CHAPTER

6 Effects of nanoparticles on the blood coagulation system (nanoparticle interface with the blood coagulation system)

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6.1 Introduction

The blood coagulation system, which comprises cells and plasma coagulation factors that mediate hemostasis at the injury sites, is considered to be critical to the human body (Ilinskaya & Dobrovolskaia, 2013; Martin et al., 2018). Upon injury, damaged endothelial cells expose subendothelial collagens for the initiation of primary hemostasis where platelets aggregate and form a temporary platelet plug. It is followed by secondary hemostasis where a coagulation cascade with the involvement of clotting factors occurs. This results in a fibrin mesh that entraps the platelet plug and red blood cells (RBCs) to form a blood clot and stops the bleeding (Gaston et al., 2018; Rumbaut & Thiagarajan, 2010). Interaction between the normal coagulation system and the fibrinolytic system maintains the delicate thrombohemorrhagic balance in the body. Any interruption in the blood coagulation system might lead to the consequences of either abnormal thrombosis or hemorrhage (de la Harpe et al., 2019; Hante et al., 2019).

The pivotal role of nanoparticles in biomedicine has been affirmed with the continuously increasing number of their applications (Arndt et al., 2020; Bao et al., 2018; Do et al., 2020; Gu et al., 2018; Le, Bach, et al., 2019; Le, Pham, et al., 2019; Nguyen, Nguyen-Tran, et al., 2019; Reimhult, 2019). Nanoparticles can potentially be employed for diagnosis, prevention, and treatment of various diseases (e.g., cancer, cardiovascular disease, degenerative disease, infectious diseases) or for regenerative medicine (de la Harpe et al., 2019; Gu et al., 2018; Hoang Thi et al., 2019; Matus et al., 2018; Nguyen, Bach, et al., 2019; Nguyen, Nguyen-Tran, et al., 2019; Thi et al., 2020; Tran et al., 2019; Tran et al., 2020). Despite the extensive modification and development of nanoparticles with versatile designs, very few can be translated into the clinic due to the lack of the full assessment of their health risks as there are always cell−nanoparticle or blood−nanoparticle interactions in the blood (de la Harpe et al., 2019; Setyawati et al., 2015). Regardless of the administration route and the intended target, nanoparticles can reach the circulatory system due to the ability to permeate epithelium after dermal penetration, oral ingestion, or inhalation

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(de la Harpe et al., 2019; Fröhlich, 2016). Once inside the bloodstream, they encounter components of the complex physiological environments, including the coagulation system (Hante et al., 2019; Ilinskaya & Dobrovolskaia, 2016; Sobot et al., 2014) (Fig. 6.1). Interaction between nanoparticles and the coagulation system components can potentially interfere with the hemostatic balance in unintended ways, causing lethal coagulation disorders such as disseminated intravascular coagulation and deep vein thrombosis, and thus raise concerns about the clinical safety of these nanoparticles (Fröhlich, 2016; Ilinskaya & Dobrovolskaia, 2016). Therefore making efforts to understand the effect of nanoparticles on the blood coagulation system is highly essential.

The purpose of this chapter is to give a complete depiction of the interface between nanoparticles and the blood coagulation system, which is beneficial for the engineering of nanoparticles and their successful translation to the clinic and market. We present how the nanoparticles interact and affect each component of the coagulation system, and then discuss common in vitro methods to

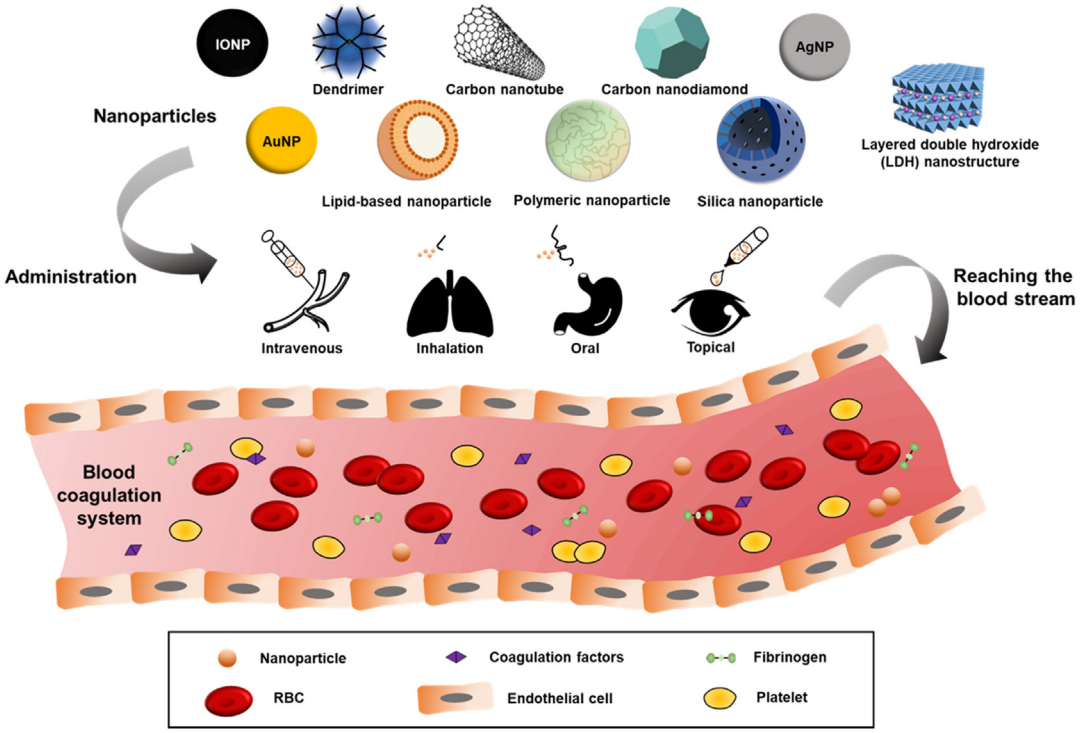

FIGURE 6.1

Nanoparticles encounter the blood coagulation system. Owing to their ability to permeate epithelium, nanoparticles can reach the circulatory system regardless of the administration routes. Once inside the bloodstream, nanoparticles encounter and interact with one or more components of the coagulation system, namely platelets, red blood cells (RBCs), endothelial cells, and plasma coagulation factors. RBCs tend to move to the center of vessels and push platelets toward the periphery, facilitating the collision of platelets and nanoparticles with the vascular endothelium for hemostatic events.

evaluate their effects. Various nanoparticles' parameters that influence the nanoparticle−coagulation system interface will also be discussed. The final section of this chapter addresses two-side effects of engineered nanoparticles for the desirable alteration of hemostasis.

6.2 Interaction of nanoparticles with the blood coagulation system—the underlying mechanisms

Being inside the bloodstream, nanoparticles encounter many blood components and biological systems, including the blood coagulation system. Unintended interactions of nanoparticles with the coagulation system can result in a dysregulation of the hemostatic balance (de la Harpe et al., 2019; Hante et al., 2019). The roles of each component in the coagulation system and possible influences of nanoparticles on them along with the underlying molecular mechanisms will be discussed in the following subsections.

6.2.1 Nanoparticles and vascular endothelium

The studies of nanoparticles associated with the coagulation system usually focus on blood cells and coagulant factors. However, vascular endothelial cells play an important role in the regulation of platelet adhesion, thrombosis, and fibrinolysis (Fröhlich, 2016). Healthy endothelial cells are protected by a glycocalyx layer consisting of heparan sulfate that has the affinity for plasma inhibitory proteins such as antithrombin III and tissue factor pathway inhibitor (TFPI). These proteins, anticoagulant mediators (heparin cofactor II, endothelial protein C receptor (EPCR), and thrombomodulin) expressed on the endothelium surface together with platelet adhesion and aggregation inhibitors [nitric oxide (NO), prostacyclin (PGI_2), and CD39/NTPDase1] secreted by endothelium, help to maintain the thrombo-resistant nature of intact vascular endothelial cells (Ekdahl et al., 2019; Hangge et al., 2017; Reitsma et al., 2007; Yau et al., 2015).

Damage to endothelial cells not only leads to the exposure of tissue factor (TF) (CD142 or FIII), which activates the extrinsic pathway of hemostasis, but also exposes subendothelial collagens that bind FXII to initiate the intrinsic pathway. Moreover, von Willebrand factor (vWF), thromboxane A2 (TXA2), P-selectin (CD62P/GMP-140/PADGEM), and platelet-activating factor (PAF) released by injured endothelial cells along with the exposed collagens are associated with platelets recruitment, adhesion, and activation (Fröhlich, 2016; Ilinskaya & Dobrovolskaia, 2013). Gelderman et al. reported that fullerenol $C_{60}(OH)_{24}$ nanoparticles at 100 μg/mL significantly triggered the expression of TF (CD142) on human umbilical vein endothlial cells (HUVECs) after 24 hours of in vitro culture (4% ± 2% $CD142^+$ cells in control versus 54% ± 20% $CD142^+$ cells in treatment group) (Gelderman et al., 2008). As also reported, silica nanoparticles (58 nm), especially at high concentration of 50 and 100 μg/mL, interrupted the NO balance, leading to HUVECs dysfunction (Guo et al., 2015). The interactions between silver nanoparticles (AgNPs) and endothelial cells' membrane, the induction of vWF release, and the reduction of tissue plasminogen activator (tPA) expression at high nanoparticles concentration are the reasons behind endothelium dysfunction caused by Ag NPs and are probably associated with thromboembolic complications (Ragaseema et al., 2012; Sun et al., 2016). After 24 hours of incubation with HUVECs, Ag NPs

(<20 nm) induced cytotoxicity at the concentration of 64 μg/mL (Danielsen et al., 2015), while the toxicity threshold for ZnO NPs (70 nm) toward human aortic endothelial cells (HAECs) was ≥15 μg/mL (Liang et al., 2016). Similar to Ag NPs, cationic dendrimer nanoparticles interacted with HUVECs' membrane, and poly(amidoamine) (PAMAM) dendrimer generation 4 and 7 (G4 and G7) (administration doses >10 mg/kg) caused disseminated intravascular coagulation in mice (Greish et al., 2012). Silica nanoparticles, as demonstrated by Feng et al., caused hypercoagulation through inducing vascular endothelial cells dysfunction (Feng et al., 2019). The increased expression of TF and platelet endothelial cell adhesion molecule-1 (PECAM-1 or CD31), as well as the imbalance of the NO/NOS (nitric oxide synthase) system, were detected after the exposure to silica nanoparticles (starting from 1.8 mg/kg of rat).

Organic nanoparticles, by contrast, have little toxicity to vascular endothelial cells. For instance, Liu et al. demonstrated that exposure of HUVECs to mPEG-PLA nanoparticles (around 20 nm) showed no significant effect on the cell viability at the concentration up to 200 μg/mL (Liu et al., 2017). Liposomes (109 and 139 nm) and lipid NPs (50−120 nm) had no cytotoxicity to HUVECs at the concentration up to 100 μg/mL (Matuszak et al., 2016).

6.2.2 Nanoparticles and platelets

Platelet (thrombocyte) is a crucial cellular component in the coagulation system. It is originated from megakaryocytes, anucleate, discoid in shape, and around 2−4 μm in diameter. Around 33% of all platelets is stored in the spleen while the rest circulates in the circulatory system (~150,000−450,000 platelets/mm^3) without adhering to the intact vascular endothelium (Matus et al., 2018; Nabeshi et al., 2012). Upon injury, the damaged endothelium exposes TF, collagen, and other thrombogenic factors, such as vWF, TXA2, and PAF, for the initiation of primary hemostasis. Once platelets come in contact with vWF and subendothelial collagens for the adhesion to the injured endothelium and vessel wall, they become activated (Broos et al., 2011; Demir et al., 2013; Palta et al., 2014; Rumbaut & Thiagarajan, 2010). The platelet activation process is portrayed by a drastic increase in cytosolic Ca^{2+}, which elicits the reorganization of platelet cytoskeleton, resulting in the shape change (from disk to sphere shape), pseudopodia formation, aggregation, and exocytosis of contents stored inside platelet's granules (De La Cruz et al., 2018) (Table 6.1). Adhesive glycoproteins (vWF, fibrinogen, P-selectin, thrombospondin, and vitronectin), coagulation factors (plasminogen, kininogen, factor V, XI, XIII), plasminogen activator inhibitor-1 (PAI-1), TXA2, PAF, adenosine diphosphate (ADP), and serotonin secreted by activated platelets mediate vasoconstriction and platelet aggregation, activate more platelets and attract them to come to form a weak platelet plug that temporarily seals the injured area (De La Cruz et al., 2018; Hangge et al., 2017; Nabeshi et al., 2012; Rumbaut & Thiagarajan, 2010). There are a certain number of glycoprotein IIb/IIIa (GpIIb/IIIa) receptors presented on the surface of resting platelets (approximately 50,000/platelet) (Sims et al., 1991). Upon activation, GpIIb/IIIa stored in the internal pool of platelets will move to their surface, increasing the number of expressed GpIIb/IIIa. These receptors, both the newly expressed and the already presented ones, undergo a conformation change process, which is related to extracellular ionized calcium and the expression of ligand-induced binding sites to become high-affinity for fibrinogen (Kleiman et al., 1995; Matzdorff & Voss, 2006; Sims et al., 1991). Fibrin forms the bridge between platelets and entraps the platelet plug and other surrounding

Table 6.1 Platelet storage granules and their contents.

Granules	Content class	Factors released
Alpha granules	Adhesive glycoproteins	vWF, thrombospondin, P-selectin, fibrinogen, fibronectin, vitronectin
	Coagulation factors	Plasminogen, kininogens, protein S, factor V, factor XI, factor XIII
	Growth factors	IGF, EGF, PDGF, TGF-β
	Angiogenic factors	PF4 inhibitor, VEGF
	Protease inhibitors	C1-inhibitor, PAI-1, TFPI, α2-antiplasmin, α2-antitripsin, α2-macroglobulin
	Immunoglobulins−chemokines	IL8, IL1β, CD40, CXCL4 (platelet basic protein/NAP-2), CXCL (PF4), CXCL1, CXCL5, CCL5 (RANTES), CCL (MIP-1α)
	Proteases	MMP2, MMP9
Dense granules (or delta granules)	Amines	Serotonin, histamine
	Bivalent cations	Ca^{2+}, Mg^{2+}
	Polyphosphates	ADP, ATP, GDP, GTP
Lysosome granules	Enzymes	Acid proteases, glycohydrolases
Other soluble mediators	NO, TXA2, defensins, PAF	

ADP, *adenosine diphosphate;* ATP, *adenosine triphosphate;* EGF, *epidermal growth factor;* GDP, *guanosine diphosphate;* GTP, *guanosine triphosphate;* IGF, *insulin-like growth factor;* MMP, *matrix metalloproteinase;* NO, *nitric oxide;* PAF, *platelet-activating factor;* PAI-1, *plasminogen activator inhibitor-1;* PDGF, *platelet-derived growth factor;* PF4, *platelet factor 4;* TFPI, *tissue factor pathway inhibitor;* TGF-β, *transforming growth factor β;* TXA2, *thromboxane A2;* VEGF, *vascular endothelial growth factor;* vWF, *von Willebrand factor.*
Reproduced with permission from de la Harpe, K. M., Kondiah P. P., Choonara Y. E., Marimuthu T., du Toit L. C., & Pillay V. (2019). The hemocompatibility of nanoparticles: A review of cell−nanoparticle interactions and hemostasis. Cells, *8(10), 1209.*

blood cells to form a stable clot (De La Cruz et al., 2018; Hangge et al., 2017; Nabeshi et al., 2012; Rumbaut & Thiagarajan, 2010).

Generally, the interactions of nanoparticles with platelets can affect platelet functions. Different types of nanoparticles with varied size, charge, coating materials, and composition may lead to different outcomes, including activating effect, inhibitory effect, or no effect on platelets.

6.2.2.1 Inorganic nanoparticles

6.2.2.1.1 Carbon-based nanoparticles

The tendency to stimulate platelet aggregation of various types of carbon nanoparticles, including mixed carbon nanoparticles (MCN), single-wall carbon nanotubes (SWCNT), and multiwall carbon nanotubes (MWCNT) (0.2−300 μg/mL), was evaluated and compared with standard urban particulate matter (SRM1648, 1.4 μm) in a study by Radomski et al. Radomski et al. (2005). The results showed that all tested materials induced the platelet aggregation and increased the vascular thrombosis rate in rat carotid arteries model in the order from highest to lowest: MCN ≥ SWCNT > MWCNT > SRM1648. The platelet aggregation induced by these carbon nanoparticles

corresponded to the activation of the GpIIb/IIIa receptors and correlated with platelet degranulation, the translocation of P-selectin to the platelet surface, and the tendency to mimic molecular bridges in platelet−platelet interaction. The prothrombotic effect of carbon nanotubes regarding platelet activation and aggregation was further explored in studies by Simak group (Semberova et al., 2009). The results were consistent with the previous study in which SWCNTs (outer diameter <2 nm, 5−15 μm in length for S1 SWCNT and 1−2 nm of outer diameter, 5−30 μm in length for S2 SWCNT) had higher platelet aggregation (34% ± 5% for S1 and 32% ± 6% for S2) than MWCNTs (outer diameter was 60−100 nm, 1−2 μm in length for M60 and 30 ± 15 nm of outer diameter, 1−5 μm in length for M30) with platelet aggregation of 27% ± 3% (M60) and 38% ± 9% (M30). Amorphous carbon nanopowder (outer diameter was ∼30 nm) showed a weak effect on platelet aggregation (15% ± 2%) while fullerenol C60 (∼1.3 nm), fullerene C60 (∼0.7 nm), and polystyrene nanobeads (PBs) (20 and 200 nm) had no effect. They reported that the effects of carbon nanotubes on platelet activation, degranulation, and aggregation were accompanied by elevated intracellular [Ca^{2+}] in platelets which is the second key messenger mediating platelet activation. Platelets raised intracellular [Ca^{2+}] by either releasing it from intracellular stores or entering of extracellular Ca^{2+} through plasma membrane channels including SOCE, second messenger-operated Ca^{2+} entry (SMOC), and receptor-operated Ca^{2+} entry (Semberova et al., 2009). As the carbon nanotube-facilitated extracellular Ca^{2+} influx was sensitive to calcium entry blockers 2-APB and SKF 96365, SOCE was proved to be involved in platelet activation induced by carbon nanotubes (De Paoli Lacerda et al., 2011; Semberova et al., 2009). Corbalan et al. proposed that MWCNTs ruptured the dense tubular system—a Ca^{2+} pool—after penetrating the instantly resealed platelet membrane, leading to intracellular Ca^{2+} depletion and activating SOCE (Corbalan et al., 2012).

Carbon nanodiamonds (CNDs) with the size range of 4−10 nm can evoke platelet activation at low concentration (1 μg/mL). Kumari et al. demonstrated that CNDs elevated the intracellular Ca^{2+} level in platelets and increased the expression of phosphatidylserine on the platelet membrane (Kumari et al., 2014). CND-treated platelets showed reduced viability and altered morphology with developed lamellipodia or filopodia. In vivo results evidenced extensive pulmonary thromboembolism in mice after IV injection of CNDs (Kumari et al., 2014).

6.2.2.1.2 Silver nanoparticles

The accumulation of silver nanoparticles (AgNPs) within platelets can interfere with intraplatelet activities (Jun et al., 2011; Krajewski et al., 2013; Ragaseema et al., 2012; Shrivastava et al., 2009). It has been found that AgNPs, 10−100 nm in diameter, induced intracellular [Ca^{2+}] (250 μg/mL of AgNPs), which upregulated GpIIb/IIIa (100 μg/mL of AgNPs) and P-selectin expression (100 μg/mL of AgNPs), and serotonin secretion (250 μg/mL of AgNPs) (Jun et al., 2011). Enhanced thrombin and phosphatidylserine generation (250 μg/mL of AgNPs) were observed in fresh human platelets as evidence for platelet aggregation induced by AgNPs. Both AgNPs-induced platelet activation and aggregation were concentration-dependent. Exposure to AgNPs (0.05−0.1 mg/kg I.V. or 5−10 mg/kg intratracheal instillation) in vivo enhanced venous thrombus formation, platelet aggregation, and PS externalization in rat. Accumulated AgNPs (stabilized with sodium polyacrylate, 30 mg/L, 10−15 nm) triggered α-granule secretion and induced kallikrein-like, FXIIa-like, and thrombin−antithrombin III complex (Krajewski et al., 2013). Further exposure of AgNPs in rat (0.05−0.1 mg/kg intravenous or 5−10 mg/kg intratracheal

instillation) induced platelet aggregation, phosphatidylserine externalization, and vascular thrombus formation ex vivo (Jun et al., 2011; Krajewski et al., 2013). In another study, AgNPs (16 nm) only promoted platelet adhesion but not platelet aggregation at the concentration of 50 μg/mL (Laloy et al., 2014). At concentrations up to ~40 μg/mL, neither AgNPs (20 nm) with polyvinyl pyrrolidone coating nor with citrate coating exert any effect on platelet aggregation and coagulation (Huang et al., 2016). However, some other studies reported the antiplatelet properties of AgNPs (stabilized with either citrate or D-glucose) (Bandyopadhyay et al., 2012; Shrivastava et al., 2009). Accumulative AgNPs within platelet granules impeded integrin-mediated platelet responses such as adhesion to immobilized fibrinogen and platelet conformation change, namely retraction of a fibrin clot, in a concentration-dependent manner in vitro and in vivo, regardless of agonists used (Bandyopadhyay et al., 2012; Shrivastava et al., 2009). AgNPs also inhibited platelet aggregation induced by either ADP, thrombin, or collagen in vitro and in mouse whole blood in a dose-dependent manner (Bandyopadhyay et al., 2012). Different dispersing media/coatings/stabilizers used for synthesized AgNPs may be one of the possible reasons for the variability between these studies (Strojan et al., 2017).

6.2.2.1.3 Gold nanoparticles

The effect of gold nanoparticles (AuNPs) on platelets was first demonstrated in rat by Berry et al. (1977). The presence of a high amount of AuNPs in platelets of alveolar capillaries affected platelet aggregation, leading to microthombus and atheromatous plaques formation. Deb et al. presented that the molecular mechanism of platelet aggregation induced by AuNPs (stabilized with citrate) is linked to degranulation and the increased expression level of P-selectin and tyrosine phosphorylation (Deb et al., 2011). The study revealed that platelet response constantly decreased with the increment in the size of AuNPs where AuNPs greater than 60 nm (>40 μM) were inert to platelet as compared to the maximal platelet activation effect of smaller ones (~ 20 nm) at 40 μM. This might be attributed to the higher accumulation of small AuNPs in platelets (Deb et al., 2011). By contrast, Love et al. found that either AuNPs, Au(+) nanoparticles, or Au(−) nanoparticles (respectively stabilized with either citrate, 11-mercaptoundecanoic acid, or 11-mercaptoundecylamine) of around 30 nm and up to 50 μg/mL did not induce platelet aggregation after short-term exposure probably because of protein corona formation on the surface of examined AuNPs (Love et al., 2012).

6.2.2.1.4 Iron oxide nanoparticles

The effect of iron oxide nanoparticles (IONPs) on platelets is somehow contradictory as they can have either induced (Bircher et al., 2014), inhibitory (Deb et al., 2012; Villegas et al., 2019), or neutral effect (Bircher et al., 2014; Deb et al., 2012; Easo & Mohanan, 2015) on platelet, highly depending on the stabilizing agents coated on the nanoparticle surface. According to the report by Bircher et al., iron carbide nanoparticles coated with carbon (~ 30 nm) increased the expression of GpIIb/IIIa and P-selectin by platelets, which led to reduced blood clotting time by 25% at the concentration of 1 mg/mL (Bircher et al., 2014). By contrast, PEGylation of iron carbide nanoparticles attenuated the influence of the nanomagnets on coagulation parameters. At the concentration of 0.5 mg/mL, there was no significant effect observed. In other comparable studies, starch-coated IONPs (45 nm, 128−256 μM) (Deb et al., 2012) and dextran-stabilized IONPs (25.3 ± 0.97 nm, 1 mg/mL) (Easo & Mohanan, 2015) did not show any effect on platelet function. However, Deb

et al. indicated that citric acid-stabilized iron oxide nanoparticles (FeNP(C)) (35 nm, tested concentration range was 64, 128, 192, and 256 μM) had an antiplatelet property, which was higher than that citric acid has by itself, as reflected in various molecular events including ATP release of dense granules, the level of tyrosine phosphorylation, and the expression of GpIIb/IIIa and CD62P (P-selectin) (Deb et al., 2012). In addition, poly(acrylic acid)-coated IONPs (PAC-IONs) presented the antagonistic effect on platelet aggregation and no effect on platelet activation even up to 62 μg/mL of the nanoparticles (Villegas et al., 2019).

6.2.2.1.5 Silica nanoparticles

As explored in a study by Tavano et al., synthetic amorphous silica nanoparticles (SAS-NPs), bare, and PEGylated organically modified silica nanoparticles (ORMOSIL) had no appreciable effect on platelet activation and aggregation (Tavano et al., 2010). On the contrary, anionic amorphous silica nanoparticles (SiNPs) (10−500 nm) with the concentration varied from 10 to 200 μg/mL were reported to induce platelet activation and aggregation, accompanied by GpIIb/IIIa and CD62P upregulation (Corbalan et al., 2012). Since the thrombotic activity of SiNPs was hindered by inhibitors of ADP and the matrix metalloproteinase-2 (MMP2) pathway, the author discussed that the nanoparticles interact with the Ca^{2+} ion channel and result in extracellular Ca^{2+} influx into platelets cytoplasm, leading to the activation of eNOS for NO generation. After the substrate (L-arginine) is used up, eNOS is uncoupled, and superoxide is produced to interact with NO to form ONOO- (peroxynitrite anion). Low ratio of NO/ONOO- is a marker of oxidative stress and diminished NO-availability, which promotes platelet activation. In other studies, silica nanoparticles (around 58 and 245 nm) were reported to enhance the expression of PECAM-1 (starting from1.8 mg/kg·bw of rat), result in NO/NOS system imbalance (>1.8 mg/kg · bw of rat), and an increase in platelet number on endothelial cells (both 10 and 250 μg/mL), promoting platelet adhesion and prethrombotic state (Feng et al., 2019; Saikia et al., 2018). Such a phenomenon is in contrast to another study where silica nanoparticles at 20−200 μg/mL led to the decrease in adhered platelet number as compared to the control and the treatment group at higher concentrations of the nanoparticles ($\sim$1000 μg/mL) (Nishikawa et al., 2009). The differences between the two studies might be attributed to the porosity, the size (50 vs 250 nm), and the fabrication method (Stöber vs mesoporous silica nanoparticles) of the particles.

6.2.2.1.6 Other inorganic nanoparticles

An in vivo study carried out by Singh et al. depicted an extremely thrombotic effect in mice after intravenous (IV) injection of atomically thin graphene oxide sheets (GO) (Singh et al., 2011). As explored in in vitro tests, GO sheets triggered platelet aggregation through the intracellular release of Ca^{2+} and the activation of Src kinases. At the concentration of 2 μg/mL, this effect of GO sheets was higher than that induced by 1 U/mL of thrombin. Continuing this study, Singh et al. found that amine-modified GO sheets (GO-NH_2) (2 and 10 μg/mL) did not show any induced or inhibitory effect on platelets, without noticeable change in the ROS level (Singh et al., 2012). There was no in vivo pulmonary thromboembolism after GO-NH_2 exposure.

Rutile titanium (TiO_2) nanorods (0.4−10 μg/mL, 4−6 nm) were reported to cause significant platelet aggregation in rat blood in a concentration-dependent manner (Nemmar et al., 2008). After intratracheal instillation of TiO_2 nanorods in rats, the platelet count was significantly decreased, indicating the platelet aggregation in vivo. The molecular mechanism for platelet response to TiO_2

nanorods is still ambiguous but could be associated with the shape and/or surface feature of the material. However, rutile TiO_2 nanoparticles (67 nm in size) showed no effect on murine platelets with the injection dose of 1 mg/kg in other studies (Bihari et al., 2010; Haberl et al., 2015). As described in some studies, nickel nanoparticles (0.05 mg/mL) or zinc oxide nanoparticles (3:1 v/v ratio of platelet-rich plasma) also cause changes in the platelet shape (Guildford et al., 2009) and promote platelet activation (Šimundić et al., 2013).

6.2.2.2 Organic nanoparticles

6.2.2.2.1 Dendrimers

Several studies have demonstrated that large, cationic poly(amidoamine) (PAMAM) dendrimers (above G4) induced platelet aggregation. By evaluating 12 PAMAM dendrimers of different generations (G3 to G6) functionalized with succinamic acid (anionic), amidoethanol (neutral), and amine (cationic), Marrink et al. revealed that only large and cationic PAMAM dendrimers (amine-G4, amine-G5, and amine-G6) induced platelet aggregation (Dobrovolskaia et al., 2012). Moreover, the aggregation effect was proportional to the number of amine groups on the surface. Since the observed platelet aggregation was neither accompanied with the release of membrane microparticle nor sensitive to inhibitors interfering with platelet activation's pathway, the proposed mechanism is supposed to involve the capability of cationic PAMAM to disrupt platelet membrane integrity and thus induce the aggregation. Computational simulations also supported this proposal (Marrink et al., 2004). In study by Jones et al., large and cationic PAMAM G7 dendrimer nanoparticles (100 μg/mL) showed their effect in altering platelet morphology, which substantially interfered with platelet function, and induced platelet adhesion and aggregation (Jones et al., 2012). Greish et al. also reported that G4 and G7 PAMAM dendrimer nanoparticles caused DIC-like manifestations in mice at a dose >10 mg/kg (Greish et al., 2012). As compared to PAMAM dendrimers, triazine dendrimers (0.01−1 μM) evoked less aggressive platelet aggregation due to differences in the assembly of supramolecular structure and/or cationic charge (Enciso et al., 2016).

6.2.2.2.2 Lipid-based nanoparticles

The effect of lipid-based nanoparticles on platelet is also correlated with surface charge. It has been presented that anionic lipid-based (cetyl alcohol/polysorbate) nanoparticles (50−150 μg/mL) (Koziara et al., 2005) and both anionic and cationic liposome prepared from a photopolymerizable phosphatidylcholine derivative (100−360 μg/0.5 mL platelet) (Juliano et al., 1983) inhibited platelet activation and aggregation in a concentration-dependent manner. However, Reinish et al. reported the reduction in the platelet number after IV injection of anionic liposomes (dose level of 25 mg/kg) in rats in the first 5 minutes (Reinish et al., 1988). The platelet count was recovered 60 minutes postinjection. Similarly, anionic liposomes (phosphatidylcholine: phosphatidic acid = 8:1), not cationic and neutral liposomes, provoked platelet aggregation in vitro and in vivo after IV injection in guinea pigs (Zbinden et al., 1989). The effect was probably due to the interaction between anionic liposomes and FXIII/XI. Moreover, Constantinescu et al. suggested that the interaction of liposomes with platelet was independent of opsonization but dependent on the liposome concentration (Constantinescu et al., 2003). The discrepancies between studies might be attributed to not only the surface charge but also the composition of the lipid-based nanoparticles.

6.2.2.2.3 Other polymeric nanoparticles

Unmodified, carboxyl-modified, and amine-modified polystyrene latex nanoparticles from 50 to 100 nm caused aggregation of platelet in a dose-dependent manner (15−60 μg/mL) except the 50 nm amine-modified ones (Smyth et al., 2015). This aggregation was mediated by secondary agonists released from platelet granules and induced GpIIb/IIIa expression depending on Ca^{2+} influx and protein kinase C signaling pathway. The author also described that these effects were associated with both size and surface modification. In another study, carboxyl-modified polystyrene nanoparticles (∼80 nm, 260 μg/mL) induced platelet aggregation by disrupting platelet membrane and upregulating platelet-activating markers P-selectin and PAC-1, respectively (McGuinnes et al., 2011).

Ramtoola et al. (2011) and Li et al. (2009) found that chitosan (CS), poly(lactic-co-glycolic acid) (PLGA), PLGA-macrogel, and PLGA-CS nanoparticles did not exert any effect on platelet activation in the concentration range of 0.1−500 μg/mL. In Li 's study, PLGA, CS, and PLGA-CS nanoparticles (0.01−100 μg/mL) had slight inhibitory effect toward platelet aggregation induced by collagen (Li et al., 2009). This could be due to the reduced platelet−platelet interaction and/or reduced adsorption of platelets onto collagen fibers.

6.2.3 Nanoparticles and red blood cells

Another significant cellular component for blood coagulation is RBCs (erythrocytes), which has been underestimated in the past. Detailed mechanisms of how RBCs play their roles in hemostasis has been reviewed in-depth previously (Weisel & Litvinov, 2019). Briefly, RBCs attribute to hemostasis through hemorheological properties owning to their abundance and large size (Du et al., 2014). The influence of hemorheology—flow property of blood and its elements—on hemostasis and thrombosis depends on the blood shear rates and viscosity, of which RBC is a main contributor (Mehri et al., 2018; Sriram et al., 2014). The blood viscosity affects platelet distribution within vessels based on the axial margination phenomenon in which RBCs tend to move to the center of vessels and push platelets toward the periphery, facilitating their collision with the vasculature for hemostatic events (Walton et al., 2017).

Interactions of nanoparticles with RBCs can cause RBC aggregation (Wu et al., 2018). For instance, nanodiamonds (100 nm) were found to greatly increase attraction forces between RBCs' membrane, leading to the formation of large and abnormal RBCs aggregates (Avsievich et al., 2019). Meanwhile, no anomalous aggregate was depicted when RBCs were treated with polymeric nanoparticles (600 nm) with platelet-free blood plasma. The concentration of tested nanoparticles was kept at 0.01%. Also, Fe_3O_4 magnetic nanoparticles (∼73 nm, 200 μg/mL) (Ran et al., 2015) induced the aggregation of RBCs. Aggregation of RBCs, especially in small vessels, normally increases the blood viscosity in the center of vessels and platelet margination, resulting in induced endothelium activation and platelet aggregation (Mehri et al., 2018).

Furthermore, nanoparticle interactions with RBCs can also alter the deformability of RBCs, which is the ability of RBCs to change their shape in response to applied stress without resulting in hemolysis (Yedgar et al., 2002). Decrease in RBCs deformability is related to higher risk of thrombosis, since rigid RBCs can block small vessels easily, change the blood flow, and provoke platelet activation (Kwaan & Samama, 2019). Pan et al. demonstrated that the absorption of polystyrene

nanoparticles (PSNPs) on murine RBCs significantly reduced RBCs' deformability as a function of elongation index (EI) value at both sizes (200 and 300 nm) as well as both low and high nanoparticles:RBCs ratio (200:1 and 1000:1) (Pan et al., 2018). In contrast, lysozyme-dextran nanogels (LDNGs) did not affect deformability of RBCs even at the nanoparticles:RBCs ratio of 1000:1.

In addition to hemorheology, RBCs also contribute to blood coagulation via the exposure of phosphatidylserine (PS) on the cell surface (Guo et al., 2018). PS is a key phospholipid localized within the plasma membrane. Upon the high shear stress, oxidative stress, or complement attack, damaged RBCs expose PS on the membrane surface, providing a procoagulant surface for the accumulation of coagulation complexes such as prothrombinase and intrinsic tenase that facilitate thrombus formation (Du et al., 2014). Ran et al. reported that IONPs (72.6 ± 0.57 nm, 200 μg/mL) dramatically altered RBCs' rigidity by externalizing PS on the cell surface (the PS-expressed cells reached 40% after 48 hours), which ultimately changed the thrombotic potential of blood (Ran et al., 2015). Moreover, PSNPs exerted mechanical, oxidative, and osmotic stresses on murine RBCs (Pan et al., 2018). As a result, the proportion of RBCs expressing PS increased up to 87% and 92% respectively for low and high nanoparticles: RBCs loading ratios, in comparison to only 0.1% of RBCs only and 0.3% of LDNGs loading for the control.

6.2.4 Nanoparticles and plasma coagulation factors

The majority of circulating plasma coagulation factors are zymogens, precursors of enzymes, which will be converted into the active form once the coagulation cascade is initiated. The other plasma coagulation factors are nonenzymatic that act as either cofactor (e.g., TF (or FIII), FV and FVIII, high-molecular-weight kininogen (HMWK or HK), and protein S) or substrate (e.g., fibrinogen). These factors form a coagulation cascade in secondary hemostasis, which can be divided into extrinsic and intrinsic pathways. Both pathways lead to thrombin generation and ultimately fibrin formation to create a stable blood clot at the injury site. The extrinsic pathway is activated by TF exposed on damaged endothelial cells, initializing the coagulation cascade. In a parallel manner, the intrinsic pathway begins with FXII, prekallikrein (PK), and HMWK (Palta et al., 2014). FXII can be activated via the contact with negatively charged molecules and nanoparticle surfaces such as dextran sulfate, glass, kaolin, celite, and silica (Simak & De Paoli, 2017; Tankersley et al., 1983; van der Graaf et al., 1982; Wiggins & Cochrane, 1979). It can also be autoactivated by the membrane of activated platelets (Bendapudi et al., 2016), resulting in the activation of the kallikrein–kinin system and FXI as well as other downstream zymogens in the intrinsic pathway (Ilinskaya & Dobrovolskaia, 2016). It is important to note that apart from activated FXII (FXIIa), a small amount of thrombin generated by the extrinsic pathway can in turn activate FXI and thus facilitate the activation of the intrinsic pathway and amplification of thrombin generation.

Since nanoparticle surfaces can activate coagulation factor XII to initiate the intrinsic pathway of coagulation, it is reasonable to anticipate that nanoparticles might unintendedly interfere with the coagulation cascade and overall hemostasis. For example, Baker et al. reported that mesocellular foams (MCFs) with the window size >11 nm and the total pore volume at 0.0006 cm^3 facilitated clotting in an FXII-dependent mechanism (Baker et al., 2008). The authors stated that FXII, with a hydrodynamic size of 7.5 nm, can diffuse into and adhere to MCFs' cells, thus they can be activated and initiate a coagulation cascade. Silica nanoparticles (70–1000 nm) at 0.02 mg/mL were reported to activate the intrinsic pathway via their interaction with FXII (Nabeshi et al., 2012).

Decreasing the silica particle size from micrometer to nanometer (30 and 70 nm), that is, increasing the particle surface, resulted in a higher degree of FXII activation after intranasal exposure in mice for 7 days at 500 μg/mouse (Yoshida et al., 2013). Kushida et al. reported that silica nanoparticles at varied concentrations of 0.01−100 nM with the size of 12−85 nm had significant coagulation activity, while those with very small sizes (4−7 nm) did not (Kushida et al., 2014). The reason may be that very small nanoparticles (4−7 nm) have a higher surface curvature, which does not distort the configuration of FXII after its adsorption on the surface of the nanoparticles and affects the activation of other factors such as kallikrein, leading to a coagulant "silent" surface. Besides, coagulant factors such as FXa and vWF were induced whilst anticoagulant factors were reduced after 30 days of exposure to silica nanoparticles (58.11 ± 7.30 nm)in rats (Feng et al., 2019). The tested concentration of the nanoparticles was 1.8−16.2 mg/kg. By evaluating activated partial thromboplastin time (APTT) or partial thromboplastin time (PTT), Burke et al. concluded that MWCNTs (range of diameter was 26−31 nm, median length was 490−580 nm) at the concentration of 100 μg/mL triggered the intrinsic pathway by preferentially interacting with FIXa and acting as a platform to promote its enzyme activity (Burke et al., 2011). Oslakovic et al. reported that amine-modified polystyrene nanoparticles (57.1 and 284 nm in size, 0.5 mg/mL) bound to FVII and IX, which inhibited thrombin formation due to the depletion of these coagulation factors in solution (Oslakovic et al., 2012). By contrast, carboxyl-modified polystyrene nanoparticles (27.8 or 223.9 nm in size, 0.5 mg/mL) act as an active surface to trigger the intrinsic pathway.

Fibrinogen can strongly bind to gold nanoparticles (stabilized with citrate) thanks to cysteine residues presented in alpha, beta, and gamma chains of fibrinogen for Au-S bond formation, which induced the blood clot (Chen et al., 2011). However, another study reported that fibrinogen bound on the gold nanoparticle surface, which was stabilized with citrate, only increased the nanoparticle size but did not usually cause blood coagulation as in the previous study (Dobrovolskaia et al., 2009). Several studies described that interactions between silver nanoparticles and fibrin caused conformation change of fibrin (Ragaseema et al., 2012; Shrivastava et al., 2009, 2011), leading to the inhibition of fibrin polymerization and thrombus formation in vitro (Shrivastava et al., 2011). Nevertheless, it is worth noting that this effect is less pronounced in plasma than in a purified system due to nonspecific interactions of silver nanoparticles with other plasma proteins such as globulin and albumin.

6.3 Common in vitro methods to evaluate the effect of nanoparticles on blood coagulation

There are several methods based on different working principles that can be employed to access the effect of nanoparticles on components of the coagulation system and hemostatic process. A combination of more than one method is usually required to reach any solid conclusion about the nanoparticle effect. Methods that are commonly used are summarized below.

Standard laboratory coagulation tests or standard plasma coagulation tests (SLTs): (Activated) partial thromboplastin time (aPTT, PTT), prothrombin time (PT), and thrombin time (TT) are measured using an automated analyzer to access coagulation. Respectively, PT and aPTT/PTT reflect the activities of coagulation factors during blood coagulation. TT reflects the activity of fibrinogen (Fröhlich, 2016; Simak & De Paoli, 2017; Sperling et al., 2018). Nanoparticles are incubated with

citrate-anticoagulated plasma for the test. Interpretation of changes in obtained values is useful to determine the procoagulant/coagulant or proanticoagulant/anticoagulant effects of tested nanoparticles (Burke et al., 2011; Cenni et al., 2008; Dobrovolskaia et al., 2009; Martínez-Gutierrez et al., 2012).

Viscoelastic test: In comparison to standard plasma-based coagulation test, viscoelastic test is performed in citrated whole blood to measure viscoelastic properties during thrombus formation until fibrinolysis (Paniccia et al., 2015; Peng, 2010). Hence, this test provides a global assessment of the entire hemostatic process (da Luz et al., 2013), and thus can be used to evaluate the effect of nanoparticles on clot development, stabilization, and dissolution (Ajdari et al., 2017; Bircher et al., 2014; He et al., 2020; Meng et al., 2012; Zhang et al., 2016). Currently, three commercial systems for the viscoelastic test are available, namely thromboelastography, rotational thromboelastometry, and Sonoclot analysis (da Luz et al., 2013).

Immunoassays: Nanoparticles' effect on blood coagulation can be identified by immunoassay, such as enzyme-linked immune assay (ELISA)—one of the most frequently used. Based on the specificity of the antigen−antibody interaction, ELISA can be used to detect and quantify platelet activation markers such as β-TG, PF4, serotonin, P-selectin (Ferraz et al., 2008; Jones et al., 2012; Mayer et al., 2009; Stevens et al., 2009), prothrombin activation fragments D-dimer (Burke et al., 2011; Feng et al., 2019; Mayer et al., 2009), TF, vWF exposed by damaged endothelial cells (Burke et al., 2011; Feng et al., 2019; Yoshida et al., 2013), eNOS, FXa in serum (Feng et al., 2019), and plasmatic markers indicating the activation of the coagulation cascade (Krajewski et al., 2013).

Synthetic substrate assay: A variety of commercial assay kits have been developed to detect the activity of coagulation factors such as thrombin generation assay (Jones et al., 2012; Kushida et al., 2014; Stevens et al., 2009), FXII activity assay (Yoshida et al., 2013), lactate dehydrogenase (LDH) assay to detect platelet membrane integrity (Guo et al., 2015; Liang et al., 2016; Liu et al., 2017; Mayer et al., 2009; Shrivastava et al., 2009; Singh et al., 2011; Smyth et al., 2015), and NO measurement (Guo et al., 2015; Semberova et al., 2009). These assays are useful to investigate the effect of nanoparticles−coagulation system interactions. The assay is normally based on the detection of chromogenic or fluorogenic substrates, such as intracellular free Ca^{2+} assay (De Paoli Lacerda et al., 2011; Gelderman et al., 2008; Kumari et al., 2014; Shrivastava et al., 2009; Singh et al., 2011, 2012), or intracellular ROS measurement (Guo et al., 2015; Kumari et al., 2014; Liang et al., 2016; Liu et al., 2017; Ran et al., 2015; Singh et al., 2011, 2012; Sun et al., 2016).

Aggregometry: Light transmission aggregometry (LTA) and multiple electrode aggregometry (MEA) are used to assess platelet reactivity and measure platelet aggregation in response to agonists. LTA uses citrated platelet-rich plasma (PRP) and the change in light transmission to detect aggregation while MEA uses whole blood and works by detecting electrical impedance between electrodes (Sun et al., 2019). These tests have been used to study platelet−nanoparticles interactions (Bihari et al., 2010; Corbalan et al., 2012; Deb et al., 2011, 2012; Dobrovolskaia et al., 2012; Haberl et al., 2015; Jones et al., 2012; Jun et al., 2011; Koziara et al., 2005; Kumari et al., 2014; Laloy et al., 2014; Li et al., 2009; Love et al., 2012; Ragaseema et al., 2012; Ramtoola et al., 2011; Santos-Martinez et al., 2012, 2015; Shrivastava et al., 2009; Singh et al., 2011, 2012; Smyth et al., 2015; Tavano et al., 2010; Villegas et al., 2019; Zbinden et al., 1989).

Quartz crystal microbalance with dissipation (QCM-D): QCM-D is a new potential method to investigate the effect of nanoparticles on platelets by detecting platelet aggregation under flow conditions (Santos-Martinez et al., 2012; Santos-Martinez et al., 2015). It has been demonstrated that QCM-D is more sensitive than LTA (Santos-Martinez et al., 2012, 2015).

Flow cytometry: Flow cytometry is a powerful method and provides statistical data related to platelet activation by accessing physical interactions between platelet and nanoparticles (Constantinescu et al., 2003; Singh et al., 2012), platelet surface activation markers such as P-selectin, CD63, PS, GpIIIb/IIa, GpIbα, thrombin-mediated PAR-1 (Bihari et al., 2010; Bircher et al., 2014; Corbalan et al., 2012; Deb et al., 2011, 2012; Dobrovolskaia et al., 2012; Jones et al., 2012; Koziara et al., 2005; Kumari et al., 2014; Li et al., 2009; Radomski et al., 2005; Ragaseema et al., 2012; Santos-Martinez et al., 2012; Shrivastava et al., 2009; Singh et al., 2011; Smyth et al., 2015; Tavano et al., 2010; Villegas et al., 2019), change in intracellular Ca^{2+} level (Jun et al., 2011; Shrivastava et al., 2009), or the release of platelet microparticles (Ferraz et al., 2010). The exposure of markers, such as TF, PS, and ICAM-1 (CD54), promotes adhesion and the coagulation cascade on the surface of endothelial cells and RBCs after nanoparticle treatment can be measured as well (Gelderman et al., 2008; Pan et al., 2018). Flow cytometry can also be employed to detect the binding of nanoparticles to platelets and endothelial cells (Semberova et al., 2009; Tavano et al., 2010).

Western blot: This method can detect the presence of specific proteins. Several studies have used western blot to quantify the expression of cellular factors (Guo et al., 2015), expression of VE-cadherin on endothelial cells after exposure to nanoparticles (Sun et al., 2016), expression of other types of marker indicating platelet activation (Ragaseema et al., 2012), or the activation of SOCE (De Paoli Lacerda et al., 2011) induced by the interaction of the coagulation system with nanoparticles.

Real-time polymerase chain reaction (PCR): PCR is another quantitative method used to detect activation markers and coagulation factors indicating the effect of nanoparticles on the coagulation system. Real-time PCR can check mRNA expression of iNOS, eNOS (Guo et al., 2015), expression of VE-cadherin on endothelial cells after exposure to nanoparticles (Sun et al., 2016), the presence of coagulation factors such as TF, vWF, P-selectin (Feng et al., 2019; Semberova et al., 2009), and adhesion markers, namely ICAM-1, PCAM-1 (Semberova et al., 2009).

Microscopy: Microscopy is usually utilized to visualize the effect of nanoparticles on cellular components of the coagulation system (nanoparticle−cell interface). Direct visualization of platelet or RBC aggregates caused by nanoparticles can be easily obtained by optical microscopy (Cenni et al., 2008; Simak, 2016; Zbinden et al., 1989). However, transmission electron microscope (TEM) (Corbalan et al., 2012; De Paoli Lacerda et al., 2011; Kumari et al., 2014; Liang et al., 2016; Radomski et al., 2005; Shrivastava et al., 2009; Singh et al., 2011; Smyth et al., 2015) and scanning electron microscope (SEM) can be also used to access subcellular localization of nanoparticles and the ultrastructure of the nanoparticle surface, and the nanoparticle−blood cell interface with high resolution (Avsievich et al., 2019; Deb et al., 2011; Dobrovolskaia et al., 2012; Ferraz et al., 2008, 2010; Guildford et al., 2009; Jones et al., 2012; Laloy et al., 2014; Ragaseema et al., 2012; Ran et al., 2015; Santos-Martinez et al., 2012, 2015; Šimundić et al., 2013; Singh et al., 2011; Stevens et al., 2009; Sun et al., 2016).

6.4 Factors affecting nanoparticle−blood coagulation system interactions

Different nanoparticles have different effects on blood coagulation components. Changes in any nanoparticle parameters such as size, shape, surface charge, and coating materials might correlate with other ways of interaction and lead to an alternative effect.

6.4.1 Size

Silica nanoparticles of smaller size exert more profound impact on the coagulation system (Bauer et al., 2011; Corbalan et al., 2012; Jun et al., 2011; Nabeshi et al., 2012; Nemmar et al., 2014). Among silica nanoparticles with various size of 16, 41, 80, 212, and 304 nm, nanoparticles with the largest size resulted in the release of Weibel–Palade bodies and vWF from endothelial cells after 24 hours of incubation, while this effect only takes a few hours with nanoparticles of smaller size (Bauer et al., 2011). It has been reported that silica nanoparticles with the diameter of 10 nm triggered stronger platelet activation than those larger than 50 nm (Corbalan et al., 2012). Similarly, silica nanoparticles of 30, 50, or 70 nm exhibited increased procoagulant activity as compared to those of 100, 300, 500, or even 1000 nm, due to the increased specific surface area exposed to the coagulation system (Jun et al., 2011; Nabeshi et al., 2012; Nemmar et al., 2014). It is worthy of note that very small size silica nanoparticles (4–7 nm) did not have coagulation activity due to higher surface curvatures (Kushida et al., 2014). However, other studies reported that smaller silica nanoparticles (10–15 nm) inhibited platelet activation in vitro (Shrivastava et al., 2009), while larger nanoparticles (200 nm) caused more pronounced hemostasis in vivo (Kim et al., 2008).

Similar to silica nanoparticles, gold nanoparticles ($\leq$50 nm) were easily internalized and accumulated in platelets, inducing platelet activation. In contrast, gold nanoparticles larger than 60 nm were basically inert (Deb et al., 2011; Hecold et al., 2017; Santos-Martinez et al., 2012). In contrast, other studies reported that small gold nanoparticles (5–30 nm) had no effect on platelets while 60 nm-ones prevented platelet aggregation (Aseychev et al., 2013). All of these tested gold nanoparticles were used at 5–40 μM in PRP which corresponded to 0.94–7.5 μg/mL blood.

The effect of particle size was also demonstrated for carbon-based nanoparticles (Meng et al., 2012; Radomski et al., 2005) and silver nanoparticles (Guo et al., 2015). For example, shorter MWCNTs had less effect on platelet activation than the longer ones (Meng et al., 2012). Silver nanoparticles with the diameter of 110 nm exhibited the most effective toxicity to endothelial cells in comparison to 10 and 75 nm ones (Guo et al., 2015). The discrepancies in the size-dependent effect of nanoparticles on coagulation need to be carefully taken because the characterization of nanoparticle size might not be carried out in similar media and technique (e.g., water vs buffer solution or TEM/SEM vs dynamic light scattering). In addition, the impact of a specific nanoparticle on the coagulation system may be also associated with other factors such as surface charge and the concentration of nanoparticles.

6.4.2 Shape

The effect of nanoparticle shape on the interaction with the coagulation system has also been presented in some studies. Regarding carbon-based nanoparticles, carbon nanotubes (both multiwalled and single-walled) promoted platelet activation and aggregation while spherical C60 fullerenes did not (Radomski et al., 2005). Cuboidal γ-cyclodextrin nanoscale frameworks showed induced platelet aggregation in comparison to the spherical shape counterparts (He et al., 2019). On the contrary, there were studies showing that carbon-based nanoparticles can cause thrombus formation regardless of their shape (Holzer et al., 2014). Gold nanoparticles with either spherical, hollow sphere, or rod shape did not affect endothelial cells (Bartczak et al., 2012).

6.4.3 Surface charge

Many studies indicated that the surface charge of the nanoparticles is also a key factor orientating their interaction with coagulation system. Positively charged groups on nanoparticles' surface can neutralize and form cross-bridges with negatively charged ionizable sialic acid groups on the platelets' surface, facilitating platelet−platelet interaction and aggregation (Gobbo et al., 2015; Hante et al., 2019). Besides, positively charged nanoparticles can alter platelet morphology (Jones et al., 2012) and disrupt platelet membrane integrity (Dobrovolskaia et al., 2012), inducing the changes in the size and number of platelet aggregates. Large and cationic PAMAM ($\geq$ G4) and triazine dendrimer (G5 and G7) provoked platelet aggregation, in which the aggregation degree was proportional to the number of amine groups on the nanoparticles' surface (Dobrovolskaia et al., 2012).

Other studies showed that the coagulation cascade can also be initiated through the contact with negatively charge nanoparticles' surfaces (Simak & De Paoli, 2017; Tankersley et al., 1983; van der Graaf et al., 1982; Wiggins & Cochrane, 1979). For example, anionic polystyrene (carboxyl-modification) led to the upregulation of activation markers (P-selectin or PAC-1) of platelets whilst cationic polystyrene (amine-modification) led to the interruption of the platelet membrane (McGuinnes et al., 2011). Both positively and negatively charged polystyrene nanoparticles (McGuinnes et al., 2011) can eventually lead to thrombotic events. This is in contradiction with liposomes where both anionic and cationic nanoparticles inhibited platelet activation and aggregation (Juliano et al., 1983), and anionic liposomes reduced the platelet number in rats (Reinish et al., 1988). Nevertheless, there are still contradictory studies that reported the platelet aggregation effect of anionic liposomes (Zbinden et al., 1989), or the independence of the surface charge of polystyrene nanoparticles toward platelet activation (Smyth et al., 2015). Apparently, the charge-dependent effect of nanoparticles on the coagulation system is unpredictable. In physiological conditions, the influence of nanoparticle charge is even more difficult to clarify due to the absorption of plasma proteins on the surface of nanoparticles.

6.4.4 Coating materials

A layer of coating material on the nanoparticle surface can alter its reactivity to the blood coagulation system. Among all, polyethylene glycol (PEG) is the most commonly used polymeric material. Several studies have demonstrated that the presence of PEG on the nanoparticle surface reduced their interference with endothelial cells and platelets, probably due to the capability to prevent protein binding. As a result, unattended hemostasis is reduced and the compatibility of nanoparticles is improved (Koziara et al., 2005; Ragaseema et al., 2012; Santos-Martinez et al., 2014; Su et al., 2017; Tavano et al., 2010; Yu et al., 2012). However, PEGylation of nanoparticles is not successful for all nanoparticles (Burke et al., 2011; Vakhrusheva et al., 2013). In addition to PEG, other polymers, namely dextran (Chowdhury et al., 2013), albumin (Vakhrusheva et al., 2013), starch (Deb et al., 2012), and poly(acrylic acid) (PAA) (Villegas et al., 2019) did not cause any effect on endothelial cells and platelets, or reduce platelet aggregation. It was reported that PAA conjugated on the surface of gold nanoparticles reduced platelet aggregation by binding to fibrinogen and promoting the changes in its conformation (Deng et al., 2011). Gold nanoparticles coated with polyethylenimine and polyvinylpyrrolidone, however, induced platelet aggregation (Hecold et al., 2017).

All the findings above have demonstrated that specific coating material is worth investigating for these commonly used nanoparticles during their interactions with the coagulation system.

6.4.5 Other factors

The surface charges of the nanoparticle can be altered in the physiological fluids due to the binding of plasma proteins or simply pH value, which could come along with the alteration of nanoparticle hydrophobicity (Fröhlich, 2016; Setyawati et al., 2015). A study clarifying the influence of latex polystyrene nanoparticles' hydrophobicity on the blood coagulation carried out by Miyamoto et al. (1990) revealed that hydrophobic latex nanoparticles provoked platelet aggregation to a higher extent than the hydrophilic ones. This could be due to their ability to interact more closely with the cell membrane and activate platelets (Kou et al., 2013). However, further investigation relating to the relationship between hydrophobicity of nanoparticles and the blood coagulation system is rarely found.

Interestingly, the concentration of nanoparticle metal cores (such as gold) had an impact on coagulation. Hsu et al. incorporated polyurethane nanocomposites with gold and revealed that incorporation of a lower gold concentration (43.5 ppm) resulted in less platelet adhesion and activation compared to a higher amount of gold (174 ppm) (Hsu et al., 2006).

6.5 Two-side effect of engineered nanoparticles on the blood coagulation system

Nanoparticles can be purposely engineered for specific interactions with the blood coagulation system to either facilitate or prevent coagulation in order to avoid bleeding or prevent thrombosis, respectively. Usually, nanoparticles can be loaded with drugs and/or decorated with peptides, recombinant factors, or markers on the surface to obtain the desirable effect. Some reviews have discussed nanoparticles that are intended to promote coagulation (Gaston et al., 2018; Ilinskaya & Dobrovolskaia, 2013). For instance, "synthetic platelets" comprising poly(lactic-co-glycolic acid)-poly-L-lysine (PLGA-PLL) nanospheres decorated with PEG terminated RGD peptide were developed by Bertram et al. (2009). This system induced platelet aggregation to halt bleeding at the injury site owning to the interaction between RGD peptide and GpIIb/IIIa on the surface of activated platelets for cross-linking. In the study by Shafir et al., maghemite nanoparticles with recombinant coagulant factor VII (rVII) physically bound on the surface showed comparable activity to free rVII (Shafir et al., 2009). On the other hand, nanoparticles designed to prevent coagulation have also been reviewed elsewhere (Ilinskaya & Dobrovolskaia, 2013). Regarding the target and working mechanism, these nanoparticles can be engineered to have the antithrombotic, antiplatelet, and fibrinolytic effects. To exert the antithrombotic effect, nanoparticles can incorporate anticoagulant drugs inside (e.g., heparin, rutin, dipeptide IleTrp, and adenosine) (Argyo et al., 2012; Jiao et al., 2001, 2002; Nguyen, Nguyen et al., 2019; Wu et al., 2020; Zhao et al., 2018) or are conjugated with a ligand (e.g., thrombin-specific aptamer) (Shiang et al., 2011) that inhibits or delays thrombus formation. Nanoparticles with the antiplatelet effect prohibit platelet activation and aggregation. Liposomes with CD39 incorporated inside (Haller et al., 2006), PAMAM dendrimers

conjugated with $P2Y_1$ receptor antagonist MSR2500 (de Castro et al., 2010) or A2A receptor agonist CGS21680 (Kim et al., 2008; Kim et al., 2009), and cubosomes loaded with antiplatelet drug clopidogrel bisulfate (El-Laithy et al., 2018) are representative examples of antiplatelet engineered nanoparticles. Besides, some nanoparticles with PEG functionalization possess an antiplatelet property as well (Koziara et al., 2005; Ragaseema et al., 2012; Santos-Martinez et al., 2014; Su et al., 2017; Tavano et al., 2010; Yu et al., 2012).

Moreover, nanoparticles can also be designed as a carrier of fibrinolytic agents to dissolve existing thrombi (fibrinolytic/thrombolysis effect). Several nanoparticles (e.g., liposomes and polymeric nanoparticles) have been successfully engineered to improve the efficacy of fibrinolytic agents such as urokinase, streptokinase, and tissue plasminogen activator (t-PA) with reduced side effects (Chapurina et al., 2016; Chung et al., 2008; Elbayoumi & Torchilin, 2008; Heeremans et al., 1995; Leach et al., 2003; Nguyen et al., 1990; Su et al., 2020; Zamanlu et al., 2019).

6.6 Conclusion and prospects

Nanoparticles in the bloodstream come into contact and interact with one or more components of the blood coagulation system. This chapter presents a thorough review of possible interactions and influences of various nanoparticles on coagulation system components such as platelets, RBCs, endothelial cells, and plasma coagulation factors. However, there is still plenty of room for more studies in the future as not all commonly examined nanoparticles are investigated and fully understood with regard to the underlying mechanisms. Further research investigating the effects of common nanoparticles on RBCs and specific coagulation factors is going to be of high interest as most of current studies have focused more on the interaction of platelets and endothelial cells with nanoparticles. Several in vitro methods that are often used to assess the effects of nanoparticles on hemostasis have also been briefly mentioned. These methods are usually used in combination. Alterable interferences in the blood coagulation correlating to changes in nanoparticle physiochemical parameters have been examined in many studies but not in a systematic way. The discrepancies in results need to be treated with caution since the characterizations might not be carried out in the comparable methods, setting, and media.. More importantly, the effects of a specific nanoparticle on the coagulation system could be associated with more than one factor. As discussed, coating material is an important factor that can alter nanoparticles' reactivity to the blood coagulation system. However, there is a limited variety of investigated polymeric materials. The effect of metal coating of core−shell nanoparticles, regarding types of metal, thickness of metal coating, and coating method, on the coagulation system has not been explored yet. Therefore more studies are needed to give future insight into the influences of coating materials in hemostasis. It is worth examining specific coating material for commonly used nanoparticles. Moreover, the interface between the blood coagulation system and other factors of nanoparticles such as hydrophobicity, porosity, lipid composition of lipid-based nanoparticles, surface topography may attract much interest in the future. Apparently, in vivo studies are encouraged since the behavior of nanoparticles is not always predictable in physiological conditions due to the absorption of plasma proteins on their surface. Taken together, our chapter is beneficial for the establishment of nanoparticles that can avoid unintended interferences with the hemostatic balance, or purposely increase the interaction with a specific blood coagulation component.

References

Ajdari, N., Vyas, C., Bogan, S. L., Lwaleed, B. A., & Cousins, B. G. (2017). Gold nanoparticle interactions in human blood: A model evaluation. *Nanomedicine: Nanotechnology, Biology and Medicine*, *13*(4), 1531–1542.

Argyo, C., Cauda, V., Engelke, H., Rädler, J., Bein, G., & Bein, T. (2012). Heparin-coated colloidal mesoporous silica nanoparticles efficiently bind to antithrombin as an anticoagulant drug-delivery system. *Chemistry–A European Journal*, *18*(2), 428–432.

Arndt, N., Tran, H. D., Zhang, R., Xu, Z. P., & Ta, H. T. (2020). Different approaches to develop nanosensors for diagnosis of diseases. *Advanced Science*, *7*(24), 2001476.

Aseychev, A., Azizova, O., Beckman, E., Dudnik, L., & Sergienko, V. (2013). Effect of gold nanoparticles coated with plasma components on ADP-induced platelet aggregation. *Bulletin of Experimental Biology and Medicine*, *155*(5), 685–688.

Avsievich, T., Popov, A., Bykov, A., & Meglinski, I. (2019). Mutual interaction of red blood cells influenced by nanoparticles. *Scientific Reports*, *9*(1), 1–6.

Baker, S. E., Sawvel, A. M., Fan, J., Shi, Q., Strandwitz, N., & Stucky, G. D. (2008). Blood clot initiation by mesocellular foams: Dependence on nanopore size and enzyme immobilization. *Langmuir.*, *24*(24), 14254–14260.

Bandyopadhyay, D., Baruah, H., Gupta, B., & Sharma, S. (2012). Silver nano particles prevent platelet adhesion on immobilized fibrinogen. *Indian Journal of Clinical Biochemistry*, *27*(2), 164–170.

Bao, B. Q., Le, N. H., Nguyen, D. H. T., Tran, T. V., Pham, L. P. T., Bach, L. G., et al. (2018). Evolution and present scenario of multifunctionalized mesoporous nanosilica platform: A mini review. *Materials Science and Engineering: C.*, *91*, 912–928.

Bartczak, D., Muskens, O. L., Nitti, S., Sanchez-Elsner, T., Millar, T. M., & Kanaras, A. G. (2012). Interactions of human endothelial cells with gold nanoparticles of different morphologies. *Small.*, *8*(1), 122–130.

Bauer, A. T., Strozyk, E. A., Gorzelanny, C., Westerhausen, C., Desch, A., Schneider, M. F., et al. (2011). Cytotoxicity of silica nanoparticles through exocytosis of von Willebrand factor and necrotic cell death in primary human endothelial cells. *Biomaterials.*, *32*(33), 8385–8393.

Bendapudi, P. K., Deceunynck, K., Koseoglu, S., Bekendam, R. H., Mason, S. D., Kenniston, J., et al. (2016). *Stimulated platelets but not endothelium generate thrombin via a factor XIIa-dependent mechanism requiring phosphatidylserine exposure*. Washington, DC: American Society of Hematology.

Berry, J., Arnoux, B., Stanislas, G., Galle, P., & Chretien, J. (1977). A microanalytic study of particles transport across the alveoli: Role of blood platelets. *Biomedicine/[publiée pour l'AAICIG]*, *27*(9–10), 354–357.

Bertram, J. P., Williams, C. A., Robinson, R., Segal, S. S., Flynn, N. T., & Lavik, E. B. (2009). Intravenous hemostat: Nanotechnology to halt bleeding. *Science Translational Medicine*, *1*(11), 11ra22–11ra22.

Bihari, P., Holzer, M., Praetner, M., Fent, J., Lerchenberger, M., Reichel, C. A., et al. (2010). Single-walled carbon nanotubes activate platelets and accelerate thrombus formation in the microcirculation. *Toxicology.*, *269*(2–3), 148–154.

Bircher, L., Theusinger, O. M., Locher, S., Eugster, P., Roth-Z'graggen, B., Schumacher, C. M., et al. (2014). Characterization of carbon-coated magnetic nanoparticles using clinical blood coagulation assays: Effect of PEG-functionalization and comparison to silica nanoparticles. *Journal of Materials Chemistry B.*, *2*(24), 3753–3758.

Broos, K., Feys, H. B., De Meyer, S. F., Vanhoorelbeke, K., & Deckmyn, H. (2011). Platelets at work in primary hemostasis. *Blood Reviews*, *25*(4), 155–167.

Burke, A. R., Singh, R. N., Carroll, D. L., Owen, J. D., Kock, N. D., D'Agostino, R., Jr, et al. (2011). Determinants of the thrombogenic potential of multiwalled carbon nanotubes. *Biomaterials.*, *32*(26), 5970–5978.

Cenni, E., Granchi, D., Avnet, S., Fotia, C., Salerno, M., Micieli, D., et al. (2008). Biocompatibility of poly (D, L-lactide-co-glycolide) nanoparticles conjugated with alendronate. *Biomaterials.*, *29*(10), 1400–1411.

Chapurina, Y. E., Drozdov, A. S., Popov, I., Vinogradov, V. V., Dudanov, I. P., & Vinogradov, V. V. (2016). Streptokinase@ alumina nanoparticles as a promising thrombolytic colloid with prolonged action. *Journal of Materials Chemistry B.*, *4*(35), 5921–5928.

Chen, G., Ni, N., Zhou, J., Chuang, Y.-J., Wang, B., Pan, Z., et al. (2011). Fibrinogen clot induced by gold-nanoparticle in vitro. *Journal of Nanoscience and Nanotechnology*, *11*(1), 74–81.

Chowdhury, S. M., Kanakia, S., Toussaint, J. D., Frame, M. D., Dewar, A. M., Shroyer, K. R., et al. (2013). In vitro hematological and in vivo vasoactivity assessment of dextran functionalized graphene. *Scientific Reports*, *3*, 2584.

Chung, T.-W., Wang, S.-S., & Tsai, W.-J. (2008). Accelerating thrombolysis with chitosan-coated plasminogen activators encapsulated in poly-(lactide-co-glycolide)(PLGA) nanoparticles. *Biomaterials.*, *29*(2), 228–237.

Constantinescu, I., Levin, E., & Gyongyossy-Issa, M. (2003). Liposomes and blood cells: A flow cytometric study. *Artificial Cells, Blood Substitutes, and Biotechnology*, *31*(4), 395–424.

Corbalan, J. J., Medina, C., Jacoby, A., Malinski, T., & Radomski, M. W. (2012). Amorphous silica nanoparticles aggregate human platelets: Potential implications for vascular homeostasis. *International Journal of Nanomedicine*, *7*, 631.

da Luz, L. T., Nascimento, B., & Rizoli, S. (2013). Thrombelastography (TEG®): Practical considerations on its clinical use in trauma resuscitation. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, *21*(1), 1–8.

Danielsen, P. H., Cao, Y., Roursgaard, M., Møller, P., & Loft, S. (2015). Endothelial cell activation, oxidative stress and inflammation induced by a panel of metal-based nanomaterials. *Nanotoxicology.*, *9*(7), 813–824.

de Castro, S., Maruoka, H., Hong, K., Kilbey, S. M., Costanzi, S., Hechler, B., et al. (2010). Functionalized congeners of P2Y1 receptor antagonists: 2-Alkynyl (N)-methanocarba 2′-deoxyadenosine 3′, 5′-bisphosphate analogues and conjugation to a polyamidoamine (PAMAM) dendrimer carrier. *Bioconjugate Chemistry*, *21*(7), 1190–1205.

De La Cruz, G. G., Rodríguez-Fragoso, P., Reyes-Esparza, J., Rodríguez-López, A., Gómez-Cansino, R., & Rodriguez-Fragoso, L. (2018). Interaction of nanoparticles with blood components and associated pathophysiological effects. *Unraveling the Safety Profile of Nanoscale Particles and Materials-From Biomedical to Environmental Applications*.

de la Harpe, K. M., Kondiah, P. P., Choonara, Y. E., Marimuthu, T., du Toit, L. C., & Pillay, V. (2019). The hemocompatibility of nanoparticles: A review of cell–nanoparticle interactions and hemostasis. *Cells.*, *8*(10), 1209.

De Paoli Lacerda, S. H., Semberova, J., Holada, K., Simakova, O., Hudson, S. D., & Simak, J. (2011). Carbon nanotubes activate store-operated calcium entry in human blood platelets. *ACS Nano*, *5*(7), 5808–5813.

Deb, S., Patra, H. K., Lahiri, P., Dasgupta, A. K., Chakrabarti, K., & Chaudhuri, U. (2011). Multistability in platelets and their response to gold nanoparticles. *Nanomedicine: Nanotechnology, Biology and Medicine*, *7*(4), 376–384.

Deb, S., Raja, S., Dasgupta, A. K., Sarkar, R., Chattopadhyay, A. P., Chaudhuri, U., et al. (2012). Surface tunability of nanoparticles in modulating platelet functions. *Blood Cells, Molecules, and Diseases*, *48*(1), 36–44.

Demir, E., Burgucu, D., Turna, F., Aksakal, S., & Kaya, B. (2013). Determination of TiO_2, ZrO_2, and Al_2O_3 nanoparticles on genotoxic responses in human peripheral blood lymphocytes and cultured embryonic kidney cells. *Journal of Toxicology and Environmental Health, Part A*, *76*(16), 990–1002.

Deng, Z. J., Liang, M., Monteiro, M., Toth, I., & Minchin, R. F. (2011). Nanoparticle-induced unfolding of fibrinogen promotes Mac-1 receptor activation and inflammation. *Nature Nanotechnology*, *6*(1), 39–44.

Do, V. M. H., Bach, L. G., Tran, D.-H. N., Nguyen, T. N. Q., Hoang, D. T., Nguyen, D. H., et al. (2020). Effective elimination of charge-associated toxicity of low generation polyamidoamine dendrimer eases drug delivery of oxaliplatin. *Biotechnology and Bioprocess Engineering*, 1–11.

Dobrovolskaia, M. A., Patri, A. K., Simak, J., Hall, J. B., Semberova, J., De Paoli Lacerda, S. H. ,, et al. (2012). Nanoparticle size and surface charge determine effects of PAMAM dendrimers on human platelets in vitro. *Molecular Pharmaceutics*, *9*(3), 382–393.

Dobrovolskaia, M. A., Patri, A. K., Zheng, J., Clogston, J. D., Ayub, N., Aggarwal, P., et al. (2009). Interaction of colloidal gold nanoparticles with human blood: Effects on particle size and analysis of plasma protein binding profiles. *Nanomedicine: Nanotechnology, Biology and Medicine*, *5*(2), 106–117.

Du, V. X., Huskens, D., Maas, C., Al Dieri, R., de Groot, P. G., & de Laat, B. (Eds.), (2014). *New insights into the role of erythrocytes in thrombus formation. Seminars in thrombosis and hemostasis*. Thieme Medical Publishers.

Easo, S. L., & Mohanan, P. (2015). In vitro hematological and in vivo immunotoxicity assessment of dextran stabilized iron oxide nanoparticles. *Colloids and Surfaces B: Biointerfaces*, *134*, 122–130.

Ekdahl, K. N., Fromell, K., Mohlin, C., Teramura, Y., & Nilsson, B. (2019). A human whole-blood model to study the activation of innate immunity system triggered by nanoparticles as a demonstrator for toxicity. *Science and Technology of Advanced Materials*, *20*(1), 688–698.

Elbayoumi, T. A., & Torchilin, V. P. (2008). Liposomes for targeted delivery of antithrombotic drugs. *Expert Opinion on Drug Delivery*, *5*(11), 1185–1198.

El-Laithy, H. M., Badawi, A., Abdelmalak, N. S., & El-Sayyad, N. (2018). Cubosomes as oral drug delivery systems: A promising approach for enhancing the release of clopidogrel bisulphate in the intestine. *Chemical and Pharmaceutical Bulletin*, c18–00615.

Enciso, A. E., Neun, B., Rodriguez, J., Ranjan, A. P., Dobrovolskaia, M. A., & Simanek, E. E. (2016). Nanoparticle effects on human platelets in vitro: A comparison between PAMAM and triazine dendrimers. *Molecules.*, *21*(4), 428.

Feng, L., Yang, X., Liang, S., Xu, Q., Miller, M. R., Duan, J., et al. (2019). Silica nanoparticles trigger the vascular endothelial dysfunction and prethrombotic state via miR-451 directly regulating the IL6R signaling pathway. *Particle and Fibre Toxicology*, *16*(1), 1–13.

Ferraz, N., Carlsson, J., Hong, J., & Ott, M. K. (2008). Influence of nanoporesize on platelet adhesion and activation. *Journal of Materials Science: Materials in Medicine*, *19*(9), 3115–3121.

Ferraz, N., Hong, J., & Karlsson Ott, M. (2010). Procoagulant behavior and platelet microparticle generation on nanoporous alumina. *Journal of Biomaterials Applications*, *24*(8), 675–692.

Fröhlich, E. (2016). Action of nanoparticles on platelet activation and plasmatic coagulation. *Current Medicinal Chemistry*, *23*(5), 408–430.

Gaston, E., Fraser, J. F., Xu, Z. P., & Ta, H. T. (2018). Nano-and micro-materials in the treatment of internal bleeding and uncontrolled hemorrhage. *Nanomedicine: Nanotechnology, Biology and Medicine*, *14*(2), 507–519.

Gelderman, M. P., Simakova, O., Clogston, J. D., Patri, A. K., Siddiqui, S. F., Vostal, A. C., et al. (2008). Adverse effects of fullerenes on endothelial cells: Fullerenol C60 (OH) 24 induced tissue factor and ICAM-1 membrane expression and apoptosis in vitro. *International Journal of Nanomedicine*, *3*(1), 59.

Gobbo, O. L., Sjaastad, K., Radomski, M. W., Volkov, Y., & Prina-Mello, A. (2015). Magnetic nanoparticles in cancer theranostics. *Theranostics.*, *5*(11), 1249.

Greish, K., Thiagarajan, G., Herd, H., Price, R., Bauer, H., Hubbard, D., et al. (2012). Size and surface charge significantly influence the toxicity of silica and dendritic nanoparticles. *Nanotoxicology.*, *6*(7), 713–723.

Gu, Z., Yan, S., Cheong, S., Cao, Z., Zuo, H., Thomas, A. C., et al. (2018). Layered double hydroxide nanoparticles: Impact on vascular cells, blood cells and the complement system. *Journal of Colloid and Interface Science*, *512*, 404–410.

Guildford, A., Poletti, T., Osbourne, L., Di Cerbo, A., Gatti, A., & Santin, M. (2009). Nanoparticles of a different source induce different patterns of activation in key biochemical and cellular components of the host response. *Journal of the Royal Society Interface*, *6*(41), 1213–1221.

Guo, C., Xia, Y., Niu, P., Jiang, L., Duan, J., Yu, Y., et al. (2015). Silica nanoparticles induce oxidative stress, inflammation, and endothelial dysfunction in vitro via activation of the MAPK/Nrf2 pathway and nuclear factor-κB signaling. *International Journal of Nanomedicine*, *10*, 1463.

Guo, H., Zhang, J., Boudreau, M., Meng, J., Yin, J.-j, Liu, J., et al. (2015). Intravenous administration of silver nanoparticles causes organ toxicity through intracellular ROS-related loss of inter-endothelial junction. *Particle and Fibre Toxicology*, *13*(1), 1–13.

Guo, L., Tong, D., Yu, M., Zhang, Y., Li, T., Wang, C., et al. (2018). Phosphatidylserine-exposing cells contribute to the hypercoagulable state in patients with multiple myeloma. *International Journal of Oncology*, *52*(6), 1981–1990.

Haberl, N., Hirn, S., Holzer, M., Zuchtriegel, G., Rehberg, M., & Krombach, F. (2015). Effects of acute systemic administration of TiO_2, ZnO, SiO_2, and Ag nanoparticles on hemodynamics, hemostasis and leukocyte recruitment. *Nanotoxicology.*, *9*(8), 963–971.

Haller, C. A., Cui, W., Wen, J., Robson, S. C., & Chaikof, E. L. (2006). Reconstitution of CD39 in liposomes amplifies nucleoside triphosphate diphosphohydrolase activity and restores thromboregulatory properties. *Journal of Vascular Surgery*, *43*(4), 816–823.

Hangge, P., Stone, J., Albadawi, H., Zhang, Y. S., Khademhosseini, A., & Oklu, R. (2017). Hemostasis and nanotechnology. *Cardiovascular Diagnosis and Therapy*, *7*(Suppl. 3), S267.

Hante, N. K., Medina, C., & Santos-Martinez, M. J. (2019). Effect on platelet function of metal-based nanoparticles developed for medical applications. *Frontiers in Cardiovascular Medicine*, *6*.

He, H., Adili, R., Liu, L., Hong, K., Holinstat, M., & Schwendeman, A. (2020). Synthetic high-density lipoproteins loaded with an antiplatelet drug for efficient inhibition of thrombosis in mice. *Science Advances*, *6*(49), eabd0130.

He, Y., Xu, J., Sun, X., Ren, X., Maharjan, A., York, P., et al. (2019). Cuboidal tethered cyclodextrin frameworks tailored for hemostasis and injured vessel targeting. *Theranostics.*, *9*(9), 2489.

Hecold, M., Buczkowska, R., Mucha, A., Grzesiak, J., Rac-Rumijowska, O., Teterycz, H., et al. (2017). The effect of PEI and PVP-stabilized gold nanoparticles on equine platelets activation: Potential application in equine regenerative medicine. *Journal of Nanomaterials*, *2017*.

Heeremans, J., Prevost, R., Bekkers, M., Los, P., EMEIS, L., Kluft, C., et al. (1995). Thrombolytic treatment with tissue-type plasminogen activator (t-PA) containing liposomes in rabbits: A comparison with free t-PA. *Liposomes in Thrombolytic Therapy*, 102.

Hoang Thi, T. T., Nguyen Tran, D.-H., Bach, L. G., Vu-Quang, H., Nguyen, D. C., Park, K. D., et al. (2019). Functional magnetic core-shell system-based iron oxide nanoparticle coated with biocompatible copolymer for anticancer drug delivery. *Pharmaceutics.*, *11*(3), 120.

Holzer, M., Bihari, P., Praetner, M., Uhl, B., Reichel, C., Fent, J., et al. (2014). Carbon-based nanomaterials accelerate arteriolar thrombus formation in the murine microcirculation independently of their shape. *Journal of Applied Toxicology*, *34*(11), 1167–1176.

Hsu, Sh, Tang, C. M., & Tseng, H. J. (2006). Biocompatibility of poly (ether) urethane-gold nanocomposites. *Journal of Biomedical Materials Research Part A*, *79*(4), 759–770.

Huang, H., Lai, W., Cui, M., Liang, L., Lin, Y., Fang, Q., et al. (2016). An evaluation of blood compatibility of silver nanoparticles. *Scientific Reports*, *6*(1), 1–15.

Ilinskaya, A. N., & Dobrovolskaia, M. A. (2013). Nanoparticles and the blood coagulation system. Part I: Benefits of nanotechnology. *Nanomedicine*, *8*(5), 773–784.

Ilinskaya, A. N., & Dobrovolskaia, M. A. (2016). *Nanoparticles and the blood coagulation system. Handbook of immunological properties of engineered nanomaterials: Volume 2: Haematocompatibility of engineered nanomaterials* (pp. 261–302). World Scientific.

Jiao, Y., Ubrich, N., Marchand-Arvier, M., Vigneron, C., Hoffman, M., Lecompte, T., et al. (2002). In vitro and in vivo evaluation of oral heparin−loaded polymeric nanoparticles in rabbits. *Circulation.*, *105*(2), 230−235.

Jiao, Y., Ubrich, N., Marchand-Arvier, M., Vigneron, C., Hoffman, M., & Maincent, P. (2001). Preparation and in vitro evaluation of heparin-loaded polymeric nanoparticles. *Drug Delivery*, *8*(3), 135−141.

Jones, C. F., Campbell, R. A., Franks, Z., Gibson, C. C., Thiagarajan, G., Vieira-de-Abreu, A., et al. (2012). Cationic PAMAM dendrimers disrupt key platelet functions. *Molecular Pharmaceutics*, *9*(6), 1599−1611.

Juliano, R., Hsu, M., Peterson, D., Regen, S., & Singh, A. (1983). Interactions of conventional or photopolymerized liposomes with platelets in vitro. *Experimental Cell Research*, *146*(2), 422−427.

Jun, E.-A., Lim, K.-M., Kim, K., Bae, O.-N., Noh, J.-Y., Chung, K.-H., et al. (2011). Silver nanoparticles enhance thrombus formation through increased platelet aggregation and procoagulant activity. *Nanotoxicology.*, *5*(2), 157−167.

Kim, Y., Hechler, B., Gao, Z.-G., Gachet, C., & Jacobson, K. A. (2009). PEGylated dendritic unimolecular micelles as versatile carriers for ligands of G protein-coupled receptors. *Bioconjugate Chemistry*, *20*(10), 1888−1898.

Kim, Y., Hechler, B., Klutz, A. M., Gachet, C., & Jacobson, K. A. (2008). Toward multivalent signaling across G protein-coupled receptors from poly (amidoamine) dendrimers. *Bioconjugate Chemistry*, *19*(2), 406−411.

Kleiman, N. S., Raizner, A. E., Jordan, R., Wang, A. L., Norton, D., Mace, K. F., et al. (1995). Differential inhibition of platelet aggregation induced by adenosine diphosphate or a thrombin receptor-activating peptide in patients treated with bolus chimeric 7E3 Fab: Implications for inhibition of the internal pool of GPIIb/IIIa receptors. *Journal of the American College of Cardiology*, *26*(7), 1665−1671.

Kou, L., Sun, J., Zhai, Y., & He, Z. (2013). The endocytosis and intracellular fate of nanomedicines: Implication for rational design. *Asian Journal of Pharmaceutical Sciences*, *8*(1), 1−10.

Koziara, J., Oh, J., Akers, W., Ferraris, S., & Mumper, R. (2005). Blood compatibility of cetyl alcohol/polysorbate-based nanoparticles. *Pharmaceutical Research*, *22*(11), 1821−1828.

Krajewski, S., Prucek, R., Panacek, A., Avci-Adali, M., Nolte, A., Straub, A., et al. (2013). Hemocompatibility evaluation of different silver nanoparticle concentrations employing a modified Chandler-loop in vitro assay on human blood. *Acta Biomaterialia*, *9*(7), 7460−7468.

Kumari, S., Singh, M. K., Singh, S. K., Grácio, J. J., & Dash, D. (2014). Nanodiamonds activate blood platelets and induce thromboembolism. *Nanomedicine.*, *9*(3), 427−440.

Kushida, T., Saha, K., Subramani, C., Nandwana, V., & Rotello, V. M. (2014). Effect of nano-scale curvature on the intrinsic blood coagulation system. *Nanoscale.*, *6*(23), 14484−14487.

Kwaan, H. C., & Samama, M. (2019). *Clinical thrombosis*. CRC Press.

Laloy, J., Minet, V., Alpan, L., Mullier, F., Beken, S., Toussaint, O., et al. (2014). Impact of silver nanoparticles on haemolysis, platelet function and coagulation. *Nanobiomedicine*, *1*, 4.

Le, N. T. T., Pham, L. P. T., Nguyen, D. H. T., Le, N. H., Tran, T. V., Nguyen, C. K., et al. (2019). Liposome-based nanocarrier system for phytoconstituents. *Novel Drug Delivery Systems for Phytoconstituents*, 45.

Le, V. T., Bach, L. G., Pham, T. T., Le, N. T. T., Ngoc, U. T. P., Tran, D.-H. N., et al. (2019). Synthesis and antifungal activity of chitosan-silver nanocomposite synergize fungicide against Phytophthora capsici. *Journal of Macromolecular Science, Part A*, *56*(6), 522−528.

Leach, J. K., Edgar, A., Patterson, E., Miao, Y., & Johnson, A. E. (2003). Accelerated thrombolysis in a rabbit model of carotid artery thrombosis with liposome-encapsulated and microencapsulated streptokinase. *Thrombosis and Haemostasis*, *90*(07), 64−70.

Li, X., Radomski, A., Corrigan, O. I., Tajber, L., De Sousa Menezes, F., Endter, S., et al. (2009). Platelet compatibility of PLGA, chitosan and PLGA−chitosan nanoparticles. *Nanomedicine.*, *4*(7), 735−746.

Liang, S., Sun, K., Wang, Y., Dong, S., Wang, C., Liu, L., et al. (2016). Role of Cyt-C/caspases-9, 3, Bax/Bcl-2 and the FAS death receptor pathway in apoptosis induced by zinc oxide nanoparticles in human aortic endothelial cells and the protective effect by alpha-lipoic acid. *Chemico-Biological Interactions*, *258*, 40−51.

Liu, F., Huang, H., Gong, Y., Li, J., Zhang, X., & Cao, Y. (2017). Evaluation of in vitro toxicity of polymeric micelles to human endothelial cells under different conditions. *Chemico-Biological Interactions*, *263*, 46−54.

Love, S. A., Thompson, J. W., & Haynes, C. L. (2012). Development of screening assays for nanoparticle toxicity assessment in human blood: Preliminary studies with charged Au nanoparticles. *Nanomedicine.*, *7*(9), 1355−1364.

Marrink, S. J., De Vries, A. H., & Mark, A. E. (2004). Coarse grained model for semiquantitative lipid simulations. *The Journal of Physical Chemistry B*, *108*(2), 750−760.

Martin, K., Ma, A. D. „ & Key, N. S. (2018). *Molecular basis of hemostatic and thrombotic diseases*. *Molecular pathology* (pp. 277−297). Elsevier.

Martínez-Gutierrez, F., Thi, E. P., Silverman, J. M., de Oliveira, C. C., Svensson, S. L., Hoek, A. V., et al. (2012). Antibacterial activity, inflammatory response, coagulation and cytotoxicity effects of silver nanoparticles. *Nanomedicine: Nanotechnology, Biology and Medicine*, *8*(3), 328−336.

Matus, M. F., Vilos, C., Cisterna, B. A., Fuentes, E., & Palomo, I. (2018). Nanotechnology and primary hemostasis: Differential effects of nanoparticles on platelet responses. *Vascular Pharmacology*, *101*, 1−8.

Matuszak, J., Baumgartner, J., Zaloga, J., Juenet, M., Da Silva, A. E., Franke, D., et al. (2016). Nanoparticles for intravascular applications: Physicochemical characterization and cytotoxicity testing. *Nanomedicine.*, *11*(6), 597−616.

Matzdorff, A., & Voss, R. (2006). Upregulation of GP IIb/IIIa receptors during platelet activation: Influence on efficacy of receptor blockade. *Thrombosis Research*, *117*(3), 307−314.

Mayer, A., Vadon, M., Rinner, B., Novak, A., Wintersteiger, R., & Fröhlich, E. (2009). The role of nanoparticle size in hemocompatibility. *Toxicology.*, *258*(2−3), 139−147.

McGuinnes, C., Duffin, R., Brown, S. ,L., Mills, N., Megson, I. L., MacNee, W., et al. (2011). Surface derivatization state of polystyrene latex nanoparticles determines both their potency and their mechanism of causing human platelet aggregation in vitro. *Toxicological Sciences*, *119*(2), 359−368.

Mehri, R., Mavriplis, C., & Fenech, M. (2018). Red blood cell aggregates and their effect on non-Newtonian blood viscosity at low hematocrit in a two-fluid low shear rate microfluidic system. *Plos One*, *13*(7), e0199911.

Meng, J., Cheng, X., Liu, J., Zhang, W., Li, X., Kong, H., et al. (2012). Effects of long and short carboxylated or aminated multiwalled carbon nanotubes on blood coagulation. *PLoS One*, *7*(7), e38995.

Miyamoto, M., Sasakawa, S., Ozawa, T., Kawaguchi, H., & Ohtsuka, Y. (1990). Mechanisms of blood coagulation induced by latex particles and the roles of blood cells. *Biomaterials*, *11*(6), 385−388.

Nabeshi, H., Yoshikawa, T., Matsuyama, K., Nakazato, Y., Arimori, A., Isobe, M., et al. (2012). Amorphous nanosilicas induce consumptive coagulopathy after systemic exposure. *Nanotechnology*, *23*(4), 045101.

Nemmar, A., Albarwani, S., Beegam, S., Yuvaraju, P., Yasin, J., Attoub, S., et al. (2014). Amorphous silica nanoparticles impair vascular homeostasis and induce systemic inflammation. *International Journal of Nanomedicine*, *9*, 2779.

Nemmar, A., Melghit, K., & Ali, B. H. (2008). The acute proinflammatory and prothrombotic effects of pulmonary exposure to rutile TiO_2 nanorods in rats. *Experimental Biology and Medicine*, *233*(5), 610−619.

Nguyen, D. H., Bach, L. G., Nguyen Tran, D.-H., Cao, V. D., Nguyen, T. N. Q., Le, T. T. H., et al. (2019). Partial surface modification of low generation polyamidoamine dendrimers: Gaining insight into their potential for improved carboplatin delivery. *Biomolecules*, *9*(6), 214.

Nguyen, P. D., O'rear, E., Johnson, A. E., Patterson, E., Whitsett, T. L., & Bhakta, R. (1990). Accelerated thrombolysis and reperfusion in a canine model of myocardial infarction by liposomal encapsulation of streptokinase. *Circulation Research*, *66*(3), 875−878.

Nguyen, T. D., Nguyen, T. T. T., Ivanov, I. A., Nguyen, K. C., Tran, Q. N., Hoang, A. N., et al. (2019). Nanoencapsulation enhances anticoagulant activity of adenosine and dipeptide IleTrp. *Nanomaterials*, *9*(9), 1191.

Nguyen, T. N. T., Nguyen-Tran, D.-H., Bach, L. G., Du Truong, T. H., Le, N. T. T., & Nguyen, D. H. (2019). Surface PEGylation of hollow mesoporous silica nanoparticles via aminated intermediate. *Progress in Natural Science: Materials International*, *29*(6), 612–616.

Nishikawa, T., Iwakiri, N., Kaneko, Y., Taguchi, A., Fukushima, K., Mori, H., et al. (2009). Nitric oxide release in human aortic endothelial cells mediated by delivery of amphiphilic polysiloxane nanoparticles to caveolae. *Biomacromolecules*, *10*(8), 2074–2085.

Oslakovic, C., Cedervall, T., Linse, S., & Dahlbäck, B. (2012). Polystyrene nanoparticles affecting blood coagulation. *Nanomedicine: Nanotechnology, Biology and Medicine*, *8*(6), 981–986.

Palta, S., Saroa, R., & Palta, A. (2014). Overview of the coagulation system. *Indian Journal of Anaesthesia*, *58*(5), 515.

Pan, D. C., Myerson, J. W., Brenner, J. S., Patel, P. N., Anselmo, A. C., Mitragotri, S., et al. (2018). Nanoparticle properties modulate their attachment and effect on carrier red blood cells. *Scientific Reports*, *8*(1), 1–12.

Paniccia, R., Priora, R., Liotta, A. A., & Abbate, R. (2015). Platelet function tests: A comparative review. *Vascular Health and Risk Management*, *11*, 133.

Peng, H. T. (2010). Thromboelastographic study of biomaterials. *Journal of Biomedical Materials Research Part B: Applied Biomaterials*, *94*(2), 469–485.

Radomski, A., Jurasz, P., Alonso-Escolano, D., Drews, M., Morandi, M., Malinski, T., et al. (2005). Nanoparticle-induced platelet aggregation and vascular thrombosis. *British Journal of Pharmacology*, *146*(6), 882–893.

Ragaseema, V., Unnikrishnan, S., Krishnan, V. K., & Krishnan, L. K. (2012). The antithrombotic and antimicrobial properties of PEG-protected silver nanoparticle coated surfaces. *Biomaterials*, *33*(11), 3083–3092.

Ramtoola, Z., Lyons, P., Keohane, K., Kerrigan, S. W., Kirby, B. P., & Kelly, J. G. (2011). Investigation of the interaction of biodegradable micro-and nanoparticulate drug delivery systems with platelets. *Journal of Pharmacy and Pharmacology*, *63*(1), 26–32.

Ran, Q., Xiang, Y., Liu, Y., Xiang, L., Li, F., Deng, X., et al. (2015). Eryptosis indices as a novel predictive parameter for biocompatibility of Fe_3O_4 magnetic nanoparticles on erythrocytes. *Scientific Reports*, *5*, 16209.

Reimhult, E. (2019). Nanoparticle interactions with blood proteins and what it means: A tutorial review. *Blood and Genomics*, *3*(2), 73–87.

Reinish, L., Bally, M., Loughrey, H., & Cullis, P. (1988). Interactions of liposomes and platelets. *Thrombosis and Haemostasis*, *59*(03), 518–523.

Reitsma, S., Slaaf, D. W., Vink, H., Van Zandvoort, M. A., & Oude Egbrink, M. G. (2007). The endothelial glycocalyx: Composition, functions, and visualization. *Pflügers Archiv: European Journal of Physiology*, *454*(3), 345–359.

Rumbaut, R. E., & Thiagarajan, P. (2010). Platelet-vessel wall interactions in hemostasis and thrombosis. *Synthesis Lectures on Integrated Systems Physiology: From Molecule to Function*, *2*(1), 1–75.

Saikia, J., Mohammadpour, R., Yazdimamaghani, M., Northrup, H., Hlady, V., & Ghandehari, H. (2018). Silica nanoparticle–endothelial *I*nteraction: Uptake and effect on platelet adhesion under flow conditions. *ACS Applied Bio Materials*, *1*(5), 1620–1627.

Santos-Martinez, M. J., Inkielewicz-Stepniak, I., Medina, C., Rahme, K., D'Arcy, D. M., Fox, D., et al. (2012). The use of quartz crystal microbalance with dissipation (QCM-D) for studying nanoparticle-induced platelet aggregation. *International Journal of Nanomedicine*, *7*, 243.

Santos-Martinez, M. J., Rahme, K., Corbalan, J. J., Faulkner, C., Holmes, J. D., Tajber, L., et al. (2014). Pegylation increases platelet biocompatibility of gold nanoparticles. *Journal of Biomedical Nanotechnology*, *10*(6), 1004–1015.

Santos-Martinez, M. J., Tomaszewski, K. A., Medina, C., Bazou, D., Gilmer, J. F., & Radomski, M. W. (2015). Pharmacological characterization of nanoparticle-induced platelet microaggregation using quartz

crystal microbalance with dissipation: Comparison with light aggregometry. *International Journal of Nanomedicine*, *10*, 5107.

Semberova, J., De Paoli Lacerda, S. H., Simakova, O., Holada, K., Gelderman, M. P., & Simak, J. (2009). Carbon nanotubes activate blood platelets by inducing extracellular Ca^{2+} influx sensitive to calcium entry inhibitors. *Nano Letters*, *9*(9), 3312–3317.

Setyawati, M. I., Tay, C. Y., Docter, D., Stauber, R. H., & Leong, D. T. (2015). Understanding and exploiting nanoparticles' intimacy with the blood vessel and blood. *Chemical Society Reviews*, *44*(22), 8174–8199.

Shafir, G., Galperin, A., & Margel, S. (2009). Synthesis and characterization of recombinant factor VIIa-conjugated magnetic iron oxide nanoparticles for hemophilia treatment. *Journal of Biomedical Materials Research Part A: An Official Journal of the Society for Biomaterials, the Japanese Society for Biomaterials, and the Australian Society for Biomaterials and the Korean Society for Biomaterials*, *91*(4), 1056–1064.

Shiang, Y. C., Hsu, C. L., Huang, C. C., & Chang, H. T. (2011). Gold nanoparticles presenting hybridized self-assembled aptamers that exhibit enhanced inhibition of thrombin. *Angewandte Chemie International Edition*, *50*(33), 7660–7665.

Shrivastava, S., Bera, T., Singh, S. K., Singh, G., Ramachandrarao, P., & Dash, D. (2009). Characterization of antiplatelet properties of silver nanoparticles. *ACS Nano*, *3*(6), 1357–1364.

Shrivastava, S., Singh, S. K., Mukhopadhyay, A., Sinha, A. S., Mandal, R. K., & Dash, D. (2011). Negative regulation of fibrin polymerization and clot formation by nanoparticles of silver. *Colloids and Surfaces B: Biointerfaces*, *82*(1), 241–246.

Simak, J. (2016). *The effects of engineered nanomaterials on the plasma coagulation system*. *Handbook of immunological properties of engineered nanomaterials: Volume 2: Haematocompatibility of engineered nanomaterials* (pp. 163–192). World Scientific.

Simak, J., & De Paoli, S. (2017). The effects of nanomaterials on blood coagulation in hemostasis and thrombosis. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, *9*(5), e1448.

Sims, P. J., Ginsberg, M., Plow, E., & Shattil, S. (1991). Effect of platelet activation on the conformation of the plasma membrane glycoprotein IIb-IIIa complex. *Journal of Biological Chemistry*, *266*(12), 7345–7352.

Šimundić, M., Drašler, B., Šuštar, V., Zupanc, J., Štukelj, R., Makovec, D., et al. (2013). Effect of engineered TiO_2 and ZnO nanoparticles on erythrocytes, platelet-rich plasma and giant unilamelar phospholipid vesicles. *BMC Veterinary Research*, *9*(1), 7.

Singh, S. K., Singh, M. K., Kulkarni, P. P., Sonkar, V. K., Grácio, J. J., & Dash, D. (2012). Amine-modified graphene: Thrombo-protective safer alternative to graphene oxide for biomedical applications. *ACS Nano*, *6*(3), 2731–2740.

Singh, S. K., Singh, M. K., Nayak, M. K., Kumari, S., Shrivastava, S., Grácio, J. J., et al. (2011). Thrombus inducing property of atomically thin graphene oxide sheets. *ACS Nano*, *5*(6), 4987–4996.

Smyth, E., Solomon, A., Vydyanath, A., Luther, P. K., Pitchford, S., Tetley, T. D., et al. (2015). Induction and enhancement of platelet aggregation in vitro and in vivo by model polystyrene nanoparticles. *Nanotoxicology.*, *9*(3), 356–364.

Sobot, D., Mura, S., Couvreur, P., Kobayashi, S., & Müllen, K. (2014). *Nanoparticles: Blood components interactions*. *Encyclopedia of polymeric nanomaterials* (pp. 1–10). Berlin, Heidelberg: Springer.

Sperling, C., Maitz, M., & Werner, C. (2018). *Test methods for hemocompatibility of biomaterials*. *Hemocompatibility of biomaterials for clinical applications* (pp. 77–104). Elsevier.

Sriram, K., Intaglietta, M., & Tartakovsky, D. M. (2014). Non-Newtonian flow of blood in arterioles: Consequences for wall shear stress measurements. *Microcirculation.*, *21*(7), 628–639.

Stevens, K. N., Knetsch, M. L., Sen, A., Sambhy, V., & Koole, L. H. (2009). Disruption and activation of blood platelets in contact with an antimicrobial composite coating consisting of a pyridinium polymer and AgBr nanoparticles. *ACS Applied Materials & Interfaces*, *1*(9), 2049–2054.

Strojan, K., Leonardi, A., Bregar, V. B., Križaj, I., Svete, J., & Pavlin, M. (2017). Dispersion of nanoparticles in different media importantly determines the composition of their protein corona. *PLoS One*, *12*(1), e0169552.

Su, M., Dai, Q., Chen, C., Zeng, Y., Chu, C., & Liu, G. (2020). Nano-medicine for thrombosis: A precise diagnosis and treatment strategy. *Nano-Micro Letters*, *12*, 1−21.

Su, Y., Zhao, L., Meng, F., Wang, Q., Yao, Y., & Luo, J. (2017). Silver nanoparticles decorated lipase-sensitive polyurethane micelles for on-demand release of silver nanoparticles. *Colloids and Surfaces B: Biointerfaces*, *152*, 238−244.

Sun, P., McMillan-Ward, E., Mian, R., & Israels, S. J. (2019). Comparison of light transmission aggregometry and multiple electrode aggregometry for the evaluation of patients with mucocutaneous bleeding. *International Journal of Laboratory Hematology*, *41*(1), 133−140.

Sun, X., Shi, J., Zou, X., Wang, C., Yang, Y., & Zhang, H. (2016). Silver nanoparticles interact with the cell membrane and increase endothelial permeability by promoting VE-cadherin internalization. *Journal of Hazardous Materials*, *317*, 570−578.

Tankersley, D. L., Alving, B. M., & Finlayson, J. S. (1983). Activation of factor XII by dextran sulfate: The basis for an assay of factor XII. *Blood.*, *62*(2), 448−456.

Tavano, R., Segat, D., Reddi, E., Kos, J., Rojnik, M., Kocbek, P., et al. (2010). Procoagulant properties of bare and highly PEGylated vinyl-modified silica nanoparticles. *Nanomedicine.*, *5*(6), 881−896.

Thi, T. T. H., Nguyen, D. H. T., Nguyen, D. T. D., Nguyen, D. H., & Truong, M.-D. (2020). Decellularized porcine epiphyseal plate-derived extracellular matrix powder: Synthesis and characterization. *Cells Tissues Organs*, *209*(1), 1−9.

Tran, D. H. N., Nguyen, T. H., Vo, T. N. N., Pham, L. P. T., Vo, D. M. H., Nguyen, C. K., et al. (2019). Self-assembled poly (ethylene glycol) methyl ether-grafted gelatin nanogels for efficient delivery of curcumin in cancer treatment. *Journal of Applied Polymer Science*, *136*(20), 47544.

Tran, H. D., Park, K. D., Ching, Y. C., Huynh, C., & Nguyen, D. H. (2020). A comprehensive review on polymeric hydrogel and its composite: Matrices of choice for bone and cartilage tissue engineering. *Journal of Industrial and Engineering Chemistry*.

Vakhrusheva, T. V., Gusev, A. A., & Gusev, S. A. (2013). Vlasova II. Albumin reduces thrombogenic potential of single-walled carbon nanotubes. *Toxicology Letters*, *221*(2), 137−145.

van der Graaf, F., Keus, F. J., Vlooswijk, R. A., & Bouma, B. N. (1982). The contact activation mechanism in human plasma: Activation induced by dextran sulfate. *Blood*, *59*(6), 1225−1233.

Villegas, M. G., Ceballos, M. T., Urquijo, J., Torres, E. Y., Ortiz-Reyes, B. L., Arnache-Olmos, O. L., et al. (2019). Poly (acrylic acid)-coated iron oxide nanoparticles interact with mononuclear phagocytes and decrease platelet aggregation. *Cellular Immunology*, *338*, 51−62.

Walton, B. L., Lehmann, M., Skorczewski, T., Holle, L. A., Beckman, J. D., Cribb, J. A., et al. (2017). Elevated hematocrit enhances platelet accumulation following vascular injury. *Blood, The Journal of the American Society of Hematology*, *129*(18), 2537−2546.

Weisel, J., & Litvinov, R. (2019). Red blood cells: The forgotten player in hemostasis and thrombosis. *Journal of Thrombosis and Haemostasis*, *17*(2), 271−282.

Wiggins, R. C., & Cochrane, C. C. (1979). The autoactivation of rabbit Hageman factor. *The Journal of Experimental Medicine*, *150*(5), 1122−1133.

Wu, H., Su, M., Jin, H., Li, X., Wang, P., Chen, J., et al. (2020). Rutin-loaded silver nanoparticles with antithrombotic function. *Frontiers in Bioengineering and Biotechnology*, *8*, 1356.

Wu, Y.-F., Hsu, P.-S., Tsai, C.-S., Pan, P.-C., & Chen, Y.-L. (2018). Significantly increased low shear rate viscosity, blood elastic modulus, and RBC aggregation in adults following cardiac surgery. *Scientific Reports*, *8*(1), 1−10.

Yau, J. W., Teoh, H., & Verma, S. (2015). Endothelial cell control of thrombosis. *BMC Cardiovascular Disorders*, *15*(1), 1−11.

Yedgar, S., Koshkaryev, A., & Barshtein, G. (2002). The red blood cell in vascular occlusion. *Pathophysiology of Haemostasis and Thrombosis*, *32*(5−6), 263−268.

Yoshida, T., Yoshioka, Y., Tochigi, S., Hirai, T., Uji, M., Ichihashi, K.-I., et al. (2013). Intranasal exposure to amorphous nanosilica particles could activate intrinsic coagulation cascade and platelets in mice. *Particle and Fibre Toxicology*, *10*(1), 1−12.

Yu, M., Huang, S., Yu, K. J., & Clyne, A. M. (2012). Dextran and polymer polyethylene glycol (PEG) coating reduce both 5 and 30 nm iron oxide nanoparticle cytotoxicity in 2D and 3D cell culture. *International Journal of Molecular Sciences*, *13*(5), 5554−5570.

Zamanlu, M., Eskandani, M., Barar, J., Jaymand, M., Pakchin, P. S., & Farhoudi, M. (2019). Enhanced thrombolysis using tissue plasminogen activator (tPA)-loaded PEGylated PLGA nanoparticles for ischemic stroke. *Journal of Drug Delivery Science and Technology*, *53*, 101165.

Zbinden, G., Wunderli-Allenspach, H., & Grimm, L. (1989). Assessment of thrombogenic potential of liposomes. *Toxicology.*, *54*(3), 273−280.

Zhang, Y., Cai, J., Li, C., Wei, J., Liu, Z., & Xue, W. (2016). Effects of thermosensitive poly (N-isopropylacrylamide) on blood coagulation. *Journal of Materials Chemistry B.*, *4*(21), 3733−3749.

Zhao, W., Liu, Q., Zhang, X., Su, B., & Zhao, C. (2018). Rationally designed magnetic nanoparticles as anticoagulants for blood purification. *Colloids and Surfaces B: Biointerfaces*, *164*, 316−323.