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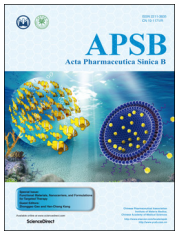

REVIEW

# Charge-reversal nanoparticles: novel targeted drug delivery carriers

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**Abstract** Spurred by significant progress in materials chemistry and drug delivery, charge-reversal nanocarriers are being developed to deliver anticancer formulations in spatial-, temporal- and dosage-controlled approaches. Charge-reversal nanoparticles can release their drug payload in response to specific stimuli that alter the charge on their surface. They can elude clearance from the circulation and be activated by protonation, enzymatic cleavage, or a molecular conformational change. In this review, we discuss the physiological basis for, and recent advances in the design of charge-reversal nanoparticles that are able to control drug biodistribution in response to specific stimuli, endogenous factors (changes in pH, redox gradients, or enzyme concentration) or exogenous factors (light or thermos-stimulation).



*Abbreviations:* Abs, integrin aVb3 mAbs; B-PDEAEA, poly[(2-acryloyl) ethyl (*p*-boronic acid benzyl) diethylammonium bromide]; BPS, bridged polysilsesquioxanexerogel; BSA, bovine serum albumin; CA4, combretastatin A4; CAPL, charge reversible pullulan-based; CHPNH2, cationic cholesteryl group–bearing pullulans; Cit, citraconic anhydride; CMC, carboxymethyl cellulose; CPLAs, cationic polylactides; Cya, cysteamine hydrochloride; DAP, 2,3-diamino-propionate; DCL, dimethyl maleamidic acid-*ε*-caprolactone; DDS, drug delivery system; DM, dimyristeroyl; DMA, 2,3-dimethylmaleic anhydride; DMPA, dimethylol propionic acid; DOX, doxorubicin; FITC, fluorescein isothiocyanate; Glu, glutamic acid; GO, graphene oxide; GSH, glutathione; HCC, hepatocellular carcinoma; HEP, 1,4-bis(2-hydroxyethyl) piperazine; His, histidine; HMP, *p*-hydroxylmethylenephenol; MG, microgels; MMPs, matrix metalloproteinases; MNP, magnetic nanoparticles; NPs, nanoparticles; PAEP, poly(allyl ethylene phosphate); pA-F, fluorescein-labeled polyanion; PAH, poly(allylamine) hydrochloride; PBAE, poly(*β*-amino ester); PCL, poly(*ε*-caprolactone); PDADMAC, poly(diallyldimethylammonium chloride); PEG, polyethylene glycol; PEI, polyethylenimine; PEO, poly(ethylene oxide); PK, protein kinase; PLA, ploylactic acid; PLGA, poly(lactic-*co*-glycolic acid); PLL, poly(L-lysine); PMA, poly(methacrylic acid); PS, pH sensitive; PSS, poly(sodium 4-styrenesulfonate); PSSS, poly(styrene-*co*-4-styrene-sulfonate); PTX, paclitaxel; PU, polyurethane; PVPON, poly(*N*-vinylpyrrolidone); ROS, reactive oxygen species; SOD, superoxide dismutase; TMA, 2-(mercaptoethyl) trimethylammonium chloride; TUNA, thioundecyl-tetraethyleneglycolester-*o*-nitrobenzy-lethyldimethyl ammonium bromide

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## 1. Introduction

Cancer is a leading cause of death around the world. According to the mortality data from World Health Organization in 2015, there were an estimated 84 million cancer deaths in the last decade[1]. Cancer development has been defined as a multistep process by which an initiating event (*e.g.*, environmental insult) leads to malignant proliferation. As a small tumor mass forms, the surrounding healthy tissue is unable to compete with the cancer cells for an adequate supply of nutrients from the blood system, leading to apoptosis and necrosis of the normal cells followed by dysfunction of primary organs and death[2]. Current therapeutic strategies for most cancers involve a combination of surgical resection, radiation therapy, and chemotherapy. However, significant morbidity and mortality are always associated with these therapies due to their off-target effects on the "normal" cells. The efficacy of a chemotherapy regimen is directly correlated with the ability to selectively target tumor tissue, overcome biological barriers, and "smartly respond" to the tumor environment to release therapeutic agents[3]. In conventional drug delivery, the drug is exposed directly to serum without protection. The drug concentration in the blood increases rapidly after administration and then declines. The purpose of an ideal drug delivery system (DDS) is to adjust the drug concentration within a desired therapeutic range after a single dose, and carry the drug to a targeted region while simultaneously lowering the systemic levels of the drug[4]. Charge-reversal nanoparticles exert significant potential for the specific targeting and release of anti-cancer drugs. Nanoparticles are defined as submicronic colloidal systems. Nanosized drug carriers have a variety of intrinsic advantages over conventional drug delivery systems, such as large payload capacity for anticancer formulations, protection from degradation, multivalent targeting moieties, and controlled or sustained release that reduces adverse effects while enforcing the safety margin of the antitumor agents[5–7]. Nanoparticles are usually taken up by various metabolic systems depending on their surface characteristics. Generally, the positive charge facilitates the binding of nanoparticles to the cell membrane, leading to a significant improvement in membrane transport properties because of the intrinsic negative surface charge of the cell membrane. However, this positive charge might also strengthen the nonspecific binding of vectors to normal tissue[8]. The luminal surface of blood vessels is well known to have a negatively charged surface contributed by sulfated and carboxylate sugar moieties, meaning that nanoparticles with high positive charges will bind nonspecifically to the luminal surface of vascular walls and be rapidly cleared from the blood circulation[9]. Charge-reversal nanoparticles combine the targeting advantages of a conventional "smart" nanoparticle with a charge-switch characteristic for drug release. Surface charge is designed to be obscured during the blood circulation and uncovered at tumor sites. Thus, these novel anti-cancer drug carriers have attracted tremendous attention for delivery of anticancer agents. Herein, we provide a brief review of several possible targeting delivery strategies for charge-reversal nanoparticles.

## 2. Endogenous stimuli-responsive charge-reversal delivery

### 2.1. *pH-triggered charge-reversal delivery*

Low cellular pH has been widely used to design sensitive drug delivery strategies. Previous reports demonstrated that pH values vary significantly in different tissues or organs, (such as stomach and brain), and in morbid states, (such as diabetes, infection, inflammation, and tumor)[10]. The pH in tumor tissue is lower than that in normal tissues because of the high rate of glycolysis in cancer cells. Compared with the pH 7.4 of normal tissue, the pH in a tumor has been demonstrated to range from 5.7 to 7.8. Additional pH differences are observed at the subcellular level. The late endosomes and lysosomes have a much lower pH, in the range of 4.5–5.5. Several drug carriers are absorbed through endocytosis and assimilated within endosomes and lysosomes. This pH gradient is significant for cancer drug delivery. pH-Sensitive nano-systems are designed to stabilize the cargo at physiological pH, and release the drug rapidly when the pH triggering-point is reached (Fig. 1A). Kim et al.[11] synthesized a

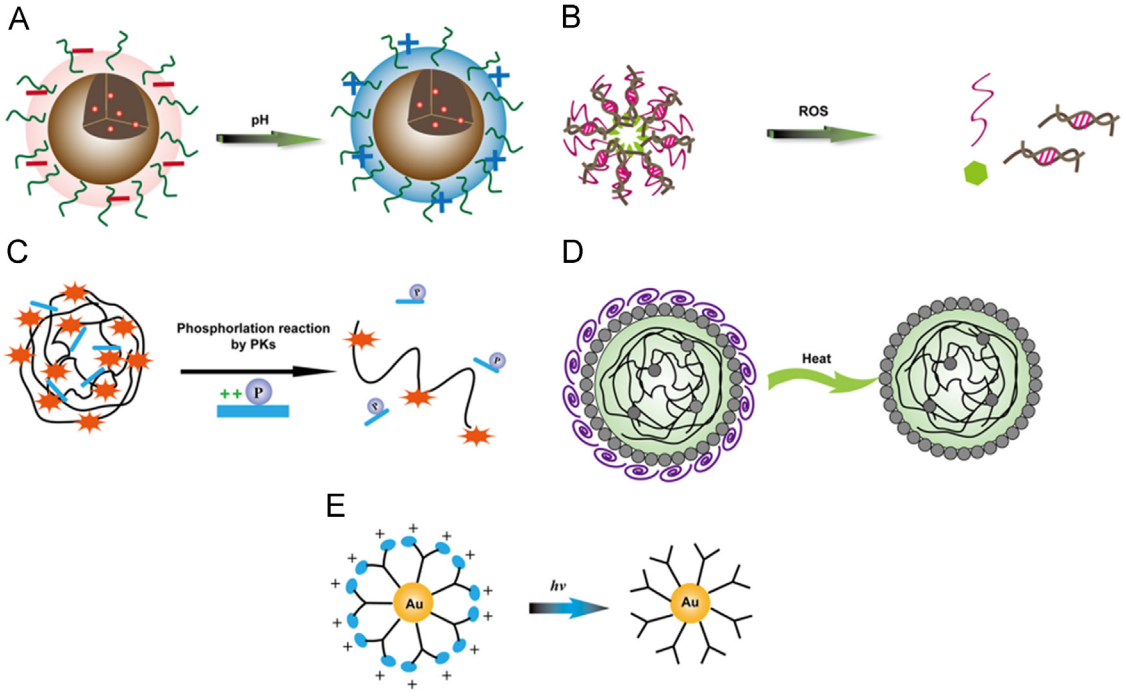


**Figure 1** Endogenous and exogenous stimuli-responsive charge-reversal delivery. (A) pH-triggered charge-reversal delivery; (B) tumor redox environment–triggered charge-reversal delivery; (C) tumor protease-triggered charge-reversal nanoparticles; (D) light-triggered charge-reversal drug delivery; and (E) thermo-responsive charge-reversal drug delivery.