Journal of Nanobiotechnology

REVIEW

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Emerging strategies against accelerated blood clearance phenomenon of nanocarrier drug delivery systems

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Abstract

Nanocarrier drug delivery systems (NDDS) have gained momentum in the field of anticancer or nucleic acid drug delivery due to their capacity to aggrandize the targeting efficacy and therapeutic outcomes of encapsulated drugs. A disadvantage of NDDS is that repeated administrations often encounter an obstacle known as the "accelerated blood clearance (ABC) phenomenon". This phenomenon results in the rapid clearance of the secondary dose from the bloodstream and markedly augmented liver accumulation, which substantially undermines the accurate delivery of drugs and the therapeutic effect of NDDS. Nevertheless, the underlying mechanism of this phenomenon has not been elucidated and there is currently no effective method for its eradication. In light of the above, the aim of this review is to provide a comprehensive summary of the underlying mechanism and potential countermeasures of the ABC phenomenon, with a view to rejuvenating both the slow-release property and expectation of NDDS in the clinic. In this paper, we innovatively introduce the pharmacokinetic mechanism of ABC phenomenon to further elucidate its occurrence mechanism after discussing its immunological mechanism, which provides a new direction for expanding the mechanistic study of ABC phenomenon. Whereafter, we conducted a critical conclusion of potential strategies for the suppression or prevention of the ABC phenomenon in terms of the physical and structural properties, PEG-lipid derivatives, dosage regimen and encapsulated substances of nanoformulations, particularly covering some novel high-performance nanomaterials and mixed modification methods. Alternatively, we innovatively propose a promising strategy of applying the characteristics of ABC phenomenon, as the significantly elevated hepatic accumulation and activated CYP3A1 profile associated with the ABC phenomenon are proved to be conducive to enhancing the efficacy of NDDS in the treatment of hepatocellular carcinoma. Collectively, this review is instructive for surmounting or wielding the ABC phenomenon and advancing the clinical applications and translations of NDDS.

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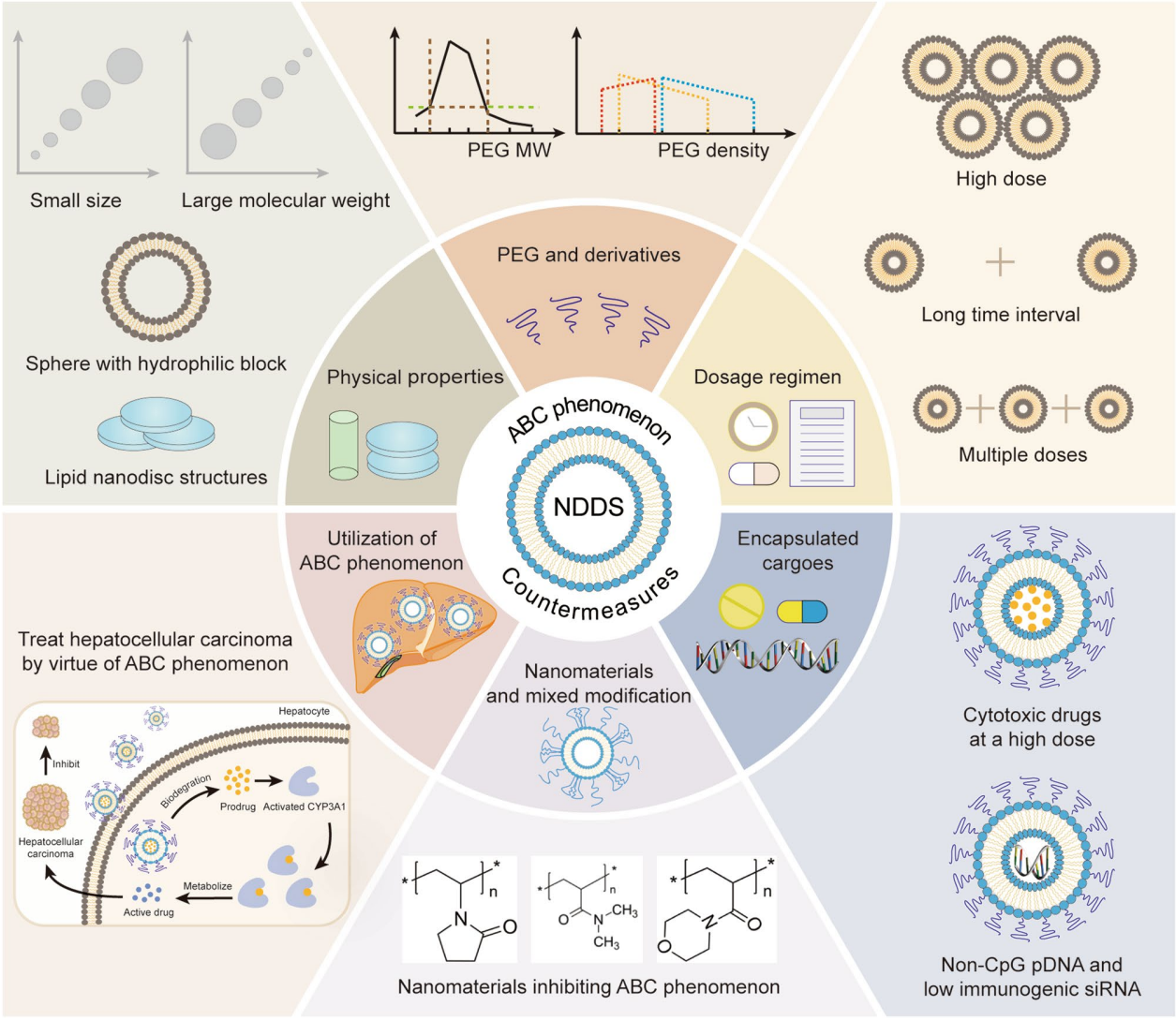
Graphical abstract



Keywords Nanocarrier drug delivery systems, Nanotechnology, Nanomedicine, Accelerated blood clearance phenomenon, Nanomaterials, Clinical application, Countermeasures

Background

The application of nanocarrier drug delivery systems (NDDS) in clinical disease treatment has received considerable attention due to their excellent quality, which includes the improvement of pharmacokinetic profiles and bioavailability of the carried drugs, accurate delivery of drugs to tumor or target sites, and other benefits [1–4]. But the nanoparticles circulating in the blood are easily recognized and opsonized by opsonin, making nanoparticles more susceptible to phagocytic clearance from blood by phagocytes in the mononuclear phagocyte system (MPS), which includes opsonin-mediated phagocytosis of nanoparticles by phagocytes and the direct capture of nanoparticles by phagocytes through opsonin-independent scavenger receptors [5, 6]. The MPS, previously known as the reticuloendothelial system (RES), consists of dendritic cells, monocytes, granulocytes, and macrophages in the liver, spleen, and lymph nodes, along with their bone marrow progenitors [5–7]. Endothelial cells within organs related to the MPS are commonly fenestrated, which aids in the filtering of substances in the bloodstream. Nanoparticles with 100 nm size can pass through the endothelial fenestrations in the liver and spleen, as well as the vascular endothelium in lymph nodes [6]. Hence, the MPS offers a pivotal defense mechanism that is responsible for the degradation and

removal of exogenous substances from the blood, such as foreign pathogens and therapeutic nanoparticles. Polyethylene glycol (PEG) modification is widely recognized as a promising nanotechnology due to its established safety in humans and its ability to extend the circulation time of nanocarriers [5, 6]. This is achieved through the hydrophilic PEG chains forming a hydration layer around nanoparticles, which reduces the recognition and binding of nanoparticles by opsonin via spatial repulsion. Consequently, PEG modification evades recognition by the MPS, thereby decreasing phagocytosis and clearance from the bloodstream. However, some adverse reactions have occurred during the application of PEGylated liposomes (PL), such as hand-foot syndrome (or palmar-plantar erythrodysesthesia), hypersensitivity reactions, and accelerated blood clearance (ABC) phenomenon [8–10].

The focus of this article is the ABC phenomenon that is characterized by an anomalous pharmacokinetic and biodistribution alteration following repeated intravenous administrations of PL, which challenges the prevailing assumption that PEG is hypoimmunogenic [10]. In this phenomenon, the second dose of PL is rapidly eliminated from the bloodstream following the initial injection, accompanied by a significantly increased accumulation in the liver. This results in the loss of the long circulation time associated with PEGylation, leading to reduced delivery efficiency and efficacy of the nanoformulations. In addition to intravenous injection, the ABC phenomenon was occasioned by subsequently intravenous injection of PEGylated solid lipid nanoparticles (PSLN) when subcutaneous injection of PSLN first, meanwhile, the strength of accelerated clearance caused by subcutaneous injection was tantamount or even lower compared to intravenous injection first [11]. Furthermore, intraperitoneal injection of PEGylated nanoemulsions (PE) has also been observed to induce the ABC phenomenon [12]. The nanocarrier types that have been demonstrated to induce the ABC phenomenon are summarized in Table 1; Fig. 1, ranging through liposome, nanoparticle, micelle, emulsion, solid lipid nanoparticle, lipid nanoparticle (LNP), microbubble, and exosome [10, 11, 13–18]. Worth the whistle, ABC phenomenon can be apparently induced by repeated injections of conventional liposomes (CL) without PEGylation, which displayed that PEG modification is not a prerequisite for ABC phenomenon [19]. Additionally, the ABC phenomenon has been observed in a diverse range of animal species, including Wistar rats, mice, beagle dogs, cynomolgus monkeys and minipigs [20, 21]. It is a cause for concern that repeated dosing resulted in the accelerated clearance of PEGylated asparaginase in humans, meaning that NDDS that require

Table 1 Nanocarrier types eliciting ABC phenomenon and some specific nanoformulations

Nanocarrier type	Nanoformulation	Ref.
Liposome	PEGylated liposome	[10, 105]
	Conventional liposome	[19]
	PEGylated liposomal doxorubicin	[20, 31]
	PEGylated cationic liposome	[38, 137]
	DSPE-PEG_{2000}-4-aminophenyl-α-D-mannopyranoside and DSPE-PEG_{2000}-4-aminophenyl-β-L-fucopyranoside co-modified PEGylated liposome	[40]
	PEGylated liposomal Gambogenic Acid	[64]
	PEGylated liposomal topotecan	[120]
	PEGylated liposome containing pDNA	[123]
	PEGylated cationic liposome encapsulating small interfering RNA	[124]
	PEGylated thermosensitive liposome	[127]
Nanoparticle	PEGylated gold nanoparticle	[13]
	PEGylated PLGA nanoparticle	[75]
	Etoposide-encapsulated PEGylated PLGA nanoparticle	[99]
	Prostaglandin E1-encapsulated PEG-PLA nanoparticle	[108]
Micelle	Lactosome	[51, 98]
	Polymeric micelle	[70, 144]
	PEGylated micelle	[14]
Emulsion	PEGylated emulsion	[15, 86]
	PEGylated nanoemulsion	[12, 42]
Solid lipid nanoparticle	PEGylated solid lipid nanoparticle	[11, 85]
Lipid nanoparticle	PEGylated lipid nanoparticle	[18, 33, 96, 133]
Microbubble	PEGylated microbubble	[16]
	Optison microbubble	[16]
Exosome	PEGylated exosome	[17]

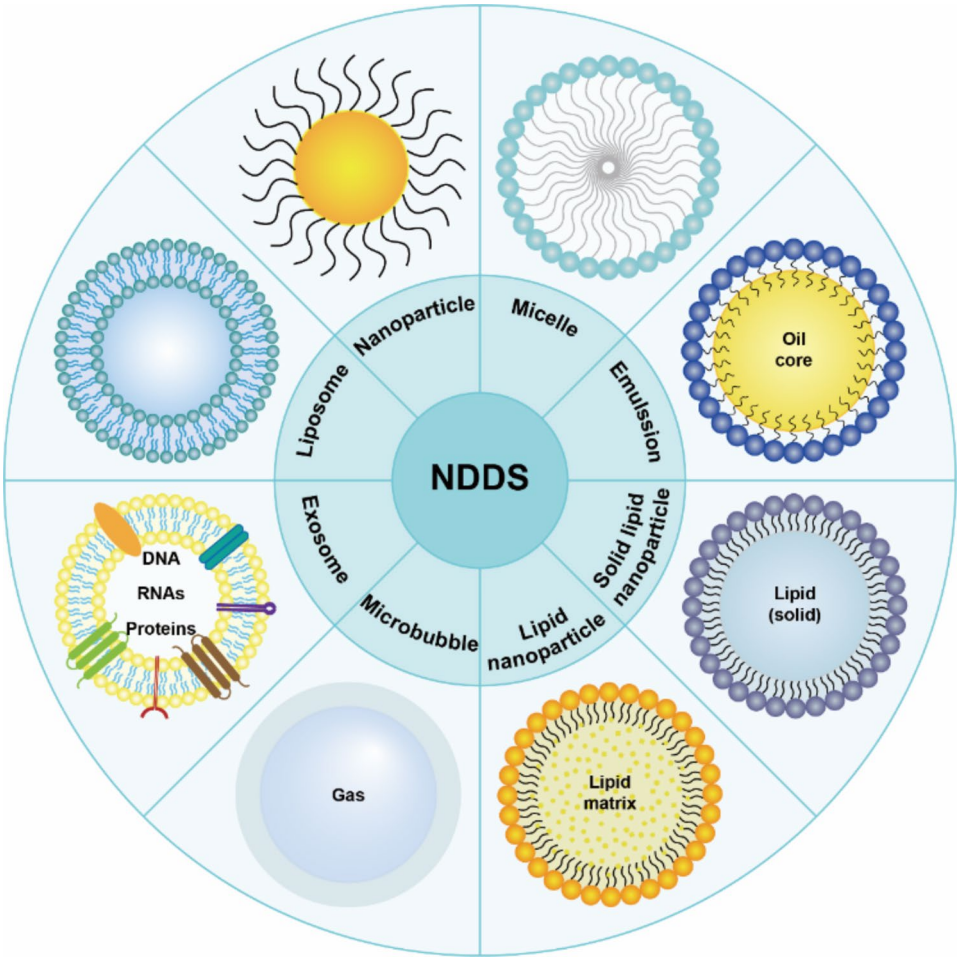


Fig. 1 Basic structure drawing of nanocarrier types engendering ABC phenomenon. The nanocarrier types engendering ABC phenomenon range through liposome, nanoparticle, micelle, emulsion, solid lipid nanoparticle, lipid nanoparticle, microbubble, and exosome

repeated administration may be got into hot water in clinical practice [22].

Despite the plethora of literature on the ABC phenomenon, the majority of it is centered on the investigation of immunological mechanisms and the development of innovative nanomaterials with immunosuppressive properties. Moreover, the existing reviews presents an overview lacking a systematic delineation of specific interventions to address the ABC phenomenon. The objective of this paper is to present practical and feasible strategies for NDDS to effectively address the ABC phenomenon and to provide a comprehensive exploration of the underlying mechanisms. This paper discusses the countermeasures of the ABC phenomenon from various perspectives and proposes innovative strategies of leveraging the characteristics of the ABC phenomenon. It also places particular emphasis on the study of the pharmacokinetic mechanism of the ABC phenomenon, discussing its research value and potentiality. Finally, an outlook on the development and potential direction of research on coping strategies and mechanisms of ABC phenomenon is offered.

Mechanisms related to the ABC phenomenon

The ABC phenomenon induced by repeated administrations of NDDS, as an obstacle, hampers the favorable development and treatment potency of numerous NDDS. Accordingly, it is imperative and prerequisite to gain an understanding of latent mechanism of ABC phenomenon, for the sake of contriving feasible countermeasures of ABC phenomenon. The focus on the mechanism of the ABC phenomenon is primarily within the immunological field. However, the application of immunological knowledge alone is inadequate, as evidenced by critical thinking and experimental results. Thus, we propose an innovative approach that integrates pharmacokinetic studies to complement and expand our understanding of the ABC phenomenon. In the following, the interrelated mechanism studies are expounded from both immunological and pharmacokinetic perspectives.

Immunological perspective

As an early report, ABC phenomenon was induced in normal rats that were given an infusion of serum from rats with a pretreatment of PL, exhibiting that some undefined serum factors participated in producing the phenomenon [10]. Subsequently, some researchers suggested that the prime protein having a binding behavior to PEGylated formulations was anti-PEG IgM antibody, which was the reason of their ABC phenomenon [19, 23]. High anti-PEG IgM concentration was also induced by injection of PEGylated exosomes, peginterferon alfa-2a and PL containing toll-like receptor agonists, and then triggering accelerated clearance of second dose, which indicated that ABC phenomenon was in tight correlation with opsonization of anti-PEG IgM antibody [9, 17, 24]. In addition, anti-PEG IgG antibodies were also induced by intravenous injection of PE, which could bind to PE and accelerate its clearance, showing that IgG antibody was also responsible for the accelerated elimination of PEGylated formulations [25]. Interestingly, subsequent studies reported that anti-PEG IgM and IgG reactions were produced concurrently when repeated administration of PEGylated gold nanoparticles, PEGylated microbubbles, and methoxy polyethylene glycol (mPEG)-epoetin beta, which gave them all a significant ABC phenomenon [13, 16, 26]. It was the affinity of anti-PEG antibody to bind PEG that probably may have a variation based on whether they are congenital or acquired, and higher antibody affinity brought about bigger combination trend and fiercer clearance [27]. Notably, anti-PEG antibodies in the circulation, either treatment-elicited or pre-existing, are able to bind PEG molecules, leading to ABC phenomenon of PEGylated formulations [28].

Spleen is well known to play a vital role in immune reactions and produce IgM antibodies following an external pathogen infection [29]. Previously, it had stated that ABC phenomenon intensity and serum concentration of anti-PEG IgM were seriously diminished in rats treated by a splenectomy in advance of first administration of PL [30]. Moreover, after first subcutaneous injection of PSLN, a slight number of particles accumulated in spleen and the majority was drained into lymphatics, which presented increased uptake in regional lymph nodes, subsequently bringing into contact with a bulk of lymphocytes and initiation of specifically immune reaction to PEG, testifying the contribution of lymph nodes in ABC phenomenon [11].

It was reported that PEG polymer was featured as a repetitious structure with resemblance to T cell-independent type 2 antigens and the repetitious subunits might be a binding site of anti-PEG IgM and function as antigen epitopes of PEG, displaying that PL may arouse anti-PEG IgM responses in a T cell-independent manner and run as T cell-independent type 2 antigens [31, 32]. The B-1 lymphocytes and B-2 lymphocytes were activated in order by repeated injections of mRNA-loaded LNP, which brought about generation of anti-phosphorylcholine IgM and a classic anti-PEG immune reaction respectively, synergistically inducing the ABC phenomenon of mRNA-loaded LNP [33]. Specially, anti-PEG IgM response induced by a recombinant PEGylated human granulocyte colony-stimulating factor was dreadfully mitigated in athymic nude mice lacking T cells, being different from other nanoformulations [34]. PL predominantly cumulated in the splenic marginal zone upon intravenous injection and the splenic marginal zone B cells were dominant IgM-positive B cells, tightly associated with induction of anti-PEG IgM [35, 36]. The marginal zone B cells could recognize the immune complex of anti-PEG IgM-PEGylated liposomes-complement system and operate the drainage of the complex to follicle region in spleen. Thereby, both marginal zone and follicular B cells had an integral role in anti-PEG IgM production attracted by PEGylated formulations. When depleting hepatosplenic phagocytes, anti-PEG IgM generation and accelerated elimination elicited by PL and PEGylated cationic liposomes were appreciably mitigated, exhibiting the involvement of hepatosplenic phagocytes in induction of ABC phenomenon [37, 38]. Kupffer cells, a sort of hepatic phagocytes, had the capability to phagocytize extrinsic pathogens and substances, deemed to account for hepatic aggregation of nanoparticles [39]. The augmentation of opsonization-independent phagocytic activity of Kupffer cells coupled with hyperresponsiveness of Kupffer cells to antigen-antibody complexes was the reason of ABC phenomenon induced by repeated injections of PE [15]. Besides, a di-ligand modified PEGylated liposome (MFPL) with potent ability to target Kupffer cells elicited enhanced ABC phenomenon in rats compared to PL, which illustrated that fiercer ABC phenomenon was aroused behind more Kupffer cells were evoked [40]. Correspondingly, ABC phenomenon was outstandingly suppressed by applying MFPL to load alendronate sodium to deplete Kupffer cells [41]. Of attention, the inborn immune memory of Kupffer cells against PE was ignited, which can be adoptively transferred into the naïve rats and persist 21 days, raising hepatic distribution of PE in the naïve rats without antibody [42]. Furthermore, the systemic clearance of nanoparticles may require coordinated collaboration among many MPS cell populations. Beyond hepatosplenic phagocytes, it was shown that antibody binding could promote the recognition and phagocytic clearance of nanoparticle in circulation by antigen-presenting dendritic cells [43]. Kupffer cells, dendritic cells and other immune cells have been reported to be concurrently related to the rapid clearance of virus-like nanoparticles to the liver after injection into mice [44]. Following intravenous administration, blood

monocytes were demonstrated to mediate nanoparticle clearance in mice [45]. The cellular uptake of nanoparticles was able to enhance the phagocytic capacity of monocytes, macrophages, and neutrophils [46]. Recent studies have further revealed that marginated neutrophil granulocytes in the lung actively compete for and efficiently clear intravascular nanoparticles [47]. Therefore, although existing literature has predominantly focused on hepatosplenic macrophages as key contributors to the blood clearance of nanoparticles in the ABC phenomenon, the potential involvement of other MPS cell types remains an important area for further exploration.

The complement system could be activated after recognition of exogenous materials and immunocomplexes, and then mediate their clearance from systemic circulation [48]. The complement system was mostly actuated by a classical pathway mediated by anti-PEG IgM, whose activation degree had a positive correlation with anti-PEG IgM concentration, of which the C1 and C3 fragments were primary proteins associated with PL in complement system [23]. The combination of anti-PEG IgM with PL led to strong complement activation, and Kupffer cells mediated by complement-receptor increased liver accumulation of second dose [19]. Moreover, anti-PEG IgG antibody also had the potentiality to achieve complement activation [49]. The opsonization and elimination of nanoparticles by relevant macrophages and dendritic cells could be triggered after antibody binding and complement system actuation [43]. However, the second injection of PE still could spring up faint ABC phenomenon after exhausting complement system, certifying that complement inhibition might only squash ABC phenomenon to some extent [50].

The connection between non-PEGylated formulations and ABC phenomenon was proved as well. Previously, it had been discovered that ABC phenomenon could be caused by CL without PEGylation [19]. The first dosage of liposome was able to trigger anti-PEG IgM responses and modest responses specific to other lipid ingredients, and there was a compact correlation among the amount of IgM antibody produced by conventional liposomes, complement system activation extent and strength of ABC phenomenon. In a similar vein, Lactosome without PEGylation ignited ABC phenomenon in that B lymphocytes mediated immune response generating anti-Lactosome IgM and IgG3, meanwhile, antigenic epitope moiety of Lactosome was reduplicative poly(sarcosine) subunits [51]. Repeated injections of microbubbles without PEGylation unveiled alteration of clearance, indicating that immune factors out of anti-PEG immunity were involved in ABC of non-PEGylated formulations [16].

Based on the foregoing, the immunological mechanism of ABC phenomenon rendered by repetitious administrations of NDDS might be described as follows (Fig. 2A). Upon repeated administrations of NDDS in animals, the first dose of NDDS chiefly shifts towards spleen to contact with responded B cells in splenic marginal zone and set up a crosslinking with surface immunoglobulins existed on these cells, which generated the anti-PEG IgM and IgG antibodies or antibodies against else ingredients independent on assistance of T lymphocytes. Afterwards, the ensuing dose of NDDS is recognized and attached by these antibodies in blood circulation, which mediates

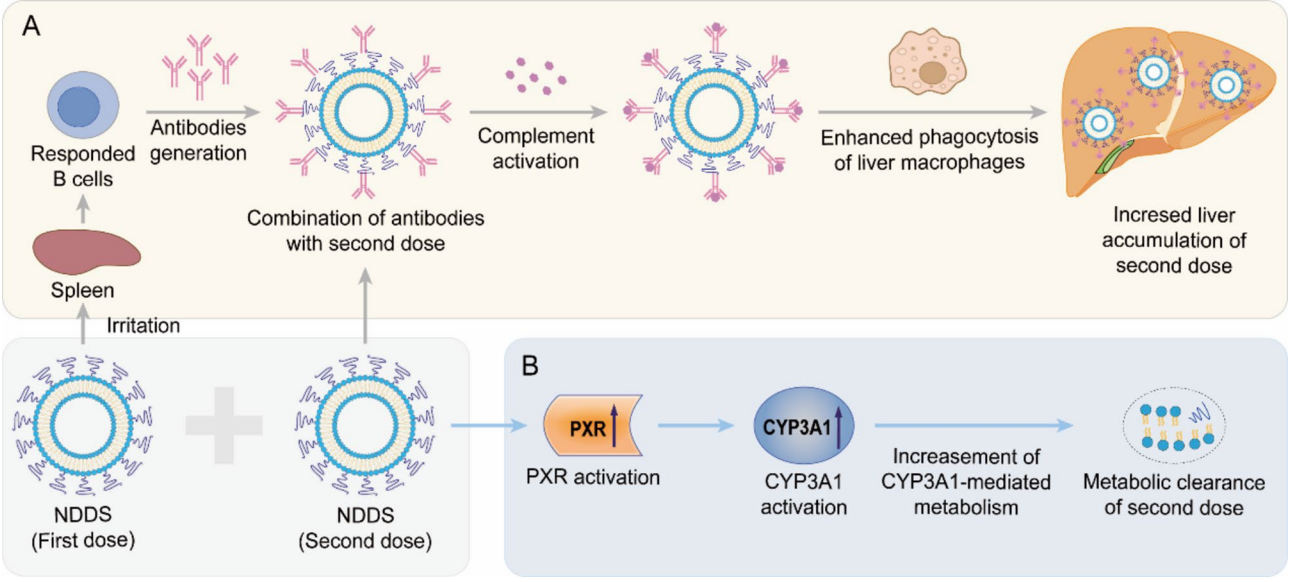


Fig. 2 Occurrence mechanism to interpret ABC phenomenon. (**A**) The immunologic mechanism of ABC phenomenon. (**B**) The preliminarily pharmacokinetic mechanism of ABC phenomenon

complement system activation. The opsonization of complement C1 and C3 fragments to the subsequent dose increases the uptake of NDDS by Kupffer cells in liver via complement receptor-mediated endocytosis. What's more, the augmentation of opsonization-independent phagocytic activity of Kupffer cells and responsiveness of Kupffer cells to antigen-antibody complexes induced by NDDS also have a participation in elicitation of ABC phenomenon. To sum up, accelerated clearance of NDDS from blood system is the outcome occasioned by synergistic effect of splenic B cells, antibodies against NDDS and complement system in concomitance with phagocytes just from immunological perspective [52].

Furthermore, after the administration of NDDS into blood circulation, NDDS could be identified and bound by some proteins, which constitute either a soft protein corona through loosely attaching on polymer nanoparticles or a hard protein corona through being firmly adsorbed on nanoparticles, influencing the distribution and clearance of NDDS in body [53, 54]. Another report proposed that the protein corona was primarily composed by apolipoproteins and complement proteins, meanwhile, the protein adsorption and liposomal surface affinity of apolipoproteins could be inhibited by prolonging PEG chain length [55]. The function of apolipoprotein low-density-lipoprotein receptor in accelerated clearance of nanoparticles had been testified [56]. Thus, the subject of the correlation between ABC phenomenon and protein corona has colossal space for study.

Pharmacokinetic perspective

There are other inducements in ABC phenomenon except immunologic elements since ABC phenomenon was still induced following splenectomy, depletion of phagocytic cells and exhausted complement [30, 38, 41, 50]. As reported, the physiologically based pharmacokinetic model could be used to comprehend the pharmacokinetic process of antibody-caused clearance of NDDS, which prompted us to innovatively explore the mechanisms underlying the ABC phenomenon from a pharmacokinetic perspective [57]. We had declared that the enhanced activity and expression of hepatic CYP3A1, CYP2C6, and CYP1A2 were found in male rats that were repeatedly injected PL [58]. In the meantime, the suppression of hepatic CYP3A1 was in concomitance with a slashed ABC phenomenon through employing selective inhibitors of cytochrome P450 enzymes (CYP450s), presenting that CYP450s were contributed to the generation of ABC phenomenon. Subsequently, we testified that the expression of pregnane X receptor (PXR) in the rat hepatocyte nucleus, the mainly upstream transcriptional regulatory factors of CYP450 genes, was prohibitively augmented in ABC phenomenon prompted by PL, accompanied by remarkable nuclear translocation [59]. Additionally, pre-administration with dexamethasone, the specifically inductive agent of PXR, literally elicited ABC phenomenon as well, together with raised nuclear translocation of PXR and activated CYP450s. These results unsealed that involvement of CYP450s might highly be attributable to activation of PXR in ABC phenomenon, verifying the contribution of PXR-CYP450s signal axis in ABC phenomenon. The preliminarily pharmacokinetic mechanism could be depicted as that, behind repeated administration of NDDS, incremental expression and nuclear translocation of nuclear receptor PXR in hepatocyte are activated, accompanied by strengthened activity and expression of CYP450s, and CYP450s-mediated metabolic clearance of subsequent dose could account for the appearance of ABC phenomenon induced by NDDS (Fig. 2B).

Drug transporters control the process that molecules pass into and out of cells, which can regulate drug absorption, distribution, metabolism and excretion regardless of running alone or in line with drug metabolic enzymes, influencing the pharmacokinetic behavior and/or pharmacodynamic characteristics of drug formulations at last [60]. ATP binding cassette family is one of transporter super family, which contains ATP-binding cassette transporters B1 (ABCB1), multidrug resistance proteins (MRPs) and breast cancer resistance protein (BCRP), mediating the efflux of drugs from cells [61]. Of note, PXR can also regulate the expression and function of ABCB1, MRP2 and BCRP apart from CYP450s-mediated metabolism of exogenous substances [62]. Some efflux transporters participated in the regulation of various aspects of immune cell infiltration [63]. We previously had also claimed that potentiated expression of efflux transporters, ranging over ABCA1, ABCB1, and ABCG1, was detected along with risen secretion of anti-PEG IgM in ABC phenomenon induced by PEGylated liposomal Gambogenic Acid [64]. Nevertheless, it is a pity that whether efflux transporters-mediated efflux role of extrinsic materials from cells accounts has an involvement in the elicitation of ABC phenomenon has not been investigated. Therefore, the tole of efflux transporters and nuclear receptor-transporter signal axis to ABC phenomenon should be elucidated by conducting more rigorous experiments. Such as, whether efflux transporters mediated the immigration of anti-PEG antibody from immune cells to blood circulation to hamper repetitive doses of NDDS, detecting the expression level of efflux transporters on splenic B cells and liver, inquiring the variation of anti-PEG antibody concentration and ABC phenomenon degree via wielding efflux transporter human-specific inducers or inhibitors and transporter knockout. Regrettably, the researches employing PXR-specific inhibitor or PXR knockdown and human-specific PXR inducer to study the effect on ABC phenomenon are still inexistent,

which has tremendous research value and significance to grope pharmacokinetic mechanism of ABC phenomenon. What's more, diversified humanized or transgenic mouse models for nuclear receptors, metabolic enzymes and efflux transporters might furnish compelling results and novel clews for the mechanism. In general, the depth and breadth of researching ABC phenomenon by applying pharmacokinetic knowledge is far from enough, and further studies that may offer more unambiguous clues and innovative hypotheses about the pharmacokinetic mechanism of ABC phenomenon are warranted, which is bound to avail the regulation of the untoward effect of ABC phenomenon on controlled release property of NDDS.

Recent progress in countermeasures for ABC phenomenon

In line with the intricate property of the ABC phenomenon mechanism, a multitude of factors exert influence over the phenomenon. In this section, we will discuss some strategies that have the potential to inhibit the phenomenon (Table 2). These strategies are based on several major aspects, including the physical and structural properties of nanocarriers, PEG-lipid derivatives, the medication regimen and encapsulated drugs for nanoformulations, nanomaterials as polymer coatings, and the clinical availability of the ABC phenomenon.

Strategies based on physical and structural properties of nanocarriers

Physical properties influence the bioavailability and in vivo fate of NDDS [65, 66]. The liver and spleen are closely related to the blood clearance of nanoparticles. The gaps between the endothelial cells of the splenic venous sinus are about 200 nm, which are prone to capture larger particles [67]. In contrast, nanoparticles below 100 nm are primarily cleared by the liver [68]. Therefore, the size of nanoparticles affects their uptake by MPS by means of their biodistribution. It was reported that ABC phenomenon of PL was discovered in mice pre-given polymeric micelles or PL with 50.2–795 nm compared to the polymeric micelles with 9.7–31.5 nm [69]. Repeated injections of AlexaFluor594-labeled polymeric micelles with 76.2 nm diameter could elicit ABC phenomenon, but the one with 33.6 nm only induced less obvious ABC phenomenon [70]. While descending the polymer size to 30–40 nm, ABC phenomenon of PEGylated uricase conjugates was not observed and PEGylated micelles induced descended IgM titers [71]. These results indicated that NDDS with small size (~ 30 nm) might suppress the ABC phenomenon by averting the discernment from immune cells and the clearance by MPS cells, whereas larger-sized NDDS perhaps only stimulated immune systems and MPS. It is generally required that the polydispersity index (PDI) value be as small as possible to ensure good stability when preparing liposomes, e.g., less than 0.2. Liposomes reported in the literatures have small PDI values, and they are generally capable of inducing the ABC phenomenon. We hypothesize that liposomes with larger PDI values may be outside the range of particle size inducing the ABC phenomenon because of the uneven particle size distribution, which in turn inhibits the ABC phenomenon, but then the stability of the liposomes will also be greatly reduced. Alternatively, PEGylated interferon with 40 kDa molecular weights (MW) could not trigger ABC phenomenon in human after repetitive injections [72]. The nanoparticles prepared by polylactide with 28,100 MW diminished the secretion of anti-PEG IgM, compared to 17,500 MW [73]. Thus, it may perhaps utilize nanocarriers with smaller size and larger

Table 2 The prime influence elements for ABC phenomenon and corresponding countermeasures

Prime influence element	Countermeasure	Ref.
Polymer size	Smaller size	[69–71]
Polymer molecular weight	Larger molecular weight	[72, 73]
Hydrophobic structure of nanocarrier	Bring in hydrophilic block or obscure PEG-hydrophobic portions	[69, 74–76]
Subunit structure of nanocarrier	Structure with low immunogenicity	[32, 51, 77, 78]
PEG molecular weight	Larger or lower molecular weight	[14, 86–89]
PEG terminal group	Low immunogenic group	[90–93]
PEG-lipid type	Low immunogenic PEG-lipid	[11, 94–97]
Administrated dose	High dose	[17, 98–101]
Lipid dose	High dose	[32, 102, 103]
Administrated time interval	Long time interval	[64, 103, 105, 106]
Number of doses	Multiple doses	[99, 107, 108]
Cytotoxic drug	Cell cycle nonspecific drug	[31, 99, 117, 120]
Nucleic acid	Non-CpG pDNA and low immunogenic siRNA	[123–126]
Immune system	Apply immunosuppressor	[30, 37, 38, 50]
Nanomaterials	Low immunogenic nanomaterials	[108, 127–147, 149–152]
Modification strategy	Mixed modification	[35, 38, 153–155]

molecular weight to attenuate ABC phenomenon. However, it appears to be a technical ordeal to prepare NDDS with too small size, and the lower limit value of size and the upper limit value of molecular weight igniting ABC phenomenon remain to be determined. Therefore, it is imperative need to adopt more detailed researches to acquire sufficient understanding about the effect of physical properties of nanocarriers on ABC phenomenon, and then probing rational solutions.

The influence of structural features of NDDS on ABC phenomenon also was considered. It was showed that no specific IgM antibody against PEG main chain was found in mice given PL, and that anti-PEG IgM combined with PEG-hydrophobic portions, which could be curbed via bringing in hydrophilic blocks between every hydrophobic block and PEG chain [74, 75]. Likewise, 1,2-distearoyl-snglycero-3-phosphorglycerol could obscure the interface between hydrophobic blocks and PEG chain in PE and hamper the occurrence of ABC phenomenon by hindering discernment and binding of IgM for PE [76]. These results demonstrated that hydrophobic blocks were required for the association of NDDS with anti-PEG IgM, in other words, anti-PEG IgM may not bind to PEG without hydrophobic blocks. Thereby, employing nanocarriers devoid of hydrophobic blocks or masking the hydrophobic portions of nanocarriers represents an effective approach to mitigate ABC phenomenon. Besides, the reduplicated subunit structure in polymers was deemed as antigenic epitope moiety of polymers [32, 51]. The polyhydroxy structure in nanoemulsion could transmit more immune information to Kupffer cells in contrast with polycarboxyl group in nanocarriers, meaning that the polycarboxyl structure had the potentiality of averting ABC phenomenon [77].

It is worth mentioning that in contrast to spherical liposome, the lipodisc is a kind of applanate circular lipid-based nanocarrier with distribution of PEG-lipids on the highly crooked edge, which could bypass the opsonization of IgM and impede the formation of membrane-bound conformation for IgM to circumvent complement activation because the bound IgM were constrained to this rim [78]. The ability of lipid nanodiscs to shun ABC phenomenon was not affected by phospholipid components [79]. Another report showed that nanodiscs and nanorods are more likely to be sequestered in the splenic reticular fiber network than spherical nanoparticles, thus non-spherical nanoparticles are more likely to activate immune responses [80]. The nanorods facilitate protein unfolding on the particle surface and promote adsorption of immunoglobulin and complement proteins [81, 82]. Although non-spherical nanoparticles may trigger a stronger immune response, the larger contact angle between non-spherical nanoparticles and cells results in a slower rate of their uptake by the MPS cells, which may allow them to be cleared slower than spherical nanoparticles even after repeated injections [83]. Hence, based on the lower cellular uptake rate, changing the shape of nanoparticles appears to have the potential to reduce their phagocytic clearance by MPS cells from circulation. However, studies on the effect of the nanoparticle shape on anti-PEG immune responses and the ABC phenomenon are lacking, which requires further research. To sum up, the nanocarriers whose structure has low immunogenicity should be chosen for delivery of drugs. The effect of physical and structural properties of NDDS on ABC phenomenon should not be neglected, and there is momentous meaning to mount investigation about the interplay among them for the development of strategies to inhibit ABC phenomenon (Fig. 3).

Strategies based on PEG-lipid derivatives

PEGylated modification of nanocarriers has a significant impact on the elicitation of the ABC phenomenon. The intensity of ABC phenomenon induced by PL gradually diminished when the PEG density was increased from 5 mol% to 15 mol%, surmising that higher PEG density could bestow liposome much more "stealth" [32]. The compromised anti-PEG response and ABC phenomenon were generated by a PEGylated polyamidoamine dendrimer with a high PEG density [84]. That PSLN with 10 mol% PEG density occasioned more drastic ABC phenomenon than PSLN with 20 mol% PEG density was also attested [85]. These findings suggested that in contrast to low PEG density, high PEG density attenuate the ABC phenomenon and that PEG density greater than 20% may be recommended to inhibit the ABC phenomenon (Fig. 4A). However, it can be found that the influence of PEG density on ABC phenomenon was dictated by nanocarrier types and others. Thus, the practical PEG density to inhibit ABC phenomenon should be selected based on specific nanoformulations.

It was reported that the strength of ABC phenomenon induced by PE enhanced first and then dipped with the rise of PEG MW ranged 400–5000 MW, out of which ABC phenomenon of PE with 2000 PEG MW was the strongest [86–88]. Analogously, a predominant ABC phenomenon was provoked by PE prepared by distearoylphosphatidylethanolamine (DSPE)-mPEG$_{2000}$, while PE prepared by DSPE-mPEG$_{40000}$ did not [89]. PEGylated Micelle (PM) with 2000 and 5000 PEG MW rendered the most potent ABC phenomenon in comparison with PM with 350, 550, 10,000, and 20,000 PEG MW [14]. Consequently, these results proved that PEG MW less than 550 or more than 10,000 inhibited the ABC phenomenon and that applying PEG derivatives with lower or higher PEG MW to modifying NDDS might be a promising tactic to alleviating ABC phenomenon (Fig. 4B).

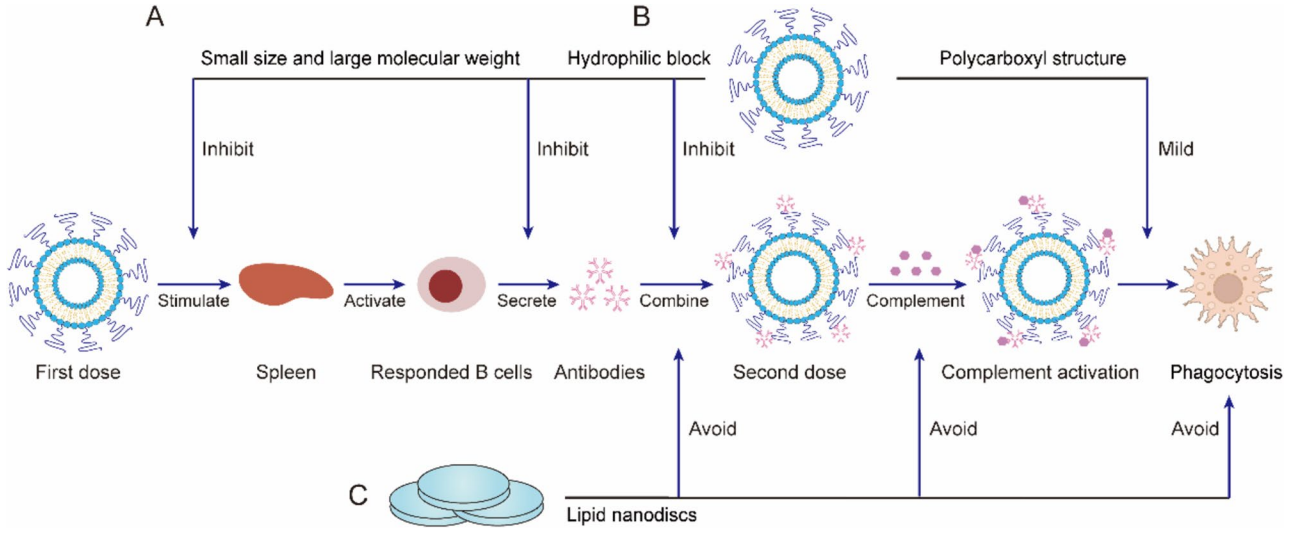


Fig. 3 Strategies based on physical and structural properties of NDDS to elude ABC phenomenon. (**A**) NDDS with small size and large molecular weight can decrease the stimulation to immune system and inhibit the secretion of antibodies [69–73]. (**B**) Replacing hydrophobic blocks with hydrophilic blocks and applying polycarboxyl structure can inhibit the combination of antibodies with NDDS and the activation of phagocytes respectively [74–77]. (**C**) Lipid nanodisc structures have the advantage of avoiding ABC phenomenon by shunning antibody adsorption, complement activation and macrophage capture [78, 79]

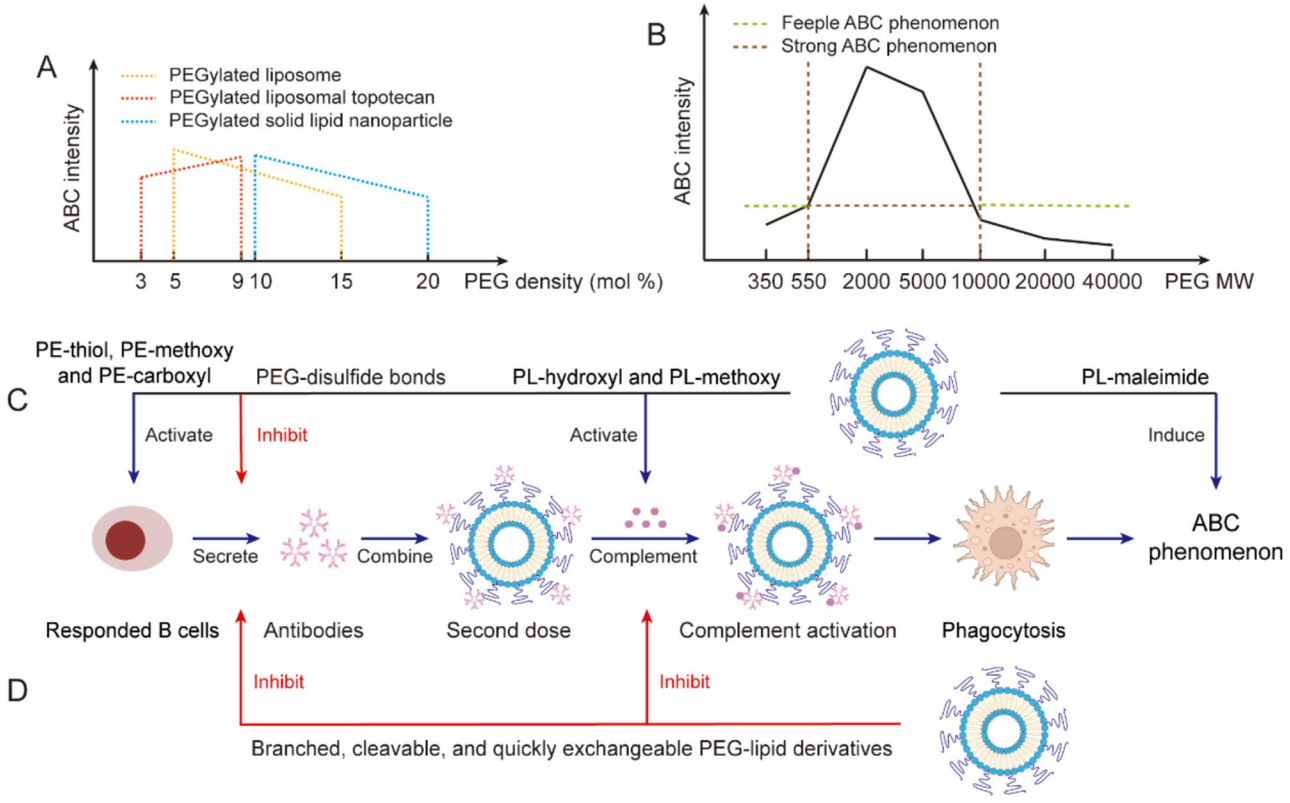


Fig. 4 Strategies based on PEG-lipid types to inhibit ABC phenomenon. (**A**) Schematic representation of the relationship between PEG content and ABC intensity for the three PEGylated formulations [32, 85]. (**B**) Rough diagram of the relationship between PEG molecular weight and ABC intensity [14, 86–89]. (**C**) Effect of representative PEG-terminal functional groups on the ABC phenomenon [90–93]. (**D**) Branched, cleavable, and quickly exchangeable PEG-lipid derivatives are capable of suppressing ABC phenomenon by inhibiting antibody production and complement activation [94–97]

It was shown that the accelerated clearance induced by PE terminated thiol group in rats was stronger compared to PE terminated methoxy and carboxyl group, which may be due to the ability of thiol group to motivate propagation and differentiation of B cells or reaction with follicular dendritic cells [90]. The strong complement-activating effect of PL with hydroxyl at PEG terminal in vitro was responsible for ABC phenomenon induced by PL-hydroxyl of second dose [91]. Apparent ABC phenomenon was prompted by repetitious injections of PL with maleimide at PEG terminal, although only small quantities of anti-PEG IgM antibodies were detected [92]. Specially, a PEG-nanoparticles cross-linked with disulfide bonds could evade generation of antibodies against PEG and realize the suppression to ABC phenomenon, in tandem with effective anti-tumor property [93]. What's more, ABC phenomenon was not produced by repetitive injections of liposomes or nanoemulsions modified by branched PEG-lipid derivatives in contrast with linear PEG-lipid derivatives, which might be in that branched PEG-modified nanocarriers triggered virtually lower anti-PEG IgM concentration and no activation to complement [94, 95]. Of attention, PEG with a short acyl chain was used to modify nanocarriers to diminish ABC phenomenon since it could fleetly break away from lipid bilayer after injection [96]. After repeated injections, faint ABC phenomenon was operated by liposomes modified by cleavable PEG-lipid because of low antibody concentrations and no complement activation [11, 97]. These outcomes unraveled that compared to ordinary PEG, the cleavable and branched PEG-lipid derivatives could badly stem the ABC phenomenon. Therefore, when designing PEGylated formulations for repeated administration regimens, it is essential to consider functional groups on the PEG terminus and PEG-lipid types that exhibit low irritative level to immune system (Fig. 4C and D).

Strategies based on dosage regimen of nanoformulations

The anti-PEG IgM concentration elicited by single dose of PEGylated exosome increased at the dose range from 0.2 to 3 mg exosome protein/kg but reduced at 5 mg/kg [17]. Additionally, the first Lactosome dose had negative correlation with quantity of anti-Lactosome IgM within the dose range of 5 to 250 mg/kg, and the ABC phenomenon could not attract when the second dose of Lactosome has a dose over 50 mg/kg [98]. The elimination of ABC phenomenon and a higher AUC value of the second dose of PEGylated poly(lactic-co-glycolic acid) (PLGA) nanoparticles were observed after further increasing the first polymer dose over 20 mg/kg [99]. The ABC phenomenon could also be bounded by repeated injections of PEGylated gold nanoparticles with 2 mg/kg dose compared to dose below 1 mg/kg [100]. Furthermore, it was reported that the first dose of pegfilgrastim less than 0.06 mg/kg was insufficient to trigger an anti-PEG immune response [101]. Thus, the administered dose of NDDS seriously affects the occurrence and intensity of ABC phenomenon. Although there was some discrepancy in these results, on the whole, they consistently suggested that bigger initial and subsequent dose was in favor of ameliorating ABC phenomenon, inferring that a higher dose may make immune systems produce immunologic tolerance and the saturation of phagocytic ability of phagocytes. By contrast, doses in the range of 0.1–20 mg/kg for the first injection have been reported to induce the ABC phenomenon of the second dose, so in practice, doses above 20 mg/kg might be considered to reduce the occurrence of the ABC phenomenon. However, there are differences between the properties of different preparations and high doses may be accompanied by potential adverse effects, and therefore their specific threshold dose for reducing ABC phenomena needs to be experimentally determined.

On the other hand, the ABC phenomenon intension evoked by PL was adversely proportional to the preinjected lipid dose at a range of 0.001-5 μmol/kg [32]. The hike of first lipid dosage (1–20 μmol phospholipids/kg) of PL containing topotecan or nothing was accompanied by progressively moderated ABC phenomenon of second dosage [102]. Moreover, the accelerated clearance of subsequent dose was not detected when going up lipid dose of first injection of ^{64}Cu-labeled PL from 5 to 25 μmol/kg [103]. The first dose of DNA-loaded LNP with a 0.05 mg lipid/kg dose could not remarkably increase anti-PEG IgM level and affect blood clearance of subsequent PEGylated liposomal doxorubicin (Doxil) compared with the first dose of 0.005 mg/ml PL [104]. These results indicated that bigger initial lipid dose was conducive to mitigating ABC phenomenon, which was in accord with the effect of dose of nanoformulations (Fig. 5). Initial lipid doses of 0.001-20 μmol/kg have been reported to induce the ABC phenomenon of the second dose, thereby lipid doses above 20 μmol/kg may be used to attenuate the ABC phenomenon, with the exact dose varying according to conditions. Hence, determining a reasonable injection dose and lipid dosage for nanoformulations is a reliable way to restrict the ABC phenomenon.

It was claimed that the ABC phenomenon was discovered when PEGylated ^{64}Cu-liposome was injected with a 7-day interval in clinical canine cancer models [103]. Nevertheless, when administrated time interval had an expansion from 3 days to 7 days, ABC phenomenon elicited by PEGylated liposomal gambogenic acid was also suppressed [64]. It was reported that PL promoted ABC phenomenon was in a time-dependent manner and the phenomenon was remitted and even eradicate following expanding administered interval beyond 2 or 4 weeks [105, 106]. Those reports keenly demonstrate

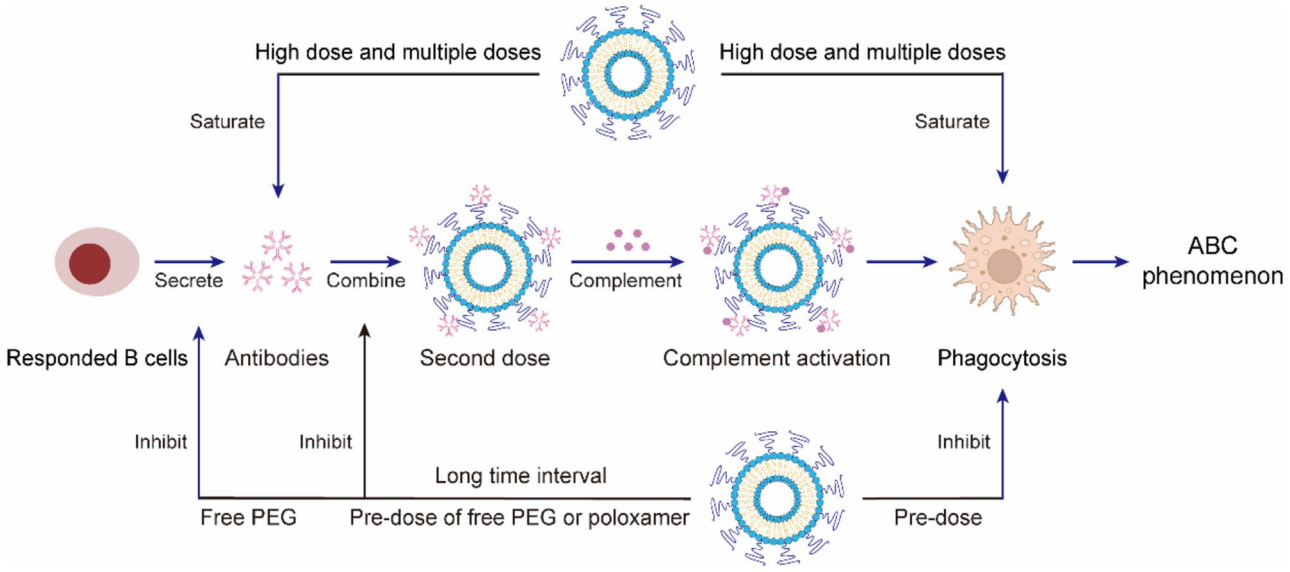


Fig. 5 Strategies based on dosage regimen of NDDS to inhibit ABC phenomenon. High dose and multiple doses of NDDS will saturate the antibodies and phagocytes, which in turn inhibit ABC phenomenon [98–100, 103, 104, 107, 108]. Long time interval and pre-dose of free PEG or poloxamer can curb the combination of antibodies with NDDS and phagocytosis of NDDS by macrophages [106, 109–114]. The free PEG with high MW can repress antibody production

that compared to the short time interval, the longer time interval has a suppression effect on the ABC phenomenon, and therefore protracting administrated time interval of NDDS beyond 1 week or more might be an alleviation way for ABC phenomenon (Fig. 5).

It was disclosed that the third dose could rejuvenate blood circulation time of PL and etoposide-encapsulated PEGylated nanoparticles, besides, ABC phenomenon was inhibited after the fourth dose of PL together with almost normal pharmacokinetics in contrast with second dose [10, 99]. Anti-PEG immunoreactions, complement activation and ABC phenomenon were all not observed in patients when administrated PEGylated liposomal methyl prednisolone-succinate with 8 doses [107]. Upon serial administrations of prostaglandin E1-loaded PEGylated nanoparticles, the third dose prominently inhibited IgM level and ABC phenomenon intensity [108]. Accordingly, compared with twice doses, it is a significant strategy to apply multiple doses to attenuate ABC phenomenon (Fig. 5). The pretreatment with free PEG as a competitive inhibitor prior to administration of PEGylated microbubble also could inhibit the binding of anti-PEG antibodies and PEGylated microbubble, significantly skyrocketing its cycle time [16]. It was complemented that the ABC phenomenon encountered with PL could be surmounted by pre-infusion of high MW free PEG to suppress the induction of anti-PEG antibodies, like 40 kDa rather than 10 kDa [109–112]. In a similar vein, pre-injection of free poloxamer-407 barely affected the circulation time of PEGylated particles and antitumor effect of Doxil [113]. A developed anti-PEG single-chain variable fragment with high binding tendency to PEG could highly vie the combination of anti-PEG antibodies with PL in rats and human plasma, thereby forestalling complement activation and ABC phenomenon [114]. Therefore, these studies suggested that adopting free PEG or other competitive inhibitors as a pre-dose to curb the binding of anti-PEG antibodies with NDDS is a way with feasibility to curb the ABC phenomenon caused by repetitive injections of NDDS (Fig. 5).

Strategies based on encapsulated cargoes in nanoformulations

NDDS are generally served as a promising approach for cancer treatment via efficiently delivering anticancer drugs into tumor sites [4, 115, 116]. Yet, whether the therapeutic efficacy of repeatedly administered anticancer drug delivery systems is affected by the ABC phenomenon needs to be discussed. It was shown that the pre-injection with Doxil could deracinate ABC phenomenon of PL, but the combined pre-treatment of free doxorubicin and PL did not, suggesting that doxorubicin packed in PL may kill immunocytes related to ABC phenomenon by being delivered by liposomes into the liver and spleen [31]. Meanwhile, repeated administrations of PEGylated liposomal oxaliplatin did not ignite noticeable immune responses against PEG, showing the capability of oxaliplatin uprooting ABC phenomenon [117]. Although both of these cytotoxic drugs were able to inhibit the ABC phenomenon, it was certified that sequential administrations of Doxil at a lower dose less than 2 mg doxorubicin/m^2 could induce ABC phenomenon in

beagle dogs, monkeys, minipigs, mice and rats, while a higher dose of 20 mg doxorubicin/m^2 did not [19]. The intravenously injected PEGylated liposomal oxaliplatin distinctly weakened ABC phenomenon at a dose of 2.3–2300 μg oxaliplatin/kg instead of 0.023 μg oxaliplatin/kg in that PEGylated liposomal oxaliplatin could stem anti-PEG IgM responses in a dose-dependent manner [118]. Multiple injections of PEGylated liposomal epirubicin also could cause dramatical reduction of epirubicin level in blood and tumor tissue at a dose range of 0.08–1.2 mg epirubicin/kg [119]. These researches demonstrate that the injected dose of cytotoxic drugs play a salient influence on ABC phenomenon induction. It appears that cytotoxic drugs at a lower dose can stimulate immune system and then attract immune responses against PEG, whereas crippling splenic B cells proliferation at a higher dose and thereby waning the ABC phenomenon. On the other hand, a noticeable ABC phenomenon was caused by repetitive administrations of PEGylated liposomal topotecan in Wistar rats, beagle dogs and mice, at a dose of 12, 9.5, 12 mg topotecan/m^2 respectively [120]. The repeated administrations of PEG-PLGA nanoparticles incorporating etoposide also evoked ABC phenomenon at a dose of 8 mg etoposide/kg [99]. It was deduced that both topotecan and etoposide are cytotoxic drugs specific to cell cycle, which could not completely eliminate the whole splenic B cell population since only acting on the S phase and G2/M phase of cell cycle respectively, thus ABC phenomenon still existed. Consequently, NDDS encapsulating cytotoxic drugs with immunosuppressive effect at an optimal administrated dose should conduce to avoid the generation of ABC phenomenon and enhance their therapeutic efficacy (Fig. 6A).

NDDS are also widely applied in the delivery of nucleic acids [121, 122]. It was uncovered that anti-PEG IgM generation and obvious ABC phenomenon were induced by repetitive injections of PL containing plasmid DNA (pDNA) [123]. The ABC phenomenon could also be rendered by repeated administrations of PEGylated cationic liposome encapsulating small interfering RNA (siRNA) [124]. It is worth mentioning that repeated injections of PL encapsulating non-CpG pDNA prohibitively reduced anti-PEG IgM secretion and increased the accumulation of second dosage in tumor site compared to the general pDNA-contained PL, demonstrating that the CpG motif was a main inducement of ABC phenomenon stimulated by pDNA-contained PL [125]. Additionally, the siRNA-coated PEGylated wrapsome motivated fainter anti-PEG IgM reaction in comparison with the conventional siRNA-coated PL, coupled with abolishment of IgM response after inserting 2'-O-methyl uridine, which suppressed cytokine activation, into siRNA sequence [126]. Thus, applying non-CpG pDNA and siRNA with low immune stimulation may be a practicable method to recuperate the clinical significance of nanoformulations containing nucleic acids without ABC phenomenon (Fig. 6B). Analogously, building up immunosuppressive models by co-delivery with immunosuppressors

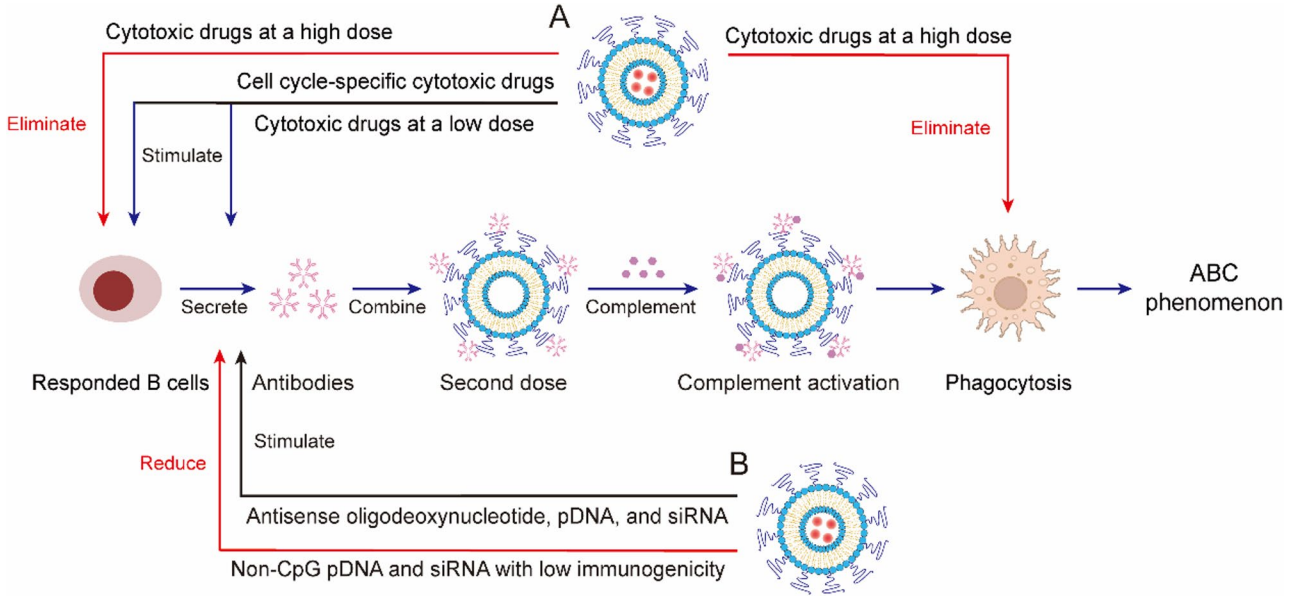


Fig. 6 Strategies based on encapsulated cargos in NDDS to inhibit ABC phenomenon. (**A**) NDDS encapsulating cytotoxic drugs at a high dose can eliminate responded B cells and phagocytes, thus inducing no ABC phenomenon [118, 119]. Cytotoxic drugs at a low dose and cell cycle-specific cytotoxic drugs only stimulate the immune system and elicit ABC phenomenon of NDDS [99, 120]. (**B**) NDDS encapsulating antisense oligodeoxynucleotide, pDNA, and siRNA induce apparent ABC phenomenon, whereas NDDS encapsulating non-CpG pDNA and low immunogenic siRNA can mitigate ABC phenomenon by reducing antibody production [123–126]

also might be a workable approach to largely bridle the incurrence of ABC phenomenon facilitated by repeated administrations of NDDS as accelerated clearance of NDDS was conspicuously retarded in splenectomy, hepatosplenic phagocytic cell depletion and complement inhibition models, yet, possibly ensuing adverse reactions and health risks should be thought over [30, 37, 38, 50].

Strategies based on nanomaterials and mixed modifications

Except for PEG coating, herewith, some novel polymer coatings (Table 3) and modification methods kindling slight ABC phenomenon are described. Compared to PEGylation, 1,2-dipalmitoyl-sn-glycero-3-phosphodiglycerol modified thermosensitive liposomes had extended half-life without ABC phenomenon in that 1,2-dipalmitoyl-sn-glycero-3-phosphodiglycerol subdued complement actuation [127]. The ABC phenomenon and biodistribution alteration of second dose were not induced when administrating self-assembled amphiphilic polylactic acid (PLA)–hyaluronic acid (HA) block copolymer nanoparticles [128]. The maleimide-modified nanoparticles had ability to keep nanoparticles from phagocytosis of macrophages, avoiding ABC phenomenon of subsequent injection [129]. Poly(N-vinyl pyrrolidone) (PVP), poly(N, N-dimethyl acrylamide) (PDMA), poly(N-acryloyl morpholine) (PAcM), and poly[N-(2-hydroxypropyl) methacrylamide] (PHPMA) did not elicit ABC phenomenon of nanoparticles or liposomes [130, 131]. Besides, poly(oligo(ethylene glycol) methyl ether methacrylate) (POEGMA) polymer modified uricase occasioned no anti-polymer antibody and was not identified by anti-PEG antibody [132]. Poly(2-ethyl-2-oxazoline) lipid modification could downscale the blood clearance of LNP and anti-lipid IgM concentrations than PEG-lip [133]. In like manner, ABC phenomenon was not fostered by poly(thioglycidyl glycerol)-modified ovalbumin and liposomes due to the inhibition of anti-polymer antibody generation and hepatosplenic accumulation [134]. Similarly, the linear and hyperbranched polyglycerol-modified polylactide-NPs had no induction ABC phenomenon because of inhibition of anti-PEG IgM production and poor binding properties to IgM antibodies [135].

Table 3 Nanomaterials engendering faint or no ABC phenomenon

Nanomaterial	Nanocarrier	Mechanism	Ref.
1,2-dipalmitoyl-sn-glycero-3-phosphodiglycerol	Liposome	Potentiate apolipoprotein E adsorption and subdue complement actuation	[127]
Polylactic acid–hyaluronic acid block copolymer	Nanoparticle	Weak IgM response	[128]
Maleimide	Nanoparticle	Covalently conjugate plasma albumin to avoid phagocytosis of macrophages	[129]
Poly(N-vinyl pyrrolidone)	Nanoparticle, liposome	No IgM generation	[108, 130, 131]
Poly(N, N-dimethyl acrylamide)	Liposome	No IgM response	[130]
Poly(N-acryloyl morpholine)	Liposome	No IgM response	[130]
Poly[N-(2-hydroxypropyl) methacrylamide]	Liposome	No IgM response	[130]
Poly(oligo(ethylene glycol) methyl ether methacrylate)	Uricase	No anti-polymer antibody and not identified by anti-PEG antibody	[132]
Poly(2-ethyl-2-oxazoline) lipids	Lipid nanoparticle	Lower levels of anti-lipid IgM	[133]
Poly(thioglycidyl glycerol)	Ovalbumin, liposome	Low complement activation and lack of antibody recognition	[134]
Polyglycerol	Liposome, nanoparticle	IgM secretion inhibition	[135]
Poly(carboxybetaine)	Liposome	Evasion to immune protein adherence	[137]
Poly(N-methyl-N-vinylacetamide)	Liposome	Reduction of immunological reactions	[138]
Zwitterionic peptide	Nanoparticle	No IgM and IgG response	[13]
Poly(carboxybetaine-γ-(2-(2-(2-methoxyethoxy) ethoxy)ethoxy)esteryl L-glutamate)	Asparaginase	Little antibody production	[139]
Polysarcosine	Liposome, nanoparticle	IgM and IgG response mitigation	[140–144]
Polysialic acid and sialic acid	Micelle	Suppression of IgM generation and phagocytosis	[145]
Ginsenoside Rg3	Liposome	Low immunogenicity	[147]
Red blood cell membrane	Nanoparticle	Immunological tolerance specialty	[149–152]
Monosialylganglioside	Liposome	IgM response inhibition	[153]
Ganglioside	Liposome	Render B cell tolerance	[35, 38]
4-arm PEG5000 cholesteryl methyl amide	Emulsion	Decrease antibody binding	[154]
Polymethyloxazoline	Nanoparticle	Lessen antibody response	[155]

In addition, polyzwitterionic materials are deemed as an adorable selection to supersede PEG [136]. Zwitterionic poly(carboxybetaine) (PCB) and poly(N-methyl-N-vinylacetamide) modified liposomes could keep away from ABC phenomenon via shunning immune reactions [137, 138]. The increased IgM and IgG concentrations and ABC phenomenon were prevented from gold nanoparticles modified by a zwitterionic peptide sequence alternating positively charged lysine and negatively charged glutamic acid upon repeated administrations [13]. Contrary to PEGylated asparaginase conjugate, an urchin-like helical polypeptide-asparaginase conjugate P(CB-EG_3Glu)-asparaginase did not trigger ABC phenomenon because of little antibody production [139]. Thereby, zwitterionic material has broad prospects for application of modification of NDDS due to averting ABC phenomenon appearance and prolonging circulation time.

Recent studies showed that liposomes modified by polysarcosine attracted lower concentration of anti-polymer antibodies and inhibited hepatosplenic accumulation upon repeated injections [140, 141]. The polysarcosine modification was capable of promoting the immunogenic cell death and antitumor effects, compared to PEGylation [142]. Peptide-nanosheets composed of poly(sarcosine)$_{60}$-block-(L-Leu-Aib)$_6$ and nanoparticle consisted of (poly(sarcosine)$_{23}$)$_3$-block-poly(L-lactic acid)$_{30}$ were found having no stimulation to immune system and thus abrogating ABC phenomenon, which might be due to high surface density of poly-(sarcosine) chains on the peptide-nanosheet [143, 144]. Analogously, the ABC phenomenon aroused by micelles was waned by polysialic acid, a polysaccharide homopolymer with immune camouflage function [145]. The inulin-g-poly-D, L-lactide amphiphilic copolymers was contrived in that the natural polysaccharide inulin was selected as PEG substitution in view of structural similarity, hydrophilicity, flexibility, and safety [146]. These studies showed that polysaccharide had potentiality of inhibiting ABC phenomenon. Of note, the liposomes modified with ginsenoside Rg3 and an anionic γ-zein-based proline-rich peptide showed extended circulation time and lessened ABC phenomenon [147, 148]. Besides, the biomimetic red blood cell membrane coated nanoparticles engendered no ABC phenomenon by reason of innate immunological tolerance specialty, such as red blood cell membrane coated Fe_3O_4 nanoparticles, biotin modified red blood cell membrane coated large pore-sized mesoporous silica nanoparticles, and red blood cell membrane wrapped Au nanocages, demonstrating the significance of exploiting natural biomaterials as coatings to surmount ABC phenomenon [149–152]. Although all of the aforementioned nanomaterials can inhibit the ABC phenomenon, there are differences in the extent to which they inhibit the production of anti-polymer antibodies. After comparative analysis of the abundance of antibody production, we summarized the nanomaterials reported above that inhibit the production of anti-PEG IgM and IgG antibodies more effective, which are promising modifying delivery systems to inhibit the occurrence of the ABC phenomenon. They included PVP, PDMA, PAcM, PHPMA, POEGMA, PG, PCB, Ginsenoside Rg3, and red blood cell membrane, among which the natural product Ginsenoside Rg3 and the biomaterial erythrocyte membranes showed the most superior ability to inhibit antibody production. Some of their structures are schematically shown in Fig. 7.

On the other hand, mixed modification of PEGylated epirubicin liposome by monosialylganglioside was accompanied by mightily attenuated ABC phenomenon when monosialylganglioside contents account for 10% or 15% mol [153]. Analogously, anti-PEG immune reactions and ABC phenomenon were extremely impeded by drawing ganglioside into PL, which was probably due to rendering B cell tolerance [35, 38]. The mixed PEGylated surfactant modifying system that modifying tocopheryl nicotinate-loaded nanoemulsions with 4-arm PEG_{5000} cholesteryl methyl amide and $mPEG_{2000}$-DSPE could stem ABC phenomenon [154]. Innovatively, desirably sustaining pharmacokinetic behaviors were realized by a tactic that alternates nanocoating between PEG and polymethyloxazoline polymers when injected repeatedly to inhibit immune reactions towards each dosage [155]. Therefore, it would be a promising strategy to construct NDDS via inaugurating mixed modification system for prevention of ABC phenomenon. Alternatively, the first dose of both PL and PEGylated ovalbumin elicited anti-PEG IgM response and decrease of plasma concentration of PEGylated exosomes, whereas plasma concentration of PEGylated ovalbumin was not influenced by anti-PEG IgM attracted by PEGylated exosomes [17]. Hence, the cross-administration of PEGylated nanocarriers is probably provided with non-negligible potentiality to shun ABC phenomenon, and devising an apt combined treatment regimen employing NDDS has critical significance to potentiate therapeutic efficacy.

Strategies based on utilization of ABC phenomenon

The ABC phenomenon ignited by repetitive administrations of NDDS brings about the loss of targeted delivery capacity and circulatory time of NDDS along with compromised treatment effect, which imposes significant challenges to the application and development of NDDS in preclinical research and clinical practice [10, 105, 156]. Nevertheless, the potential impact of the ABC phenomenon on NDDS has yet to be fully realized. Recently, it has been demonstrated that a mouse model generating monoclonal anti-PEG IgM to imitate pre-existing

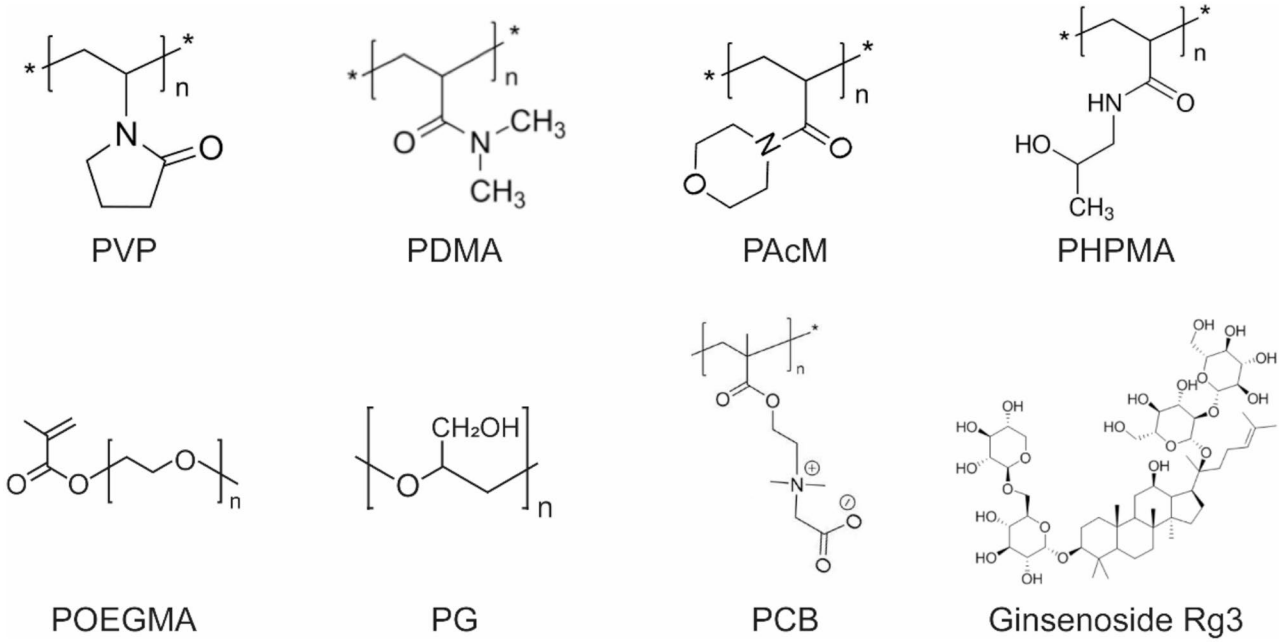


Fig. 7 Schematic structure of representative nanomaterials capable of inhibiting ABC phenomenon by reducing IgM production effectively. These polymeric nanomaterials are promising for modification of nanoformulations without ABC phenomenon, including PVP [130, 131], PDMA [130], PAcM [130], PHPMA [130], POEGMA [132], PG (linear PG is shown) [135], PCB [137], and Ginsenoside Rg3 [147]

anti-PEG antibodies in the blood circulation can serve as a valuable prognostic indicator for the efficacy of preclinical studies of distinct PEGylated formulations [157]. It is our contention that this mouse model could also be employed to detect whether NDDS can induce the ABC phenomenon. Furthermore, it is noteworthy that, based on the increased liver accumulation observed in the ABC phenomenon, we propose that this phenomenon endows NDDS with liver targeting capacity, promoting the delivery of drugs to the liver. Therefore, it is theoretically feasible to utilize drug-loaded NDDS for the treatment of hepatopathy and/or liver cancer by virtue of the ABC phenomenon. It is also important to note that the enhancement of CYP3A1 expression and activity in the liver has been demonstrated in the context of the ABC phenomenon [58]. Accordingly, we devised PEGylated liposomes of anticancer prodrugs metabolized by CYP450s to ascertain whether the augmented hepatic accumulation and CYP450s activity characteristics of the ABC phenomenon could be harnessed to augment the therapeutic efficacy against hepatocellular carcinoma. It was demonstrated that the ABC phenomenon could be effectively employed in the treatment of hepatocellular carcinoma through the repeated administration of NDDS encapsulating CYP3A1-metabolised anticancer prodrugs. This approach involves the targeted accumulation of the prodrugs in the liver, where they are metabolized into active products by CYP3A1, thereby enhancing the therapeutic efficacy while reducing the toxicity to other normal tissues (Fig. 8) [158]. Consequently, it is recommended that further investigation be conducted into the potential of utilizing the properties of hepatic accumulation and activated CYP450s associated with the ABC phenomenon as a treatment for liver diseases. This approach may prove to be a highly effective method for addressing the adverse effects of the ABC phenomenon.

Conclusion and perspectives

The ABC phenomenon casts an ordeal on the targeted delivery accuracy and treatment efficacy of NDDS, which prominently clogs clinical application and development of NDDS. On the basis of summarizing the immunological mechanism of ABC phenomenon, we innovatively bring in pharmacokinetic mechanism and hypotheses to replenish and consummate the mechanism of ABC phenomenon, providing a breakthrough to carry out further mechanism research and contrive practical strategies against ABC phenomenon. Currently, researchers are engaging in the active pursuit of strategies to inhibit the ABC phenomenon. Strategies based on optimizing the physical and structural properties of nanocarriers, rationally controlling the time interval of repeated injections, dose and number of administrations, encapsulating drugs with low immunogenicity, applying PEG derivatives with immunosuppressive effects or novel nanomaterials instead of PEG, and mixed modification system have shown the potential to significantly attenuate the ABC phenomenon. What's more, researchers have also cleverly utilized the properties of ABC phenomenon, including its rapid accumulation in liver tissues and

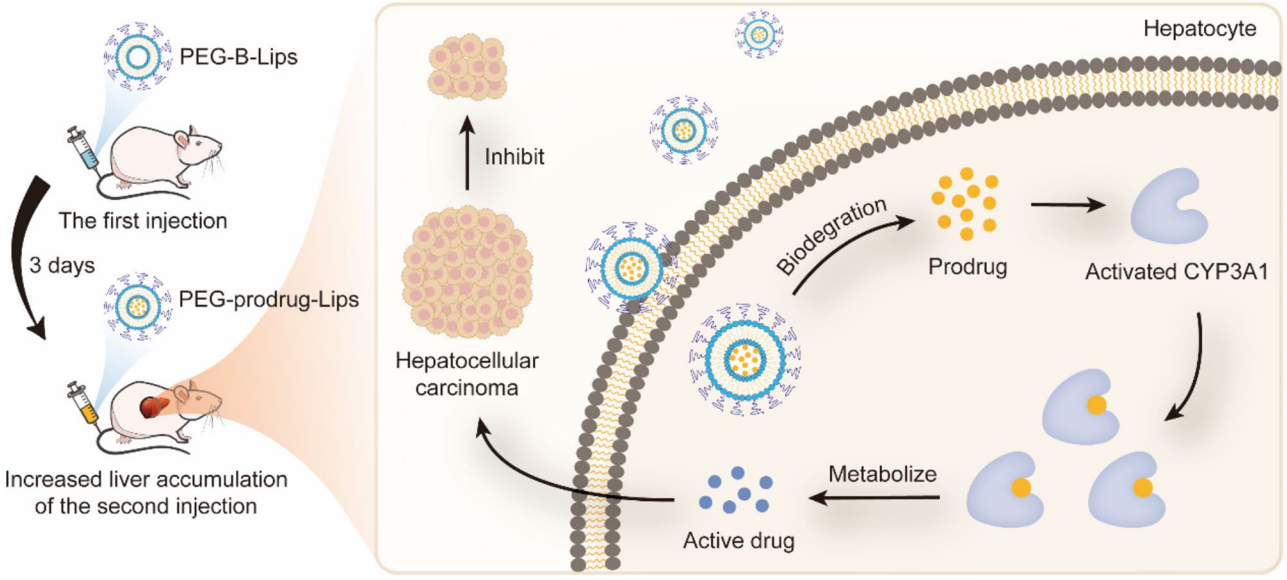


Fig. 8 Schematic conceptualization of applying the ABC phenomenon to treat hepatocellular carcinoma

activation of CYP450s, to explore a novel drug delivery system for precise targeting of hepatocellular carcinoma. This approach has the potential to enhance therapeutic efficacy, underscoring the significant promise of the ABC phenomenon in the treatment of liver disease and cancer. Herewith, perhaps it is a promising avenue to cope with ABC phenomenon and drive clinical translations of NDDS by converting the drawback of ABC phenomenon into an advantage. After conducting a comparative analysis, we believe that among the strategies described above, the dose and time interval of administration have a greater effect on the ABC phenomenon. Because even the commonly used PEG-Lip can inhibit the ABC phenomenon by adjusting to the appropriate dose and time interval, this strategy is practical and easy to realize. But at the same time, its effect on the efficacy and side effects could not be neglected. Compared with optimizing the physicochemical properties of nanocarriers, the development of novel PEG derivatives or alternative materials has been a hot research topic in recent years, and a series of novel nanomaterials have been reported. Meanwhile, the establishment of mixed modification delivery systems is also a new concept, implying more possibilities for the modification strategies of nanocarriers. In contrast, the study of the effect of encapsulated drugs on the ABC phenomenon has been at a standstill. It is noteworthy that all of above-mentioned strategies for inhibiting the ABC phenomenon are based on the suppression of the immune response. In addition, the application of ABC phenomenon to the treatment of hepatocellular carcinoma is an innovative strategy in this field, which not only broadens the idea of dealing with ABC phenomenon, but also provides new possibilities for the future treatment of the disease.

Although some research progress has been made in understanding the occurrence mechanisms and coping strategies of the ABC phenomenon, some challenges remain, including the elucidation of its occurrence mechanism, the formulation of the optimal administration regimen of NDDS, the development of novel nanomaterials without immunogenicity and nanomaterials based on the inhibition of pharmacokinetic mechanism, its eradication measures, and the optimization of strategies for its clinical application. Moreover, while NDDS characterized by small size and elevated dose have demonstrated efficacy in mitigating the ABC phenomenon, the preparation of NDDS with ultra-small size may be faced with technological hurdles, and the administration of high-dose NDDS may also be associated with adverse effects. Even if immunosuppression models or some NDDS can eliminate immune cells and inhibit immune system, immunosuppressive strategies could potentially induce unforeseen complications and health risks. These multifaceted challenges must be carefully considered in practical applications. Accordingly, we have also looked forward to the possible research directions of the ABC phenomenon in the future, which include the following points. First, the exploration of the pharmacokinetic mechanism of ABC phenomenon is still in the preliminary stage, which still requires in-depth research to form a mature theoretical system, while the exploration of other new mechanisms, like protein crowns, also has a potential that should not be ignored. Second, the optimization of the administration regimen by determining the appropriate dose, time interval, and times of NDDS, as well as the encapsulation of drugs with immunosuppressive effects are also feasible research areas. As for the challenge posed by high dose of NDDS, strategies for designing safer nanoparticles, such

as the application of biocompatible materials and controlled release mechanism, should be developed. Third, the development and use of alternative materials to PEG or novel PEG derivatives with low or even no immunogenicity and antigenicity have great potential to reduce or avoid PEG-specific immune responses, which has still a good research prospect. Fourth, there is a gap regarding strategies to inhibit the ABC phenomenon based on the inhibition of nuclear receptors, metabolic enzymes, and transporters. Intensive research should be conducted in this area to achieve further results and progress, like the development of delivery systems based on the inhibition of pharmacokinetic mechanisms. Fifth, although the establishment of mixed modification delivery systems has good innovativeness, there are relatively few achievements based on this strategy to suppress the ABC phenomenon. Therefore, it has considerable space for development and should be further investigated. Sixth, the effect of the shape of nanocarriers on the ABC phenomenon also deserves to be investigated. Nanocarriers generally reported to cause ABC phenomenon are spherical nanoparticles, and few studies have been conducted on how non-spherical nanocarriers affect the ABC phenomenon. But the lipodiscs have demonstrated the ability to inhibit ABC phenomenon, and thus non-spherical nanoparticles with low cellular uptake rates show significant research promise for attenuating the ABC phenomenon. Seventh, the strategy of applying the characteristics of ABC phenomenon for the treatment of hepatocellular carcinoma is not well developed, and its research scope should be further expanded to maximize its value. For example, the hepatic accumulation property could be utilized to treat other liver diseases, or applied to promote the delivery of drugs and vaccine to the liver. The activated metabolizing enzymes could be used to develop specific prodrugs, or used to ameliorate the toxic side effects of drugs on other organs. With further research on the ABC phenomenon, we may also be able to explore the potential applications of its rapid clearance properties, for instance, the development of disease-specific rapid clearance therapies to enhance the efficiency and safety of clinical treatments by accelerating the metabolism and elimination of drugs. Taken together, we deem that this work serves as a guiding role for further research on the ABC phenomenon. It aids in advancing the exploration of the intrinsic mechanisms behind ABC phenomenon, offers potential avenues for addressing the ABC phenomenon issues of NDDS, and provides a theoretical foundation for the innovation of new drug design and drug delivery strategies. Furthermore, we have an expectation to stimulate profound lucubration for overcoming or harnessing the ABC phenomenon and facilitating application of NDDS in clinical settings by affording an overview of research progress of the ABC phenomenon. This research area deserves sustained commitment and persistence to dig out novel insights from it.

Abbreviations

ABC	Accelerated blood clearance
ABCB1	ATP-binding cassette transporters B1
BCRP	Breast cancer resistance protein
CL	Conventional liposomes
CYP450s	Cytochrome P450 enzymes
Doxil	PEGylated liposomal doxorubicin
DSPE	Distearoylphosphatidylethanolamine
Gadolinium-micelles	Gadolinium-loaded PEG-poly(L-lysine)-based polymeric micelles
HA	Hyaluronic acid
LNP	Lipid nanoparticles
MFPL	A di-ligand modified PEGylated liposome
mPEG	Methoxy polyethylene glycol
MRPs	Multidrug resistance proteins
MW	Molecular weights
NDDS	Nanocarrier drug delivery systems
PAcM	Poly(N-acryloyl morpholine)
PCB	Poly(carboxybetaine)
PDI	Polydispersity index
PDMA	Poly(N, N-dimethyl acrylamide)
pDNA	Plasmid DNA
PE	PEGylated emulsions
PEG	Polyethylene glycol
PEG-PBLA	PEG-b-poly(β-benzyl-L-aspartate)
PG	Polyglycerol
PHPMA	Poly[N-(2-hydroxypropyl) methacrylamide]
PL	PEGylated liposomes
PLA	Polylactic acid
PLGA	Poly(lactic-co-glycolic acid)
PM	PEGylated micelles
POEGMA	Poly(oligo(ethylene glycol) methyl ether methacrylate
PSLN	PEGylated solid lipid nanoparticle
PVP	Poly(N-vinyl pyrrolidone)
PXR	Pregnane X receptor
siRNA	Small interfering RNA

Author contributions

Pan J.Q.: Conceptualization, Writing - original draft, Writing - review & editing, Visualization. Wang Y.Y.: Writing - review & editing. Chen Y.N.: Writing - review & editing. Zhang C.: Investigation. Deng H.Y.: Investigation. Lu J.Y.: Investigation. Chen W.D.: Conceptualization, Writing - review & editing, Supervision. All authors read and approved the final manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (Grant No. 82073923).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 31 October 2024 / Accepted: 9 February 2025
Published online: 25 February 2025

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