Chapter 19
Blood Interactions with Nanoparticles During Systemic Delivery

Wing-Fu Lai, Eric M. Huang, and Wing-Tak Wong

Abstract In the preceding chapter, different physiological, chemical, and biochemical barriers in systemic drug delivery have been introduced. In this chapter, we will talk about the interactions between nanoparticles and blood components, and will delineate strategies to enhance the compatibility of the nanoparticles in blood. In fact, in order to achieve systemic delivery, blood circulation plays an important role because it is the blood that helps deliver the therapeutics to tissues bodywide. A good understanding of the interactions between nanoparticles and various components in blood is, therefore, pivotal to proper design of nanoparticulate systems as effective systemic carriers. The objective of this chapter is to introduce the methods of manipulating the pharmacokinetics and biodistribution of nanoparticulate systems by manipulating the interactions between nanoparticles and blood components during systemic delivery. Strategies to improve the hematocompatibility of the nanoparticulate systems will also be discussed for enhancing the use of the carriers in practical interventions at the preclinical and clinical levels.

Keywords Hematocompatibility · Hemolysis · Systemic administration · Complement activation · Thrombogenicity

19.1 Introduction

Over the years, several routes of drug delivery using nanoparticulate systems have been examined, ranging from intratracheal instillation and intratissue injection to intravenous administration. Among them, systemic delivery is the most challenging

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one. This is because when a carrier is administered intravenously, the clearance by the reticuloendothelial systems (RES) and the interactions with diverse blood components will diminish the chance of the carrier to reach tissues for action. Despite this, systemic delivery has its unique merits, including higher **bioavailability**, a higher rate of drug absorption, and a lower chance of removal by the first-pass metabolism in the liver. In addition, to tackle or ameliorate bodywide symptoms (e.g., chromosomal abnormalities and cellular aging), systemic delivery is the only choice.

In fact, systemic drug delivery has been adopted in different studies on disease treatment, and various levels of success have been achieved. For example, dystrophin expression has been restored bodywide in skeletal muscles of the dystrophic *mdx* mouse, with significant improvement in muscle function observed, after intravenous administration of morpholino phosphorodiamidate antisense oligonucleotides (AONs) on a weekly basis (Alter et al. 2006). Upon systemic administration of nanoparticles synthesized by using the three-way junction (3WJ) motif derived from bacteriophage phi29 packaging RNA (pRNA) as a scaffold harboring various functional motifs (including therapeutic anti-miRNA, Alexa647 as a fluorescent imaging module, and an epidermal growth factor receptor-targeting RNA aptamer as a targeting ligand), accumulation in tumor tissues and the onset of miRNA knockdown have been observed in orthotopic triple-negative breast cancer (TNBC) tumor-bearing mice (Shu et al. 2015). More recently, by using lipid nanoparticles for systemic delivery of factor IX mRNA, protein replacement therapy has been executed in a Factor IX (FIX)-deficient mouse model of hemophilia B (Ramaswamy et al. 2017). All these have demonstrated the versatility and technical feasibility of systemic delivery of therapeutics using various nanoparticulate systems as carriers.

19.2 Roles of Nanoparticulate Systems in Systemic Delivery

Our current understanding of the fate of an exogenous agent upon administration into a body is based on the absorption, distribution, metabolism, and excretion (ADME) concept (Fig. 19.1) (Markovsky et al. 2012). In general, upon intravenous injection, the first tissue that will be encountered by the nanoparticle is blood, which contains both acellular and cellular portions. The former comprises the plasma (in which over 90% is water) and various biomolecules; whereas the cellular portion consists of erythrocytes, leukocytes, lymphocytes, and platelets. Both the acellular and cellular portions may interact with the surface of the nanoparticle. This constitutes the so-called "synthetic identity" and "biological identity" of the nanoparticle, which denote the surface characteristics of the nanoparticle before and after exposure to serum (Albanese et al. 2014). Through the blood flow, the carrier will be transported to the heart through the right ventricle (Fig. 19.2) (Bertrand and Leroux 2012). After that, it will enter the pulmonary circulation. Due to their small diameter (around 2–13 μm), lung capillaries form the first sieving constraint for drug carriers (Bertrand and Leroux 2012). In general, rigid nanoparticles with a diameter of 10 μm will be

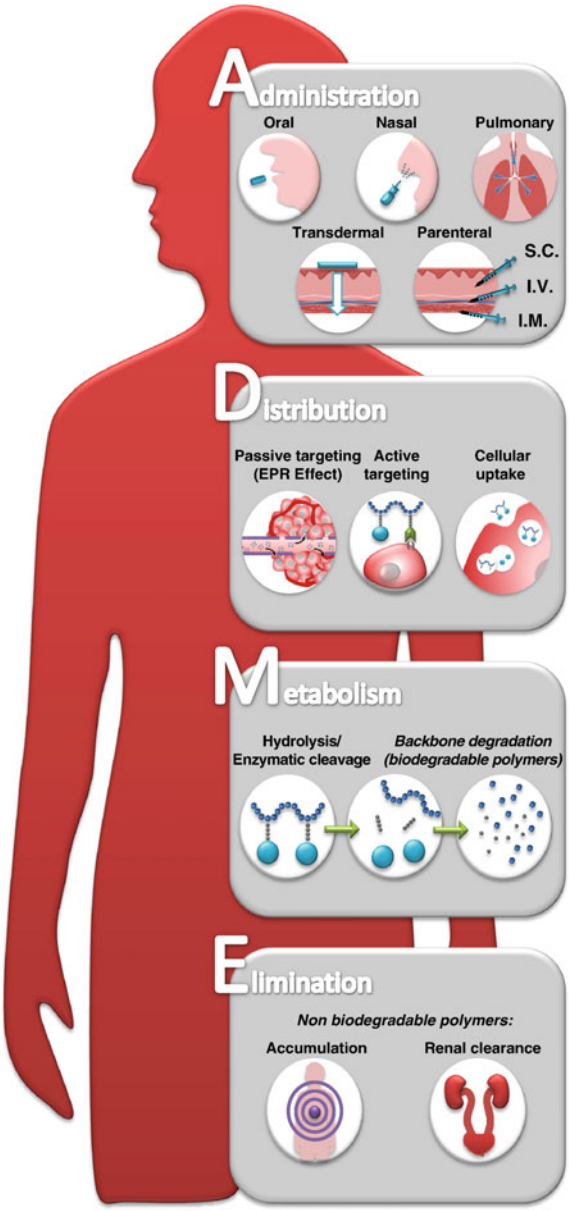

Fig. 19.1 The ADME concept. Reproduced from Markovsky et al. (2012) with permission from Elsevier B.V.

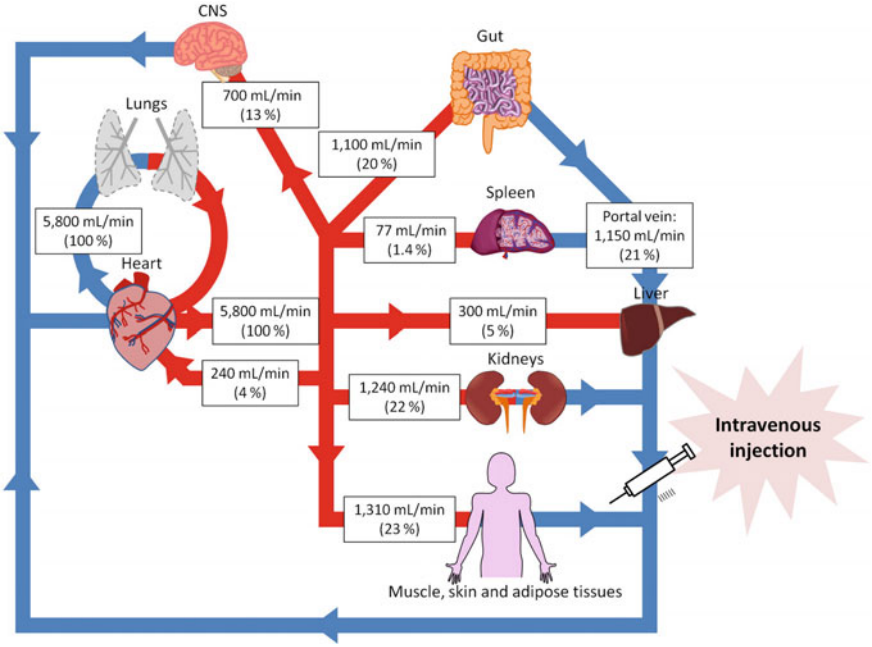

Fig. 19.2 Distribution of the blood flow in the systemic and pulmonary circulation. The percentage of the total blood flow is shown in parentheses in each organ. Abbreviation: CNS, central nervous system. Reproduced from Bertrand and Leroux (2012) with permission from Elsevier B.V.

permanently trapped inside lung capillaries (Kutscher et al. 2010); whereas those with a diameter less than 3 μm can escape from pulmonary retention (Kutscher et al. 2010). For those with a diameter of 3–6 μm, they may be initially trapped but can escape at the end (Kutscher et al. 2010). Due to the small diameter of lung capillaries, pulmonary retention has been exploited for systemic delivery of mRNA, which is complexed with polymer-lipid nanoparticles generated from poly(β-amino esters) and lipid-PEG, to the lung (Kaczmarek et al. 2016); however, in general, pulmonary retention is not desired. Proper control of the nanoparticle size, therefore, plays an important role. Those particles that successfully escape from pulmonary retention can return to the heart through the left ventricle, and enter the systemic circulation.

In addition, when a hydrophilic drug is administrated intravenously into a body, the drug can be eliminated easily via renal excretion. On the contrary, if the drug is more hydrophobic in nature, the extent of serum protein binding experienced by the drug will be increased. This may reduce the rate of renal clearance in the beginning; however, a hydrophobic drug can often be metabolized in the liver to enhance hydrophilicity, and at the end be excreted either into bile or into urine before it can effectively get into tissues bodywide. Because of this, systemic delivery of a free drug is generally difficult. This problem can be partially tackled by using nanoparticles, which may increase the molecular size to reduce the rate of renal clearance (whose

cutoff size has been estimated to be around 5.5 nm by using quantum dots (Choi et al.)) and may also protect the drug from attack by metabolizing enzymes in the liver. In addition, while bodywide distribution of a drug is desired when systemic aging symptoms (e.g., **telomere** shortening and cell senescence) are tackled, treatment of more localized age-associated diseases (e.g., Parkinson's diseases and primary tumors) may necessitate more localized accumulation of a drug to specific tissues so as to obtain enhanced therapeutic effects and to avoid unnecessary systemic toxicity. By changing the physical properties (including size and **zeta potential**) and surface chemistry of a drug, the use of nanoparticles can help manipulate the pharmacokinetic (PK) profiles of the parent drug to achieve the desired profile of tissue distribution.

While small-molecule compounds can easily diffuse through the capillary wall and get into tissues for action, nanoparticulate systems, owing to its bigger size, usually have to make use of the intercellular pores in the endothelium for getting into tissues. The pore size of the endothelial wall, therefore, becomes one of the barriers to the accumulation of the carrier in tissues. This explains the occurrence of passive targeting of a carrier to tumor tissues via the **enhanced permeability and retention (EPR) effect**. Apart from tumor tissues, a carrier may tend to accumulate in the liver, spleen, and bone marrow. This is because these tissues contain a large amount of macrophages, which can capture particulates and macromolecules in blood. Upon intravenous administration of a carrier, the carrier surface is subjected to **opsonization** and subsequently is recognized by the scavenger receptor on the macrophage for internalization. Minimizing opsonization is required if the development of a carrier for effective bodywide distribution is needed.

19.3 Manipulation of Pharmacokinetics and Biodistribution

The success of manipulation of the pharmacokinetics and biodistribution of a carrier can be examined by determining the concentration of a drug in all major tissues from the time of drug administration until the elimination phase. Based on the pharmacokinetic (PK) profile, various parameters can be calculated to quantitatively describe the way the drug or the nanoparticle is processed in a body. Examples of these parameters include the half-life ($t_{1/2}$), maximum concentration ($C_{\max}$), clearance (Cl), mean resident time (MRT), and the area under the curve (AUC). Successful enhancement of a drug carrier for blood retention is usually manifested by an increase in AUC, MRT, and $t_{1/2}$, as well as a decrease in Cl. Apart from determining the efficiency of a strategy for enhancing a drug carrier for blood retention, PK parameters can help optimize the dose and dose regimen during the execution of an anti-aging intervention so that the therapeutic agent can stay in the blood circulation long enough for therapeutic effects to manifest while having minimal side effects.

To alter the PK and biodistribution profiles of a carrier, several properties of the carrier can be modulated. One important property is the particle size. For instance, by using a mesoporous silica (MS) templating method, the size of poly(ethylene glycol) (PEG) hydrogel particles has been successfully controlled. During particle fabrication, mesoporous silica particles with different average diameters (viz., 1000, 500, 280, and 110 nm) are first constructed as templates (Cui et al. 2015). 8-arm-PEG-NH_2 with a hexaglycerol core structure is then infiltrated into the mesoporous silica particles, followed by crosslinking between 8-arm-PEG-NH_2 and succinimidyl carboxyl methyl ester-functionalized 8-arm-PEG (Cui et al. 2015). Upon the dissolution of the templates and the incorporation of Alexa Fluor 488 carboxylic acid succinimidyl ester (AF488) into the PEG particles for fluorescence visualization, PEG particles, denoted as PEG40-1000, PEG40-500, PEG40-280, and PEG40-110, are successfully generated from mesoporous silica particles with an average diameter of 1000, 500, 280, and 110 nm, respectively (Fig. 19.3) (Cui et al. 2015). An ex vivo assay using human whole blood reveals that an increase in the PEG molecular weight, or a decrease in the PEG particle size, can reduce the association of the PEG particles with phagocytic blood cells (Cui et al. 2015). This is consistent with the observation in vivo, in which PEG particles with a smaller size (150 nm) have been found to be more effective in blood retention than the larger counterparts (>400 nm) (Cui et al. 2015).

Another important factor to be tuned is the surface properties. One example is the surface charge, whose effect on biodistribution has been demonstrated by a previous study (Arvizo et al. 2011), which examined the PK and biodistribution profiles of four types of gold nanoparticles that display different surface charges (neutral, positive, negative, and zwitterionic). Results showed that, upon intravenous and intraperitoneal administration, neutral and zwitterionic nanoparticles exhibit longer blood circulation time and more effective tumor uptake, whereas those having a negative or positive surface charge show shorter half-lives. The surface chemistry of a carrier can affect the profile of biodistribution, too. This factor, however, can be easily manipulated by both chemical and engineering methods. One example of the latter is the layer-by-layer (LbL) assembly approach, which has previously been adopted to generate electrostatically assembled nanoparticles for systemic delivery. By using carboxyl functionalized gold nanoparticles or carboxyl functionalized quantum dots as cores (with polylysine, dextran sulfate, and hyaluronic acid for layer deposition), an increase in the number of deposited layers has been found to lead to an increase in in vivo stability (Poon et al. 2011). In addition, the outermost deposited layer has been demonstrated to form a critical surface cascade, affecting not only the degree of non-specific particle uptake but also the ultimate tissue distribution profile (Poon et al. 2011).

Apart from the aforementioned factors, the shape of a carrier should be carefully designed in order to obtain the desired bodywide distribution. This is revealed by the difference in biodistribution experienced by fluorescent mesoporous silica nanoparticles (MSNs) (Huang et al. 2011a). While intravenously administrated short-rod MSNs predominately accumulate in the liver in mice, long-rod MSNs localize largely in the spleen (Huang et al. 2011a). In addition, short-rod MSNs are found to be more susceptible to be removed by renal and fecal excretion when compared with the

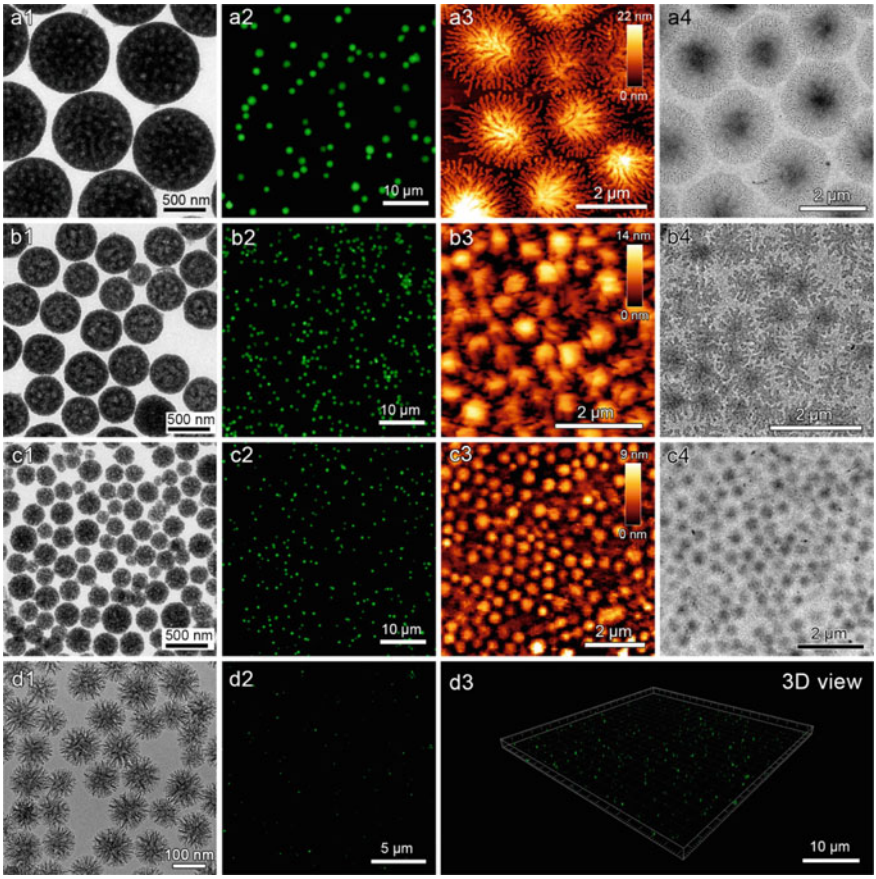

Fig. 19.3 Transmission electron microscopy (TEM) images of the mesoporous silica particles with different average diameters: **a1** 1000 nm, **b1** 500 nm, **c1** 280 nm, and **d1** 110 nm. Fluorescence microscopy images of different AF488-labeled PEG particles: **a2** PEG40-1000, **b2** PEG40-500, **c2** PEG40-280, and **d2**, **d3** PEG40-110. **a3**–**c3** Atomic force microscopy images and **a4**–**c4** TEM images of different PEG particles: **a3**, **a4** PEG40-1000, **b3**, **b4** PEG40-500, and **c3**, **c4** PEG40-280. Reproduced from Cui et al. (2015) with permission from American Chemical Society

long-rod counterparts (Huang et al. 2011a). Recently, the shape effect on biodistribution has been further corroborated by using magnetic mesoporous silica (MS) nanoparticles, which have been generated with different shapes and have been labeled with fluorescein isothiocyanate (FITC) for fluorescence monitoring (Fig. 19.4) (Shao et al. 2017). The spherical nanoparticles with a diameter of 200 nm are denoted as M-MSNP0, whereas those rod-shaped cylinders with dimensions of 200–250/120–150 nm and 400–450/120–150 nm are denoted as M-MSNP1 and M-MSNP2, respectively. Upon intravenous administration to tumor bearing mice, M-MSNP2 has been found to be most effectively deposited in the spleen and tumor (Shao et al. 2017),

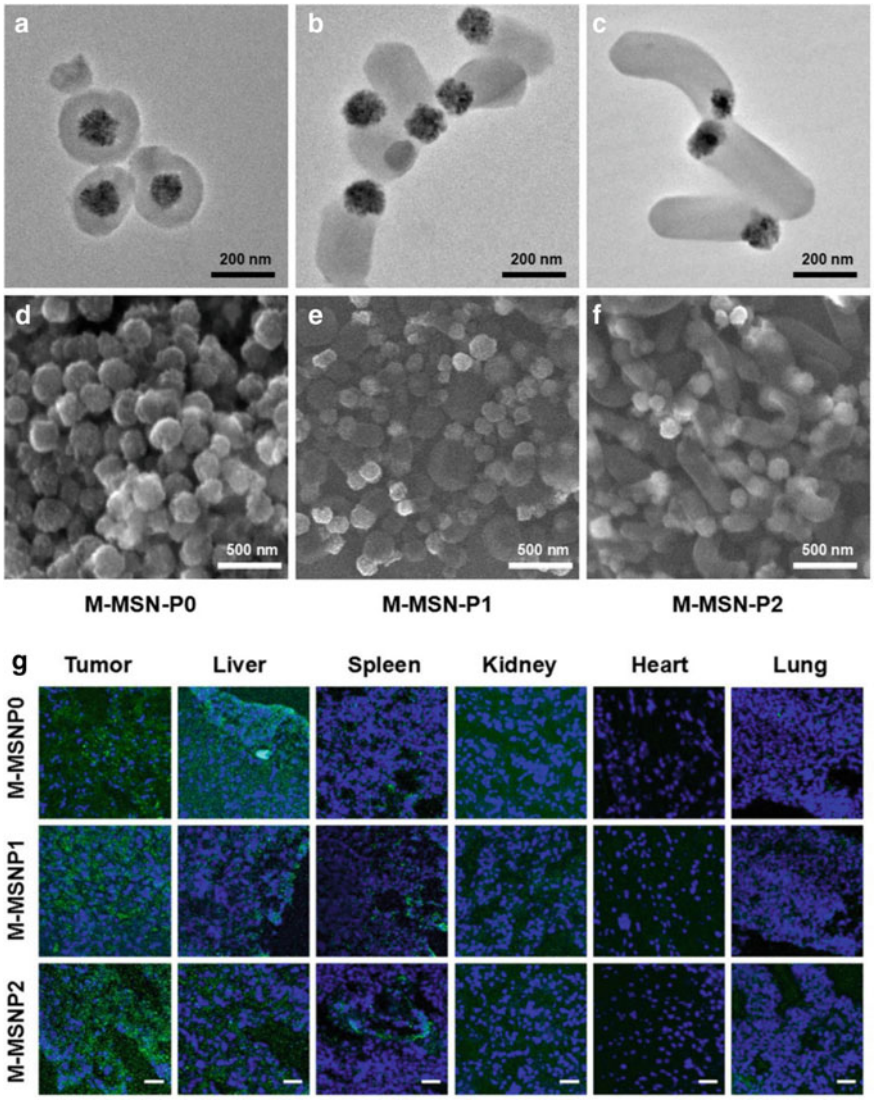

Fig. 19.4 **a**–**c** TEM and **d**–**f** SEM images of different magnetic MS nanoparticles: **a**, **d** M-MSNP0, **b**, **e** M-MSNP1, and **c**, **f** M-MSNP2. Scale bars in **a**–**c** represent 200 nm; whereas those in **d**–**f** represent 500 nm. **g** Confocal microscopy images of tissue sections taken from different tissues of HepG2 tumor-bearing mice 3 h after intravenous administration of FITC-labeled magnetic MS nanoparticles. Scale bars represent 100 μm. Reproduced from Shao et al. (2017) with permission from Elsevier B.V.

whereas M-MSNP0 has accumulated at a much higher level than those rod-like counterparts in the liver (Shao et al. 2017).

Finally, the number of times of drug administration may affect the PK profile. This is revealed by Dams and coworkers (2000), who have studied the pharmacokinetics and biodistribution of repeated injections of radiolabeled PEGylated liposomes. They have observed that, 4 h after the second dose in rats, a significant reduction in the blood content (from 52.6 ± 3.7 to $0.6 \pm 0.1\%$ injected dose, $P < 0.01$) occurs (Dams et al. 2000). Such reduction is accompanied by a dramatic increase in the uptake of the liposomes in the liver (from 8.1 ± 0.8 to $46.2 \pm 9.8\%$ injected dose, $P < 0.01$) and in the spleen (from 2.2 ± 0.2 to $5.3 \pm 0.7\%$ injected dose, $P < 0.01$). Similar observations have been found in rhesus monkeys (Dams et al. 2000). This suggests that previous administration of a carrier may lead to changes in the PK behavior of subsequently injected doses in time- and frequency-dependent manners. Because aging is a progressive process and tackling it requires repeated administration of an intervention, the impact of repeated administration on the PK profile, and hence on the efficiency of a biogerontological intervention, is a problem that shall be solved for future anti-aging medicine.

19.4 Enhancement of Hematocompatibility for Systemic Delivery

Because the extension of the blood retention time is one of the important tasks to be achieved during the development of a systemic drug carrier, the **hematocompatibility** of a carrier has to be seriously considered. This compatibility can be partially enhanced by modulating the effect of the carrier on **hemolysis** (Dobrovolskaia et al. 2008). Changes in hemolytic properties can be achieved by optimizing the surface properties (especially surface charge) of the carrier. This has been revealed in dendrimers generated from polypropylene imine (PPI) (Dutta et al. 2007; Agashe et al. 2006), polylysine (PLL) (Shah et al. 2000), carbosilane (Bermejo et al. 2007), and polyamidoamine (PAMAM) (Domanski et al. 2004). The presence of unprotected primary amines on the surface of these dendrimers has been found to lead to erythrocyte damage in a dose-dependent manner; whereas blocking of those primary amines has successfully reduced **hematotoxicity**. In addition to hemolysis, the extent of complement activation induced by a carrier largely affects hematocompatibility. Complement activation by a systemically administered carrier cannot only lead to rapid clearance of the carrier from blood circulation and hence failure of bodywide biodistribution, but may also result in life-threatening conditions such as hypersensitivity reactions and anaphylaxis. The latter is supported by a clinical study (Chanan-Khan et al. 2003), which has confirmed that the observed hypersensitivity led by PEGylated liposomal doxorubicin (Doxil) is mediated largely by complement activation. For this, unlike the case of vaccination in which local complement activation may be needed for enhanced antigen presentation to boost the vaccine

efficacy, complement activation by a carrier is not desired during systemic interventions. The surface charge of a carrier is one of the factors determining the extent of complement activation. As suggested by various systems (including polystyrene nanospheres (Nagayama et al. 2007), lipid nanocapsules (Vonarbourg et al. 2006), polypropylene sulfide nanoparticles (Reddy et al. 2007), and cyclodextrin-containing polycation-based nanoparticles (Bartlett and Davis 2007)), charged nanoparticles are generally more effective than the neutral counterparts in inducing complement activation. In addition, the choice and structure of the coating material can affect the capacity of the carrier to activate the complement system. For instance, while the presence of a PEG coating or a poloxamine 908 coating can reduce the activation of the complement system (Al-Hanbali et al. 2006; Vonarbourg et al. 2006), the incorporation of a dextran coating may lead to an increase in complement activation (Bertholon et al. 2006), whose extent increases with the coating thickness (Bertholon et al. 2006). Further studies are required to determine the relationship between the properties (including the thickness, density, and structure) of the polymer coating and the extent of complement activation.

Last but not least, **thrombogenicity** significantly governs the hematocompatibility of a carrier. This factor is especially important when a systemic carrier is developed. This is because when a carrier is used for systemic delivery, extended blood circulation time is required. In this case, the interaction of the carrier with components of the coagulation system will be long too. This may activate the coagulation cascade, leading to blood clotting and the occlusion of a blood vessel by thrombus. Thrombogenicity of a carrier can possibly be modulated by changing the surface properties of a carrier. This has been shown by the case of cetyl alcohol/polysorbate-based nanoparticles, in which the extent of platelet aggregation is reduced upon the incorporation of a PEG coating (Koziara et al. 2005). However, at the moment the association between the surface properties of a carrier to thrombogenicity is poorly understood. Apart from manipulating the carrier per se, co-administration of the carrier with anticoagulants may be a feasible method of reducing platelet aggregation. However, a recent study has observed that while micron-sized carbon particles require protein kinase C (PKC) for the upregulation of the glycoprotein integrin receptor GPIIb/IIIa to induce platelet aggregation (Radomski et al. 2005), carbon nanoparticles can induce integrin receptor activation in a PKC-independent manner (Radomski et al. 2005). This implies that platelet aggregation may be induced via multiple pathways, and the use of common anticoagulants may not necessarily be effective. To enhance the effectiveness of systemic delivery, elucidation of the exact mechanism underlying platelet aggregation induced by nanoparticulate systems is in dire need.

19.5 Other Factors to be Considered for Intervention Execution

Apart from the issues mentioned above, there are other technical factors to be considered during intervention execution. One is the route of administration. Oral/intranasal administration is usually not an option for many diseases such as cancer whose target site is not readily accessible by the oral and intranasal routes (Tatiparti et al. 2017). In addition, these routes may be associated with other issues such as enzymatic degradation in the intestine (Allemann et al. 1998; Bernkop-Schnurch and Krajicek 1998), mucociliary clearance in the nasal epithelium (Brime et al. 2000), and insufficient permeability across the intestinal epithelium into the systemic circulation (Haussecker 2014). Another option is subcutaneous injection which has the advantage of bypassing the first-pass effect of the liver and accessing to the circulation through capillaries or lymphatic drainage from interstitial space (Tatiparti et al. 2017). Nevertheless, the hydrophobicity and particle size of some drug carriers may trigger phagocytosis by the immune system (Tatiparti et al. 2017). Hitherto, intravenous injection is the most common method for systemic administration. In addition, as the administered agents are able to be passively delivered to tissues with an irregular fenestration (such as the bone marrow, liver, and spleen) (Lungwitz et al. 2005; Lai 2011), intravenous injection is suitable for treatments of localized diseases like primary cancer. Other administration means such as buccal/sublingual, pulmonary, and transdermal routes suffer from similar limitations mentioned above (e.g., compromised stability, immune response, etc.), leading to a dose loss issue. However, increasing the dose might not be an appropriate solution, as the additional dose required to compensate the dose loss might be too high to be practically applicable and safe, especially when a viral delivery system is used.

Crossing the vascular barrier is a crucial step for drug delivery to reach the target tissues, too. The most important feature determining the success of delivery within the vasculature is particle size (Tatiparti et al. 2017). Liver generally allows the entrance of particles with a size below 100 nm (Fang et al. 2011). In case of tumor tissues, carriers should be made in a smaller size as the capillaries have smaller pores (60–80 nm) and the endothelium there is covered with the continuous basal lamina which prevents the diffusion of larger nanoparticles (Wang et al. 2016; Kobayashi et al. 2013). Finally, one of the major mechanisms involved in the removal of drug carriers from the bloodstream is via urine by glomerular filtration in the kidneys with a pore size of approximately 8 nm (Jarad and Miner 2009; Wartiovaara et al. 2004; Huang et al. 2011b), which sets a lower limit for the size of carrier particles.

Immune response is also an obstacle for drug delivery (Ma et al. 2005; Draz et al. 2014). To overcome this limitation, non-immunogenic carriers are often used in order to avoid being destroyed before reaching the target (Tatiparti et al. 2017). Viral vectors might not be a suitable candidate in this case for their high susceptibility toward the immune response (Xue et al. 2015). Once a carrier reaches target tissues, effective cellular internalization is required. Plasma membranes are, however, made of negatively charged phospholipids. The surface charge often acts as a barrier for

the uptake of certain carriers or therapeutic agents such as siRNA (Tatiparti et al. 2017). To address this challenge, positively charged nanoparticles (e.g., cationic lipid nanoparticles) are often used as carriers (Lappalainen et al. 1994; Mishra et al. 2004). Alternatively, the effect of **endocytosis** has to be utilized (Meade and Dowdy 2007) by surface modification of the nanocarriers with agents such as folate (Rozema et al. 2007), transferrin (Konishi et al. 2008), and aptamers (Chu et al. 2006).

19.6 Summary and Outlooks

Similar to the case of hydrophobic drugs, intravenously administered carriers also undergo protein corona formation, leading to a further increase in the carrier size by 3–35 nm (Choi et al. 2007; Monopoli et al. 2011). This may change the ADME profile of the carrier as well. This has been demonstrated by the case of lipid nanoparticles composed of 3β-[*N*-(*N*′,*N*′-dimethylaminoethane)-carbamoyl] (DC-Chol) and dioleoylphosphatidylethanolamine (DOPE). Upon exposure to plasma, a protein corona consisting of various apolipoproteins (including Apo A-I, Apo C-II, Apo D, and Apo E) is formed, and causes a 13-fold increase in the uptake of the nanoparticles in PC3 prostate cancer cells (Barran-Berdon et al. 2013). The effect of the protein corona on physiological performance has been further confirmed by the case of dihydrolipoic acid- or cysteamine-functionalized quantum dots, whose size has been found to be increased upon exposure to protein serum, resulting in a reduction in renal clearance (Choi et al. 2007). Here it is worth noting that the composition of the protein corona could be different among different types of nanoparticles, or even among the same type of nanoparticles that show different dimensions. Taking the case of gold and silver nanoparticles as examples, the composition of the protein corona on these nanoparticles differs by over 60% even though the size and charge of the particles are the same (Walkey et al. 2014). In addition, the protein corona composition for amine- and carboxy-functionalized gold nanoparticles differs by almost 53%, whereas that for 15 and 30 nm gold nanoparticles differs by around 25% (Walkey et al. 2014). Apart from the physicochemical properties of the nanoparticles per se, the local environment and the duration of blood exposure may affect the protein corona composition (Lundqvist et al. 2011; Casals et al. 2010). Along with the fact that the composition of the blood changes constantly owing to convection and changes in cellular metabolism, precisely predicting the composition of the protein corona is challenging. Yet, taking this challenge is unavoidable because the protein corona composition largely determines the biological identity of a carrier. Taking the fact that the synthetic identity and the biological identity are largely interrelated to each other (Fig. 19.5), in order to develop an effective systemic carrier, proper manipulation of the synthetic identity to enable better control of the protein corona composition is required.

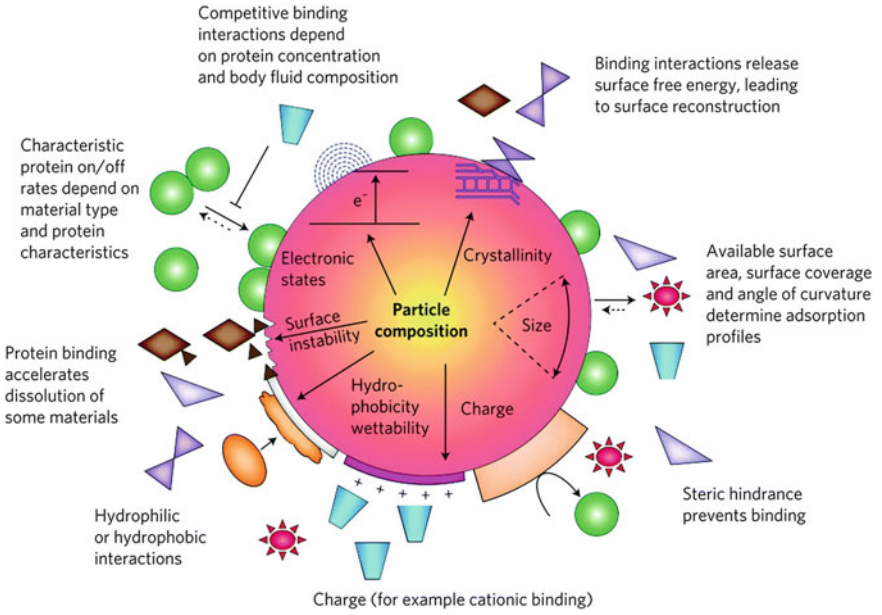

Fig. 19.5 An overview delineating the effects of the synthetic identity of a nanoparticle on protein adsorption. Reproduced from Nel et al. (2009) with permission from Springer Nature

Important Notes

- The ADME (absorption, distribution, metabolism, excretion) concept provides a framework for our understanding of the fate of an exogenous agent upon administration into a body.
- To alter the pharmacokinetics and biodistribution of a carrier, several properties (including the particle size, shape, and surface properties) of a carrier can be modulated.
- The hematocompatibility of a carrier can be partially enhanced by modulating the effect of the carrier on hemolysis.
- Thrombogenicity of a carrier is important when a systemic carrier is developed because extended blood circulation time of a carrier may activate the coagulation cascade.

Questions for Future Research

- **How can a carrier be able to reach tissues bodywide?** Aging occurs in all tissues and cells in a body. Carriers that can help deliver a bioactive agent to different parts of a body is vital for the development and execution of

a biogerontological intervention. Strategies to manipulate the pharmacokinetics and biodistribution of carriers are, therefore, required for practices in anti-aging medicine.

- **How can the physiochemical properties and the PK profile of a carrier be predicted before synthesis?** Right now carriers are usually developed in a trial-and-error manner. Their PK profiles and efficiency are known only after experimental evaluation. If the performance of a carrier can be estimated in silico based on the structure-activity relationship (SAR) and related models, candidates that are less likely to succeed can be excluded from further experimental studies. This may help facilitate the development of effective carriers.
- **How can a carrier be designed to tailor individual differences among subjects in a wider population?** The PK profile of a carrier is affected not only by the physical and chemical properties of the carrier per se but also by genetic variations and individual differences among subjects. Serious consideration shall be made on ways to accommodate such variations so that the delivery efficiency of a carrier among a wider population can be secured.

Glossary

Bioavailability The degree to which the active ingredient or moiety is absorbed from an administered dosage form and becomes available at the site of action.

Endocytosis A process that transports molecules from the extracellular milieu into cells via vesicle formation at the plasma membrane.

Enhanced permeability and retention (EPR) effect The effect of passive targeting caused by the extravasation of large molecules from the leaky tumor vasculature and hence the accumulation of those molecules in the tumor tissue.

Hematocompatibility Compatibility of a material with the components of the blood system.

Hemolysis Rupture of erythrocytes with release of hemoglobin into the plasma.

Hematotoxicity The toxicity of an agent to blood or hematopoietic tissues.

Opsonization A process in which opsonins interact with exogenous entities to make the entities more susceptible to phagocytosis.

Telomere A segment of DNA at the end of a chromosome. It gives protection to that chromosome.

Thrombogenicity The capacity of a material to induce or promote the formation of thromboemboli.

Zeta potential The electrical potential at the boundary of the hydrodynamic shear plane of a charged particle.

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