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Recent advances in stealth coating of nanoparticle drug delivery systems

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Abstract

Modifying surfaces of nanoparticles (NPs) with polyethylene glycol (PEG), the so called PEGylation, is the most commonly used method for reducing premature clearance of NPs from the circulation. However, several reports point out that PEGylation may negatively influence the performance of NPs as a drug carrier. Alternative surface modification strategies, including substitute polymers, conditional removal of PEG, and biomimetic surface modification, may provide solutions for the limitations of PEG.

Introduction

Chemotherapy is an indispensable modality in the treatment of most solid tumors, but its side effects often limit its benefits and impact the patients' quality of life. Moreover, repeated chemotherapy can induce multidrug resistance (MDR) in the tumors,[1–3] which then require extremely high doses of anticancer drugs, often making the regimens intolerable due to the significant toxicity.[2]

To address the shortcomings of existing chemotherapeutic agents, many researchers are developing new drug delivery methods that can transport medicines specifically to the target tumors without damaging healthy tissues or organs. A popular strategy is to use nanoparticles (NPs) such as polymeric NPs, liposomes, and micelles as a drug carrier. Upon systemic administration, the NP formulations display different pharmacokinetics than free drugs and enhance accumulation and release of drugs in tumors. Due to their ability to accumulate in tumors, NPs are also explored as a promising diagnostic tool.

NP delivery to solid tumors relies on the unique anatomical and physiological features of tumors and their environment. As a tumor grows, demands for nutrients, gas exchange, and waste removal of the highly metabolic cancer cells escalate as does their need for new blood vessels.[4–6] The formation of new blood vessels involves extension of existing vasculature toward the tumor tissues[4, 7] and recruitment of the progenitor endothelial cells.[8] Soluble growth factors such as vascular endothelial growth factor and basic fibroblast growth factor promote expansion of the tumor vasculature.[8–11] Due to the imbalance between pro- and antiangiogenic factors, growth of tumor blood vessels is poorly regulated, resulting in disorderly expansion of the vasculature.[11–13] Consequently, tumor vasculature tends to have

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defective architecture with pore sizes ranging from 100 to 780 nm,[14] allowing for extravasation of NPs within this size range. Another common feature of solid tumors is poor lymphatic drainage,[15, 16] which prevents efficient removal of macromolecules, including NPs, from tumors.[11, 17] This phenomenon, the so called "enhanced permeability and retention (EPR) effect,[17–21] has been the foundation of most NP-based tumor-targeting strategies[22] since the first report in 1986.[15]

"STEALTH COATING": A STRATEGY TO INCREASE BIOAVAILABAILABILITY OF NANOPARTICLES

To take advantage of the EPR effect, NPs need to circulate for a prolonged period. One significant obstacle to the long-term circulation of NPs is clearance by the reticuloendothelial system (RES),[23, 24] whose main role is to protect the body from the invasion of extraneous particles. The removal of NPs is initiated by interactions between foreign particles and the phagocytic cells in the blood (e.g., monocytes, neutrophils) and tissues (e.g., Kupffer cells, dendritic cells, macrophages).[25–27] This process is facilitated by adsorption of plasma proteins (opsonins), such as IgG or complement fragments, onto the particle surface, which labels the NPs as a foreign substance.[28–30] The opsonized NPs are ultimately eliminated by receptor-mediated phagocytosis.[30, 31]

Many studies have shown that NPs administered intravenously are cleared from the blood by RES within minutes, if the NP surface is not protected from opsonization.[23, 24, 32, 33] The circulation half-life of NPs depends on their size,[34] shape,[35, 36] surface chemistry,[37, 38] surface charge,[34, 39] and chemical composition of NP matrix.[36] Hydrophobic and/or charged NPs have shorter circulation half-lives due to significant opsonization.[34, 39] Therefore, NPs developed for systemic application are almost always coated with an electrically neutral hydrophilic surface layer, the so called "stealth coating". The circulation half-life of such NPs can be thus extended to >40 hours by the stealth coating.[40]

PEGYLATION FOR STEALTH COATING

In the past three decades, the majority of surface stabilization of NPs has been carried out with non-ionic hydrophilic polymers and/or surfactants. In particular, polyethylene glycol (PEG) (Fig. 1A) is used in the majority of current studies. In 1977, Abuchowski et al reported that covalent conjugation of 2 kDa or 5 kDa PEG ("PEGylation") to bovine liver catalase decreased immunogenicity of the protein and increased its circulating time in blood.[41] Since then PEG (typically 5 kDa[42]) has been widely used in a variety of NP systems, such as liposomes,[43–45] polymeric NPs,[29, 46, 47] and micelles.[48, 49]

PEG forms a flexible layer on the surface of NPs,[50] preventing the adsorption of opsonins[51, 52] via steric hindrance[53] and their subsequent uptake by phagocytic cells.[54] The PEG surface layer is often described as a mushroom or a brush model (Fig. 1B). When the surface PEG density is relatively low (for example, 0.5–0.7 mol% PEG 5kDa in liposomes), it forms a mushroom-like structure to maximize surface coverage.[55, 56] As the PEG density increases, the PEG chains extend to avoid overlap with other PEG molecules, resulting in a brush model.[42, 56]

The reported optimal PEG content varies by system. For example, 10 wt% PEG density was considered optimal for poly(lactic acid) (PLA) NPs[39] or poly(lactide-co-glycolide) (PLGA) NPs[57] with respect to the particle dispersibility and stealth effect. On the other hand, Gref et al reported that the optimal PEG surface coverage for PLA, PLGA, and polycaprolatone NPs was 5 wt%, and that higher levels of PEG content did not further reduce protein adsorption.[42] Five to seven mol% PEG, which is at the borderline between mushroom and

brush, is reported as optimal for obtaining thermodynamically stable liposomes.[56] In this range, PEG dehydrates the lipid head group and decreases defects in lipid bilayer. Further increase in PEG content (>10 mol%) destabilizes liposomes due to repulsion between the neighboring PEG chains.[56]

The effects of PEGylation on the prolongation of the NP circulation are well established. Verrecchia et al reported that PEGylated NPs showed higher plasma concentration and lower accumulation in the liver than non-PEGylated NPs.[58] At 6 hours after injection, 10% of PEGylated PLA NPs, but only 0.4% of non-PEGylated PLGA NPs remained in circulation.[58] Uptake of PEGylated PLA NPs by the liver was significantly lower than that of non-PEGylated PLA NPs (11% vs. 20% of injected dose).[58]

EXAMPLES OF PEGYLATED NPS

Liposomes

Liposomes consist of one or more concentric spheres of lipid bilayers, which are separated by aqueous compartments.[59] Liposomal doxorubicin (Doxil® or Caelyx®) is indicated for the treatment of patients with metastatic breast cancer, ovarian cancer, or Kaposi sarcoma.[60] For long-term circulation of liposomes, surface protection with PEG is an essential part of the preparation. Liposome PEGylation is performed by mixing PEG–lipid conjugates and other lipid components at a fixed ratio.

Polymeric NPs

Polymeric NPs are made of hydrophobic and mostly biodegradable polymers. They contain drugs in the polymer matrix and release them by diffusion and/or matrix degradation. PEGylated polymeric NPs are prepared either by making NPs with block co-polymers of PEG and hydrophobic polymer[61] or grafting PEG on the surface of pre-formed NPs. When PEG is grafted on the surface of pre-formed NPs, PEG with amine termini is covalently conjugated to reactive functional groups (e.g., carboxylic groups) exposed on the NP surface.[62] Alternatively, PEG can be attached to the NP surface using avidin-biotin interaction.[63]

Polymeric micelles

Polymeric micelles are formed by self-assembly of amphiphilic block copolymers, which consist of hydrophilic and hydrophobic segments. When dispersed in water along with hydrophobic drugs, the amphiphilic block copolymer assembles into 30–50 nm spheres with a core-shell structure, in which drugs and hydrophobic segments form the core and the hydrophilic segment interfaces with the aqueous medium.[64] Polymeric micelles usually form at a relatively low concentration compared to surfactant micelles and thus are more stable in circulation.[65] PEGylation of polymeric micelles is achieved by employing PEG as the hydrophilic segment. Polymeric micelle formulations are currently in clinical trials for the treatment of various cancers.[66–68]

THE “PEG DILEMMA”

Interference with cellular uptake and endosomal escape of NPs

While PEG has been successfully used for surface protection of various NPs, recent studies recognize its disadvantages.[69–74] Drug delivery using NPs often involves cellular uptake of NPs, especially when the drug does not freely enter the target cells by itself (e.g., nucleic acids) or when it is constantly removed from the cells (e.g., multidrug resistance). The extravasated NPs are still multiple steps away from cellular entry (Fig. 2). NPs go through (i) transport in the extracellular matrix, (ii) attachment to the cell membrane via receptors,[75]

(iii) internalization into the cells,[76] (iv) escape from intracellular vesicles and drug release to the cytosol, and (v) transport to target organelles.[77] The so-called "PEG dilemma" is that the PEG coating, an essential part of a NP until extravasation, interferes with NP-cell interactions and the endosomal escape of NPs after extravasation.[78] Although the extent of PEG interference may vary with particle types or sizes, it significantly compromises intracellular delivery of drugs or genes by various NPs.[69, 79]

For example, PEGylated liposomal doxorubicin showed less tumor accumulation than non-PEGylated liposomes, indicating PEG interference with the cell-liposome interactions.[80] Moreover, Hatakeyama et al discussed in their recent review article that PEGylated multifunctional envelope-type nano device (MEND) showed a significantly lower gene expression than unmodified MEND.[69] Mishra et al also demonstrated that PEGylation of non-viral gene vectors (branched polyethyleneimine (bPEI) or β-cyclodextrin-containing polymer) led to significant reduction in gene expression.[81] Electron microscopy revealed that the gene vectors with bare cationic surfaces entered cells as large aggregates, whereas PEGylated bPEI NPs remained small and discrete, both outside and inside the cells.[81] These results indicate that PEGylated NPs are less effective in entering cells and escaping intracellular vesicles. Remaut et al investigated the intracellular fate of oligonucleotides delivered by PEGylated liposomes using fluorescence resonance energy transfer (FRET) microscopy.[82] PEG layer interfered with endosomal escape of liposomes, resulting in degradation of the oligonucleotides.[82]

Immune responses

In addition to its effects on the cellular uptake and endosomal escape, PEGylation raises other concerns. Recently, immune reactions to PEGylated liposomes have been reported.[71, 73, 74, 83–88] Ishida et al demonstrated that PEGylated liposomes were rapidly cleared from blood upon repeated injections.[73, 83, 89, 90] The accelerated blood clearance (ABC) of the second dose of PEGylated liposomes was caused by the binding of PEG-specific IgM, produced by the first dose of liposomes,[73, 87] and the subsequent activation of the complement system.[73, 91] The liposomes cleared from the circulation accumulated in the liver and to a lesser degree in the spleen.[85, 88] Induction of the IgM response depended on the spleen[84] but not on T cells,[74] indicating that the immune response against PEGylated liposomes was mediated by splenic B cells in a T-cell independent manner. On the other hand, the ABC response was not seen with doxorubicin-loaded PEGylated liposomes and/or high dose of PEGylated liposomes, presumably due to their detrimental effects on splenic B cells[71] or depletion of blood opsonins.[92] In this case, a significant fraction of NPs tend to accumulate in the spleen, and the NPs delivering cytotoxic drugs may avoid accelerated clearance by inhibiting the proliferation of the splenic B cells. However, the immune response to PEGylated nanomedicines can be a significant issue for the delivery of other drugs or for low-dose applications, adversely affecting their pharmacokinetics and biodistribution profiles. For instance, PEG-asparaginase administered for the treatment of acute lymphoblastic leukemia was reported to be cleared rapidly in one third of the treated patients, potentially decreasing effectiveness of the treatment.[93]

ALTERNATIVE STRATEGIES FOR PROTECTING NP SURFACES

Alternative polymers

Polyoxazolines—Polyoxazolines (POZ) have been explored as a hydrophilic segment in amphiphilic block-co-polymer. Poly(2-ethyl-2-oxazoline) (Fig. 3) was coupled with poly(caprolactone),[94, 95] poly(aspartic acid),[96] or poly(1,3-trimethylene carbonate)[97] to form polymeric micelles. POZ was also used in preparing liposomes and shown to be comparable to PEG in stealth effects.[98] Poly(2-methyl-2-oxazoline) was grafted to poly(l-lysine) as a

PEG alternative for non-viral gene delivery.[99] A recent study reported a series of POZ-based amphiphiles, demonstrating versatility of synthetic manipulation of POZ and cytocompatibility of the POZ-based polymers.[100]

Poly(amino acids)—Poly(amino acids) such as poly(hydroxyethyl l-glutamine) or poly(hydroxyethyl-l-asparagine) (PHEA) (Fig. 3) have been developed as potential stealth polymers.[101] Unlike PEG, poly(amino acids) are readily degraded by proteases and thus may reduce the risk of accumulation and related toxicity.[102] These polymers were able to prolong the blood circulation of NPs to a similar extent as PEG.[101, 102] In particular, PHEA-coated liposomes were superior to PEGylated liposomes in resisting ABC after repeated administration and in maintaining the stealth effect at low lipid doses.[103]

N-(2-hydroxypropyl)methacrylamide (HPMA)—First synthesized by Kopecek et al,[104] HPMA (Fig. 3) and its derivatives have been widely explored as macromolecular drug carriers.[105] HPMA polymers have many attractive features for drug delivery, including biocompatibility, hydrophilicity, and ability to accommodate structural modifications.[105, 106] HPMA has been conjugated to various drugs[107, 108] and targeting moieties.[109, 110] HPMA conjugation increases the circulation time of low molecular weight drugs, allowing for EPR-mediated tumor accumulation.[105] To facilitate intracellular drug release, drugs are conjugated via an enzymatically cleavable peptide linker (e.g., GFLG).[111]

Polybetaines—Betaines such as sulfobetaine and carboxybetaine are zwitterionic molecules, which bind water molecules via electrostatic interactions,[112, 113] more strongly than those relying on hydrogen bonding.[114] Polymers based on betaines (Fig. 4) greatly reduce non-specific protein adsorption,[115] bacterial adhesion and biofilm formation[116, 117] on various surfaces. Moreover, poly(carboxybetaine) has multiple functional groups amenable to multivalent conjugations, providing a useful platform for multi-functional nanomedicines.[112] For these reasons, polybetaines have generated certain interest as alternative non-fouling materials for NP modification. For example, poly(carboxybetaine) has been used to modify a variety of NPs such as silica,[118] gold,[119] iron oxide,[120] PLGA,[121] and hydrogel NPs.[122, 123] These NPs showed excellent size stability in protein solutions including serum, indicating strong resistance to non-specific protein adsorption.[118–121, 123]

Polyglycerols—Polyglycerols (also known as polyglycidols) (Fig. 5) are biocompatible and flexible hydrophilic aliphatic polyether polyols, prepared in branched or linear forms.[124, 125] The anti-fouling effect of hyperbranched polyglycerols is comparable to PEG, while they are less susceptible to oxidation or thermal stress than PEG.[126] In addition, polyglycerols contain multiple hydroxyl groups, which can be further functionalized.[126] The long plasma half-lives of hyperbranced polyglycerols (33 hours for 106 kDa and 57 hours for 540 kDa) indicate their promises as stealth polymers.[127] Polyglycerols were used to prolong liposome circulation[128] and to prevent protein adsorption to gold surface.[126] A recent study reported a new liposome system covered with a block-copolymer of PEG and hyperbranched polyglycerol, where the polyglycerol moieties facilitated multivalent functionalization of the liposome.[129]

Polysaccharides—NPs are prepared with derivatives of chitosan,[130, 131] dextran,[132, 133] hyaluronic acid,[134] and heparin,[135–137] in which the polysaccharides (Fig. 6) provide hydrophilic shells on the NP surface. Advantages of polysaccharides are biodegradability, low immunogenicity and toxicity,[135, 138, 139] and abundant functional groups useful for conjugation of drugs or cell-interactive ligands. These polysaccharide-based NPs extend circulation times of the loaded drugs and enhance their accumulation in tumors. In particular, chitosans assume a positive charge and thus can improve cellular interactions of

NPs at weakly acidic pH. This property can be utilized to achieve specific drug delivery to acidifying tumors.

Papisov at al proposed to use acyclic hydrophilic polyacetals (Fig. 7) derived from polycarbohydrates to replace PEG.[140] The advantages of hydrophilic polyacetals, as compared with PEG, are biodegradability and availability of readily modifiable functional groups.[140] Moreover, a polylysine grafted with polyacetal had a much longer blood half-life than a polylysine grafted with dextran, the original polysaccharide that polyacetal was derived from.[140] This difference was attributed to elimination of rigid stereospecific structures of dextran.[140]

Conditional removal of PEG effect

Triggered by cellular cues (Fig. 8)

pH change: Environmental features unique to tumors and extracellular matrices have been exploited as a way of removing the protective effect of PEG in a tumor-specific manner. One such feature is the slight acidity of tumors,[141–143] induced by the increased glycolysis and plasma membrane proton-pump activity of tumor cells, which results in greater lactic acid production than in normal cells and in leakage of acid into the extracellular milieu.[144, 145] Moreover, many solid tumors develop hypoxia,[146, 147] which further induces or selects for hyperglycolytic cells, enhancing local acidosis.[148] Therefore, many tumor tissues show weakly acidic pH,[149–151] compared to the blood and normal tissues (pH 7.4).

pH-sensitive PEGylated liposomes have been proposed to take advantage of the tumor microenvironment pH.[152–154] Sawant et al reported a liposome system with a pH-sensitive hydrazone linker between the surface and PEG layer.[154] The PEG layer shielded liposomes at pH 7.4 and detached at pH 5–6 revealing a cell adhesive peptide, which helped liposomes to interact with cells at the acidic pH.[154] pH-sensitive micelles have been developed for a similar purpose. Lee et al reported polymeric micelles composed of poly(l-histidine)-PEG diblock copolymer,[155] where poly(1-histidine) (molecular weight: 5 kDa) lost hydrophobicity at pH 7 due to the ionization of the imidazole group.[156] Such a transition in the ionization status of the polymer allowed gradual destabilization of the micelles and release of the encapsulated drug at acidic pH. Stability of micelles, and hence the pH at which the micelle destabilization is triggered, could be controlled by blending a pH-insensitive PLA-PEG block copolymer[156] and/or introducing a pH-insensitive polymer block (poly(l-phenylalanine)) to the existing pH-sensitive polymer.[157, 158]

Depending on the trigger pH, pH-responsive PEG removal can enhance endosomal escape of NPs. Late endosomes and lysosomes have a pH of 5–5.5.[159] pH-sensitive micelles or liposomes that destabilize at this pH allow for endosomal drug release and disruption of endosomal membrane.[142, 160] Mohajer et al showed that the enhancement of endosomal drug release using pH-sensitive micelles helped cytosolic delivery of anticancer drugs and significantly increased the intracellular drug levels in MDR tumor cells.[161] A pH-sensitive micelle system, combined with a cell-interactive ligand (e.g., folate), suppressed the growth rate of MDR ovarian tumors, to a much greater extent than pH-insensitive micelles.[158] The effectiveness of the pH-sensitive micelles in MDR tumors was attributed to accelerated endosomal drug release, which enabled a high cytosolic drug concentration and increased intracellular drug diffusion, providing room for the subsequently delivered drug.[158] In another example, a pH-sensitive hydrazone linker was used in DNA-lipopolyplexes to induce endosomal removal of PEG (dePEGylation) and increase gene transfection efficiency.[162] First, cholesterol linked to PEG via a pyridine hydrazone linker was included in the liposomes. DNA-lipopolyplexes were then prepared by mixing DNA-polyethylenimine complex with the pH-sensitive liposomes.[162] Lipopolyplexes were

aggregated in pH 5.4, indicating acid-induced removal of PEG from the lipid surface.[162] Because of the intracellular dePEGylation, the lipopolyplexes with cleavable PEG were 40 times more effective in gene delivery compared to those with non-cleavable PEG.[162]

Enzymatic stimuli: Another unique property common to many solid tumors is overexpression of proteinases, such as matrix metalloproteinases (MMPs),[163] which play a critical role in invasion of tumor cells and angiogenesis.[164] Several studies have employed MMPs to trigger PEG cleavage.[163, 165, 166] Terada et al reported a galactosylated liposome system containing PEG-peptide-dioleoylphosphatidyl ethanolamine (DOPE) ternary conjugate.[165] PEG was removed as the peptide linker was cleaved by MMP-2. Upon removal of PEG, galactose moieties on liposome surface was exposed and recognized by asialoglycoprotein receptors on cancer cells. The ligand-receptor interaction increased cellular uptake of liposomes and cytotoxicity of the liposomes containing an anti-cancer drug.[165] Hatakeyama et al used the MMP-2 sensitive MEND for delivery of plasmid DNA[167] or siRNA.[166] The MMP-sensitive MEND was superior to the MMP-insensitive PEGylated MEND in cellular uptake and endosomal escape.[166] The in vitro results translated to relatively higher tumor accumulation and gene silencing effect in tumors.[166]

Enzymatically cleavable PEG linkers may be employed not only in drug/gene delivery but also in imaging agents. A quantum dot (QD) decorated with a cell-penetrating peptide was PEGylated via a MMP-2 cleavable peptide linker.[168] Cellular uptake of QDs occurred in response to the presence of MMP-2, as a result of MMP-2 induced dePEGylation of QDs.[168] Similarly, gold nanorods were coated with PEG via a peptide linker cleaved by urokinase-type plasminogen activator (uPA), specifically expressed in malignant tumors. In the presence of uPA, the PEG-peptide-modified gold nanorods showed more efficient cell-binding and tumor accumulation than control nanorods with a non-cleavable linker.[163] On the other hand, a challenge in enzymatically cleavable PEG systems is to find an optimal PEG density. While PEG density should be sufficiently high to protect the NPs during circulation, dense PEG chains can interfere with enzyme access to the substrate linker.[163]

Reductive potential: Another unique feature of many tumors is the reductive environment due to overexpression of reductase enzymes[169, 170] or release of glutathione following cell death.[171] Ren et al reported a micelle system consisting of PEG-polyleucine diblock copolymer, in which PEG and polyleucine were linked via the disulfide bond.[172] The micelles dissociated and released the incorporated drug in response to a reducing agent, which caused disulfide cleavage.[172] Cytotoxicity of doxorubicin loaded in these reducible micelles was significantly enhanced when cells were pretreated with 10 mM glutathione.[172] Based on the same principle, PEG was linked to nucleoside-lipid via disulfide bond.[173] Micelles and liposomes prepared with the reducible PEG-nucleolipid showed changes in particle size and surface charge upon treatment with a reducing agent, reflecting reduction-induced dePEGylation. Detachment of PEG increased cellular uptake of micelles and liposomes.[173]

Triggered by external cues

Thermal stimuli: Thermal stimuli can be applied to enhance drug delivery from NPs after their accumulation at tumor site.[174, 175] Li et al reported a thermosensitive liposome system containing relatively high contents (5 mol%) of 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-PEG (2000 Da) (DSPE-PEG_{2000}) as compared to typical PEGylated liposomes (< 5 mol%).[174] The thermosensitivity came from the balanced membrane stability. High density of surface-grafted polymers (PEG) disturbed membrane integrity due to the transition in PEG configuration.[176] Liposomes containing 5 mol% DSPE-PEG_{2000} had the optimal balance between stability and temperature sensitivity.[174]

This liposome system released the payload in response to mild hyperthermia at 42°C,[174] providing a way of increasing drug release at target tissues in a stimulus-dependent manner. Stability of PEGylated liposomes can be alternatively controlled by the particle size.[177] Hossann et al demonstrated that particle size was inversely proportional to the drug release rate.[177] This is because membrane curvature and permeability of phospholipids significantly increase as the vesicle size decreases.[178]

Ultrasonic stimuli: Ultrasound may also be used to trigger drug release from NPs. Ultrasound of various intensities is widely used for diagnostic imaging or therapeutic intervention.[179–181] For these purposes, ultrasounds provide thermal[179] or mechanical effects.[182] Ultrasonic heating has been employed to trigger the drug release by increasing the permeability of liposomal membrane.[183] Alternatively, pulsed ultrasound has been used to mechanically trigger the drug release from NPs.[181, 183, 184] Rapoport et al achieved tumor selective drug delivery by local tumor insonation.[182] This approach involved systemic administration of nanoemulsions, consisting of paclitaxel and echogenic liquid (perfluoropentane) stabilized with PEG-PLA or PEG-PCL block copolymers.[182] Following tumor accumulation (4 hours after the injection), pulsed ultrasound was applied to trigger droplet-to-bubble transition of perfluoropentane and subsequent drug release.[182] The ultrasonic stimulus also contributed to drug diffusion in the tumor matrix and intracellular drug uptake via perturbation of cell membrane.[185]

Biomimetic stealth coating

Red blood cell (RBC) membrane has been used for stealth coating of polymeric NPs.[186] PLGA NPs were formed first and then co-extruded with RBC-membrane-derived vesicles through a porous membrane. Thus formed RBC-membrane-camouflaged NPs were well dispersed in serum and showed a longer circulation time than those covered with PEG-lipid.[186] Clinical translation of this approach may face some challenges related to immunogenicity or disease transmission. On the other hand, this study points to the critical roles of transmembrane proteins in controlling half-lives of circulating particles. A synthetic surface recapitulating their functions may provide a new biomimetic stealth coating that overcomes limitations of PEG.

Conclusions and Perspectives

For delivery of NPs to tumors to be effective, it is critical to produce long-circulating NPs. PEGylation is the most widely used technique to achieve this; however, the popularity of PEG does not necessarily mean that it is the best polymer for stealth coating. Recent studies find that PEG can interfere with processes subsequent to the extravasation of NPs, which are required for successful drug delivery to target tissues, and that PEGylated NPs may be subject to immune surveillance after the first dose. Several approaches to replacing PEG or modifying PEGylation are worth noting. Many alternative polymers have advantages over PEG in biodegradability or ability to accommodate functional groups. These features may be useful for improving cell-NP interactions in a target-specific manner and/or avoiding immune responses, which remain a topic for future studies. pH- or enzyme-triggered removal of PEG, another promising strategy to overcome the PEG dilemma, has proven effective in several recent studies. The remaining challenge is to produce sensitive and selective linkers, which can respond to minute changes in microenvironment or to alternative biological cues. Despite potential challenges in clinical translation, biomimetic stealth coating is a stimulating idea, which taps into the nature's secret for controlling the longevity of RBCs.

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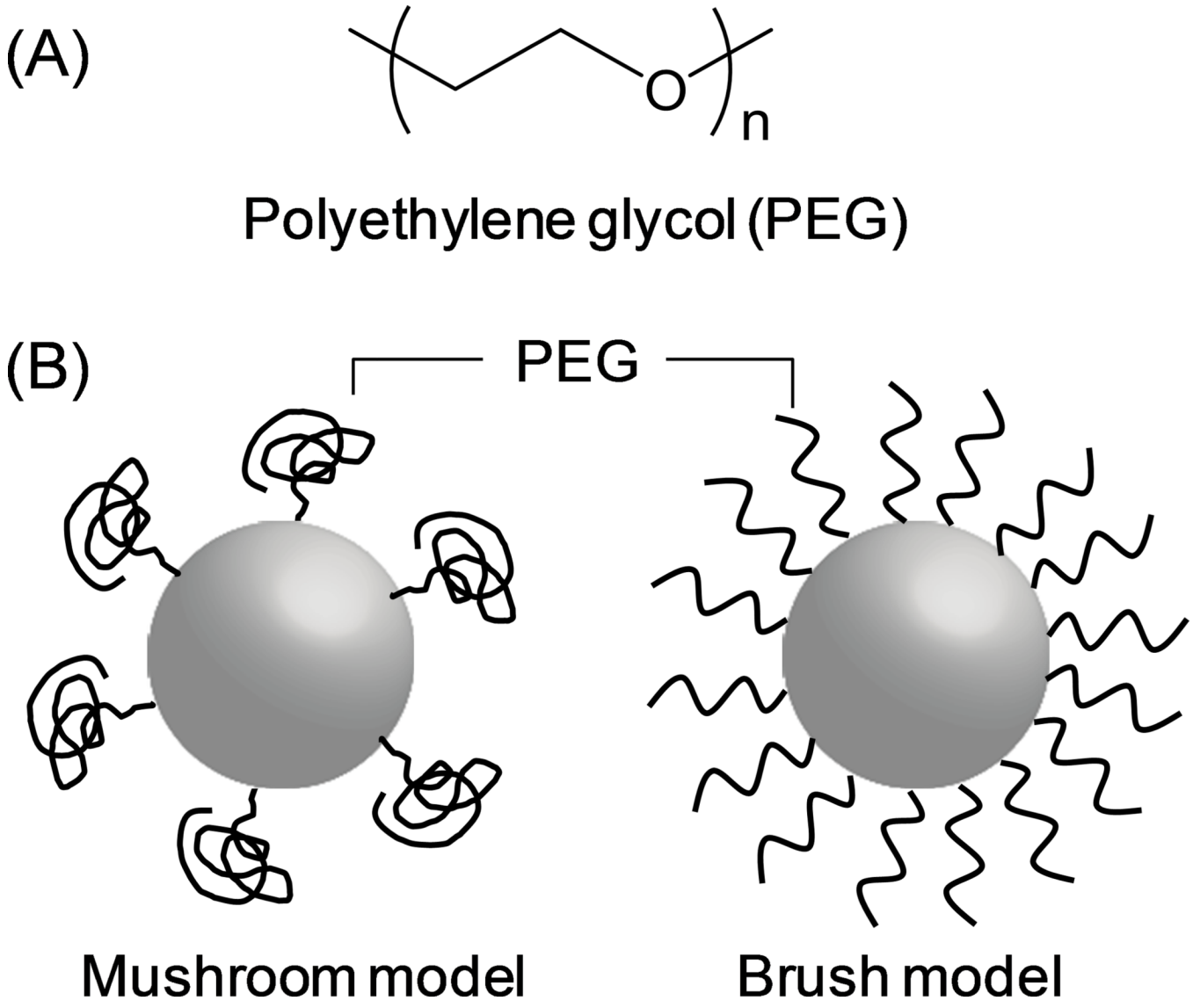

Fig. 1.
(A) PEG structure; (B) model of PEGylated NPs.

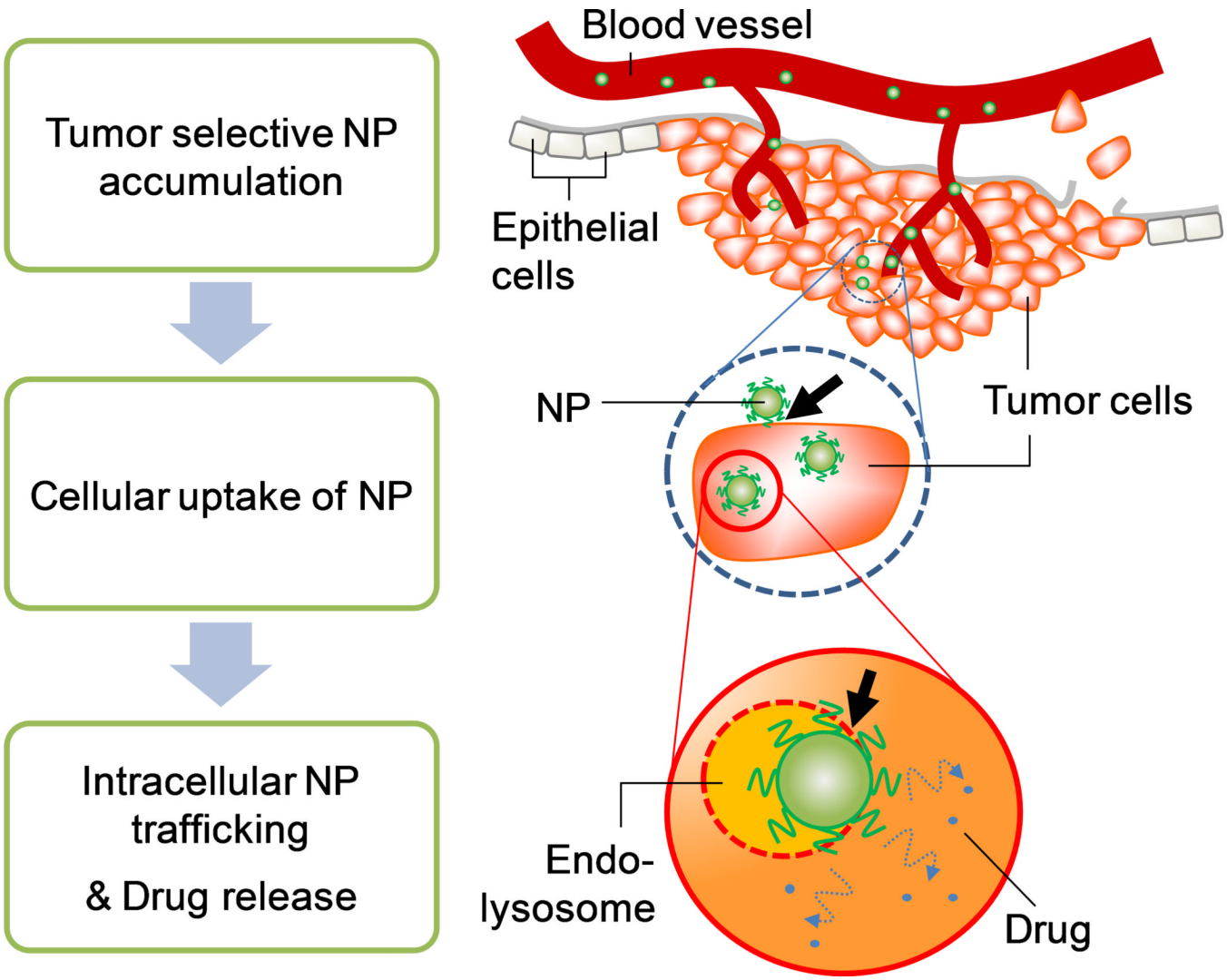

Fig. 2.
Schematic description of NP-based drug delivery to tumors. Arrows indicate steps negatively influenced by PEG layer on NP surface.

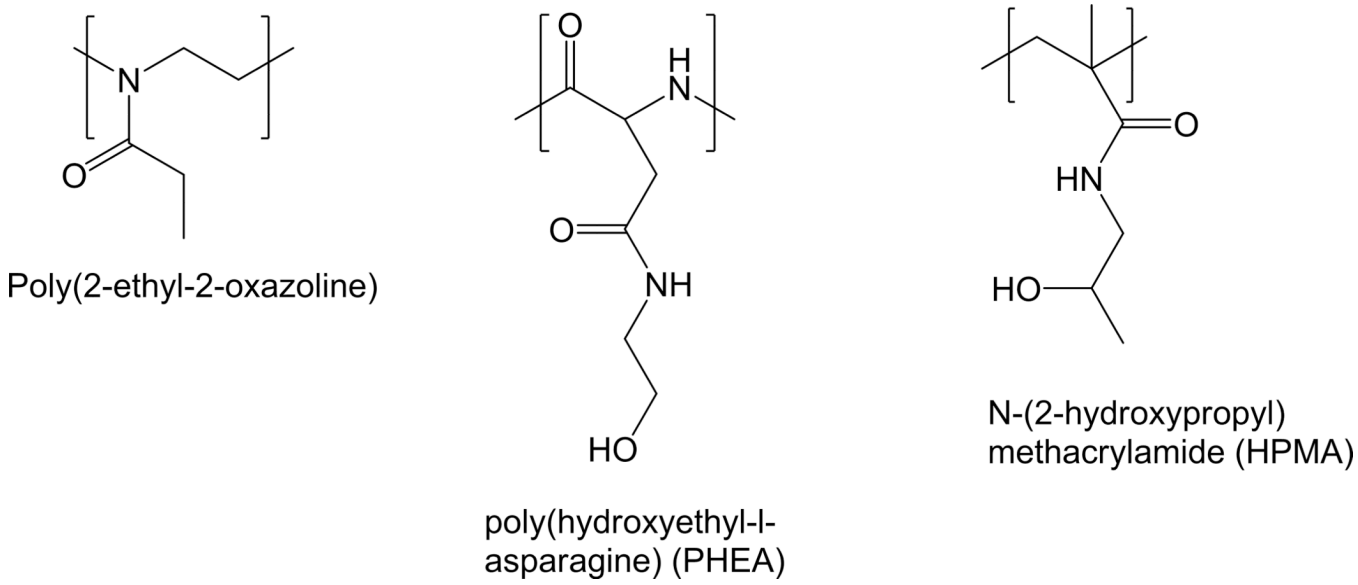

Fig. 3.
Structures of poly(2-ethyl-2-oxazoline), PHEA, and HPMA.

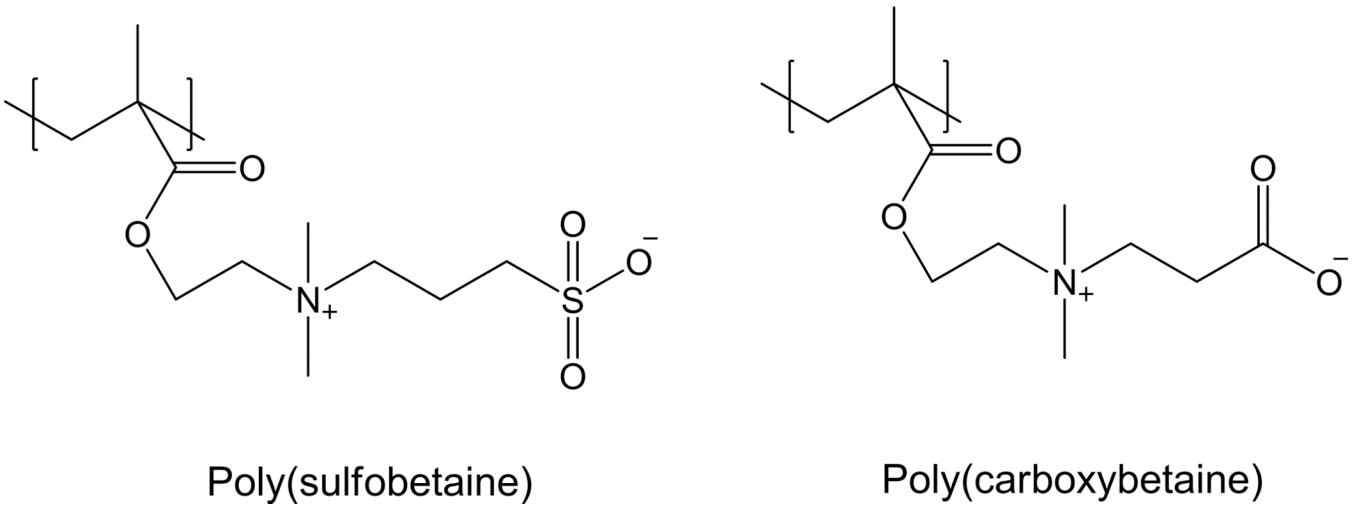

Fig. 4.
Structures of poly(sulfobetaine) and poly(carboxybetaine)

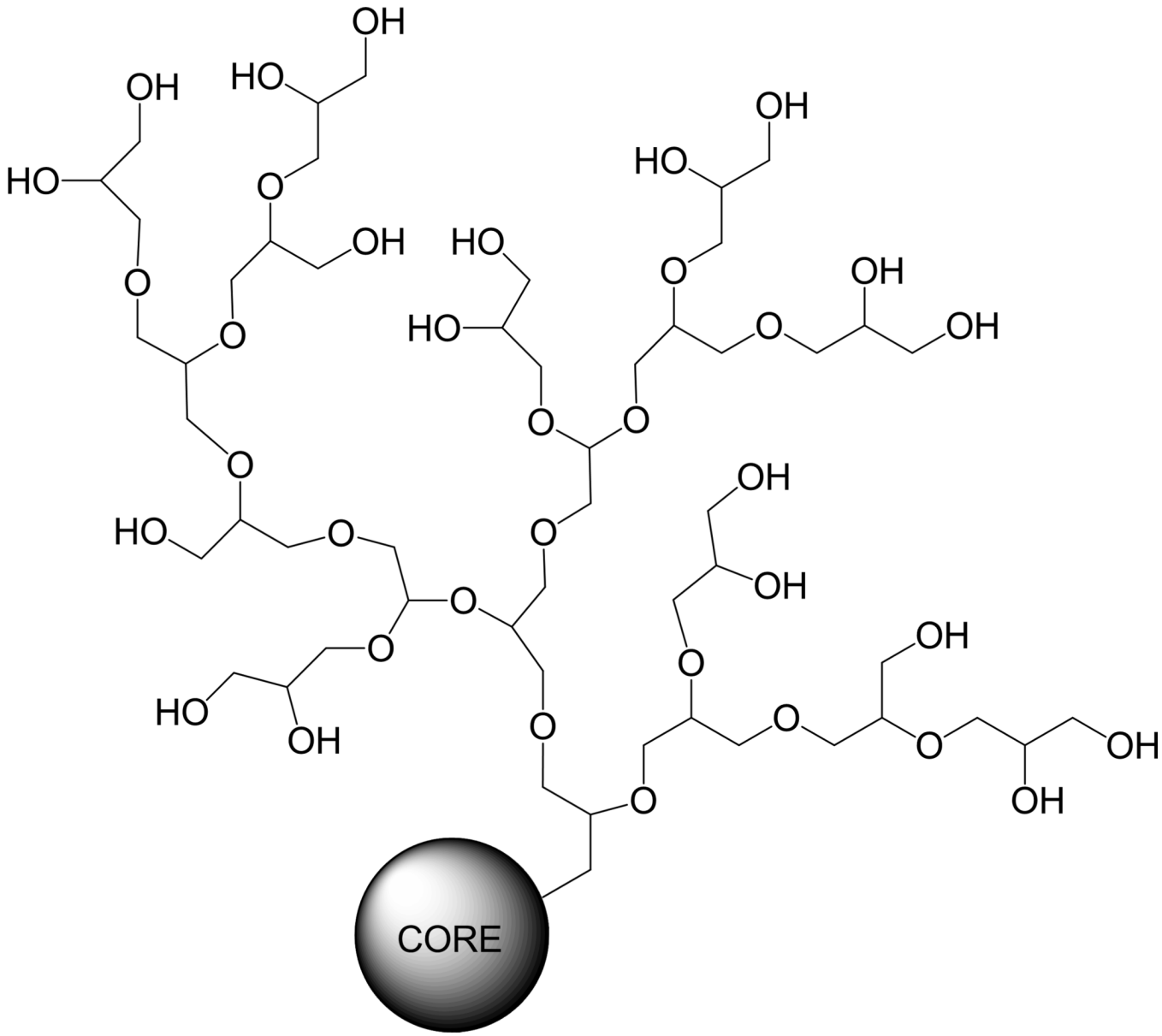

Fig. 5.
Structure of hyperbranched polyglycerol[127].

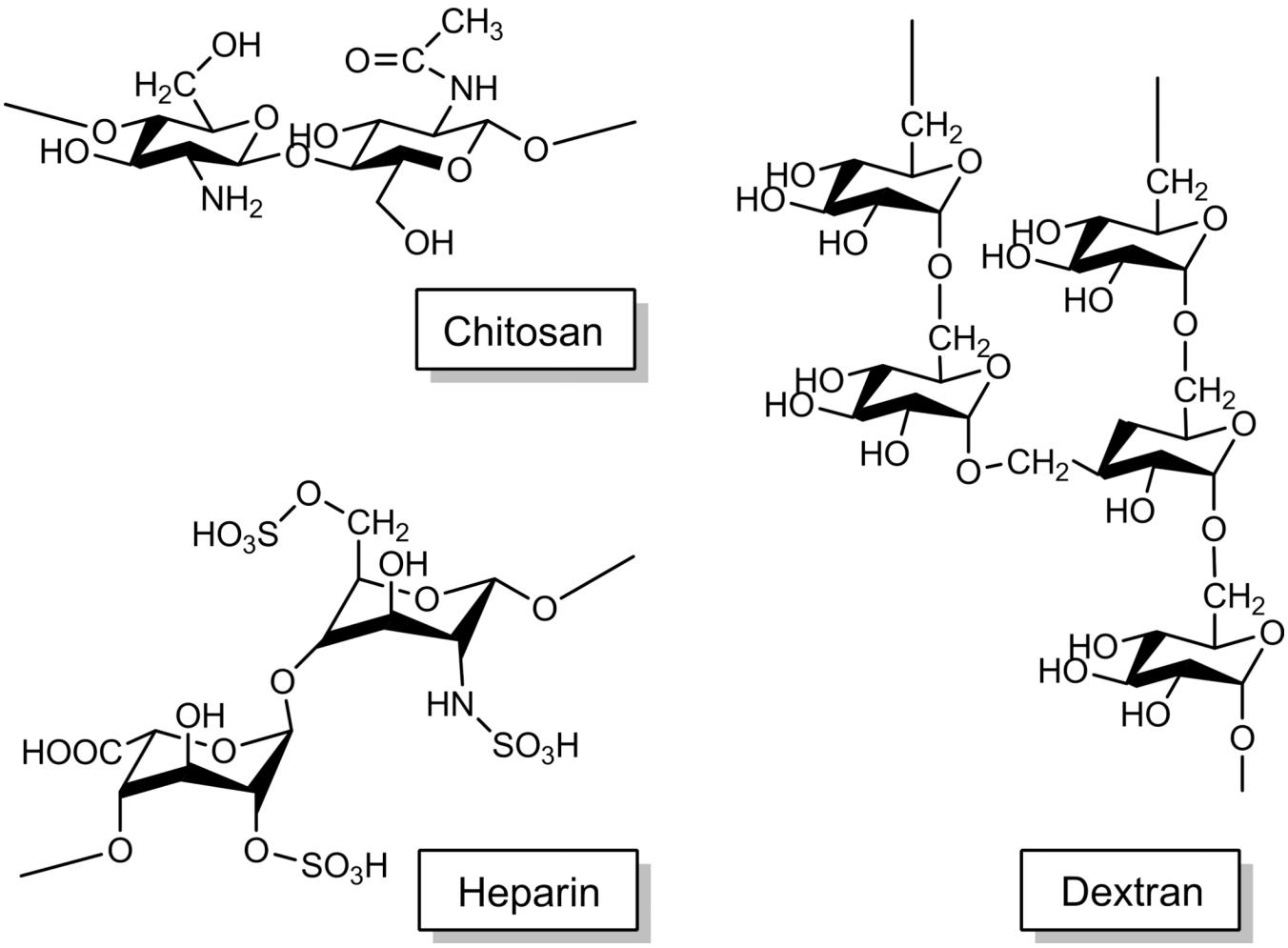

Fig. 6.
Structures of chitosan, heparin, and dextran.

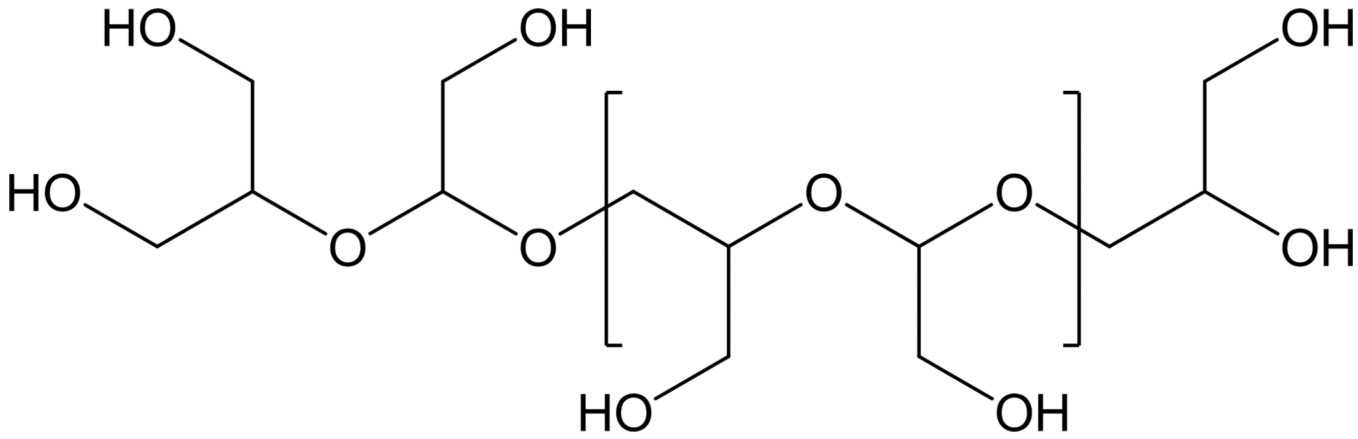

Fig. 7.
Poly(hydroxymethylethylene hydroxymethylformal)

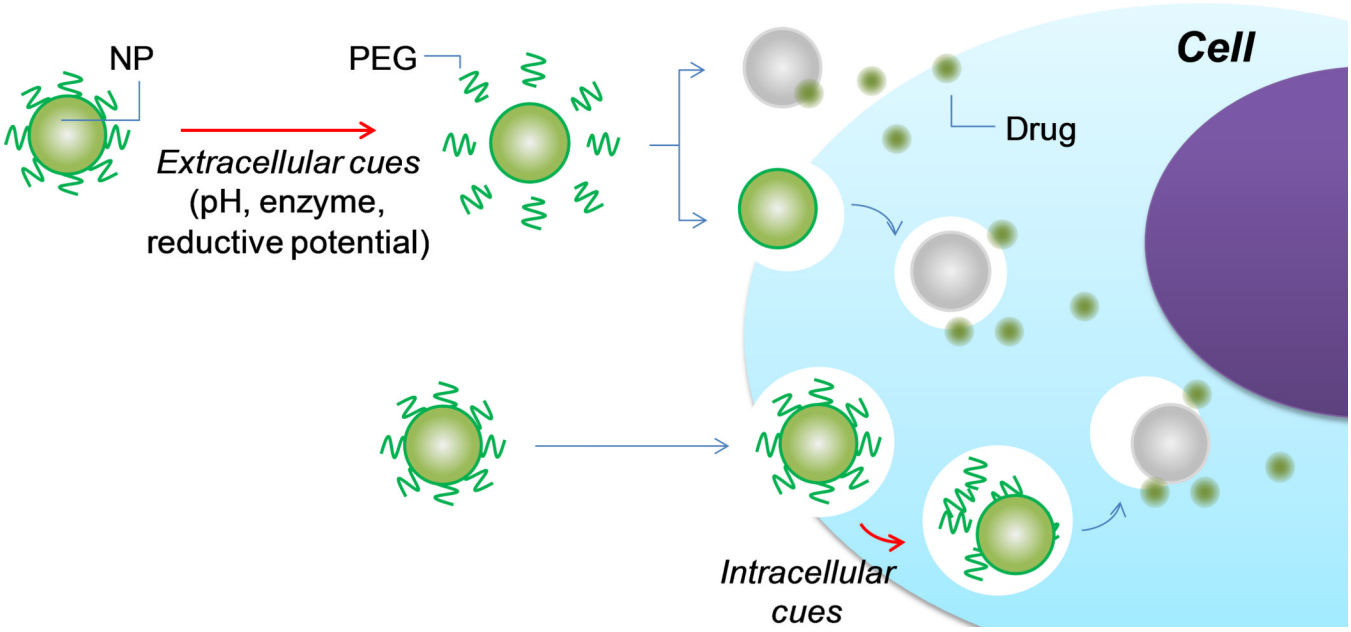

Fig. 8.
DePEGylation of NPs by cellular cues