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Understanding nanoparticle-liver interactions in nanomedicine

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Abstract

Introduction: Understanding the interactions between administered nanoparticles and the liver is crucial for developing safe and effective nanomedicines. As the liver can sequester up to 99% of these particles due to its major phagocytic role, understanding these interactions is vital for clinical translation.

Areas Covered: This review highlights recent studies on nanoparticle-liver interactions, including the influence of nanoparticle physicochemical properties on delivery, strategies to enhance delivery efficiency by modulating liver Kupffer cells, and their potential for treating certain hepatic diseases. Additionally, we discuss how aging impacts the liver's phagocytic functions.

Expert Opinion: While liver accumulation can hinder nanomedicine safety and effectiveness, it also presents opportunities for treating certain liver diseases. A thorough understanding of nanoparticle-liver interactions is essential for advancing the clinical application of nanomedicines.

Keywords

Nanomedicine; nanoparticle; drug delivery; phagocytic clearance; liver

1. Introduction

Nanomedicine is an emerging technology to diagnose, image, and treat a variety of disease indications [1]. However, the safe and effective application of nanomedicine requires efficient nanoparticle delivery to cells and tissues in the body [2]. Upon systemic administration, nanoparticles interact with complex biological environments that determine

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Declaration of interest

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the nanoparticles' in vivo fate [3,4]. As a result, nanoparticles encounter various cell-dependent and cell-independent blood removal pathways [5], leading to the accumulation of up to 99% of the administered nanoparticle dose in the liver, while often less than 1% of administered nanoparticles reach targeted tissues, such as solid tumors [2,6]. The limited accumulation in target cells and tissues underscores the need to improve nanoparticle delivery strategies [2,6].

In this review, we focus on nanoparticle-liver interactions, as the liver represents a major biological barrier limiting the safe and effective application of nanomedicines. We explore and explain recent advances in understanding nanoparticle-liver interactions and summarize published studies to overcome the rapid and efficient clearance of nanoparticles from the bloodstream. We explore the nanoparticle fate upon entering the body, specifically the nanoparticle elimination pathways such as through hepatic fecal excretion. These pathways often depend on nanoparticle interactions with non-parenchymal cells like Kupffer cells. We highlight how various nanoparticle physicochemical properties, such as size, shape, and hardness, affect their behavior at each step of this elimination pathway, ultimately determining nanoparticle fate. Additionally, we outline different strategies for modulating liver macrophage, i.e. Kupffer cell, activity to enhance targeted nanoparticle delivery. Furthermore, we extensively discuss the potential of using nanoparticles as carriers for intracellular nucleic acid delivery. Finally, we address age as a significant factor affecting the efficacy of nanotherapeutics. A better understanding of nanoparticle-liver interactions may lead to improved nanoparticle delivery strategies and accelerate the translation of nanomedicines into the clinic.

2. The majority of administered nanoparticles tend to accumulate in the liver

Researchers are harnessing the delivery potential of nanoparticles by embedding drugs and/or imaging agents into them. This delivery strategy offers many advantages, including limiting the potential rapid metabolism of these compounds in the body, prolonging their circulation time, and increasing their accumulation at disease sites, while potentially reducing adverse effects [4]. Nanoparticles are engineered materials with dimensions in the nanoscale size range (often between 1 and 100 nm) and, therefore, are capable of reaching targeted disease sites in the body upon systemic administration [1]. However, upon introduction into the bloodstream, nanoparticles promptly engage with complex biological environments.

In this environment, serum proteins often form what is known as a 'protein corona' around administered nanoparticles [1]. This protein corona typically exhibits a multilayered structure. The composition and organization of the adsorbed proteins affect the nanoparticle's *in vivo* fate. For example, opsonins in the protein corona can mark nanoparticles for phagocytosis by certain circulating white blood cells and tissue-resident macrophages [1]. Interestingly, Beever et al. recently found that the interaction between poly(ethylene glycol) (PEG)-coated nanoparticles and macrophages is more akin to the interaction between lipoproteins and macrophages, rather than the interaction between

pathogens and macrophages. The researchers concluded that the interactions between PEG-coated nanoparticles and macrophages depend on the direct interaction of the PEG component with receptors that bind lipoproteins [7].

After intravenous administration, nanoparticles are transported to the heart along with venous blood from the systemic circulation. After passing through the pulmonary circulation, nanoparticles return to the left atrium with arterial blood from the pulmonary veins, flowing into the left ventricle. From there, the nanoparticles exit the heart and enter the systemic circulation, interacting with various organs and tissues throughout the body [5]. During this journey in the circulatory system, nanoparticles often accumulate primarily in the liver, with liver accumulation reported to reach up to 99% of the injected nanoparticle dose (Figure 1(a)). The preferential accumulation of nanoparticles in the liver is a commonly observed phenomenon and remains consistent across different animal models and nanoparticle physicochemical properties, such as size, shape, surface chemistry, and composition [8].

As demonstrated by the following literature examples, liver macrophages, particularly Kupffer cells, play a crucial role in the uptake and clearance of nanoparticles. Ouyang et al. demonstrated the overlap of the gold nanoparticle imaging signal with liver macrophages in tissue slices, proving that in a dose-dependent manner, over 90% of the administered nanoparticles co-localized with liver macrophages [9]. Sadauskas and colleagues found that almost all liver macrophages contained gold nanoparticles after systemic administration [10]. Park and coworkers examined the cellular distribution of poly(lactic-co-glycolic acid) (PLGA) particles in the liver using flow cytometry, revealing a 98% positivity rate for nanoparticles in liver macrophages [11]. Tsoi et al. observed that after intravenous injection of quantum dot nanoparticles in rats, ~85% of liver macrophages, ~82% of B cells, and ~ 65% of liver endothelial cells contained these nanoparticles [12]. Considering that liver macrophages outnumber B cells approximately five-fold in the liver, the researchers concluded that liver macrophages play a crucial role in the clearance of quantum dot nanoparticles. Additionally, liver macrophages were found to retain nanoparticles in the liver for an extended period. Poon et al. reported that up to 50% of intravenously administered gold nanoparticles persisted in mice livers 14 days after injection. This finding suggests that liver macrophages sequester the nanoparticles, thereby preventing the metabolic clearance and excretion of the gold nanoparticles through the hepatobiliary route [13].

Reasons for the high nanoparticle accumulation in the liver include the large blood volume in the liver, the slow sinusoidal blood flow (Figure 1(b)), and the direct exposure of liver macrophages to circulating nanoparticles facilitating their phagocytosis and endocytosis via various cellular uptake pathways [14].

Understanding the complex interactions between nanoparticles and liver macrophages within a healthy liver is crucial for nanomedicine development. Poon et al. used gold nanoparticles as a model system for non-biodegradable nanoparticles (Figure 1(c)) to systematically identify and quantify biological barriers within the hepatobiliary pathway for non-biodegradable nanoparticle elimination in the hepatic sinusoidal context [13]. Liver non-parenchymal cells, specifically Kupffer cells and hepatic sinusoidal endothelial

cells, play a pivotal role in impeding the egress of nanoparticles from the hepatic sinusoidal endothelium, thereby limiting their access to the Disse space for interactions with hepatocytes. Within the hepatic sinuses, there exist minute pores facilitating the transport of nanoparticles to the Disse space. However, particles surpassing the physical dimensions of these pores cannot directly penetrate the Disse space. Instead, these particles may gain access through a less efficient and slower transcellular transmission process facilitated by hepatic sinusoidal endothelial cells. These endothelial cells represent the initial 'barrier,' effectively impeding the direct interaction of non-biodegradable nanoparticles with liver cells, such as hepatocytes [13]. On the other hand, if the liver is in a pathological state, the permeation pathway of nanoparticles may be influenced by the intricate complexities of tumor blood vessels and the tumor microenvironment, differing from the previously described pathways. We suggest readers refer to comprehensive review papers for more detailed information [2,15].

3. Mediating nanoparticle-liver interaction through nanoparticle design

A large amount of administered nanoparticles is trapped in hepatic macrophages, reducing the effective quantity of nanoparticles reaching the target disease site. This accumulation decreases the nanoparticle delivery efficiency, resulting in potential suboptimal therapeutic effects and potential side effects [16]. Researchers have devised strategies to minimize hepatic nanoparticle accumulation [2]. For example, researchers currently focus on two main approaches to improve nanoparticle delivery efficiency [14,17].

The first approach involves the nanoparticle design. Researchers adjust physicochemical parameters, including nanoparticle size, shape, stiffness, and surface modification, to engineer nanoparticles for specific interactions with cells [18]. These physicochemical parameters significantly impact various aspects of the interaction between nanoparticles and the biological system, including serum protein adsorption, phagocytic recognition, trajectories and margination dynamics in blood vessels, endothelial adhesion, and extravasation, as well as organ filtration [19]. Recently, Wang et al. conducted a relevant literature survey on the organ biodistribution and pharmacokinetics of various types of nanoparticles in preclinical animal models. This analysis revealed novel insights concerning the relationship between nanoparticle design and nanoparticle distribution and retention within organs, such as the liver [5].

3.1. Nanoparticle size

Nanoparticle size is a physicochemical property that affects nanoparticle diffusivity and contact surface area with cell membrane (Figure 2(a)). Kupffer cells in the liver can engulf nanoparticles within the range of a few hundred nanometers. When nanoparticles in the bloodstream are smaller than the diameter of liver sinusoidal fenestrations (maximum range ~ 150–200 nm), they can penetrate the space of Disse and potentially interact with liver cells, such as hepatocytes [13].

Bergen et al. reported that galactose-modified 50-nm gold nanoparticles outperformed 80-nm, 100-nm, and 150-nm gold nanoparticles in terms of liver hepatocyte localization [20].

The 50-nm gold nanoparticles exhibited two to three times higher hepatocyte accumulation, suggesting that the size of nanoparticles plays a crucial role.

While nanoparticle size has been established as an important factor affecting cellular interactions and uptake, various other elements, including cell type, nanoparticle sedimentation rate, density, morphology, and the formation of a protein crown, can also impact the nanoparticle internalization pathways. Consequently, identical nanoparticles may yield diverse experimental outcomes in the presence of distinct experimental conditions [21]. In the meta-analysis of animal experimental results at the 24-hour time point by Wang et al., nanoparticles with diameters ranging from 11 to 100 nm accumulate the most in the liver [5]. Meanwhile, nanoparticles with diameters larger than 200 nm exhibit lower accumulation in various organs, including the liver.

In general, nanoparticles smaller than 6 nm are typically filtered through the kidneys and excreted rapidly into the urine [22], while those larger than 6 nm tend to accumulate in various organs and tissues, with a preference for the liver [23]. In summary, the size of nanoparticles plays an essential role in nanoparticle-liver interactions.

3.2. Nanoparticle shape

In addition to size, modifications to the nanoparticle shape (Figure 2(b)) can influence their behavior and distribution in the bloodstream, thereby affecting biological interactions such as cell uptake, hemodynamics, and organ biodistribution. Nanoparticles of different shapes also exhibit variations in their interactions with organs. Short rod-shaped and spherical nanoparticles typically accumulate in the liver. Compared to non-spherical nanoparticles, spherical nanoparticles usually have shorter circulation times but are more easily internalized by cells [24].

Spherical nanoparticles are more prone to phagocytosis by macrophages, while disc-shaped and rod-shaped nanoparticles exhibit stronger adhesion to cell membranes. Rod-shaped nanoparticles accumulate most in all organs of mice. From the perspective of blood rheology, nanorods, nanoworms, and nanodiscs show distinct fluid dynamics in blood flow compared to spherical nanoparticles [25]. They have smaller curvature radii and are less prone to renal or hepatobiliary excretion. Specifically, fibrous nanoparticles like nanoworms and fibrous micelles, due to their directional distribution aligned with blood flow, mainly exist in the fluid center, reducing the chances of interaction with vessel walls or liver sinusoids. This behavior significantly decreases the uptake of fibrous nanoparticles by the mononuclear phagocytic system and helps prolong their circulation time in the bloodstream.

Researchers have demonstrated that after injecting fibrous polymer micelles into mice, the blood circulation time of nanoparticles exceeds one week, whereas the corresponding spherical particles have a circulation time of only 2 to 3 days. Additionally, disc-shaped particles in the bloodstream display rolling and migration paths, increasing their chances of binding to vessel walls. The enhanced boundary dynamics of these disc-shaped particles in blood flow strengthen their binding to endothelial cells and the possibility of extravasation through the discontinuous endothelial layer in tumor vessels [26].

3.3. Nanoparticle material and elasticity/stiffness

Various materials are used to manufacture nanoparticles (Figure 2 (c)), categorized into inorganic materials, such as gold and silver, metal oxides like iron oxide, and organic polymers, such as polylactic acid (PLA) and poly(lactic-co-glycolic acid) (PLGA), and organic biomolecules, such as liposomes and lipid nanoparticles. Different materials exhibit different mechanical properties, and the mechanical performance of nanoparticles is a key characteristic affecting biological interactions [27]. Inorganic nanoparticles often have longer *in vivo* retention times in various organs of mice, especially in the liver and spleen. For instance, gold nanoparticles tend to accumulate most in the liver. Among different organic nanoparticles, polymeric nanoparticles often exhibit the highest accumulation in the liver of mice, while liposomes and biological nanoparticles tend to have lower accumulation in the liver [5].

Different materials exhibit different elasticity/stiffness, and these two properties are particularly important for nanoparticle delivery. Nanoparticle elasticity is an inherent property of the material quantified by the Young's modulus, which represents the degree of deformation under pressure [28]. The nanoparticle stiffness is affected not only by its geometric shape but also by its physical and chemical structure. Although elasticity and stiffness have different definitions in the literature, high elasticity and stiffness are typically characteristics of hard materials, whereas low elasticity and stiffness are indicative of softer, more flexible materials [29]. Main types of tunable elastic nanoparticles include hydrogel nanoparticles and hybrid polymer-lipid nanoparticles. The nanoparticle elasticity/stiffness can affect their organ biodistribution, clearance, cellular interactions, and elimination.

It has been reported that liver Kupffer cells can more effectively engulf rigid particles. Soft nanoparticles with low elasticity typically exhibit longer circulation times in the bloodstream, suggesting reduced sensitivity to macrophage phagocytosis [30]. The potential mechanism for this phenomenon is that low elasticity nanoparticles may be more prone to deformation, thereby reducing the efficiency of macrophage engulfment.

Moreover, phagocytosis is not the only pathway for nanoparticles to enter cells. It has been reported that relatively soft lipid nanoparticles can be engulfed by tumor cells through fusion with the cell membrane, consuming less time and energy compared to engulfing hard nanoparticles [31]. However, the factors affecting these interactions are complex and include material properties, nanoparticle size and shape, and cell types, all of which may lead to variations in the observed experimental outcomes.

Elasticity and stiffness further affect the tendency of nanoparticles to migrate toward the vessel wall in the bloodstream. Generally, rigid nanoparticles are more prone to margination. However, the boundary effect is multifaceted and is influenced by the nanoparticles' physicochemical properties, including size, shape, surface modification, and stiffness, and vascular characteristics, such as blood flow rate, vessel diameter, and blood viscosity [5].

3.4. Nanoparticle charge

Nanoparticle surface charge is another physicochemical property that affects the interaction between nanoparticles and cells (Figure 2(d)). Nanoparticles with positive charges (>10 mV)

tend to interact with negatively charged cell membranes, promoting the internalization of nanoparticles, while nanoparticles with negative charges (<10 mV) and neutral nanoparticles (−10 to 10 mV) exhibit significantly lower internalization efficiency [32]. Based on the attractive forces between positive and negative charges, nanoparticles with positive charges tend to bind more firmly to cell membranes with negative charges, enhancing the internalization of nanoparticles. This binding may be nonspecific and applicable to various cell types, including hepatic cells.

On the other hand, the nanoparticle surface charge further affects the type and quantity of adsorbed plasma proteins. Cheng et al. discovered that apolipoprotein E and IgA can bind to cationic nanoparticles, in which case the nanoparticles will accumulate significantly in hepatocytes [33]. Nanoparticles with a positively charged surface are more easily cleared by the liver. Souris et al. reported that mesoporous silica nanoparticles with a positive charge, when injected into mice, could be cleared by the liver and bile within 30 minutes post-administration [34]. Additionally, positively charged particles tend to aggregate when exposed to serum proteins, making them more easily recognized, engulfed, and cleared from the bloodstream by macrophages [26].

Considering these two factors, nanoparticles with a neutral surface charge tend to have a longer residence time in the body compared to nanoparticles with a positive or negative surface charge [26]. Levchenko and colleagues demonstrated that negatively charged liposomes (~ −40 mV) accumulated more in the liver than neutral-charged liposomes [35].

Different types of liver cells exhibit distinct preferences for nanoparticle uptake, indicating that surface charge affects the nanoparticle distribution in the liver. Kupffer cells and liver sinusoidal endothelial cells (LSECs), which are rich in scavenger receptors, show strong binding affinity with nanoparticles carrying a negative charge. Liver cells tend to preferentially internalize nanoparticles with a positive charge [6].

Surface charge impacts nanoparticle biological toxicity as well. *In vivo* studies have confirmed the impact of nanoparticle surface charge on biological toxicity. For example, mice injected with lipid nanoparticles carrying a positive charge experienced more severe adverse effects, including liver toxicity, weight loss, and pro-inflammatory reactions, compared to mice injected with neutral or negatively charged nanoparticles [36].

3.5. Nanoparticle surface modification

Nanoparticle surface modification plays a crucial role in guiding their interaction with target cells or tissues [37]. The nanoparticle surface can be modified with so-called targeting ligands (Figure 2(e)) to achieve specific interactions with receptors on the surfaces of target cells, aiming to weaken the recognition and clearance by the body's macrophages and enhance targeted delivery efficiency. Targeting ligands commonly used for 'active targeting' include peptides, small molecules, proteins, antibodies, antibody fragments, nucleic acids, and more [38]. Nanoparticles without specific targeting ligands are referred to as 'passive targeting' nanoparticles, where the interaction between nanoparticles and cells is typically nonspecific [39].

‘Passive targeting’ aims to minimize the recognition of nanoparticles by macrophages [40]. This stealth effect is often achieved by modifying the nanoparticle surface with PEG or zwitterionic ligands. Another strategy is to camouflage nanoparticles as ‘self’ entities, for example, by decorating the nanoparticle surface ‘self-labeling’ proteins/peptides, or cell membranes.

One of the most common surface modification methods to reduce interactions between nanoparticles and biological entities is PEGylation [41]. When PEG polymers are attached to the nanoparticle surface, they reduce the recognition by macrophages through steric hindrance and the formation of a hydration layer around the nanoparticles.

PEGylation has been extensively studied and is known to prolong the blood half-life of various nanoparticles. However, the presence of anti-PEG antibodies in some individuals may lead to allergic reactions and accelerate the blood clearance of PEGylated nanoparticles [42,43]. To address this issue, researchers have explored alternative polymers, such as polylysine, polyoxazoline, and polysaccharides, to replace PEG. Yang and colleagues replaced PEG with heparosan (HEP) and observed that HEP-coated nanoparticles exhibited reduced protein adsorption on the nanoparticle surface and increased cellular uptake in certain immune cell types [44,45].

Zwitterionic ligands, composed of chemical groups with positive and negative charges, are often used for nanoparticle surface modification and passive targeting. Arvizo et al. found that neutral and zwitterionic nanoparticles exhibited enhanced tumor uptake capacity by comparing structurally homologous nanoparticles with different charge properties and their impact on tumor delivery ability and organ biodistribution [46]. The underlying reason behind this is that neutral and zwitterionic particles exhibit increased tumor accumulation post-administration potentially due to the EPR (Enhanced Permeability and Retention) or ATR (Active Transport and Retention) effects [47].

Plasma proteins, particularly albumin, can also be used for surface modification to improve the pharmacokinetics of nanoparticles [48]. Albumin competitively inhibits the attachment of more bioactive serum proteins. On the other hand, more biologically specific approaches involve the use of ‘self-labeling’ proteins, such as CD47 or its derived peptides [49], to modify nanoparticles [50]. These proteins are often recognized by macrophages and lymphocytes as self-components, reducing engulfment and clearance. Another type of biomacromolecule, polysaccharides, is also considered a good choice for surface modification of nanoparticles. Ji et al. found that by using Astragalus alcohol soluble polysaccharide (AASP) to surface modify selenium nanoparticles (SeNPs), they exhibited dose-dependent inhibition on liver cancer (HepG2) cells [51].

Another approach aims for lower biological specificity by encapsulating nanoparticles in cell membranes that already display various self-molecules on their surfaces. Studies have shown that nanoparticles cloaked with red blood cell membranes exhibit a longer circulating effect than ‘active targeting’ strategies and demonstrate better nanoparticle accumulation and therapeutic efficacy in liver cancer [50].

To achieve more targeted nanoparticle *in vivo* delivery, Siegwart et al. reported selective organ targeting (SORT) lipid nanoparticles. The researchers succeeded in tissue-specific mRNA delivery and CRISPR-Cas gene editing by incorporating specific SORT lipid molecules into lipid nanoparticles [52]. The SORT approach enables the targeted nanoparticle delivery to the lungs, spleen, and liver.

In summary, when designing nanoparticles for biological and medical applications, careful consideration of various nanoparticle physicochemical properties and the rational selection of surface modification strategies are essential.

4. Kupffer cell modulation

As the majority of nanoparticles are engulfed by liver macrophages upon entering the body, various approaches have been explored to reduce the ability of liver macrophages, represented by Kupffer cells, to phagocytose nanoparticles. The initial expectation was that if the Kupffer cells' phagocytic activity is reduced, more nanoparticles will remain in the bloodstream for a longer time. Longer blood circulation may increase the chance for nanoparticles to reach target tissues in the body. Three main biological modulation approaches have been employed to improve the nanoparticle delivery efficiency (Figure 3): (i) Kupffer cell saturation strategy; (ii) inhibition of Kupffer cell phagocytic function; and (iii) depletion of Kupffer cells, known as a 'suicidal strategy.'

4.1. Kupffer cell saturation strategy

The Kupffer cell saturation strategy refers to injecting an excess of nontoxic inorganic or organic materials, such as liposomes, into the body before administering therapeutic nanoparticles. This excess of nanoparticles can temporarily saturate the surface receptors of Kupffer cells and enhance the delivery of therapeutic nanoparticles to diseased tissues [9]. The principle behind this method is that although Kupffer cells can engulf a large number of circulating nanoparticles, their short-term phagocytic efficiency is limited by their capacity, i.e. the amount and rate of exogenous substances each cell can engulf [53]. Liu et al. demonstrated this by first giving mice liposomes to saturate the reticuloendothelial system, including Kupffer cells, and then injecting mice with nanoparticles containing paclitaxel [54]. They used spin echo and gradient echo magnetic resonance imaging to detect the T2 values in the tumor area before and after the administration of nanoparticles, with numerical changes from 29.1 ± 0.1% to 49.9 ± 0.1%. They concluded that this method nearly doubled the accumulation of nanoparticles in tumors and significantly slowed tumor growth. It only temporarily blocked the receptors responsible for phagocytosis without impairing the overall function of macrophages, indicating the practicality of the Kupffer cell saturation strategy.

Ouyang et al. discovered that the efficiency of nanoparticle delivery to tumors significantly increased when the number of systemically injected PEGylated gold nanoparticles exceeded one trillion in mice [9]. At this nanoparticle bolus dose, the uptake rate of Kupffer cells became saturated, prolonging the nanoparticle circulation time and thereby increasing the tumor delivery efficiency. This method achieved a 12% nanoparticle tumor delivery and improved the therapeutic effect of nanoparticles carrying drugs, such as Caelyx/Doxil.

In addition to nanoparticles, researchers have used other materials, including chitosan sulfate, natural polysaccharides, colloidal carbon, and fat emulsions, as pre-treatment agents to saturate Kupffer cells within a short time [55,56].

However, the limitations of this strategy include, on one hand, that the phagocytic function of Kupffer cells does not permanently disappear. Once lysosomal enzymes digest these inorganic or organic materials after cell uptake, the phagocytic function of Kupffer cells promptly recovers, and the entire process only lasts for ~48 hours [6]. Such recovery limits the long-term application of nanoparticles. On the other hand, high-dose blockade with nanoparticles or other substances to saturate the phagocytic activity of Kupffer cells may lead to dose-dependent toxicity and damage to other organs [57].

4.2. Endocytosis inhibition strategy

Kupffer cells internalize nanoparticles through various endocytic pathways, including phagocytosis, clathrin-mediated, caveolin-mediated endocytosis, often using scavenger receptors on their cell surface [14]. Researchers have employed drugs, such as rottlerin, colchicine, cytochalasin B, chloroquine, gadolinium chloride, and methyl palmitate [6], to limit the endocytosis of nanoparticles by Kupffer cells. Lunov et al. investigated the uptake mechanisms of 20-nm and 60-nm superparamagnetic iron oxide nanoparticles (SPIONs) on human macrophages [58]. The study results indicate that SPIONs accumulate in macrophages through endocytosis mediated by clathrin proteins and scavenger receptor A. When inhibitors for meshwork proteins and scavenger receptor A endocytosis were used, the cell uptake of SPIONs decreased by over 80%.

Wolfram et al. demonstrated that chloroquine reduced the accumulation of liposomes and disc-shaped silica particles in the liver. Meanwhile, the concentration of silica particles in the blood increased by 3.9 times, and the accumulation in the lungs increased by 1.5 times [59]. Deorukhkar et al. used gadolinium chloride to mitigate the accumulation of quantum dots in Kupffer cells to enhance tumor imaging [60].

The reduction of nanoparticle internalization by macrophages achieved through endocytosis inhibitors is relatively mild, and the inhibitory effect of these inhibitors on macrophage endocytosis is limited. The drawback is that these inhibitors do not specifically target Kupffer cells in the liver, and when they enter the bloodstream, they may have side effects on other cells throughout the body, such as hepatocytes in the liver. Currently, researchers are beginning to explore new approaches, such as using palmitic acid methyl ester nanoparticles combined with serum albumin to more effectively reduce the phagocytosis of various physicochemically distinct nanoparticles in mice [57].

4.3. Kupffer cell suicide strategy

By depleting and removing the liver Kupffer cells, nanoparticles are no longer extensively engulfed by them, leading to a natural increase in the nanoparticles' blood half-life. Researchers have used several drugs to deplete Kupffer cells in the liver. For example, Van Rooijen and colleagues developed a method using liposomes encapsulating dichloromethylene-bisphosphonate or clodronate to deplete macrophages, such as Kupffer cells [61]. Subsequently, Ohara et al. established a human pancreatic cancer model

in BALB/c nude mice and depleted Kupffer cells using clodronate liposomes before administering different doses of PEGylated liposomal doxorubicin (Doxil). The results showed that Kupffer cell depletion reduced doxorubicin accumulation in the liver, increased the plasma doxorubicin concentration threefold, increased nanoparticle tumor accumulation fourfold, and improved Doxil's anticancer efficacy [62].

Similarly, Hao et al. used clodronate liposomes to deplete Kupffer cells in melanoma mouse models. The experimental group showed an ~ 2-fold increase in the accumulation of paclitaxel-PLGA nanoparticles in tumors compared to the control group [63]. These results indicate that the removal of liver Kupffer cells can effectively reduce nanoparticle liver accumulation while increasing nanoparticle accumulation in tumors. These encouraging results inspire the development of drug delivery strategies focused on modulating the body's immune microenvironment to enhance nanoparticle delivery efficiency.

However, there are controversies regarding its clinical translation of Kupffer cell depletion strategies. For example, it has been reported that the damage caused by clodronate liposomes to liver Kupffer cells takes several days or even weeks to repair, depending on the drug dosage and the body's own condition [64]. At higher doses, a large number of apoptotic Kupffer cells are filtered in the spleen, leading to splenomegaly. Kupffer cells play a crucial role in the body's immune response to pathogenic microorganisms, and the extensive apoptosis of Kupffer cells can impair the body's immune system, resulting in potentially decreased immunity and increased susceptibility to pathogens.

Additionally, to achieve a low number of Kupffer cells in the liver over an extended period, repeated high-dose injections of clodronate liposomes are required, which can cause irreversible damage to other organs in mice. Chan et al. found that although pretreating mice with clodronate liposomes can reduce the nanoparticle uptake by Kupffer cells in the liver and improve the nanoparticle tumor delivery efficiency, this improvement is still very limited. Their statistical conclusion is that this method contributes only 2% to the overall nanoparticle tumor delivery [64]. Therefore, researchers should carefully consider the pros and cons of these Kupffer cell suicide and depletion strategies [65].

5. Liver-targeted delivery of nanoparticles in nanomedicine

Given the ability of nanoparticles to deliver drugs to liver Kupffer cells, researchers have explored various nanotechnologies for the treatment of liver diseases, with a particular focus on lipid nanoparticles and liposomes [66]. Under the influence of various disease-inducing factors, such as biological factors (hepatitis B virus, hepatitis C virus), physical factors (radioactive substances), and chemical factors (alcohol), the function of liver Kupffer cells is easily compromised. This can lead to the manifestation of diseases in the body, such as liver cell carcinoma [67], liver fibrosis [68], and cirrhosis. Furthermore, due to the widespread high expression of the cell-binding receptor – asialoglycoprotein receptor (ASGPR) on hepatocytes, the binding ligands of nanoparticles exhibit an affinity for hepatocytes. However, it is important to note that when the liver is in a diseased state, significant alterations in its histological structure can impact the efficacy of nanoparticle delivery. This enables nanoparticles with these binding ligands to more effectively deliver payloads

to the liver [69]. In this section, we will primarily delve into the impact of histological alterations in the liver under pathological conditions on nanoparticle delivery, as well as the application of nanoparticles as carriers for different payloads, including chemotherapy drugs, antibiotics, and nucleic acids to address a diverse array of liver diseases.

5.1. Influence of liver histopathological changes on nanoparticle delivery

The liver plays a crucial role in clearing and metabolizing nanoparticles from the bloodstream. Diseased liver tissue exhibits significant differences in pathology compared to normal liver tissue, thus the influence of liver histopathology on nanoparticle delivery is notable [5]. Liver histopathology refers to the microscopic examination of liver tissue to detect abnormalities or diseases. Several factors may affect nanoparticle delivery: 1. Liver diseases such as fibrosis, cirrhosis, liver cancer, hepatitis, and fatty liver can alter the structure, function, and blood flow within the liver [70]. 2. Elevated portal vein pressure resulting from increased intrahepatic vascular resistance can significantly influence the uptake, distribution, and clearance of nanoparticles [71]. 3. Activation of Kupffer cells during inflammation or liver injury increases nanoparticle uptake and clearance, reducing their circulation time and efficacy [6]. 4. Changes in liver vascular permeability affect nanoparticle penetration and distribution within liver tissues. For example, reduced vascular permeability in liver fibrosis limits nanoparticle entry into the hepatic parenchyma [72]. 5. Liver fibrosis and cirrhosis increase tissue hardness, affecting blood flow distribution and nanoparticle retention and distribution [73]. 6. Changes in cellular uptake due to liver cell pathology, such as fatty liver, influence nanoparticle uptake mechanisms and transport, impacting treatment efficacy and safety [74].

Understanding the influence of liver histopathology on nanoparticle delivery is crucial for designing and optimizing nanoparticle-based drug delivery systems, particularly for liver disease treatment. Incorporating knowledge of liver pathology into nanoparticle design can potentially enhance efficacy and tissue targeting.

5.2. Liver targeted delivery of nanoparticles with drugs

Amphotericin B, an FDA-approved formulation, harnesses the preferential accumulation of liposomes in the liver to enhance the delivery of liposomal amphotericin B, an antifungal agent [75]. Notably, Sundar et al. observed that patients with visceral leishmaniasis receiving Amphotericin B experienced milder and shorter fevers compared to those receiving free amphotericin [76].

However, the accumulation of nanoparticles carrying therapeutic components in liver Kupffer cells may lead to unexpected adverse effects. Daemen and colleagues found that the function of rat liver Kupffer cells was impaired due to the application of non-polyethylene glycolated liposomal amphotericin [77]. Given the pivotal role of liver Kupffer cells in the immune system, caution is necessary when dealing with these off-target effects of nanoparticles. Moreover, liver Kupffer cells contribute to maintaining immune tolerance to specific antigens, potentially causing unexpected immune tolerance with nanoparticle vaccines that accumulate in the liver. This becomes particularly crucial in the realm of nanoparticle immunotherapies, where treatments influence immune activity. Therefore,

when designing cancer nanomedicines, the accumulation of nanoparticles in liver Kupffer cells must be carefully considered to mitigate potential adverse effects.

5.3. Liver targeted delivery of nanoparticles with nucleic acid payloads

RNA therapy can manipulate gene expression or generate therapeutic proteins, making it applicable to pathologies with specific genetic targets, including infectious diseases, cancers, immune disorders, and Mendelian genetic diseases (including neurological disorders) [78]. Common therapeutic RNAs include gapmers composed of RNA surrounding DNA nucleotides, small interfering RNAs (siRNAs), or large RNAs, such as messenger RNA (mRNA). These RNA therapies can target RNA or proteins, encode missing or defective proteins, or mediate gene-level editing, such as DNA or RNA editing.

Therapeutic RNAs, like mRNA, are prone to degradation by RNases abundant in blood and tissues, limiting their effective cellular uptake and action. To ensure safe, effective, and efficient RNA delivery, organic nanoparticle delivery systems, represented by lipid nanoparticles and liposomes, are widely employed [78]. These nanoparticles can protect RNA payloads from degradation, significantly enhance the efficiency of RNA delivery to target cells, and reduce nucleic acid exposure to non-target cells. For example, lipid nanoparticles (LNPs) have been used to deliver mRNA to antigen-presenting cells after intramuscular administration, deliver mRNA encoding Cas9 and single-guide RNA (sgRNA) to hepatocytes, and deliver short interfering RNA (siRNA) to liver cancer cells after systemic administration [79,80]. Between 2018 and 2022, a total of 5 siRNA drugs targeting the liver were approved by the U.S. FDA: Patisiran (Onpattro), Givosiran (Givlaari), Lumasiran (Oxlumo), Inclisiran (Leqvio), and Vutrisiran (Amvutta). All these approved siRNA drugs target the mRNA expressed in the liver [81].

Building upon nucleic acid therapy, efforts are continuously made to enhance the effectiveness of nucleic acid manipulation of target genes, such as reducing dosing frequency and extending the duration of action in the body.

Small interfering RNA (siRNA) is used for gene silencing in the human body. This double-stranded RNA molecule, with a molecular weight of ~ 13 kDa, inhibits protein translation by binding to mRNA through Watson-Crick base pairing, and the target mRNA is cleaved by the catalytic action of the RISC protein Ago2 [82]. siRNA can reduce the expression of any gene encoding a protein, as demonstrated in FDA-approved therapies, such as Givosiran for treating acute hepatic porphyria, Lumasiran for type 1 primary hyperoxaluria, and Inclisiran for treating hypercholesterolemia [83].

Messenger-RNA (mRNA) can be used to replace proteins, using alternative therapies. It can also reduce protein levels through the Cas9 cleavage method or repair protein mutations through base editing of DNA [84]. mRNA can also be used for the transient expression of DNA nucleases, including zinc finger nucleases, transcriptional activation-like nucleases, or nucleases derived from the CRISPR-Cas system. This provides a simple and flexible way for therapeutic gene drugs, suitable for manipulating DNA, with a shorter protein expression lifespan, achieving once-a-year patient injections through improved delivery or siRNA design, in contrast to DNA gene drugs, avoiding long-term effects and potential

off-target effects. Lipid nanoparticles (LNPs) can deliver mRNA to different liver cells in the human body. Once the nanoparticle enters the cell cytoplasm, the mRNA is released and translated by ribosomes into functional proteins for disease treatment [85]. In addition to cancer and viral infections, the research field of nanoparticle-mRNA vaccines can also be used for prevention of parasitic infections, such as malaria. BioNTech announced plans to conduct clinical trials for mRNA vaccines against malaria, focusing on infections confined to the liver [86].

Organ-specific mRNA delivery after systemic administration remains an ongoing effort. When administered intravenously, mRNA-LNP primarily targets the liver by binding to circulating apolipoprotein E (ApoE), which, in turn, targets ApoE receptors on the surface of liver cells. Intrinsic liver regeneration serves as an example of applying nanoparticle delivery of nucleic acids [87]. Gouon-Evans et al. proposed an efficient, safe, and non-integrating method using nucleotide-modified lipid nanoparticles encapsulating mRNA (mRNA-LNP) for delivery (Figure 4) [89]. They injected mRNA-LNP into the established liver injury mouse model via retro-orbital or tail vein injections. This method achieved transient expression of hepatocyte growth factor (HGF) and epidermal growth factor (EGF) in mouse hepatocytes. The study confirmed the liver-specific targeting effect of mRNA-LNP, with protein expression sustained for approximately three days. In the liver, almost all hepatocytes were transfected, along with a portion of endothelial cells and Kupffer cells. Under steady-state conditions, HGF mRNA-LNP effectively induced hepatocyte proliferation. In a mouse model of chronic liver injury mimicking nonalcoholic fatty liver disease, co-injection of HGF and EGF mRNA-LNP significantly reversed fat deposition and accelerated liver function recovery. Similarly, HGF and EGF mRNA-LNP expedited liver regeneration after acetaminophen-induced acute liver injury, restoring the liver to baseline ALT levels rapidly. This study introduced mRNA-LNP as a potential and convertible safe therapeutic intervention, guiding liver regeneration through controlled expression of endogenous mitogens *in vivo* [89].

Dahlman et al. used a DNA barcode-based system called Fast Nanoparticle Delivery (FIND) to study the efficacy of over 100 lipid nanoparticles (LNPs) in delivering mRNA to target cell cytoplasm in mice [90]. Ultimately, an LNP with esterified cholesterol and lacking a targeting ligand proved effective at delivering Cre mRNA to liver endothelial cells and Kupffer cells at lower doses. It is noteworthy that the efficiency of these lipid nanoparticle formulations targeting microenvironmental cells surrounding liver cells is five times that of the liver cells themselves. Different biological material components of nanoparticles also affect their fate in the body. Dahlman's team quantified the fate of over 100 LNPs prepared with six cholesterol variants in 18 different cell types in mice. LNPs with esterified cholesterol were found to be more efficient in delivering nanoparticles to all tested cell types in mice compared to LNPs with ordinary or oxidized cholesterol. They also identified an LNP containing cholesteryl oleate that efficiently delivered siRNA and sgRNA to liver endothelial cells. This oleic acid LNP was distinguished from LNPs targeting hepatocytes [91]. Therefore, rational selection of cholesterol variants in nanoparticles can achieve targeted optimization of nanoparticles for more precise RNA delivery.

The CRISPR-Cas system is a naturally occurring defense system widely present in prokaryotes, designed to counteract invasion by bacteriophages and foreign genetic material. These systems consist of effector modules, either a group of proteins or a single effector, responsible for directing and cutting invading nucleic acids, and adaptation modules, which integrate foreign sequences into CRISPR arrays and express them as CRISPR RNA (crRNA) [84].

In recent years, the CRISPR-Cas gene editing approach mediated by lipid nanoparticles (LNPs) has gained significant attention. Once LNPs enter the circulatory system, their surface interacts with electrolytes, lipids, apolipoproteins, and other substances, forming a specific 'biomolecular corona.' Due to the highly perfused nature of the liver and its fenestrated capillaries, LNPs passively and predominantly accumulate in the liver [92]. Optimized designs include amino lipids with buffered ions, used to deliver mRNA encoding Cas9 and sgRNA targeting lox-Stop-lox sites. Similar lipid-like nano-materials have also been successfully used to deliver base-editing Cas systems to mouse livers. Chemical modifications specific to sgRNA can enhance the editing efficiency of mouse hepatocytes [93]. Companies like Intellia Therapeutics have reported potent gene editing of the Ttr gene after injection of biodegradable lipids (LP01), along with positive data from similar strategies in clinical trials [84]. These studies indicate the application potential of LNP-mediated gene editing in different organs and disease models.

6. Age-related hepatic macrophage clearance of nanoparticles and its impact on drug delivery to tumors

Some biological variables, such as sex [94] and age [95,96], may influence the clearance of nanoparticles and affect the therapeutic outcome of nanomedicine. These factors garner increasing research interests in the recent years as they are shown to drastically change the development and treatment outcome of human diseases [97–99].

Clinical studies observed that the pharmacokinetics of nanomedicine is different between young and old patients [94,100]. The stem cells from female or male origins also showed different uptake ability of nanoparticles [101]. It is possible that individuals of different age or sex may rely on different major pathways for nanoparticle clearance, which implies that the targeting strategies also need to be adapted to the status of the recipient.

For example, in a recent study, Jiang et al. found that tumor delivery of nanomedicine is enhanced in older mice compared to their younger counterparts, primarily due to the reduced ability of aged liver phagocytic cells to capture and clear nanoparticles [102]. This age-associated disparity of liver uptake results in improved treatment efficacy of nanomedicine for the old mice. Single-cell RNA sequencing of the liver macrophages of young and old mice revealed a striking shift of macrophage populations during aging. The young liver had large abundance of Kupffer cells, while the old liver macrophages were primarily monocyte-derived macrophages. Further transcriptomic analysis showed that young and old liver macrophages respond very differently to the stimulation of nanoparticles. For example, after nanoparticle injection, the young liver macrophages activated phagocytosis, antigen presentation, and lysosome pathways more robustly than the old counterparts. Whereas

old macrophages had higher level of reactive oxygen species and IL-17 signaling pathway activations. These differences in response to nanoparticles indicate a possible change in nano-bio interaction patterns during aging.

Analysis of phagocytosis-related receptor expressions found that higher percentage of young liver macrophages expressed a scavenger receptor named macrophage receptor with collagenous structure (MARCO). MARCO is known to be responsible for uptake of nanoparticles and bacteria by macrophages [103,104]. It was further shown by knockdown experiments that MARCO is directly responsible for the nanoparticle uptake by macrophages. The overexpression of MARCO on old macrophages can enhance their phagocytosis ability. Interestingly, nanoparticles stimulated the young livers to generate more macrophages with high expression of MARCO, but the old livers were much less responsive to nanoparticle stimulation.

Therapeutic blocking of MARCO by antibody or recombinant MARCO protein was shown to reduce nanoparticle phagocytosis by liver macrophages, thereby increasing the tumor delivery and enhancing the anti-tumor effects of clinically approved cancer nanotherapeutics in young mice. In old mice, despite the nanomedicine alone treatment was more effective compared with that in young mice, the outcome could not be further enhanced by combing with MARCO blockade. This result shows the age disparity of nanomedicine delivery efficancy and suggests that a strategy to enhance nanoparticle delivery efficiency that is effective in the young individuals may not be translatable to the old ones, due to the change of biological context (Figure 5). Furthermore, the transcriptomic and protein-level analyses at single cell and bulk levels showed that the percentage of liver macrophages expressing MARCO declined with age in mice, non-human primates, and humans, suggesting that this phenomenon is conserved and implies that it is necessary to take aging into consideration in translational study design.

These findings highlight age-related differences in nanotherapeutic phagocytosis clearance, influencing its anti-tumor response, and underscore the importance of age-appropriate strategies in cancer nanomedicine. Further study is needed to elucidate the mechanisms that cause the shift of liver macrophage populations and change of gene expression patterns, which will ultimately help the development of age-specific strategies to enhance nanoparticle delivery.

7. Conclusion

In conclusion, our review, citing papers from Google Scholar and PubMed in December 2023, underscores that administered nanoparticles predominantly accumulate in the liver, exploiting its vascular structure to access Kupffer cells in sinusoids; larger nanoparticles are preferentially sequestered, while those evading Kupffer cells pass through sinusoidal endothelium to hepatocytes in the Space of Disse for eventual elimination via bile. Strategies such as tailored nanoparticle design and modulation of Kupffer cells are essential for optimizing delivery efficiency in treating liver diseases, with LNPs and liposomes playing pivotal roles in targeting Kupffer cells and hepatocytes. Age and sex significantly influence

nanoparticle clearance and efficacy, emphasizing the importance of personalized targeting strategies in nanomedicine development.

8. Expert opinion

For future research, a deeper focus on the biological transformation of nanoparticles and their interactions with liver cells, bile ducts, and the intestinal tract is essential, as these biological components can influence the excretion efficiency and rate of nanoparticles. The liver, acting as a complex gatekeeper system, exhibits compensatory capabilities in regulating access to the liver-biliary pathway for large and non-degradable nanoparticles. Unlike degradable nanocarriers, the long-term fate and toxicity of non-degradable nanoparticles retained in the body remain unclear, necessitating a comprehensive consideration of mechanisms for nanoparticle elimination from the body. Meanwhile, introducing environmentally friendly and low-toxicity green biomaterials into the scope of research in the field of nanomedicine is also an emerging and exciting concept [105]. It is recommended to establish a comprehensive nano-bio interaction central database, facilitating trend and correlation analyses using machine learning (ML) and artificial intelligence (AI) to enhance our fundamental understanding of nano-bio interactions and guide the engineering design of the next generation of nanomedicine [5].

The substantial uptake capability of liver Kupffer cells poses a significant challenge for nanoparticle delivery to non-hepatic organs. Future research should quantify the impact of these factors on targeted nanoparticle delivery to comprehensively understand the mechanisms of nanoparticle uptake in the liver [13]. To study Kupffer cell uptake, future research may employ a library of nanoparticles with various design parameters, taking into account various physicochemical properties.

In future studies, the DNA barcode method explored by the Dahlman team can be employed to investigate the activity and stability of different nanoparticles [106]. This system, effective in various in vivo environments, can be used to study how nanoparticle delivery modes change under animal disease conditions and identify nanoparticles evading lysosomes, retained in the cytoplasm, or entering the cell nucleus. This approach will advance the study of nanoparticle drug metabolism kinetics, promote research into targeted nanoparticles for specific tissues and cells, and expedite the exploration of relationships between chemical structure and in vivo delivery.

Further research is needed to understand the complexity and extent of interactions among multiple metabolic mechanisms and confirm the conservation of these mechanisms in vivo. High-throughput techniques, such as single-cell RNA sequencing, can be employed to identify signal pathways promoting the activity of therapeutic RNA in target cell types while reducing its activity in non-target cells [107]. Despite successful mRNA delivery to immune cells through intramuscular injection of LNPs for vaccine applications, achieving clinically relevant delivery in non-hepatic tissues, such as the spleen, lungs, heart, eyes, central nervous system, and lymphatic system, requires improvements in drug delivery systems to target mRNA to these non-hepatic tissues.

Lastly, researchers need to consider age-related differences, as well as other biological variables, that affect the clearance of nanomedicines. In the future of translational medicine, emphasizing the importance of tailored cancer nanomedicine strategies suitable for different age groups is crucial [102]. Furthermore, researchers need to delve into the mechanisms underlying the heterogeneity of hepatic macrophage populations and changes in gene expression patterns under different physiological or pathological states. It will be important to understand how these parameters affect interactions between liver macrophages and nanoparticles. A better understanding of nanoparticle-liver interactions will ultimately contribute to the development of safer and more effective nanomedicines.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Pelaz B, Alexiou C, Alvarez-Puebla RA, et al. Diverse applications of nanomedicine. ACS Nano. 2017;11(3):2313–2381. doi: 10.1021/acsnano.6b06040 [PubMed: 28290206]
2. Wilhelm S, Tavares AJ, Dai Q, et al. Analysis of nanoparticle delivery to tumours. Nat Rev Mater. 2016;1(5):16014. doi: 10.1038/natrevmats.2016.14• This paper collected and analyzed the delivery efficiency of nanoparticles across numerous published studies and reported that the median nanoparticle delivery effciency to solid tumors is 0.7% of the injected nanoparticle dose.
3. Dai Q, Wilhelm S, Ding D, et al. Quantifying the ligand-coated nanoparticle delivery to cancer cells in solid tumors. ACS Nano. 2018;12(8):8423–8435. doi: 10.1021/acsnano.8b03900 [PubMed: 30016073]
4. Manzari MT, Shamay Y, Kiguchi H, et al. Targeted drug delivery strategies for precision medicines. Nat Rev Mater Nat Res. 2021;6 (4):351–370. doi: 10.1038/s41578-020-00269-6
5. Wang L, Quine S, Frickenstein AN, et al. Exploring and analyzing the systemic delivery barriers for nanoparticles. Adv Funct Mater. 2024; 34. p. 2308446. [PubMed: 38828467] • This paper extensively discussed nanoparticles removal mechanisms and proposed the concept of nanoparticle blood removal pathways. Through meta-analysis of published articles, this paper also identified the surface chemical modification as the key modulator of nanoparticle delivery.
6. Zhang YN, Poon W, Tavares AJ, et al. Nanoparticle–liver interactions: cellular uptake and hepatobiliary elimination. J Controlled Release. 2016;240:332–348. doi: 10.1016/j.jconrel.2016.01.020
7. Asoudeh M, Nguyen N, Raith M, et al. PEGylated nanoparticles interact with macrophages independently of immune response factors and trigger a non-phagocytic, low-inflammatory response. J Controlled Release. 2024;366:282–296. doi: 10.1016/j.jconrel.2023.12.019
8. Albanese A, Tang PS, Chan WCW. The effect of nanoparticle size, shape, and surface chemistry on biological systems. Annu Rev Biomed Eng. 2012;14(1):1–16. doi: 10.1146/annurev-bioeng-071811-150124 [PubMed: 22524388]
9. Ouyang B, Poon W, Zhang YN, et al. The dose threshold for nanoparticle tumour delivery. Nat Mater. 2020;19(12):1362–1371. doi: 10.1038/s41563-020-0755-z [PubMed: 32778816]
10. Sadauskas E, Danscher G, Stoltenberg M, et al. Protracted elimination of gold nanoparticles from mouse liver. Nanomedicine. 2009;5 (2):162–169. doi: 10.1016/j.nano.2008.11.002 [PubMed: 19217434]
11. Park JK, Utsumi T, Seo YE, et al. Cellular distribution of injected PLGA-nanoparticles in the liver. Nanomedicine. 2016;12 (5):1365–1374. doi: 10.1016/j.nano.2016.01.013 [PubMed: 26961463]

12. Tsoi KM, Macparland SA, Ma XZ, et al. Mechanism of hard-nanomaterial clearance by the liver. Nat Mater. 2016;15 (11):1212–1221. doi: 10.1038/nmat4718 [PubMed: 27525571]
13. Poon W, Zhang YN, Ouyang B, et al. Elimination pathways of nanoparticles. ACS Nano. 2019;13(5):5785–5798. doi: 10.1021/acsnano.9b01383 [PubMed: 30990673] • This paper elucidates the in vivo excretion mechanism of nanoparticles, providing a detailed description of the process by which nanoparticles are excreted through the hepatobiliary pathway.
14. Donahue ND, Acar H, Wilhelm S. Concepts of nanoparticle cellular uptake, intracellular trafficking, and kinetics in nanomedicine. Adv Drug Deliv Rev. 2019;143:68–96. doi: 10.1016/j.addr.2019.04.008 [PubMed: 31022434]
15. Bakrania A, Zheng G, Bhat M. Nanomedicine in hepatocellular carcinoma: a new frontier in targeted cancer treatment. Pharm MDPI. 2021;14(1):41. doi: 10.3390/pharmaceutics14010041
16. Ngo W, Ahmed S, Blackadar C, et al. Why nanoparticles prefer liver macrophage cell uptake in vivo. Adv Drug Deliv Rev. 2022;185:114238. doi: 10.1016/j.addr.2022.114238 [PubMed: 35367524]
17. Tavares AJ, Poon W, Zhang YN, et al. Effect of removing Kupffer cells on nanoparticle tumor delivery. Proc Natl Acad Sci USA. 2017;114(51):E10871–E10880. doi: 10.1073/pnas.1713390114 [PubMed: 29208719]
18. Ye H, Shen Z, Yu L, et al. Manipulating nanoparticle transport within blood flow through external forces: an exemplar of mechanics in nanomedicine. In: Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences. Royal Society Publishing; 2018. https://royalsocietypublishing.org/doi/10.1098/rspa.2017.0845
19. Zhao Z, Ukidve A, Krishnan V, et al. Effect of physicochemical and surface properties on in vivo fate of drug nanocarriers. Adv Drug Deliv Rev. 2019;143:3–21. doi: 10.1016/j.addr.2019.01.002 [PubMed: 30639257]
20. Bergen JM, Von Recum HA, Goodman TT, et al. Gold nanoparticles as a versatile platform for optimizing physicochemical parameters for targeted drug delivery. Macromol biosci. 2006;6(7):506–516. doi: 10.1002/mabi.200600075 [PubMed: 16921538]
21. De Almeida MS, Susnik E, Drasler B, et al. Understanding nanoparticle endocytosis to improve targeting strategies in nanomedicine. Chem Soc Rev R Soc Chem. 2021;50(9):5397–5434. doi: 10.1039/D0CS01127D
22. Soo Choi H, Liu W, Misra P, et al. Renal clearance of quantum dots. Nat Biotechnol. 2007;25(10):1165–1170. doi: 10.1038/nbt1340 [PubMed: 17891134]
23. De Jong WH, Hagens WI, Krystek P, et al. Particle size-dependent organ distribution of gold nanoparticles after intravenous administration. Biomaterials. 2008;29(12):1912–1919. doi: 10.1016/j.biomaterials.2007.12.037 [PubMed: 18242692]
24. Baranov MV, Kumar M, Sacanna S, et al. Modulation of immune responses by particle size and shape. Front Immunol. 2021;11. doi: 10.3389/fimmu.2020.607945
25. Truong NP, Whittaker MR, Mak CW, et al. The importance of nanoparticle shape in cancer drug delivery. Expert Opin Drug Deliv. Informa Healthcare; 2015;12(1):129–142. doi: 10.1517/17425247.2014.950564
26. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. Nat Biotechnol. 2015;33(9):941–951. doi: 10.1038/nbt.3330 [PubMed: 26348965]
27. Li Z, Xiao C, Yong T, et al. Influence of nanomedicine mechanical properties on tumor targeting delivery. Chem Soc Rev R Soc Of Chem. 2020;49(8):2273–2290. doi: 10.1039/C9CS00575G
28. Guo D, Xie G, Luo J. Mechanical properties of nanoparticles: basics and applications. J Phys D Appl Phys. 2014;47(1):013001. doi: 10.1088/0022-3727/47/1/013001
29. Anselmo AC, Zhang M, Kumar S, et al. Elasticity of nanoparticles influences their blood circulation, phagocytosis, endocytosis, and targeting. ACS Nano. 2015;9(3):3169–3177. doi: 10.1021/acsnano.5b00147 [PubMed: 25715979]
30. Shen Z, Ye H, Yi X, et al. Membrane wrapping efficiency of elastic nanoparticles during Endocytosis: size and shape matter. ACS Nano. 2019;13(1):215–228. doi: 10.1021/acsnano.8b05340 [PubMed: 30557506]

31. Tenchov R, Bird R, Curtze AE, et al. Lipid nanoparticles—from liposomes to mRNA vaccine delivery, a landscape of research diversity and advancement. ACS Nano Am Chem Soc. 2021;15 (11):16982–17015. doi: 10.1021/acsnano.1c04996
32. Sanità G, Carrese B, Lamberti A. Nanoparticle surface functionalization: how to improve biocompatibility and cellular internalization. Front Mol Biosci. 2020;7. doi: 10.3389/fmolb.2020.587012
33. Cheng SH, Li FC, Souris JS, et al. Visualizing dynamics of sub-hepatic distribution of nanoparticles using intravital multiphoton fluorescence microscopy. ACS Nano. 2012;6(5):4122–4131. doi: 10.1021/nn300558p [PubMed: 22486639]
34. Ye S, Marston G, McLaughlan JR, et al. Engineering gold nanotubes with controlled length and near-infrared absorption for theranostic applications. Adv Funct Mater. 2015;25(14):2117–2127. doi: 10.1002/adfm.201404358
35. Levchenko TS, Rammohan R, Lukyanov AN, et al. Liposome clearance in mice: the effect of a separate and combined presence of surface charge and polymer coating. Int J Pharm. 2002;240(1–2):95–102. doi: 10.1016/S0378-5173(02)00129-1 [PubMed: 12062505]
36. Friedl JD, Nele V, De Rosa G, et al. Bioinert, stealth or interactive: how surface chemistry of nanocarriers determines their fate in vivo. Adv Funct Mater. 2021;31(34). doi: 10.1002/adfm.202103347
37. Sahay G, Alakhova DY, Kabanov AV. Endocytosis of nanomedicines. J Controlled Release. 2010;145(3):182–195. doi: 10.1016/j.jconrel.2010.01.036
38. Bertrand N, Wu J, Xu X, et al. Cancer nanotechnology: the impact of passive and active targeting in the era of modern cancer biology. Adv Drug Deliv Rev. 2014;66:2–25. doi: 10.1016/j.addr.2013.11.009 [PubMed: 24270007]
39. Bazak R, Houri M, Achy SE, et al. Passive targeting of nanoparticles to cancer: a comprehensive review of the literature. Mol Clin Oncol. 2014;2:904–908. doi: 10.3892/mco.2014.356 [PubMed: 25279172]
40. Narum SM, Le T, Le DP, et al. Passive targeting in nanomedicine: fundamental concepts, body interactions, and clinical potential. Nanoparticles For Biomed Appl: Fundamental Concepts, Biol Interact Clin Appl. 2019:37–53. https://www.sciencedirect.com/science/article/abs/pii/B9780128166628000047
41. Shi L, Zhang J, Zhao M, et al. Effects of polyethylene glycol on the surface of nanoparticles for targeted drug delivery. Nanoscale R Soc Chem. 2021;13(24):10748–10764. doi: 10.1039/D1NR02065J
42. Grenier P, de O VI, Lima EM, et al. Anti-polyethylene glycol antibodies alter the protein corona deposited on nanoparticles and the physiological pathways regulating their fate in vivo. J Controlled Release. 2018;287:121–131. doi: 10.1016/j.jconrel.2018.08.022
43. Yang W, Wang L, Mettenbrink EM, et al. Nanoparticle toxicology. Annu Rev Pharmacol Toxicol. 2021;61(1):269–289. doi: 10.1146/annurev-pharmtox-032320-110338 [PubMed: 32841092]
44. Yang W, Wang L, Fang M, et al. Nanoparticle surface engineering with heparosan polysaccharide reduces serum protein adsorption and enhances cellular uptake. Nano Lett. 2022;22(5):2103–2111. doi: 10.1021/acs.nanolett.2c00349 [PubMed: 35166110]
45. Yang W, Frickenstein AN, Sheth V, et al. Controlling nanoparticle uptake in innate immune cells with Heparosan Polysaccharides. Nano Lett. 2022;22(17):7119–7128. doi: 10.1021/acs.nanolett.2c02226 [PubMed: 36048773]
46. Arvizo RR, Miranda OR, Moyano DF, et al. Modulating pharmacokinetics, tumor uptake and biodistribution by engineered nanoparticles. PLOS ONE. 2011;6(9):6. doi: 10.1371/journal.pone.0024374
47. Nguyen LNM, Ngo W, Lin ZP, et al. The mechanisms of nanoparticle delivery to solid tumours. Nat Rev Bioeng. 2024;2(3):201–213. doi: 10.1038/s44222-024-00154-9
48. Pitek AS, Jameson SA, Veliz FA, et al. Serum albumin ‘camouflage’ of plant virus based nanoparticles prevents their antibody recognition and enhances pharmacokinetics. Biomaterials. 2016;89:89–97. doi: 10.1016/j.biomaterials.2016.02.032 [PubMed: 26950168]

49. Rodriguez PL, Harada T, Christian DA, et al. Minimal 'Self' peptides that inhibit phagocytic clearance and enhance delivery of nanoparticles. Science (1979) [Internet]. 2013;339(6122):971–975. doi: 10.1126/science.1229568 [PubMed: 23430657]
50. Luk BT, Zhang L. Cell membrane-camouflaged nanoparticles for drug delivery. J Controlled Release. 2015;220:600–607. doi: 10.1016/j.jconrel.2015.07.019
51. Ji H, Lou X, Jiao J, et al. Preliminary structural characterization of selenium nanoparticle composites modified by astragalus polysaccharide and the cytotoxicity mechanism on liver cancer cells. Molecules. 2023;28(4):28. doi: 10.3390/molecules28041561
52. Cheng Q, Wei T, Farbiak L, et al. Selective organ targeting (SORT) nanoparticles for tissue-specific mRNA delivery and CRISPR–cas gene editing. Nat Nanotech. 2020;15(4):313–320. doi: 10.1038/s41565-020-0669-6
53. Weaver JL, Tobin GA, Ingle T, et al. Evaluating the potential of gold, silver, and silica nanoparticles to saturate mononuclear phagocytic system tissues under repeat dosing conditions. Part Fibre Toxicol. 2017;14(1):14. doi: 10.1186/s12989-017-0206-4 [PubMed: 28449668]
54. Liu T, Choi H, Zhou R, et al. RES blockade: a strategy for boosting efficiency of nanoparticle drug. Nano Today. 2015;10(1):11–21. doi: 10.1016/j.nantod.2014.12.003
55. Abdollah MRA, Carter TJ, Jones C, et al. Fucoidan prolongs the circulation time of dextran-coated iron oxide nanoparticles. ACS Nano. 2018;12(2):1156–1169. doi: 10.1021/acsnano.7b06734 [PubMed: 29341587]
56. Liu L, Hitchens TK, Ye Q, et al. Decreased reticuloendothelial system clearance and increased blood half-life and immune cell labeling for nano- and micron-sized superparamagnetic iron-oxide particles upon pre-treatment with Intralipid. Biochim Biophys Acta Gen Subj. 2013;1830(6):3447–3453. doi: 10.1016/j.bbagen.2013.01.021
57. Palomba R, Di Francesco M, Di Francesco V, et al. Boosting nanomedicine performance by conditioning macrophages with methyl palmitate nanoparticles. Mater Horiz. 2021;8(10):2726–2741. doi: 10.1039/D1MH00937K [PubMed: 34617542]
58. Lunov O, Zablotskii V, Syrovets T, et al. Modeling receptor-mediated endocytosis of polymer-functionalized iron oxide nanoparticles by human macrophages. Biomaterials. 2011;32(2):547–555. doi: 10.1016/j.biomaterials.2010.08.111 [PubMed: 20880574]
59. Wolfram J, Nizzero S, Liu H, et al. A chloroquine-induced macrophage-preconditioning strategy for improved nanodelivery. Sci Rep. 2017;7(1). doi: 10.1038/s41598-017-14221-2
60. Diagaradjane P, Deorukhkar A, Gelovani JG, et al. Gadolinium chloride augments tumor-specific imaging of targeted quantum dots in vivo. ACS Nano. 2010;4(7):4131–4141. doi: 10.1021/nn901919w [PubMed: 20586481]
61. Van Rooijen N. Liposomes for targeting of antigens and drugs: immunoadjuvant activity and liposome-mediated depletion of macrophages. J Drug Target. 2008;16(7–8):529–534. doi: 10.1080/10611860802228426 [PubMed: 18686122]
62. Ohara Y, Oda T, Yamada K, et al. Effective delivery of chemotherapeutic nanoparticles by depleting host Kupffer cells. Int J Cancer. 2012;131(10):2402–2410. doi: 10.1002/ijc.27502 [PubMed: 22362271]
63. Hao J, Han T, Wang M, et al. Temporary suppression the sequestrated function of host macrophages for better nanoparticles tumor delivery. Drug Deliv. 2018;25(1):1289–1301. doi: 10.1080/10717544.2018.1474965 [PubMed: 29869519]
64. Tavares AJ, Poon W, Zhang YN, et al. Effect of removing Kupffer cells on nanoparticle tumor delivery. Proc Natl Acad Sci USA. 2017;114(51):E10871–80. doi: 10.1073/pnas.1713390114 [PubMed: 29208719]
65. Li Z, Xu X, Feng X, et al. The macrophage-depleting agent clodronate promotes durable hematopoietic chimerism and donor-specific skin allograft tolerance in mice. Sci Rep. 2016;6(1):6. doi: 10.1038/srep22143 [PubMed: 28442741]
66. Wen Y, Lambrecht J, Ju C, et al. Hepatic macrophages in liver homeostasis and diseases-diversity, plasticity and therapeutic opportunities. Cell Mol Immunol. 2021;18(1):45–56. doi: 10.1038/s41423-020-00558-8 [PubMed: 33041338]
67. Tian Z, Hou X, Liu W, et al. Macrophages and hepatocellular carcinoma. Cell Biosci. 2019;9(1). doi: 10.1186/s13578-019-0342-7

68. Bertolani C, Marra F. The role of adipokines in liver fibrosis. Pathophysiology. 2008;15(2):91–101. doi: 10.1016/j.pathophys.2008.05.001 [PubMed: 18602801]
69. Hincapie R, Bhattacharya S, Baksh MM, et al. Multivalent targeting of the asialoglycoprotein receptor by virus-like particles. Small. 2023;19(52). doi: 10.1002/smll.202304263
70. Ferrell L. Liver pathology: cirrhosis, hepatitis, and primary liver tumors. Update and diagnostic problems. Mod Pathol. 2000;13 (6):679–704. doi: 10.1038/modpathol.3880119 [PubMed: 10874674]
71. Soares GA, Pereira GM, Romualdo GR, et al. Biodistribution profile of magnetic nanoparticles in cirrhosis-associated hepatocarcino-genesis in rats by AC biosusceptometry. Pharmaceutics. 2022;14 (9):14. doi: 10.3390/pharmaceutics14091907
72. Huang D, Sun L, Huang L, et al. Nanodrug delivery systems modulate tumor vessels to increase the enhanced permeability and retention effect. J Pers Med MDPI AG. 2021;11(2):124–126. doi: 10.3390/jpm11020124
73. Georges PC, Hui J-J, Gombos Z, et al. Increased stiffness of the rat liver precedes matrix deposition: implications for fibrosis. Am J Physiol-Gastrointestinal Liver Physiol. 2007;293(6):G1147–G1154. doi: 10.1152/ajpgi.00032.2007
74. He X, Chang Z, Chen F, et al. Engineering a biomimetic system for hepatocyte-specific RNAi treatment of non-alcoholic fatty liver disease. Acta Biomater. 2024;174:281–296. doi: 10.1016/j.actbio.2023.10.038 [PubMed: 37951519]
75. Stone NRH, Bicanic T, Salim R, et al. Liposomal Amphotericin B (AmBisome®): a review of the pharmacokinetics, pharmacody namics, clinical experience and future directions. Drugs. 2016;76 (4):485–500. doi: 10.1007/s40265-016-0538-7 [PubMed: 26818726]
76. Sundar S, Chakravarty J. Liposomal amphotericin B and leishmaniasis: dose and response. J Glob Infect Dis. 2010;2(2):159. doi: 10.4103/0974-777X.62886 [PubMed: 20606972]
77. Daemen T, Hofstede G, Ten Kate MT, et al. Liposomal doxorubicin-induced toxicity: depletion and impairment of phagocytic activity of liver macrophages. Int J Cancer. 1995;61(5):716–721. doi: 10.1002/ijc.2910610520 [PubMed: 7768646]
78. Paunovska K, Loughrey D, Dahlman JE. Drug delivery systems for RNA therapeutics. Nat Rev Genet Nat Res. 2022;23(5):265–280. doi: 10.1038/s41576-021-00439-4
79. Liu GW, Guzman EB, Menon N, et al. Lipid nanoparticles for nucleic acid delivery to Endothelial Cells. Pharm Res. 2023;40(1):3–25. doi: 10.1007/s11095-023-03471-7 [PubMed: 36735106]
80. El Moukhtari SH, Garbayo E, Amundarain A, et al. Lipid nanoparticles for siRNA delivery in cancer treatment. J Controlled Release. 2023;361:130–146. doi: 10.1016/j.jconrel.2023.07.054
81. Ahn I, Kang CS, Han J. Where should siRNAs go: applicable organs for siRNA drugs. Exp Mol Med. 2023;55(7):1283–1292. doi: 10.1038/s12276-023-00998-y [PubMed: 37430086]
82. van den Berg A, Mols J, Han J. RISC-target interaction: cleavage and translational suppression. Biochim Biophys Acta, Gene Regul Mech. 2008;1779(11):668–677. doi: 10.1016/j.bbagrm.2008.07.005
83. Zhang MM, Bahal R, Rasmussen TP, et al. The growth of siRNA-based therapeutics: updated clinical studies. Biochem Pharmacol. 2021;189:114432. doi: 10.1016/j.bcp.2021.114432 [PubMed: 33513339]
84. Madigan V, Zhang F, Dahlman JE. Drug delivery systems for CRISPR-based genome editors. Nat Rev Drug Discov Nat Res. 2023;22(11):875–894. doi: 10.1038/s41573-023-00762-x
85. Qin S, Tang X, Chen Y, et al. mRNA-based therapeutics: powerful and versatile tools to combat diseases. Signal Transduct Target Ther. 2022;7(1). doi: 10.1038/s41392-022-01007-w
86. Chung S, Lee CM, Zhang M. Advances in nanoparticle-based mRNA delivery for liver cancer and liver-associated infectious diseases. Nanoscale Horiz. 2022;8(1):10–28. doi: 10.1039/D2NH00289B [PubMed: 36260016]
87. Akinc A, Querbes W, De S, et al. Targeted delivery of RNAi therapeutics with endogenous and exogenous ligand-based mechanisms. Mol Ther. 2010;18(7):1357–1364. doi: 10.1038/mt.2010.85 [PubMed: 20461061]
88. Qiu M, Glass Z, Chen J, et al. Lipid nanoparticle-mediated codelivery of Cas9 mRNA and single-guide RNA achieves liver-specific in vivo genome editing of Angptl3.

89. Rizvi F, Everton E, Smith AR, et al. Murine liver repair via transient activation of regenerative pathways in hepatocytes using lipid nanoparticle-complexed nucleoside-modified mRNA. Nat Commun. 2021;12(1):12. doi: 10.1038/s41467-021-20903-3 [PubMed: 33397888]

90. Paunovska K, Da Silva Sanchez AJ, Sago CD, et al. Nanoparticles containing oxidized cholesterol deliver mRNA to the liver microenvironment at clinically relevant doses. Adv Mater. 2019;31(14):31. doi: 10.1002/adma.201807748

91. Paunovska K, Gil CJ, Lokugamage MP, et al. Analyzing 2000 in vivo drug delivery data points reveals cholesterol structure impacts nanoparticle delivery. ACS Nano. 2018;12(8):8341–8349. doi: 10.1021/acsnano.8b03640 [PubMed: 30016076]

92. Kazemian P, Yu SY, Thomson SB, et al. Lipid-nanoparticle-based delivery of CRISPR/Cas9 genome-editing components. Mol Pharm Am Chem Soc. 2022;19(6):1669–1686. doi: 10.1021/acs.molpharmaceut.1c00916

93. Kowalski PS, Rudra A, Miao L, et al. Delivering the messenger: advances in technologies for therapeutic mRNA delivery. Mol Ther. 2019;27(4):710–728. doi: 10.1016/j.ymthe.2019.02.012 [PubMed: 30846391]

94. La-Beck NM, Zamboni BA, Gabizon A, et al. Factors affecting the pharmacokinetics of pegylated liposomal doxorubicin in patients. Cancer Chemother Pharmacol. 2012;69(1):43–50. doi: 10.1007/s00280-011-1664-2 [PubMed: 21590446]

95. Chen N, Li Y, Ye Y, et al. Pharmacokinetics and pharmacodynamics of nab-paclitaxel in patients with solid tumors: disposition kinetics and pharmacology distinct from solvent-based paclitaxel. J Clin Pharmacol. 2014;54(10):1097–1107. doi: 10.1002/jcph.304 [PubMed: 24719309]

96. Jiang W, Wang Y, Wargo JA, et al. Considerations for designing preclinical cancer immune nanomedicine studies. Nat Nanotech. 2021;16(1):6–15. doi: 10.1038/s41565-020-00817-9

97. Van Herck Y, Feyaerts A, Alibhai S, et al. Is cancer biology different in older patients? Lancet Healthy Longev. 2021;2(10):e663–77. doi: 10.1016/S2666-7568(21)00179-3 [PubMed: 36098020]

98. Conforti F, Pala L, Bagnardi V, et al. Cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis. Lancet Oncol. 2018;19(6):737–746. doi: 10.1016/S1470-2045(18)30261-4 [PubMed: 29778737]

99. Li J, Lan Z, Liao W, et al. Histone demethylase KDM5D upregulation drives sex differences in colon cancer. Nature. 2023;619 (7970):632–639. doi: 10.1038/s41586-023-06254-7 [PubMed: 37344599]

100. Zamboni WC, Maruca LJ, Strychor S, et al. Bidirectional pharmacodynamic interaction between pegylated liposomal CKD-602 (S-CKD602) and monocytes in patients with refractory solid tumors. J Liposome Res. 2011;21(2):158–165. doi: 10.3109/08982104.2010.496085 [PubMed: 20626314]

101. Serpooshan V, Sheibani S, Pushparaj P, et al. Effect of Cell Sex on uptake of nanoparticles: the overlooked factor at the nanobio interface. ACS Nano. 2018;12(3):2253–2266. doi: 10.1021/acsnano.7b06212 [PubMed: 29536733]

102. Wang Y, Deng W, Lee DY, et al. Age-associated disparity in phagocytic clearance affects the efficacy of cancer nanotherapeutics. Nat Nanotechnol. 2024;19(2):255–263. doi: 10.1038/s41565-023-01502-3 [PubMed: 37723279] •• This paper demonstrates age-related disparities in the anti-tumor efficacy of cancer nanomedicine, starting from differences in the functionality of hepatic macrophages and identifying expression disparities at the transcriptomic and protein levels.

103. Hamilton RF, Thakur SA, Mayfair JK, et al. MARCO mediates silica uptake and toxicity in alveolar macrophages from C57BL/6 mice. J Biol Chem. 2006;281(45):34218–34226. doi: 10.1074/jbc.M605229200 [PubMed: 16984918]

104. Hirano S, Fujitani Y, Furuyama A, et al. Macrophage receptor with collagenous structure (MARCO) is a dynamic adhesive molecule that enhances uptake of carbon nanotubes by CHO-K1 cells. Toxicol Appl Pharmacol. 2012;259(1):96–103. doi: 10.1016/j.taap.2011.12.012 [PubMed: 22209804]

105. Rabiee N, Dokmeci MR, Zarrabi A, et al. Green Biomaterials: fundamental principles. Green Biomater. 2023;1(1):1–4. doi: 10.1080/29934168.2023.2268943

106. Dahlman JE, Kauffman KJ, Xing Y, et al. Barcoded nanoparticles for high throughput in vivo discovery of targeted therapeutics. Proc Natl Acad Sci USA. 2017;114(8):2060–2065. doi: 10.1073/pnas.1620874114 [PubMed: 28167778]

107. Dobrowolski C, Paunovska K, Schrader Echeverri E, et al. Nanoparticle single-cell multiomic readouts reveal that cell heterogeneity influences lipid nanoparticle-mediated messenger RNA delivery. Nat Nanotech. 2022;17(8):871–879. doi: 10.1038/s41565-022-01146-9

Article highlights

- Systemically administered nanoparticles often predominantly accumulate in the liver.
- Nanoparticles can be designed with specific physicochemical properties to reduce liver accumulation and enhance targeted delivery.
- Strategies, such as Kupffer cell inhibition and depletion, have been used to reduce the phagocytic activity and improve nanoparticle delivery efficiency.
- Lipid nanoparticles (LNPs) and liposomes have been extensively studied for treating liver diseases, emphasizing their capacity to deliver drugs to both Kupffer cells and hepatocytes.
- Biological variables, such as sex and age, significantly impact nanoparticle clearance and nanomedicine safety and efficacy, necessitating age- and sex-specific targeting strategies.

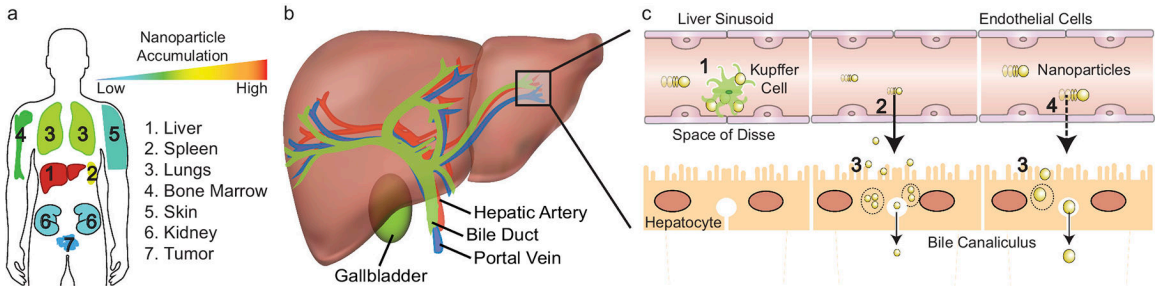

Figure 1.

Overview of nanoparticle-liver interactions. (a) The majority of administered nanoparticles often accumulate in the liver. Other organs and tissues typically exhibit lower nanoparticle accumulation. Note: The described relative biodistribution and nanoparticle accumulation may vary significantly for different nanoparticle formulations and injection doses. (b) Schematic of liver vasculature. Blood flows into the liver through the hepatic veins and arteries, forming the portal triad with the bile duct. These vessels direct blood from each portal triad to the three nearest central veins, while bile flows in the opposite direction for excretion. (c) The mechanism of nonbiodegradable nanoparticle hepatobiliary elimination in the liver sinusoid is depicted. Intravenously administered nanoparticles enter the liver and move into the liver sinusoid. (c,1) Liver-resident macrophages, called Kupffer cells, predominantly sequester circulating nanoparticles based on size, with a preference for larger nanoparticles. (c,2) Upon removing Kupffer cells from the liver sinusoid, more nanoparticles transport through the liver sinusoidal endothelium. (c,4) the transport of larger nanoparticles may be hindered by the fenestrae size limit of the liver sinusoidal endothelial cell. (c,3) Nanoparticles then accumulate in the Space of Disse, where hepatocytes gradually take them up and process them for transport into the bile canaliculus. Nanoparticles then transport out of the liver into the intestines and eventually exit the body via feces. Panel 1a, reprinted/adapted with permission by John Wiley & Sons, Inc [5]. Panel 1c, reprinted (adapted) with permission from [10.1021/acsnano.9b01383]. Copyright 2019 American Chemical Society.

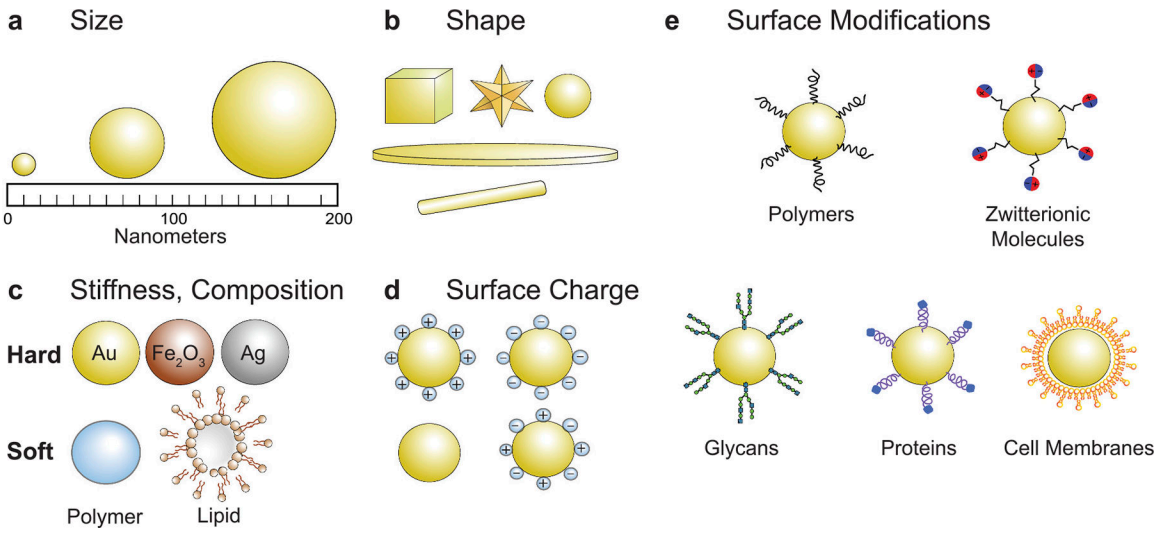

Figure 2.

Mediating nanoparticle uptake in the liver through material design approaches. The physicochemical properties of nanoparticles can be engineered to mitigate nanoparticle interactions with the liver. The design approaches span nanoparticle characteristics such as (a) size, (b) shape, (c) stiffness, composition, and (d) surface charge. In addition, (e) nanoparticle surface modifications can be used to create a variety of surface chemistries from purely synthetic to biologically-inspired modifications, thereby mitigating nanoparticle liver clearance efficiency. Reprinted/adapted with permission by John Wiley & Sons, Inc [5].

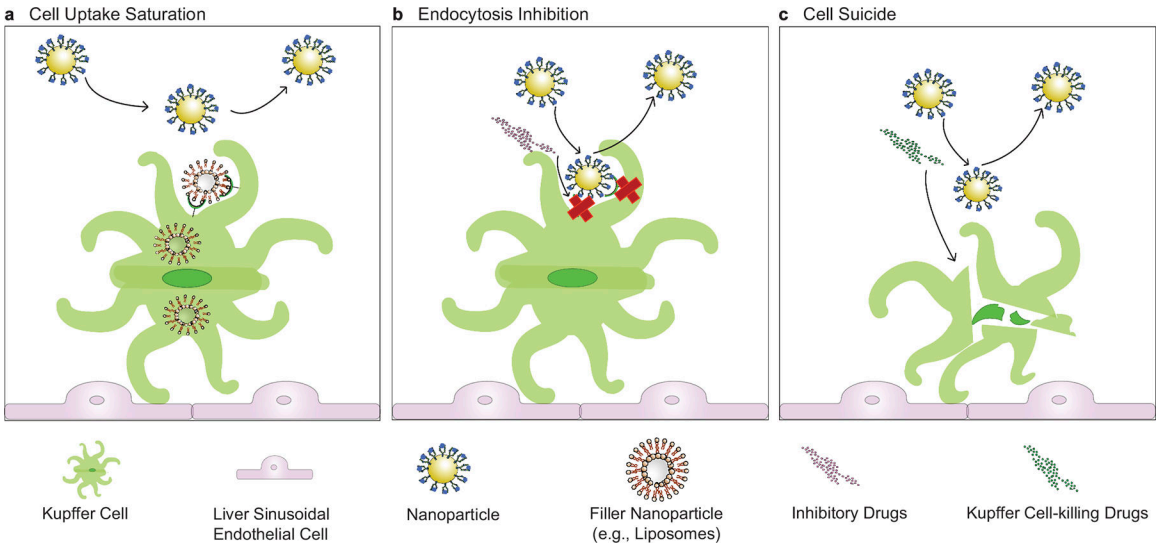

Figure 3.

Strategies for the biological modulation of nanoparticle-liver interactions. (a) Saturation preconditioning involves overloading Kupffer cells with a non-therapeutic filler nanoparticle. This chosen nanoparticle is typically nontoxic and degrades rapidly after a specific duration. The saturated Kupffer cells can no longer engulf additional nanoparticles, enabling subsequent administration of therapeutic/diagnostic nanoparticles to bypass Kupffer cells and distribute more effectively to target tissues. (b) Endocytosis inhibition strategies utilize drugs to impede interactions between Kupffer cells and nanoparticles. One mechanism involves disrupting endocytosis by blocking receptor-nanoparticle corona interactions. This prevents nanoparticles from attaching to Kupffer cell membranes, allowing more efficient interaction with target tissues. (c) The cell suicide strategy employs drugs to induce cell death in part or all of resident tissue macrophage populations, reducing nanoparticle sequestration by Kupffer cells. Reprinted/adapted with permission by John Wiley & Sons, Inc [5].

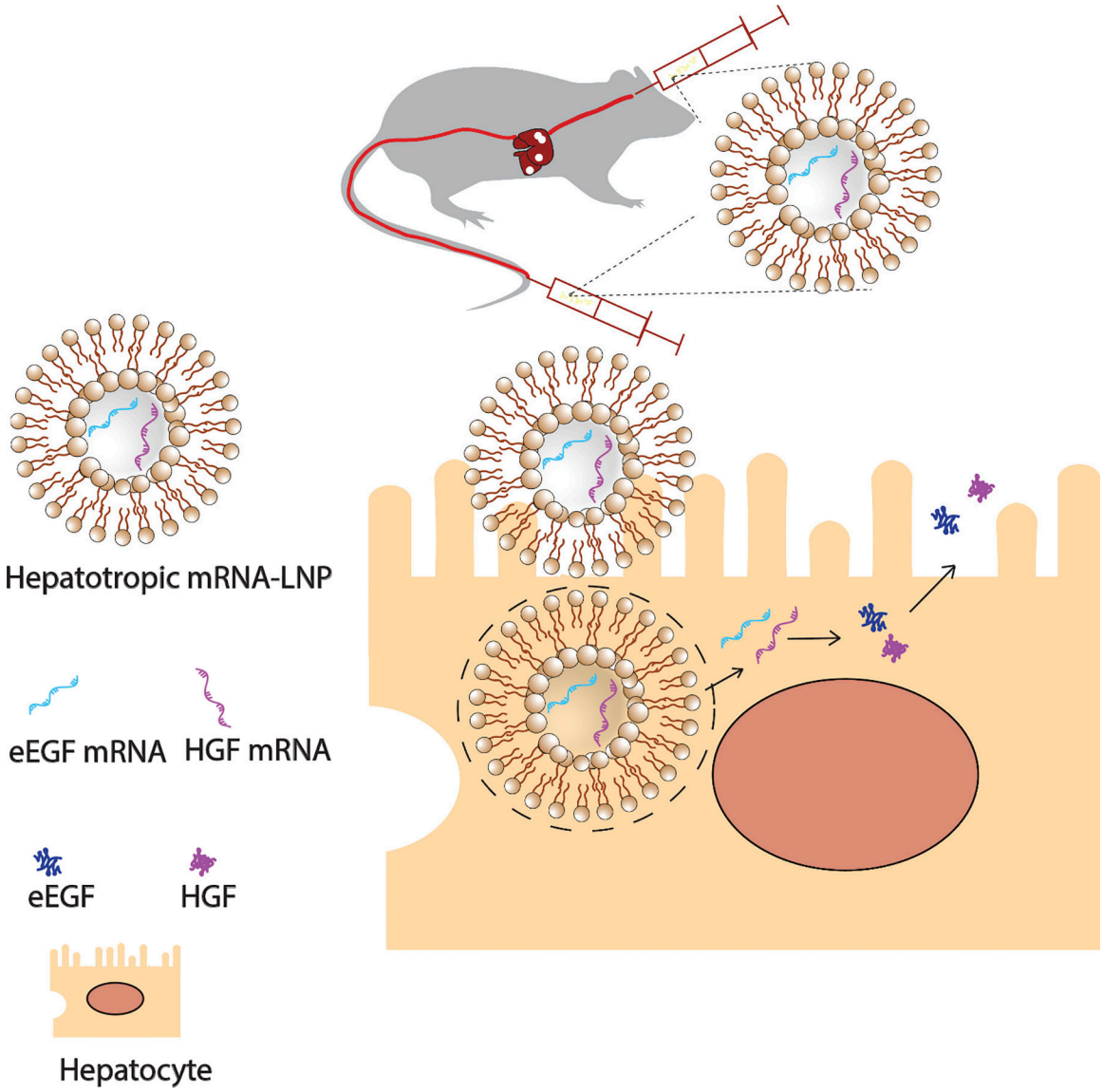

Figure 4.

Schematic representation of LNP-facilitated in vivo liver repair. HGF mRNA and EGF mRNA are encapsulated in LNPs, establishing specific hepatotropism of mRNA-LNP. These LNPs are then administered via intravenous injection to a liver injury mouse model. Subsequently, HGF mRNA and EGF mRNA are translated into proteins to assist in liver regeneration. Reprinted/adapted with permission by SpringerNature [88].

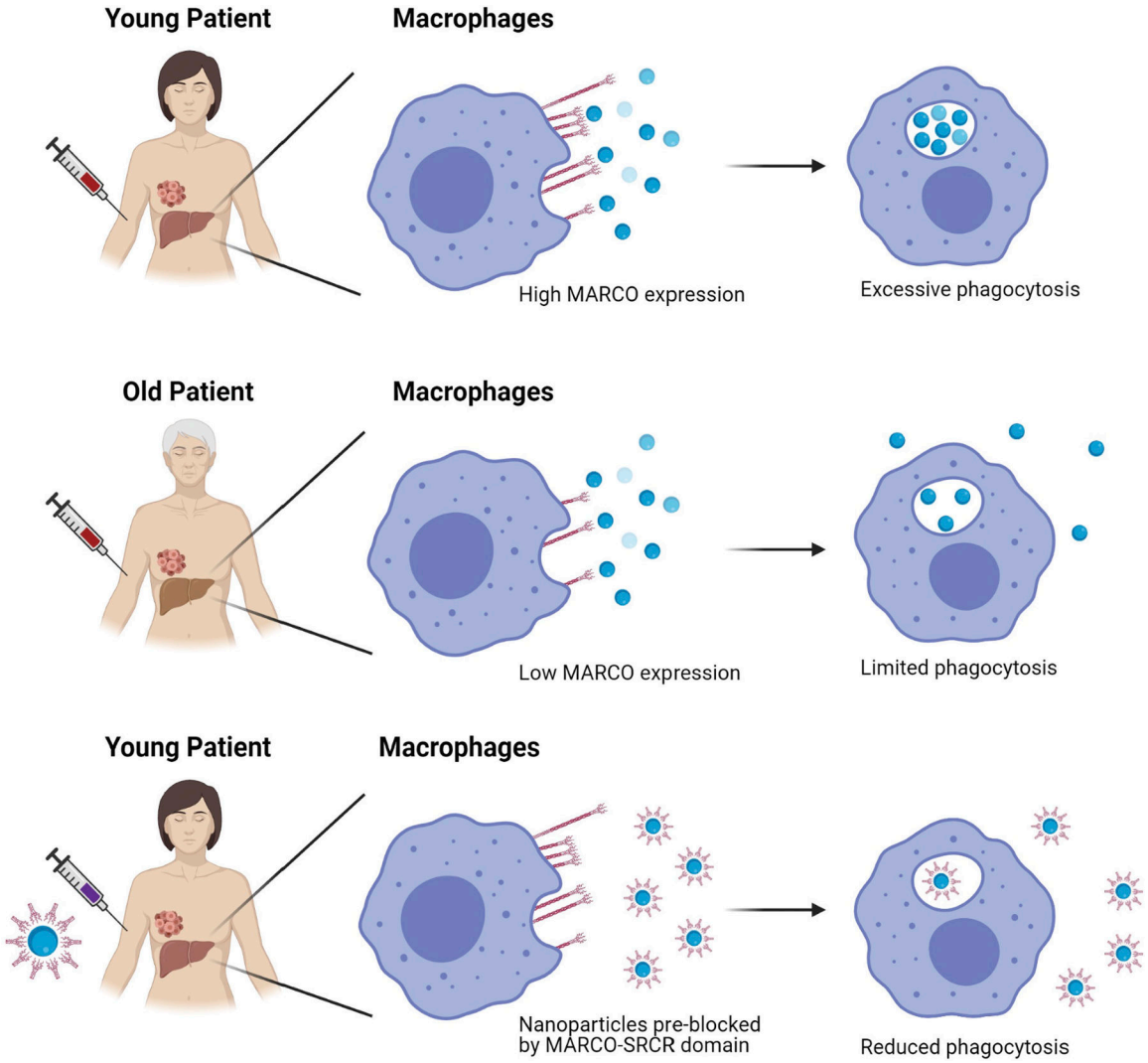

Figure 5.

Age-associated MARCO expression in the effectiveness of nanoparticle uptake by liver macrophages. the expression of macrophage scavenger receptor MARCO is generally down-regulated during biological aging, and MARCO is related to the ability of macrophages to take up nanoparticles. Blocking the interaction between nanoparticles and MARCO enhances the effect of drug delivery to tumors. Created with BioRender.