs are evidenced to be uptaken by EPCs[38], delivering TGF-ß1 from platelets to EPCs, and activating Smad3 phosphorylation which finally promotes EPC proliferation and revascularization[39]. Adipose-derived mesenchymal stem cells (ADSCs), one of the top prospects and excellent candidate in the therapeutic transplantation technique for clinical neovascularization application, have also been discovered by Tang's team to show better proangiogenic potential after culture with PMVs. In that ischemic model, PEVs were found to effectively enhance ADSCs viability, migration, and proangiogenic potential both *in vitro* and *in vivo* while the mechanism may consist of MAPK/Erk1/2 and PI3K/Akt pathways for anti-apoptotic capacities enhancing[29]. PEV was demonstrated to be a potent angiogenic stimulator and promote the proliferation and survival, migration, and tube formation in human umbilical vein endothelial cells, which was mediated via the Pertussis toxin-sensitive G protein, extracellular signal-regulated kinase and the phosphoinositide 3-kinase pathway[31]. Except for endothelial regeneration and intima regeneration, VSMCs can be stimulated to dedifferentiated by Src/Lamtor1/mTORC1 signaling pathway, and migration via TRPV4[32, 33]. In conclusion, PEVs have the ability to express and transfer functional receptors from platelet membranes, increase expression of adhesion molecules on cells, stimulate the release of cytokines, activate intracellular signaling pathways, alter vascular reactivity, induce angiogenesis, which indicated that local PEV application may be found useful for developing novel therapeutic strategies targeting angiogenesis-related conditions[40].

These studies suggest that PEVs have superior therapeutic implications in regenerative medicine and provide an exciting opportunity for therapeutic angiogenesis.

**2.3 PEVs in osteoarthritis**

PRP has been widely used in the clinical treatment of osteoarthritis (OA), and the value of PEVs in the treatment of OA is also in full swing. PEVs, which can suppress the inflammatory immune microenvironment and are often enriched by pro-inflammatory immune cells and cytokines to reduce chondrocytes apoptosis, have high therapeutic value for treating OA. Moreover, PEVs can be modified or incorporated into biomaterials for enhanced targeting and prolonged retention to treat OA effectively[41]. Bohan Yin *et al*.[41] further showed that intra-articularly injected PEVs induced more cartilage repair and OA inhibition than activated PRPs alone in a rat OA model (6-7 weeks post-surgery). Also, PEVs administration with thermosensitive Gel incorporated has a therapeutic effect in subtalar osteoarthritis and cartilage protection[42]. Ti surfaces functionalized with platelet lysate-derived EVs can improve their osteogenic properties[43]. PRP and platelet lysate have already been described as showing bone regenerative effects. [44-46] However, their clinical use was hindered by the complexity of the samples, their variability (depending on their source, production method, and storage conditions).[47] Studies by Alexander Otahal *et al*. [48] showed that platelet-derived EVs were sufficient to induce changes in chondrogenic gene expression in OA chondrocytes and inhibit the release of pro-inflammatory cytokines, which highlights the potential of PEV as a regulator of chondro-extracellular matrix metabolism and inflammation, as well as a candidate for a new cell-free treatment of OA.

PEVs may contain a functional miRNA profile which would benefit osteoarthritis regenerative therapies[49]. The promoting effect of PEVs was significantly better than activated PRP in the proliferation, migration, and scratch assay of chondrocytes. And compared with activated PRP, PEVs could significantly decrease the apoptotic rate of osteoarthritis chondrocytes.[50] PEVs present a novel therapy for osteoarthritis by activating the wingless/integrated (Wnt) /β-catenin signaling pathway[50].

**2.4 PEVs in bone regeneration and bone tissue engineering**

Synovium-derived mesenchymal stem cells (SMSCs) can adhere to damaged cartilage (a process called homing) and then repair the cartilage defect after intra-articular injection. PEVs significantly promoted the homing of SMSCs to cartilage and facilitated cartilage regeneration, which provided a safe and promising strategy for improving the outcome of stem cell therapy[51]. Antich-Rosselló *et al*.[52] demonstrate that the osteogenic effects of platelet concentrates were preserved and even increased by EVs derived from them. For this reason, PEVs, overcome platelet lysate and PRP limitations, emerging as an alternative able to platelet lysate treatments[52]. Activated platelets secret a high amount of growth factors and cytokines to promote cell proliferation and inhibit the apoptosis of chondrocytes[53, 54]. This secretion can be mediated by delivering PEVs that interact with chondrocytes for fusion and subsequent release of bioactive contents[34]. PDGF-AB, tumor necrosis factor β (TGF-β), and VEGF were secreted in PEVs to promote cell proliferation (with reduced apoptosis) and cartilaginous matrix secretion by suppressing the Wnt/β-catenin signal pathway in interleukin-1β stimulated chondrocytes[50]. Marcel Rodrigues Ferreira *et al*. provided a registry of miRNAs that play central roles in regulating osteogenic phenotype, which might have potential therapeutic applications in bone regeneration and bone tissue engineering[55].

PEVs proved to maintain the differentiation effect on mesenchymal stromal cells and present an osteogenic capability, which emerges as an alternative able to overcome PRP and platelet lysate limitations[56]. Bone marrow stromal cells treated with three different PEV concentrations (0.6 μg, 5 μg, and 50 μg) showed a significant, dose-dependent increase in cell proliferation and migration compared to the control[46]. *In vitro* and *in vivo* models of osteonecrosis have been used to test PEVs functionality, which suggest that PEVs can promote proliferation and avoid apoptosis[34]. In bone cells, PEVs rescue the osteogenic protein expression level through the Wnt/β-catenin signaling pathway, thus maintaining osteogenic differentiation and osteogenesis[34]. PEVs are important effectors for mesenchymal stromal cells osteogenic differentiation in a dose-dependent manner.

Therefore, we propose their use in bone regenerative medicine as an alternative to overcome platelet lysate and PRP limitations[57]. However, another study performed in pigs had previously reported no significant effects in bone formation[58]. Therefore, it is necessary to perform further experiments to determine the real osteogenic effect of PEVs.

**2.5 PEVs in skin regenerative**

Chronic trauma, with its long course and poor prognosis, has caused economic, social and public health burden, and it is urgent to develop advanced treatment methods. An increase of fibroblast and keratinocyte migration and proliferation *in vitro* has been reported to associate with the wound healing process[35, 59]. Shang-Chun Guo *et al*.[35] proved that PEVs increase the proliferation and migration of human dermal microvascular endothelial cells (HMEC-1) cells and fibroblasts to a greater extent than PRP in chronic wounds, and suggest that PEVs induced re-epithelialization may be triggered by activation of YAP. In the experiment of an *in vitro* model of wound healing, wound areas were assessed and find the obvious effect and advantage of PEVs in injury closure over PRP, which suggesting a key role of EVs in the healing process and a possible clinical use as an alternative to PRP[59]. Also, PMVs are evidenced have better regenerative healing outcome than PRP in rats models with post-burn scars and skin lesion[60]. These effects might be related to the PEVs cargo, which was positive in different growth factors, including PDGF, FGF2, TGF-β, and VEGF. And the exosomes subtype of PMVs have confirmed to have TGF-β loaded, hence injection of PMVs will improve chronic ischemic wound healing both *in vivo* and *in vitro*. In comparison to the renewal and repair of standard control animal models, the repair of diabetic animal models is hindered due to the lack of growth factors, vascular growth disorder, and macrovascular disorder[61, 62]. But experiments results have suggested PEVs can accelerate skin injury repair and circumvent healing impairment in models with diabetes and ultimately indicate an unexpectedly positive impact[63]. PEVs/polysaccharide (ZWP) combination therapy was more successful (a decrease of ulcer and an increase of epidermal thickness) in wound closing than ZWP single administration in a wound contraction in diabetic rats[63]. PEVs significantly promoted cell proliferation, migration, tube formation, as well as skin organoid formation *in vitro* experiment. Further research showed that PEVs promoted full-thickness healing with the reacquisition of hair follicles and sebaceous glands in topical treatment of ischemic wounds and promoted epithelial and vascular cell activity enhancing angiogenesis to restore blood flow and mature skin function[64].

In terms of the specific mechanisms of PEVs in skin repair, many research results indicate that they are related to signal pathways. Wei Zhang *et al*. found that EVs derived from platelet-rich plasma activate YAP through the phosphoinositide 3-kinase (PI3K) /Akt pathway and promote the fibrotic activity of Müller cells[65]; Shi-Cong Tao *et al*.[34] suggested that EVs derived from platelet plasma can inhibit the apoptosis of rat femoral head necrosis cells induced by glucocorticoid-related endoplasmic reticulum stress through the Akt/ BCL-2-associated death (Bad)/B-cell lymphoma 2 (Bcl-2) signaling pathway; On this basis, PEVs also have the ability to pass the stress on the endoplasmic reticulum. Under the Akt/Bad/Bcl-2 signaling pathway to promote Bcl-2 expression[34]. PEVs can also significantly enhance the proliferation, migration, and healing activity of immortalized keratinocytes (HaCaT cells). Further experiments discovered that USP15 in PEVs can enhance the functional properties of repairing skin damage by promoting EIF4A1 deubiquitination[66].

**2.6 PEVs in degenerative diseases**

Degenerative diseases are often characterized by a progressive loss of the potency of stem cell populations resident in tissues[67]. The enhanced potency of stem cell populations resident in tissues is important in preventing degenerative diseases. PEVs positively modulate the growth, migration, and differentiation potential of stem cells from different sources. The first described role of EVs derived from PRP in tissue regeneration was published in 2014 by Torreggiani *et al*.[46]. They demonstrated the potential effect of PEVs on the proliferation and migration of MSCs. The positive role of PEVs has also been evidenced in mouse bone MSCs[42]. Further study showed the promoting effect on chondrogenic differentiation of MSCs *in vitro* via the Wnt/β-Catenin Pathway[68]. In addition to bone marrow MSCs, PEVs increased the gene expression of human telomerase reverse transcriptase in umbilical cord-derived MSCs (UC-MSCs) *in vitro*[69]. And it is further been demonstrated PEVs can prolong the lifespan of UC-MSCs, probably through regulating longevity-related genes expression. In this study, PEVs prolong successfully the time before entering the process of aging after passages of culturing and maintain the viability of MSCs, which in fact overcome the key obstacle preventing MSCs from being used clinically and advancing regenerative science [70]. Baoshan Hu et al. discoverd miR-25-3p encapsulated in PEVs can be transported to nucleus pulposus (NP) cells to alleviate cell degeneration by suppressing SOX4 expression and CXCR7 transcription[71], which sheds light on the progression of intervertebral disc (IVD) degeneration.

Those findings suggested enchanting prospect that PEVs increase MSC longevity and have potential application in degenerative diseases, but this needs to be conclusively validated *in vivo*.

**2.7 PEVs and other regenerative findings**

The growth of PEV regenerative research in recent years is probably related to the study of the function of their cargo inside.

One of the main fields in which the applications of PEVs have been studied is skeleton muscle injuries and wounds[15]. In terms of muscle regeneration, PEVs can speed up recovery after a muscle strain injury in rat models likely because of factors that can modulate inflammation, fibrosis, and myogenesis[72]. Centrally nucleated fibers (CNFs) are widely accepted as a marker of muscle regeneration. And in this study, a significant increase in the number of CNFs at day 15 in muscles treated with PEVs exosomes compared to the control (saline) group[73]. In accordance with this interpretation, histological analysis revealed a shift toward smaller fiber sizes in the PEVs and MSC-exosome treated muscles, also indicative of myofiber regeneration[72]. And myogenin, a muscle regulator factor indicative of myogenesis, was significantly upregulated in muscles treated with PEVs[72] In summary, the effects of PEVs in muscle regeneration have been verified *in vivo* and *in vitro* tests[59].

In addition to muscle regeneration, PEVs have also been found their potential in pulp and gingiva regeneration. Dini Asrianti Bagio and colleagues conduct a research *in vitro* on the role of PEV exosomes in dental pulp*.* They examined the viability and migration activity of human dental pulp stem cells (hDPSCs) after co-culture with PEVs exosomes, and found PEVs can hasten wound closure and angiogenesis process by fixing the mitochondria cell function. Thus PEVs play a key role in dental pulp regeneration[74]. In contrast, Miquel's team begins their research in gingival regeneration for fibroblasts and keratinocytes promotion and successfully illustrates the new application in periodontal regeneration[75].And this is consistent with the fact PEVs can induce dermal fibroblasts and keratinocytes migration and promote wound healing as we mentioned[35].

PEVs may contribute to the renewal of blood cells and platelet regeneration. PEVs are recently evidenced to infiltrate the bone marrow, and strikingly found it restore megakaryopoiesis and bone marrow cells functional reprogramming both in vivo and in vitro, which may lead to hematopoiesis[76]. Also, A new study also evidenced the megakaryopoiesis induced by PEVs, but enhance megakaryocyte differentiation and platelet generation mechanically by miR-1915-3p transferring[77]. So PEVs may infiltrate the bone marrow and influence platelet generation, hematopoiesis. Further research should explore the mechanism and their various role in bone marrow.

Exosomes from PEVs now have been tested in vitro to verify if human endometrial cells would take them up and if they will proliferate and heal wounds in a dose-dependent way, which could be used for uterine regeneration and injury treatment in the future[78].

Also, the regenerative potential and treatment advantage of PEVs for corneal endothelial have recently been paid attention. Rifa Widyaningrum *et al.* treated Corneal endothelial cells (CECs) with PEVs to discover that CECs displayed higher viability, faster wound-healing rate, and improved adhesion rate. These evidences support the hypothesis PEVs administration are non-toxic, and can be attractive therapy forcorneal endothelial dysfunction and CECs regeneration[79].

Furthermore, PEVs exhibited proliferation promoting effect in hepatocyte, and mechanically this tied to miR-25-3p in PEVs and the autophagy pathways were involved[80].

PRP is an autologous blood-derived product. Its platelet concentration is at least 2/3 times higher than normal and contains platelet-related growth factors[81]. In clinical work, PRP has a positive effect on the healing of tissues, such as muscles, teeth, skin, joints, etc.[82-86]. In regenerative medicine, PEVs may have more significant advantages over PRP for the following reasons: (1)the concentration of growth factors in PEVs are higher as compared to PRP[34, 35, 46]; (2) PEVs are easier to transfer across biological barriers and retain stability in the extracellular environment because of the smaller size[87]; (3) PEVs have lower immunogenicity; (4) the contents of PEVs are encased in vesicles and are not easily damaged; (5) PEVs covers a large number of information molecules involved in intercellular communication, including proteins, lipids and RNA[88, 89]. Now the exosomes of PEVs have already been tested for skin rejuvenation in a six week non-randomized, controlled clinical trial, and were found it safe, well-tolerated. This unveil pleasant outcome of PEVs and its potential future[90]. We are looking forward the PMVs products refinement and more clinical trials.

**3 PEVs in hemostasis**

We have established that platelets play an essential role in hemostasis. The PEV surface is approximately 50- to 100-fold more procoagulant than the surface of activated platelets, so it is speculated that PEVs have better hemostatic activity than platelets[91].

In comparison to the control group, the PEVs group demonstrated a 24% reduction in abdominal blood loss following liver trauma in vivo experiments and also exhibited improved outcomes in blood pressure, lactate level, base excess, and plasma protein concentration (P<0.01). On the contrary, fresh platelets failed to improve these endpoints[92]. PEVs decreased endothelial cell permeability and restored endothelial cell junctions and enhanced thrombin receptor-activating peptide-mediated aggregation of whole blood. PEVs are equivalent to PLTs in attenuating VEGF-A-induced vascular permeability and uncontrolled blood loss in a tail snip hemorrhage model *in vivo*[93]. Furthermore, two rat model studies suggest that PEVs prevent uncontrolled blood loss and hemorrhagic shock. The thrombin generating assay in the rat plasma showed that the PEVs separated from the four donors in each of the four donors were exhibited, increasing the reaction rate. Similarly, the effect of PEVs on the reaction rate shows dose-dependent effects, indicating that the total amount of thrombin generated has contributed[63]. PEVs might provide a feasible product for transfusion in trauma patients to attenuate bleeding, inhibit vascular permeability, and mitigate the endotheliopathy of trauma[93].

**4 PEVs in suppress inflammation**

PEVs, which reduce the production of TNF-α by macrophages and reduce the production of TNF-α and IL-8 by plasmacytoid dendritic cells, might suppress inflammation primarily by inhibiting cytokine release and pro-inflammation factors[94, 95]. MicroRNA-34c-5p related and PODXL-mediated P38 MAPK signaling pathway is probably one of the mechanism[96]. However, other studies have suggested that PEVs promote inflammation[97-100]. Collectively, PEVs may play dual roles in the process of inflammation. The exact effect and adverse influence factors are supposed to be assessed further.

**5 PEVs as drug-delivery vehicles**

The PEVs membrane integrins and receptors inherited from parental platelet cells are the main rationale for PEVs interaction with other cells. For this, PEVs may potential be used as targeted drug-delivery vehicles[17]. Yu-Wen Wu *et al*.[101] has pointed out the capacity of platelets to be use as carriers of anticancer drugs. Jyotsna Kailashiya *et al*.[102] explored that PEVs can carry multiple drug payloads and can be harvested in large quantities in a short period. Importantly, PEVs exhibited remarkably higher toxicity towards cancer cells than free drugs and can be used as vehicles for anticancer. In the mouse model with acute lung injury, the PEVs, loading with [5-(p-fluorophenyl)-2-ureido] thiophene-3-carboxamide (TPCA-1), significantly improve therapeutic benefits by inhibiting the infiltration of pulmonary inflammatory cells and calming local cytokine storm compared with the free drug-treated group[103]. PEVs have been shown to selectively target a variety of inflammatory sites, suggesting that PEV can serve as a broad inflammatory targeting platform, including chronic atherosclerotic plaque, rheumatoid arthritis, and wounds associated with skin, with good biocompatibility and ease of preparation, demonstrating the potential for further clinical transformation[103]. Soleymani *et al*.[104] showed that the platelet microparticles have a high ability for entrapment of anti-HIV drugs such as Lamivudine and Tenofovir drugs up to 60% and 40%, respectively. James V Michael et al.[105] suggested that PEVs can inhibit tumor growth by transferring miRNA-24.

Platelets, as a cellular source of EVs, have many advantages including their established clinical value, regulated collection procedures, availability in a concentrated form, propensity to generate EVs, and unique composition and tissue-targeting capacity.

**Conclusion**

Current studies have shown that PEVs play important roles in tissue repair, disease treatment, and drug delivery. This article reviews the researches about the therapeutic action of PEVs, such as in the regenerative of nervous system, cardiovascular system, OA system, skin tissue, muscle injury, dental treatment, inhibiting inflammation, as drug carriers and many others. These indicate that PEVs have good application prospect in tissue repair and disease treatment, and can be used as carriers to bring new hope for many drugs to treat diseases efficiently, quickly and accurately. However, the current research on the clinical application of PEVs is still in its initial stage, and there are still many challenges to truly use PEVs as clinical treatment technologies or develop them into a clinical treatment product. For example, the potential molecular mechanisms of PEVs in regenerative medicine and disease treatment have not been clarified, and there is a lack of massive data evaluation on the safety and efficacy of PEVs, standardization requirements, application guidelines for preparation, etc. In the future, more studies are needed to further improve our understanding of PEVs and accurately determine their safety, efficacy and indications. And relevant laws, regulations, and clinical guidelines need to be formulated to ensure the proper and rational use of PEVs. We believe that PEVs will open up new therapeutic approaches for regenerative medicine and treatment of other diseases.

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Tables and Figure caption List:

Fig.1 Formation and components of PEVs;

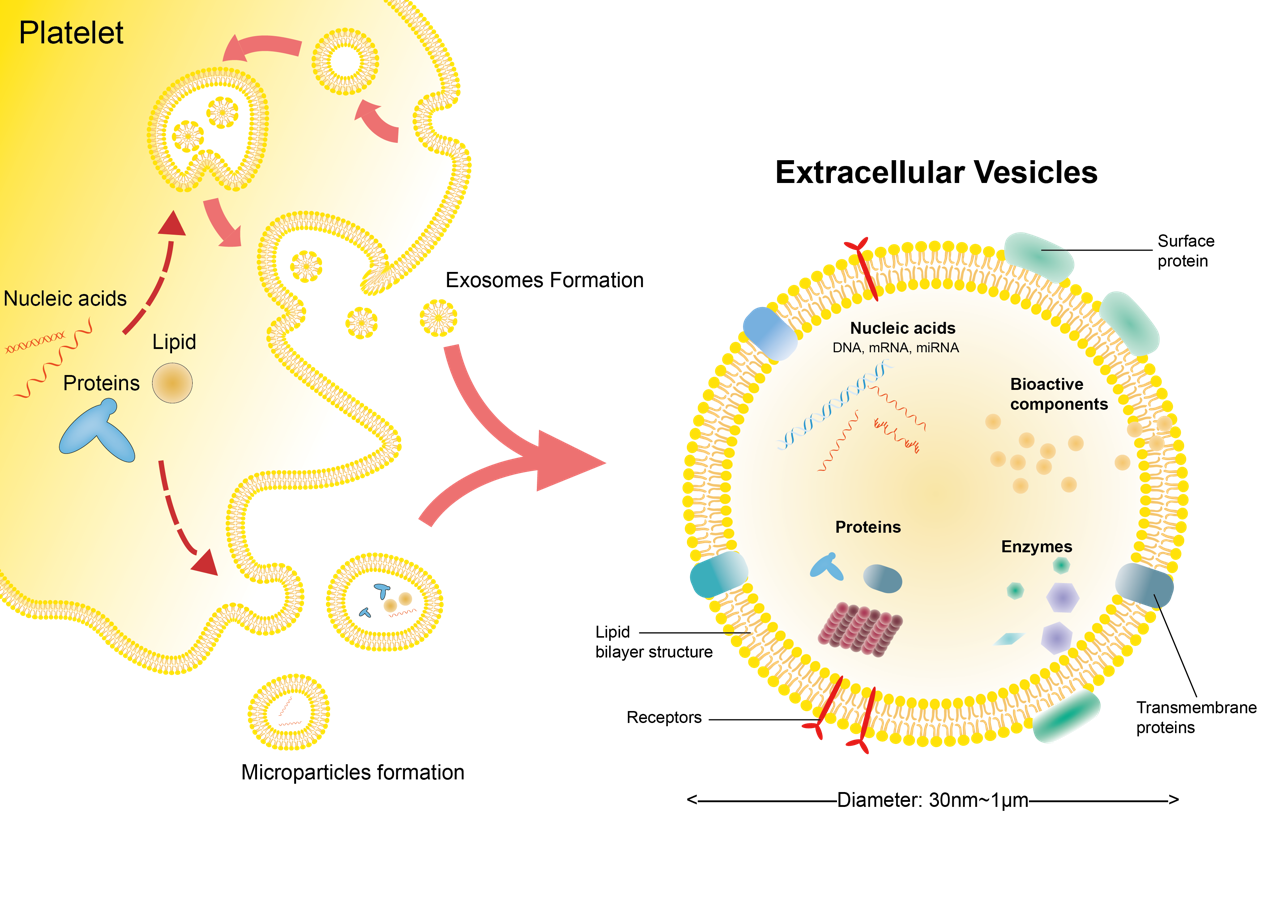


Fig.2 PEVs in regenerative medicine.

