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Recent trends in platelet membrane-cloaked nanoparticles for application of inflammatory diseases

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ABSTRACT

Platelets are multifunctional effectors of inflammatory responses and inseparable from the occurrence and development of various inflammatory diseases. The platelet membrane (PM) is integrated onto the surface of a nano-drug delivery system to form the PM-cloaked nanoparticles (PM@NPs), which can increase the biocompatibility of the nano-drug delivery system and mitigate adverse drug reactions. Owing to the strong affinity of immune regulation and adhesion-related antigens on the surface of PM to the focal sites of inflammatory diseases, which endows PM@NPs with the potential to actively target lesions and improve the therapeutic efficacy of drugs for inflammatory diseases. Based on latest developments in PM biomimetic technique and nanomedicine for the treatment of inflammatory diseases, this paper mainly elaborates three aspects: advantages of PM@NPs, experimental foundation of PM biomimetic nanotechnology, and applications of PM@NPs to the treatment of inflammatory diseases. The aim is to provide reference for the development and application of PM@NPs and novel insights into the treatment of inflammatory diseases.

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Platelet membrane; biomimetic drug delivery system; inflammation targeting; inflammatory diseases

1. Introduction

Inflammation is an immune response, a defense mechanism of the body, and the basis of a variety of physiological and pathological processes in the body (Karin & Clevers, 2016). Inflammation is closely related to many diseases, including rheumatoid arthritis (RA), atherosclerosis (AS), ischemic heart disease, cancer and bacterial infectious diseases. Given that inflammation plays a fundamental role in the development of these diseases (Jin et al., 2018), how to alleviate inflammation may be one of the important therapeutic options for these inflammatory diseases. To date, many anti-inflammatory drugs have entered clinical trials, and their therapeutic effects on various types of acute and chronic inflammation have been verified. However, although high doses of anti-inflammatory drugs (such as hormones) can actively suppress autoimmune reactions, extensive systemic immunosuppression may cause severe adverse reactions and sequelae (such as femoral head necrosis) and profoundly affect quality of life after recovery. Hence, a targeting drug delivery system that modulates local inflammatory immune responses to potentially reduce drug dosage and toxic and side effects is of great significance.

The emergence of nanotechnology has provided us with a novel drug delivery route. Nanocarriers offer many advantages, such as high drug load and good biocompatibility, and are suitable for encapsulating anti-inflammatory drugs and enhance the solubility, stability, and pharmacokinetics of drugs. Nano-drugs for treating inflammation should also have the characteristics of prolonged retention in the body circulation and specific targeting of inflammatory sites (Hu et al., 2019), so as to achieve better anti-inflammatory efficacy. Hence, targeted drug delivery systems based on functionalized modifications have attracted considerable interest, which have made the safe, efficient, and economically controllable drug delivery possible (Zhang et al., 2018). Most nanoparticles (NPs) as foreign materials can be easily recognized and cleared by the body's immune system, and the rapid elimination of these particles by the reticuloendothelial system can be slowed down by modifying the surfaces of the NPs. However, the repeated use of NPs modified by polyethylene glycol may induce immunoreactions and accelerate the clearance of NPs (Lubich et al., 2016). In addition, the targeting ability of NPs is particularly dependent on surface modification, which increases the complexity of NP preparation (Pannuzzo et al., 2020). Therefore, a safer and more effective nano-drug delivery system that is easy to prepare and enhances the treatment of inflammatory diseases is urgently needed.

In view of these above problems, researchers have focused on formulating biomimetic drug delivery systems and

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improving the biocompatibility of synthetic materials by using endogenous carriers and the targeting ability of nano-drug delivery systems. Various types of cell membranes, such as platelet membrane (PM), red blood cell (RBC) membrane, white blood cell membrane, and macrophage membrane, as well as platelet-derived extracellular vesicles (Ma et al., 2020, 2021a) have been used to encapsulate NPs, for various inflammatory diseases. Compared with RBC membrane, PM is less prone to hemolysis (Han et al., 2018) and more easily targets inflammation sites. Platelets are anucleated cells, and thus the isolation of their membranes is easier than that of nucleated cell membranes (Li et al., 2018). Therefore, PM is a promising vector for targeting inflammation. Platelets, being intrinsic components of living organisms, can escape clearance from the body's immune system and not only play a role in hemostasis but also act as multifunctional effectors for inflammation and immunoreaction. In an inflammatory response, inflammatory factors can activate platelets, which accumulate at inflammatory sites and recruit inflammatory cells to promote damage repair (Becker et al., 2018). Platelets are involved in inflammatory response because they can bind to activated or inflamed vascular walls through a range of receptor patterns, including CD40L, glycoproteins Iba, aIIb, and VI, and P-selectin. These membrane proteins in PM afford platelets multiple immunoregulation and adherence functions (Wang et al., 2020). Specific membrane proteins on PM surface mediate the different physiological and pathological functions of platelets, specifically protecting the blood vessel endothelium (Ho-Tin-Noé et al., 2018), stopping bleeding (Mancuso & Santagostino, 2017), and taking part in the body's immune and inflammatory responses (Menter et al., 2014) (Figure 1). Owing to the functional proteins retained on its surface, PM can provide good biological properties for encapsulated NPs, such as good biocompatibility, high mobility, long circulation time, inherent biodegradability, and ability to specifically target pathological tissues. In this paper, the advantages of PM-cloaked nanoparticles (PM@NPs), the experimental foundation of PM biomimetic nanotechnology, and the applications of PM@NPs to the treatment of inflammatory diseases were summarized to provide a reference for the development and application of PM@NPs.

2. Advantages of PM@NPs

2.1. Improve the targeting ability of drugs

PM@NPs inherit various components of the original PM, which provides it the ability to target disease sites. This ability may be passive or active. This camouflaged nanosystem is capable of passive targeting due to the enhanced permeation and retention effect (Narain et al., 2017). In the inflammatory state, the P-selectin receptor on PM has a strong affinity for the CD44 receptor overexpressed at the inflammation site, thereby promoting the active targeting of drugs (Vijayan et al., 2018). With multiple targeting capabilities, PM@NPs are promising drug carriers for treating different diseases. Jin's group (Jin et al., 2021) introduced a nano-drug delivery system that carries berberine (Ber) cloaked with PM (PM@Ber-NPs). They observed strong fluorescent signals in the lung tissues of the animal model of asthma after the administration of PM@Ber-NPs for 2 hours and found that the fluorescence intensities in the lungs of the PM biomimetic group were nearly twice those of bare NPs. These results suggested that PM have good performance in targeting inflammation.

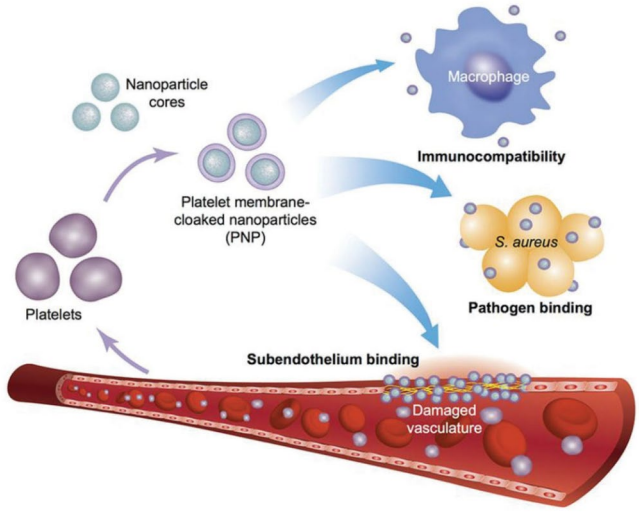

Figure 1. Several inherent platelet properties, including immunocompatibility, binding to injured blood vessels, and harmful pathogen (Zeng et al.). Copyright 2021, The Royal Society of Chemistry.

2.2. Improve the biocompatibility and prolong the circulation of drugs in the body

Common therapeutic drugs are easily cleared by the body's immune system and metabolic mechanisms during circulation in the body, and problems, such as short circulation in the body and insufficient medication, are often encountered. Despite that nano-drugs modified with PEG exhibit biocompatibility, they are easily recognized and cleared by the immune system during blood circulation. PM@NPs can utilize CD47, which regulates immune escape and CD55 and CD59 that inhibit complement activation to improve biocompatibility and prolong drug circulation (Bongoni et al., 2017). Hu et al. (2015) found that the phagocytosis rates of THP-1 macrophages increased 1.6-fold after the blocking of CD47 receptors on PM@NPs. In the complement activation experiment, PM@NPs showed no obvious complement activation. Wang et al. (2017) significantly prolonged the half-life of anti-programmed-death ligand 1 antibody (aPDL1) in the body from 5.2 to 34.8 h by coupling aPDL1 to the PM surface.

2.3. Improve the stability of drug and mitigate adverse reactions

Protein polypeptide and nucleic acid drugs are easily hydrolyzed and inactivated by enzymes in vivo, and wrapping them in PM@NPs can inhibit the degradation of enzymes and external factors, thereby increasing their stability. Tan et al. (2021) constructed a core-shell structured nano-targeted delivery platform for delivery of RNA. The core of the platform are mesoporous silica nanomicrospheres, in which miRNA-21 is high loaded, and then coated with a layer of PM on their outside, which protects miRNA-21 from degradation by RNA

enzymes in vivo and improves its stability. Cytotoxic chemotherapeutics have adverse reactions to normal cells, and the off-target toxicity of cytotoxic chemotherapeutics encapsulated in PM@NPs can be effectively reduced. Mei et al. (2020) established a biomimetic PM-cloaked paclitaxel nanocrystalline system (PPNCs). H&E staining was used to observe pathological changes in various organs. It was found that bare NPs had systemic toxicity to mice, and the effects were mainly manifested as inflammatory cell infiltration in liver. By contrast, PPNCs had no obvious organ toxicity. The safety of PPNCs may be due to the PM cloak, which effectively carries drug components, facilitates drug accumulation at tumor sites and not in normal organs, and mitigates drug toxicity.

3. Experimental basis of PM biomimetic nanotechnology

3.1. Preparation of PM@NPs

The most commonly used method for preparing PM@NPs is the top-down method (Bose et al., 2016). In this method, PM is first extracted, and a bioactive film is obtained from anucleate platelets by separating and purifying blood platelets from fresh blood. PM fragments are obtained through hypotonic, ultrasound, or repeated freeze–thaw treatment, rinsed, and extruded through a porous polycarbonate film. Vesicles from PM are then obtained. PM contains a variety of functional proteins that are essential for maintaining bioactivities (Simons & Vaz, 2004). Thus, protease inhibitors that minimize the denaturation of proteins on the cytomembrane are necessary for PM extraction (Thamphiwatana et al., 2017).

The key step in preparing PM@NPs is to effectively couple extracted PM and prepared NPs through ultrasound, coextrusion, microfluidic electroporation, or any other technique (Figure 2). In coextrusion, PM and NPs are extruded in porous films of different sizes (Hu et al., 2011), and the process relies on mechanical adsorption between membranous vesicles and the surfaces of NPs (Zou et al., 2020). However, the mechanical force provided by extrusion may damage the PM structure, and the process is time consuming and labor intensive. Thus, batch preparation is impossible. Ultrasound is preferred in the preparation of PM@NPs (Yang et al., 2021), but cloaking through an ultrasonic method is often not uniform, and a high temperature may cause the denaturation of membrane proteins. In addition, PM can be coated on the surface of NPs by electrostatic repulsion. Hu et al. (2015) separated platelets from blood. Given that PM is negatively charged and polylactic-glycolic acid (PLGA) NPs are negatively charged, the system finally obtained a 'right-side-out' structure by electrostatic repulsion, and various proteins on platelets can be retained and oriented outwards, so that the final system has the carrier properties of NPs and the activity of platelets. In recent years, microfluidic electroporation has attracted considerable interest because it allows the mass preparation of bionic NPs coated with cell membranes. A microfluidic chip system is composed of five parts: two inlets, Y-shaped merging channel, S-shaped mixing channel, electroporation zone, and outlet. NPs and PM vesicles are injected into the system via an inlet merged, and mixed via the Y-shaped merge and S-shaped hybrid channels, respectively. In the electroporation zone, the electrical pulse between two electrodes drive NPs into membranous vesicles, and PM@NPs are obtained via the outlet (Hu et al., 2015).

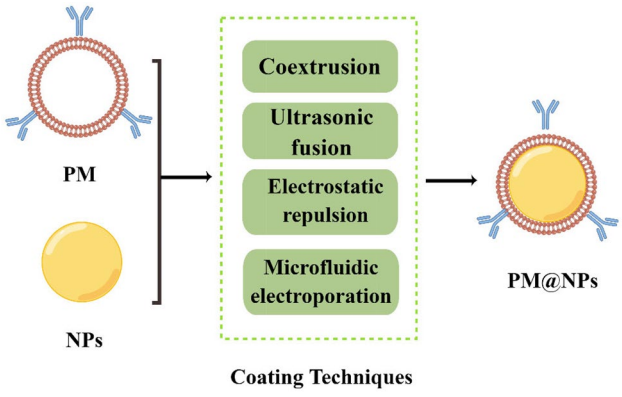

Figure 2. Schematic diagram of preparation of PM@NPs. By Figdraw, ID: TOOUW400d2.

3.2. Characterization of PM@NPs

The physicochemical structures and surface proteins of PM@NPs play vital roles in their functions. Upon the successful preparation of PM@NPs, the rationality and validity of the encapsulation process design must be ensured by validating the chemical structure, morphology, and physicochemical property of PM and integrity of surface proteins. The surface morphology of PM@NPs and the core-shell structures of NPs can be observed through transmission electron microscopy (TEM) and scanning electron microscopy. Dynamic light scattering and zeta potential can be used in characterizing the particle sizes and potential of PM@NPs, respectively. The morphology observation showed that the size of the PM@NPs increased relative to those the bare NPs. Meanwhile, given that the outer membrane of platelets is negatively charged, the negative charge of the NPs tend to increase after PM coating (Yang et al., 2021). Such properties may further influence the distribution of PM@NPs in organisms (Zhao et al., 2018).

In addition, sodium dodecyl sulfate-polyacrylamide gel electrophoresis was used to detect all-protein damage of PM@NPs. Colloidal gold immunostaining electron microscopy can be used to observe membrane proteins on PM@NPs (Xia et al., 2021). Liu et al. (Liu et al., 2019) used colloidal gold immunostaining technology to label protein CD41 on PM@NPs. The adhesion of gold NPs can be observed on PM@NPs through comparison with bare NPs. This can prove that the PM successfully encapsulates the NPs. Meanwhile, characteristic proteins on PM@NPs can be analyzed through Western blot and can be used to detect whether key surface markers, such as CD47, GPVI, CD62p, and integrin proteins on PM are successfully transferred to PM@NPs (Li et al., 2016). The protein components of platelets and PM are further identified by using liquid chromatography-tandem mass spectrometry (LC-MS/MS).

By using LC-MS/MS, Yang et al. (2021) found that the proteins they extracted from PM basically matched those of platelets and were basically not degraded during the extraction process.

4. Applications of PM@NPs in inflammatory diseases

4.1. Applications of PM@NPs in AS

AS is a chronic inflammation induced by the deposition of large amounts of lipids in the arterial intima, and platelets play an important role in the occurrence and development of AS (Lindemann et al., 2007). AS-induced local inflammation may activate endothelial cells and thereby stimulating platelet adhesion and aggregation (Langer & Gawaz, 2008). The activated platelets generate signals that act as a bridge to recruit monocytes (which are subsequently converted into macrophages) to inflammatory sites (Moore et al., 2013), while secreting proinflammatory cytokines, thereby amplifying local inflammatory responses in AS-diseased regions and forming plaques (Cervadoro et al., 2018). Arterial plaques accumulate over time and eventually endanger the lives of patients.

Considering the roles of platelets in the formation of AS, Wei's group (Wei et al., 2018) designed a naturally targeted, efficient, and noninvasive NP imaging platform to prepare about 100 nm PM-mimicking NPs (PNPs). PM was encapsulated by PLGA NPs through ultrasound. The vitro experiment results showed that compared with bare NPs, PNPs exhibited stronger binding force that was four times, 3.8 times and 2.5 times that of foam cells, collagen and activated endothelial cells, respectively. This binding force plays an important role in the formation of AS. In vivo experiment, PNPs loaded with fluorescent probes were injected into the caudal veins of AS model mice with knocked out *APOE* gene. PNPs were concentrated near atherosclerotic blood vessels, and diseased vessels were clearly visualized through fluorescent microscopy. While in the groups separately treated with bare NPs and RBC@NPs, the fluorescent signals were relatively weak and almost negligible, suggesting that PM modification can greatly enhance the ability of NPs to target AS and RBC@NPs do not have this ability. In addition, a contrast agent can afford the delivery system capability to recognize AS. With the multifactorial detection afforded by the PM functionalization, it is possible to probe for the development of AS and interrogate potentially diseased tissue in a biologically relevant manner.

PM@NPs can be used not only in AS diagnosis but also in the targeted therapy of AS. Platelets have strong affinity with plaques and can thus naturally target AS-diseased regions, and NPs that potentially target AS can be designed by mimicking the inherent adhesion function of platelets. Rapamycin (RAP) has a strong anti-AS effect, but its clinical applications are limited by its low concentration and high toxicity at AS-diseased sites. Song et al. (2019) embedded PM on the surfaces of NPs loaded with RAP and constructed a drug delivery platform (RAP-PNPs) targeting atheromatous plaque. In the mouse model of AS, RAP-PNPs may preferentially accumulate at atheromatous plaques, compared with plaque-targeting efficiency of non-biomimetically-modified NPs loaded with RAP, plaque-targeting efficiency increased 4.98 times. In addition, RAP-PNPs therapy can significantly inhibit the formation of necrotic cores in plaques compared with RAP treatment in nude mice (35.3%) and RAP-NPs treatment (42.8%). These results indicate that RAP-PNPs effectively inhibits plaque, slows down the progression of plaques, and enhances the anti-AS efficacy of RAP. Huang et al. (2020) developed novel PM biomimetic NPs based on Janus mesoporous silica nanomotor MJAMS/PTX/AV for AS treatment (Figure 3). They found that PM coated nanomotors can reduce drug leakage before reaching the plaques, and MJAMS/PTX/AV can penetrate plaques, improve the retention of drugs at diseased regions, facilitate the short-term photothermal elimination of inflammatory macrophages and the long-term antiproliferative effects of drugs, and ensure efficient AS treatment.

At the early progression stage of AS, activated endotheliocytes promote the differentiation of recruited monocytes into macrophages that may engulf lipids in plaques and thereby induce the formation of foam cells (Libby et al., 2002),

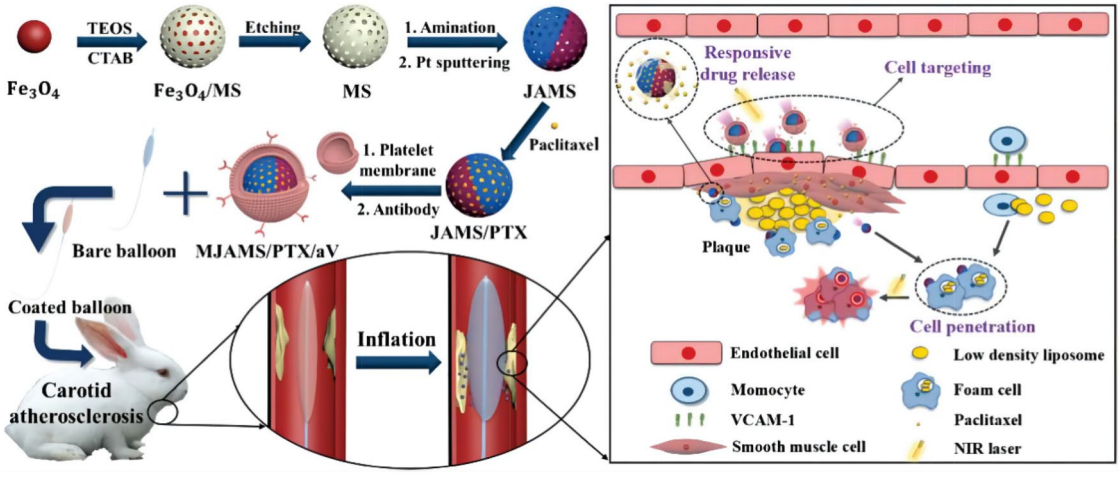

Figure 3. Schematic illustration of the synthesis process of MJAMS/PTX/AV and the mechanism of treatment of atherosclerosis using the MJAMS/PTX/AV coated balloon (Huang et al., 2020). Copyright 2020, Royal Society of Chemistry.

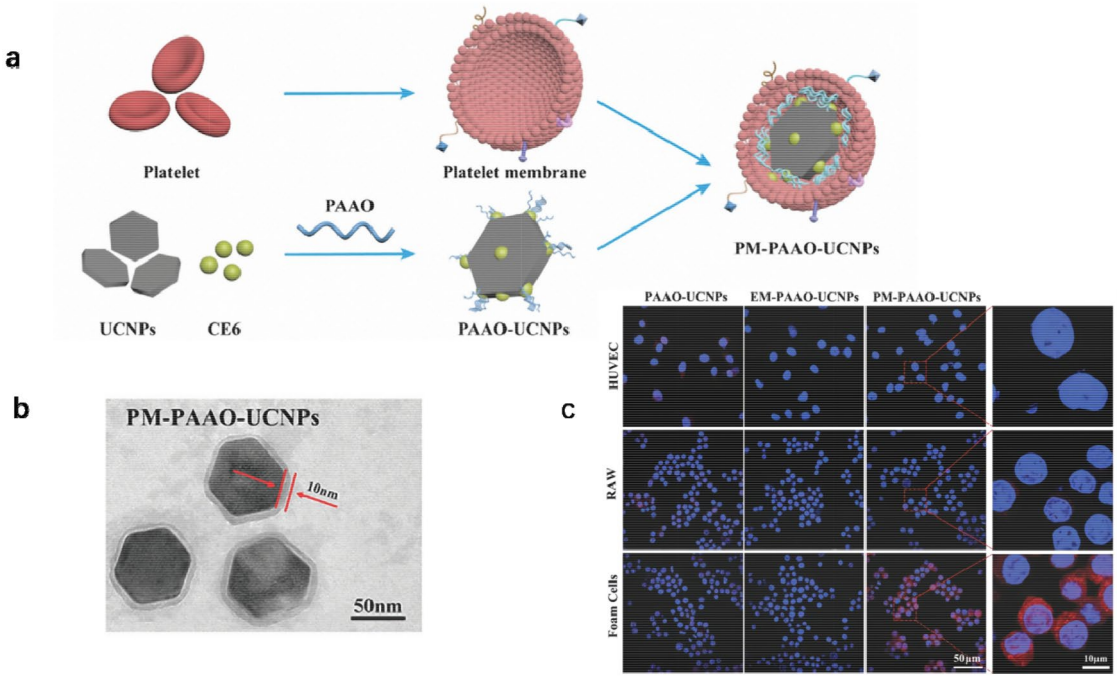

Figure 4. (a) Schematic illustration showing the composition of PM-PAAO-UCNPs. (b) TEM images of platelet member-coated PAAO-UCNPs (PM-PAAO-UCNPs). (c) Binding ability of PM-PAAO-UCNPs to foam cells in vitro. Confocal laser fluorescence imaging of RAW, HUVECs, and foam cells incubated with PAAO-UCNPs, EM-PAAO-UCNPs, and PM-PAAO-UCNPs, respectively. Blue and red fluorescence indicates nuclei and UCNPs (Ma et al., 2021b). Copyright 2021, Advanced Science published by Wiley-VCH GmbH.

which may further promote plaque formation. Therefore, a more effective and noninvasive approach for the early intervention of AS is urgently needed. Ma et al. (2021b) combined the binding abilities between platelets and plaques and radionuclide imaging and successfully developed a novel and noninvasive strategy that effectively inhibited the progression of atheromatous plaques. This PM-mimicking system added lanthanide elements doped with upconverting NPs (UCNPs) and chlorin (Ce6) photosensitizers into polyacrylate-n-octyl amine (PAAO) micelles, then PM was coated on its surface to prepare PM-PAAO-UCNPs (Figure 4(a)). A PM monolayer (≈10 nm) was observed on the unique hexagonal nanostructure through TEM (Figure 4(b)). Confocal laser imaging showed that the fluorescence signal of PM-PAAO-UCNPs was barely detectable in human vascular endothelial cells (HUVEC) and macrophages (RAW), while a strong fluorescence signal was observed in foam cells, showing that the coating of PM facilitated the immune escape of the NPs and conferred ability to specifically target AS on NPs. By contrast, bare NPs and RBC@NPs do not possess this ability (Figure 4(c)). These results suggest that this PM mimicking strategy can be used in specifically identifying foam cells during AS formation and may enable the selective delivery of therapeutic drugs. This platelet-mimicking delivery system may represent a potential noninvasive strategy to mitigate atherosclerotic plaque progression.

4.2. Applications of PM@NPs in RA

RA is an autoimmune disease mainly manifested as chronic synovitis, and many immune cells participate in the inflammation during its onset. The synovial fluids of patients with RA are rich in platelet-derived vesicles (called microparticles) carrying IL-1 (Boilard et al., 2010). Numerous studies have shown that various activated products, such as platelet-derived microparticles, are expressed and released on the PM surface after platelet activation, and these substances are involved in platelet-endothelial and platelet-leukocyte reactions in various pathways, playing important roles in the occurrence and development of inflammation (Boilard et al., 2012) and promoting the proliferation of RA synoviocytes and angiogenesis (Ripoche, 2011).

Therefore, on the basis of the intrinsic link between platelets and RA, He et al. (2018) developed the PM mimicking NPs (PNPs) for targeted drug delivery for RA treatment. PM was cloaked on NPs carrying the immunosuppressor FK506, the resulting FK506-PNPs had a mean grain size of 122.3 nm, and FK506 was highly loaded in NPs. FK506-PNPs can bond with inflammatory endotheliocytes in vitro and can accumulate in the arthritis sites of RA mice firstly. Moreover, PNPs can specifically target inflammatory sites, and this feature is likely associated with the interactions among PM proteins (GPVI, P-selectin) on FK506-PNPs and abundant type IV collagen in synovial tissue and with the binding of overexpressed CD44 (Figure 5). In addition, pharmacodynamic studies have shown that FK506-PNPs have considerable anti-inflammatory effects on mice with collagen-induced arthritis. This study provides novel insights into the targeted therapy of RA. However, these PM-coated NPs generally rely on the blood stream and passive diffusion to reach the target destination. To improve transport and therapeutic efficacy, a micromotor system that provides propelling abilities to the functional cell membrane has been proposed (Esteban-Fernández De Ávila et al., 2018). Recent studies have conjugated PM@NPs with

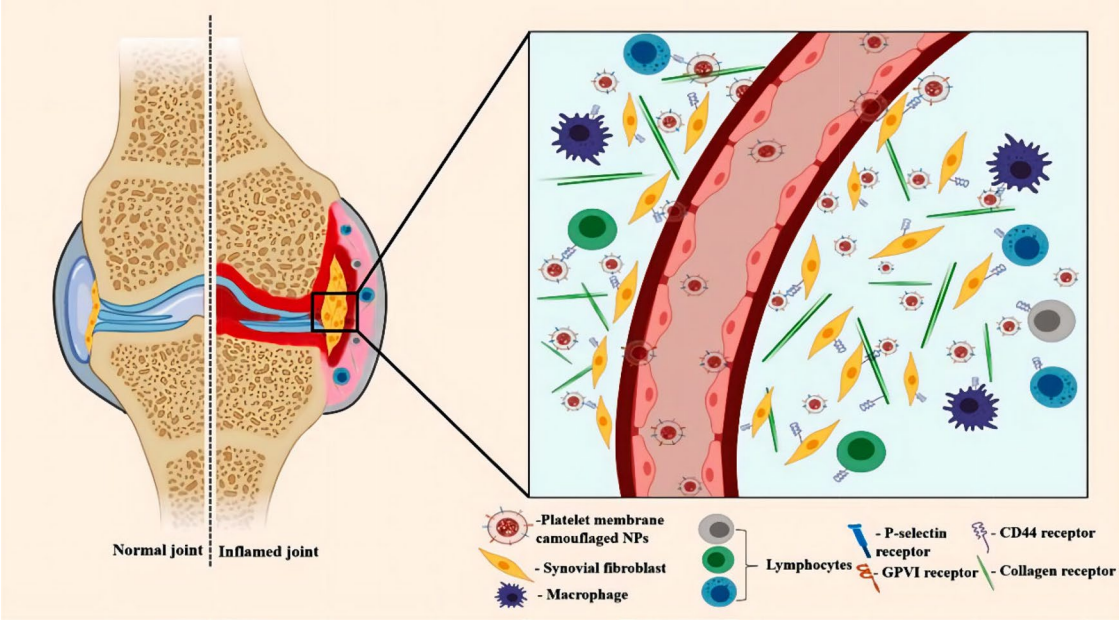

Figure 5. PM@NPs aiding retrogression of inflamed joints in RA (Kunde & Wairkar, 2021). Copyright 2021, Elsevier.

magnetic agents or enzymes for improved tissue retention, penetration, and cell-pathogen binding specificity (Tang et al., 2020). Additionally, strategies that make PM@NPs bioresponsive to inflammatory signals, such as pH-response (Liu et al., 2019), have demonstrated superior therapeutic efficacy.

4.3. Applications of PM@NPs in tumor inflammatory microenvironment

The idea that inflammation has a close connection with cancer was first proposed by Rudolph Virchow in 1863 (Balkwill, 2005). Inflammation is one of the typical features of cancer, where immune cells are activated at tumor sites. The persistence of inflammatory mediators makes an environment suitable for the proliferation of tumor cells. The exudation of tumor cells through the interstitium also requires the assistance of pro-inflammatory mediators. Inflammation can occur at all stages of tumor progression. The interaction between cancer cells as well as the surrounding stroma and inflammatory cells constitute tumor inflammatory microenvironment (Greten & Grivennikov).

Tumor blood vessels can feed and clear metabolism for tumors and are thus essential to tumor growth and metastasis (Li et al., 2019). Thus, the inhibition of tumor angiogenesis and expansion can inhibit the further development of tumor. Platelets can target adhesion to damaged tumor blood vessels via membrane surface proteins CD62p and integrin α6, enhancing the accumulation of NPs in the tumor inflammatory microenvironment (Li et al., 2021). Li et al. (2021) developed a PM-coated mesoporous silica NPs (MS-PM) for antitumor therapy via vascular disruption and anti-angiogenesis. The coincubation of NPs with tumor vascular endothelial cells induced by vascular endothelial growth factor revealed that MSCN-PM-treated cells in contrast to the bare MSN displayed significantly strong fluorescence intensity, indicating that MSNPM may target damaged tumor vessels.

In the severe stage of tumor development, metastasis contributes to over 90% of cancerous tumors and cancer-related mortality. To metastasize, circulating tumor cells (CTCs) need the inflammatory cells and cytokines for survival and dissemination. CTCs can locally induce thrombosis, including platelet activation and fibrin deposition, to form a protective cloak, which in turn protects CTCs from an immune attack (Placke et al., 2012). Inspired by the adhesion of activated platelets to CTC-associated microthrombi, synthetic silica particles encapsulated by PM (called PMDV-Si) was developed (Li et al., 2016) (Figure 6(a)). CTC_S physically interact with fibrin and activated platelets in the circulation, and PMDV-Si can exploit this interaction to target CTCs. To investigate the ability of PMDV-Si to target CTCs in circulation, FITC-labeled PMDV-Si or bare Si NPs were injected into mice. The number of NPs aggregated at the thrombus site was determined and compared with the number of PMDV–Si and bare Si NPs. The PMDV–Si particles effectively targeted cancer cell–fibrin clusters, whereas the bare particles did not (Figure 6(b)). In conclusion, camouflaged platelets have been used to target CTCs and their microthrombi in circulation, and the metastasis of the tumor is greatly inhibited. These results demonstrate a 'Trojan Horse' strategy of neutralizing CTCs to attenuate metastasis.

4.4. Applications of PM@NPs in bacterial-induced inflammatory disease

In bacterial infectious diseases, platelets have innate immune responses to invading pathogens, and they can kill microorganisms directly by releasing antimicrobial peptides that accumulate at infection sites, trap microorganisms, and limit the spread of pathogens (Gaertner et al., 2017). Platelets

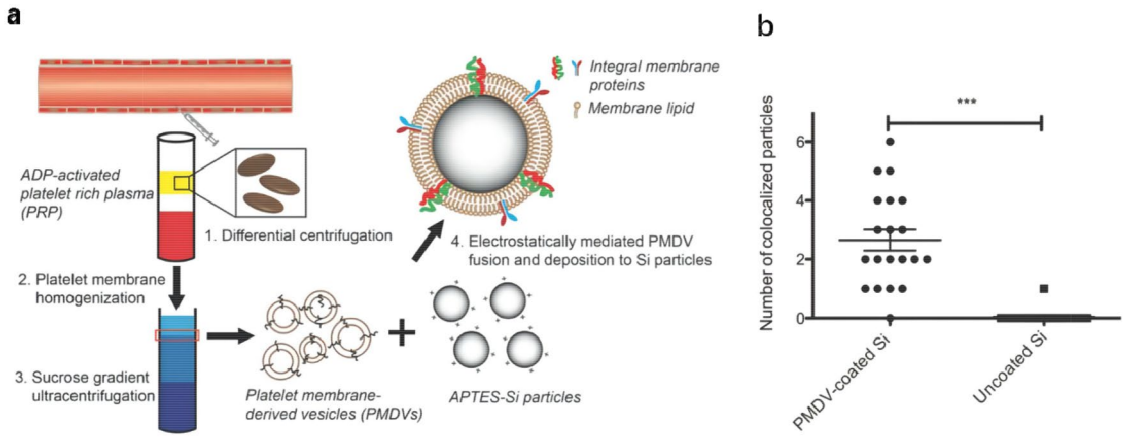

Figure 6. (a) Schematic of PMDV-Si particles preparation. (b) Quantification of PDMV-Si particles versus uncoated particles colocalized within cancer cell/fibrin 'clusters'. One cluster is defined by having at least one cancer cell or a few cancer cells that are physically close to each other (Li et al., 2016). Copyright 2015, Elsevier Ltd.

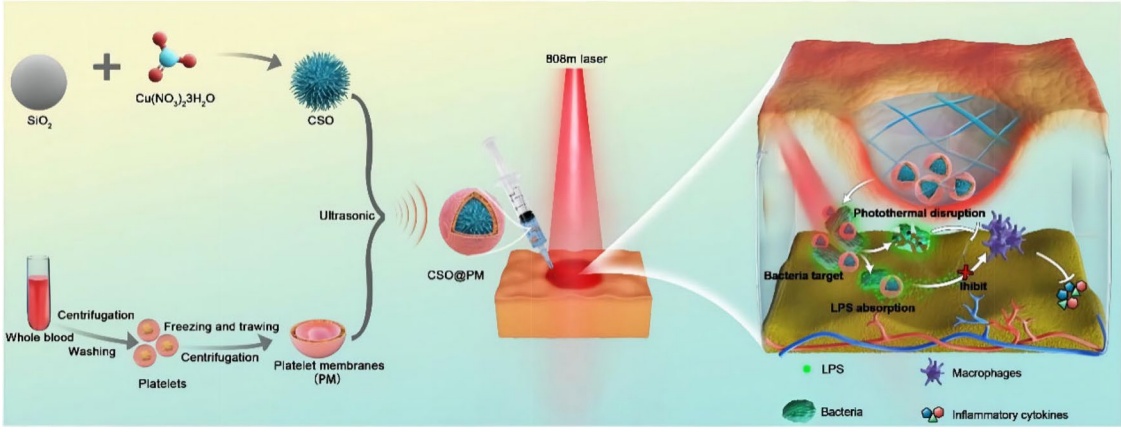

Figure 7. Schematic showing the preparation of CSO@PM NPs and the treatment of wounds infected with multi-drug-resistant Gram-negative bacteria. CSO@PM NPs specifically target bacteria, adsorbing their LPS and, in combination with NIR laser irradiation, effectively kill them, reducing inflammatory reactions and ultimately promoting wound healing (Peng et al., 2021). Copyright 2021, The Author(s).

regulate the release of various intracellular mediators in cell granules through a variety of mechanisms. These granules can directly or indirectly induce inflammation and influence the recruitment and activities of the effector cells of the immune system (Rossaint et al., 2018). These functions indicate the key roles of platelets in maintaining the balance between host immune and inflammatory responses.

Gram-negative bacteria have strong antibacterial resistance systems and secrete lipopolysaccharides (LPS), which are inherently toxic and may induce the release of inflammatory mediators that trigger persistent inflammation at infection sites (Hersoug et al., 2018). Phospholipids, the primary components of PM, can be used to adsorb toxins, meanwhile the unique surface properties of platelets can be activated to express the key mediators of inflammation (Boulaftali et al., 2013). Given the functional diversity of platelets and their close relationships with inflammation and bacterial infection, Peng et al. (2021) prepared a novel antimicrobial platform (CSO@PM) with mesoporous copper silicate microsphere (CSO) as the core and PM as the shell (Figure 7). Compared with exposed CSO, CSO@PM has a well-organized nuclear–shell structure. After Pseudomonas aeruginosa was incubated with CSO and CSO@PM, 23.5% of CSO@PM adhered to the bacterium, versus 7.69% of CSO. The bacteria in the group with CSO remained fully active and showed a typical rod-like and intact surface. By contrast, the bacteria in the CSO@PM-treated group showed twists, folds, and minor damage, and openings the cell wall and cell membrane appeared probably because the formyl peptide receptors on PM enabled CSO@PM to target bacteria. Moreover, CSO@PM adsorbed LPS secreted from gram-negative bacteria, thereby relieving inflammation. That is, CSO@PM had potent antibacterial actions and a high adsorption capacity for toxins and may be useful in the clinical treatment of multiple bacterial infections and development of next-generation antimicrobial NPs.

Staphylococcus aureus, including methicillin-resistant *Staphylococcus aureus* (MRSA) is a gram-positive bacterial pathogen that can cause a variety of diseases. *Staphylococcus aureus* toxin receptor has been identified on PM (Maurer et al., 2020), and thus platelets are the key targets of *Staphylococcus aureus* toxins. Hu et al. (2015) prepared PM cloaked polymeric NPs (PNPs) and used MRSA252 as a model pathogen to explore particle adhesion. They found that bacteria preferentially bind to PNPs, compared with non-PM-cloaked NPs, and 12-fold increase in the bonds between PNPs

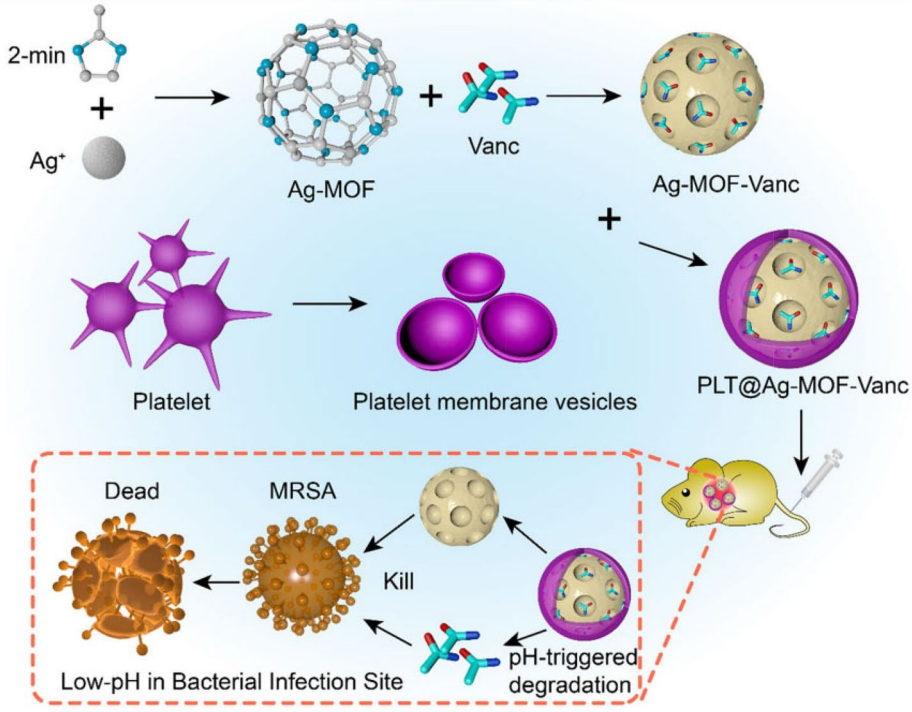

Figure 8. Schematic diagram of PLT@Ag-MOF-Vanc in the treatment for MRSA infection (Huang et al., 2021). Copyright 2021, The Author(s).

and bacteria were observed. Such adhesive is unique to PM because the rate of bonding between erythrocyte-cloaked NPs and bacteria is much lower than that between PM-cloaked NPs and bacteria. In vivo antibacterial results showed that vancomycin-loaded PNPs showed a considerable antibacterial effect, and the number of bacteria in the liver and spleen was reduced 1000 times compared with the number of bacteria exposed vancomycin when the dose was reduced to one-sixth of the original dose. This result indicates that this method can greatly improve the antibacterial effect of antibiotics. Given the ineffectiveness of many antibiotics in the treatment of MRSA infection, Huang's group (Huang et al., 2021) prepared a nano-silver metal-organic framework with 2-methylimidazole as the ligand and silver nitrate as the ion provider and developed PM-cloaked NPs loaded with vancomycin (PLT@Ag-MOF-Vanc; Figure 8). In vitro antibacterial experiments showed that the antimicrobial zone of Ag-MOF-Vanc or PLT@Ag-MOF-Vanc was larger than that of bare vancomycin, and the minimal inhibitory concentration of PLT@Ag- MOF-VANC was 0.5 μg/mL, which was far below that of bare vancomycin (2 μg/mL). In the MRSA-pneumonia model, PLT@Ag-MOF-Vanc accumulated in the lungs within 48 h after administration, and a lower degree of accumulation was observed in other normal organs, indicating that Ag-MOF-Vanc can target diseased regions efficiently and be used for the treatment of infectious diseases.

Shiga toxin (STX) is a related protein toxin produced by *shigella dysentery* and some strains of *E. coli*. STX may cause severe gastrointestinal diseases and has certain cytotoxicity, enterotoxicity and neurotoxicity. Given that STX binds to platelets via specific glycophospholipid receptors, Li et al. (2018) prepared PM-cloaked magnetic spiral nanomotors with immune escape and adsorption functions, the binding of pathogens was facilitated by PM. In vitro experiments have shown that this biomimetic nanomotors can be selectively bind to STX. Other opportunistic bacteria, such as several strains of *Staphylococcus* and *streptococcus*, can adhere to biomimetic nanomotors, and each nanomotor may capture 15 bacteria. Therefore, the PM cloaking of biomimetic nanomotors results in strong affinity for platelet-adhered toxins and pathogens and affords nanomotors efficient detoxification, offering a novel approach for the targeted therapy of bacteriotoxin infections. Furthermore, these PM-cloaked magnetic spiral nanomotors might also protect and support the innate immune function of macrophages or other phagocytic cell types. This biomimetic detoxification strategy merits further exploration as a highly efficient adjunctive therapy.

5. Conclusions and perspectives

PM@NPs are novel drug delivery systems that have attracted considerable interest, and combinations of PM and drug delivery system compensates for the deficiencies in common nano-drug delivery systems in terms of bio-performance and provides insights into the development of novel drug delivery systems. The benefits that PM@NPs offer to the treatment of various diseases have been explored in related studies. On the one hand, the biomimetic modification of PM greatly reduces the immunogenicity of a nano-drug delivery system, prolongs drug retention, and promotes immune escape. On the other hand, the tendency of PM at inflammatory sites enables nano-drug delivery systems to actively target lesion sites.

Although PM@NPs show considerable potential as tools for inflammation targeted therapy, some technical obstacles have hindered their clinical application. This field is still in its early stages as most studies have only been performed in

cells and animals. The following considerations for clinical translation deserve attention: (1) problems regarding the source of platelets, that is, whether platelets must come from a patient himself, whether platelets of different individuals or races affect curative effects, and whether individual rejection and phenomena will produce the same results. For PM, well-established protocols and infrastructures are needed to obtain blood supplies. Although the use of autologous sources may be possible, a more pragmatic way may be to acquire PM from donor matches of type and bank it. (2) In addition, infusing PM with artificial phospholipids and binding them is a potential solution to the cost of PM. Owing to the simple and easy availability of artificial phospholipids, fusing them with PM can not only save platelets, but also allow the combination of properties for better therapeutic effect. (3) PM extraction and coating requires a stringent protocol that ensures the uniformity and reproducibility of PM@NPs. Some losses are incurred at each step of PM collection and coating, and the uniformity of the film can be difficult to control. To address these issues, as presented in the previous section, microfluidic method may be a good future option for easy scale-up and high-quality fabrication. It has been shown to achieve more complete membrane coatings, better colloidal stability, and targeting efficiency. (4) How to retain the bioactivity of PM@NPs is a serious challenge because their shelf lives are short. Although no precise conclusion about the storage method of PM@NPs has been formulated, increasing the storage time of the product through a freeze-drying method with reference to the storage method of liposomal drugs may be possible. (5) Current studies on PM@NPs mostly focus on the cellular and animal levels, and the safety and potential side effects of PM@NPs as carriers in the human body need to be further investigated. Continuous development of nanotechnology and biomedical engineering technologies may result in the wide use of PM@NPs.

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