Drug Targeting Strategies Based on Charge Dependent Uptake of Nanoparticles into Cancer Cells

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ABSTRACT - The aim of this review was to describe the preferred charged nano-particles (CNPs) for targeted delivery in tumor cells. Zeta Potential (ZP), which represents the surface charge of NPs was highlighted in cell entrance and interactions. In this regard, various types of endocytosis pathways which are involved in NPs' uptake were first introduced. Then, significance of positively charged NPs (PCNPs) in proton sponge effect corresponding to lysosomal escape was discussed. Cells prefer to endocyte the NPs with positive charge in passive targeting and gene delivery, while in active targeting; the charge of receptors' ligand binding site determines the NPs cellular uptake. Moreover, pH-sensitive NPs represent charge reversible behavior depending on pH changes which leads to longer blood circulation residence and higher uptake at acidic microenvironment of the cancer media. Role of the CNPs in overcoming multidrug resistance (MDR) and bypassing p-glycoprotein was further investigated.

INTRODUCTION

In recent years, using particles prepared by Nano-technology is ever-growing in cancer diagnosis, treatment, and also in theranostic preparations. Nanoparticles (NPs) are able to deliver genes, pharmaceutical agents, proteins, peptides, and diagnostic agents (1). Targeted NPs possess further advantages compared to the traditional forms. They can guide the encapsulated agent to the special cell or tissue so the off-target side effects will be reduced. NPs can improve the oral bioavailability and preserve pharmaceutical agents against enzymatic degradation. In addition, they increase the solubility of less-soluble drugs as a matter of reduced size and increased surface area. NPs can also have a sustained release of the encapsulated agent at the target tissue (2). Despite the vast information regarding several NPs beneficial aspects in target delivery, the fundamental details about the molecular interactions of various NPs with specific cells are still remained unclear. Characterization of NPs specifications has high importance in target delivery. The physico-chemical characteristics as well as composition, size, shape, charge and surface chemistry have to be explored in detail. Cellular entrance variables such as the intended cell type, cell treatment, nanomaterial cell incubation conditions, and the types of NPs, which all have undeniable effects on the amount, kinetics, and mechanism of uptake, have to be elucidated too.

Transportation of vital substances into normal cells and drugs into target cells is a critical process. Nano-sized range proteins and pivotal ions are internalized into cells through channels of cell membrane lipid bilayer (3). Nano-sized Macromolecules and NPs containing therapeutic and diagnostic agents are delivered into cells by endocytosis. Endocytosed materials which are entrapped in lysosomes are not able to reach the cytosol (4). Instead, they are exposed to digestion by lysosomal enzymes. Thus, well designing NPs in targeting to the cell cytoplasm is essential for imaging and therapy goals (5), phototherapy (6) and drug targeting (7). There are different methods to transport NPs to the cytosol such as using chloroquine (8), direct microinjection of NPs into cells (9), use of electroporation (10), and connection of natural chaperons to NPs (11).

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One of the most common ways in this regard is disruption of endosomes and cell entrance through the "sponge-effect" phenomenon by positively charged NPs (PCNPs) (12). However, crossing process of materials through cell membrane is a challenging issue. Most NPs, such as needle-shaped NPs, cell-penetrating peptides (CPPs) (13), very small molecules (14), and PCNPs (15) can penetrate through the cell membranes successfully.

Recent studies showed that size of the NPs has a significant place in cellular absorption (16). However, inductively coupled plasma mass spectroscopy (ICP-MS) results have proved that zeta potential (ZP) which represents the surface charge has a more significant duty in cellular absorption of NPs (17). Understanding the electrostatic connections between NPs and cancer target cells has an important role in designing targeted NPs and predicting their cytotoxicity.

Surface charge of cell membranes is negative (typically -40 to -80 mV) which facilitates delivery of PCNPs (18). Cancer cell surfaces contain strong negatively charged elements as well as chorionic gonadotropin, sialic acid and anionic residues of RNA as compared to normal cell surfaces which have more neutral zwitterion phospholipids (19). Furthermore, concentration of sodium ions inside tumor cells (20) and presence of anionic glycocalyx on the tumor cells, contributes to their low ZP (19). Therefore, PCNPs have a high tendency to accumulate in cancer cells (21). However, neutral and anionic NPs could also be taken up by tumor cells (22).

Composition, size, and morphology of NPs in addition to surface charge have an inevitable role in their biologic behavior and cellular uptake. In order to explain the charge effect comprehensively, every other interfering contributors have to be excluded or remained constant.

This review discusses the fundamental issues related to NPs and cancer cells ZP by diverse cellular uptake mechanisms; in continue the effects of ZP in charged NPs' (CNPs) uptake into specific tumor cells are explained. In this regard, charge related uptake of metal, metal oxide, polymeric, lipidic and dendrimeric NPs in target delivery are discussed. Moreover, the uptake routes of neutral, anionic and cationic NPs in active and passive targeting are explained. Molecular interactions of the CNPs with the cell membrane and the charge of receptors binding sites and their ligands are also reviewed in detail.

The novelty of this work is evaluation of electrostatic interactions between specific cells and distinct CNPs regarding different strategies of passive targeted CNPs. Moreover, molecular and charge dependent interactions of specific receptors with actively targeted NPs decorated with specific ligands are discussed in more details which have not been reported before.

Cellular uptake of CNPs

NPs enter cells via various endocytosis routes, which are mostly affected by their charge and size. The surface charge of NPs is indicated by ZP which will be explained thoroughly in continue. Surface charge of NPs affects their uptake by intra-cellular organelles and their lysosomal digestion. Charge of NPs determines the blood circulation time, uptake rate and the intended target cells. Different routes of NPs endocytosis, quantification of surface charge as ZP, and lysosomal escape of NPs will be discussed. Specific charged NPs have some advantages and disadvantages in targeted delivery, which will be further explained.

Cellular uptake mechanisms of NPs

Small molecules are mostly taken up by endocytosis (23). This pathway requires ATP to create vesicles through lipid bilayer wrapping. Phagocytosis (cell eating by phagocytic cells including macrophages, neutrophils, dendritic cells, etc. which engulf the particles larger than 1 μm) and pinocytosis (cell drinking, uptake of liquid and particles smaller than 50 nm in diameter) are two categories of endocytosis mechanisms (24). The major subgroups of pinocytosis are adsorptive and receptor-mediated internalization. The second pathway is related to absorption of NPs through various routes such as macropinocytosis, caveolin-dependent/independent pinocytosis and clathrin-mediated pinocytosis (25).

Clathrin- and caveolae-mediated endocytosis are dependent on specific protein–receptor interactions. NPs which are internalized by the caveolae-dependent pathway can penetrate into the endoplasmic reticulum, while clathrin- mediated pathway entraps the NPs into endo/lysosomes (26). Figure 1 schematically illustrates various cellular entrance ways of the NPs.

Different kind of NPs: hard, soft and hybrid

There are vast number of NPs which have been prepared using verity of materials so far (31-35). Based on type of initial material used in NPs

fabrication, NPs are classified into soft, hard and hybrid ones. Soft NPs are composed of organic compounds which are soft materials such as polymers, lipids, proteins and cyclodextrin derivatives. Inorganic materials such as metals, metal oxides, metal hydroxides, silica and metal salts are primary materials applied for preparation of hard NPs. In some cases, hard NPs are coated with soft materials, resulting in hybrid NPs production. Examples of hard, soft and hybrid NPs are presented in Table 2 (36).

Cell uptake studies in the presence of inhibitors help us understand the cell entrance mechanisms of NPs. For example, Amiloride is an inhibitor of macropinocytosis. There is no cellular uptake when Amiloride and NPs are added to the cellular culture plate confirming inhibition of macropinocytosis pathway (27). Therefore, macropinocytosis is the main uptake mechanism of these NPs. Other inhibitors for different uptake mechanisms are listed in Table 1.

Surface charge of NPs

When the particles are dispersed in the solution, formation of the interfacial charge causes rearrangement of the local free ions surrounding particles resulting in electrical double layer formation. Electrical double layer (EDL) around NPs is composed of a stationary layer and a diffuse layer (37). Stationary layer (compact layer) is composed of a thin layer of counter ions immediately next to the solid face (Stern layer) containing ions with opposite charge and some solvent molecules. Slipping plane is the outer plane of stationary layer (37). At potentials higher than 150 mV, slipping plane is shifted extensively from the particle surface and though ZP will not change anymore. That is because of the polar orientation of water molecules in the electric filed and their binging to the surface (38). The stationary layer is immobile; while the NPs in the solution are randomly moving. Thus, with the motion of materials in the solution, ZP does not change. ZP is the potential difference between slipping plane and solution medium (37, 39). ZP indicates the superficies charge of NPs, which affects the cellular absorption. Position of the stern layer, slipping plane and ZP are schematically shown in Figure 2.

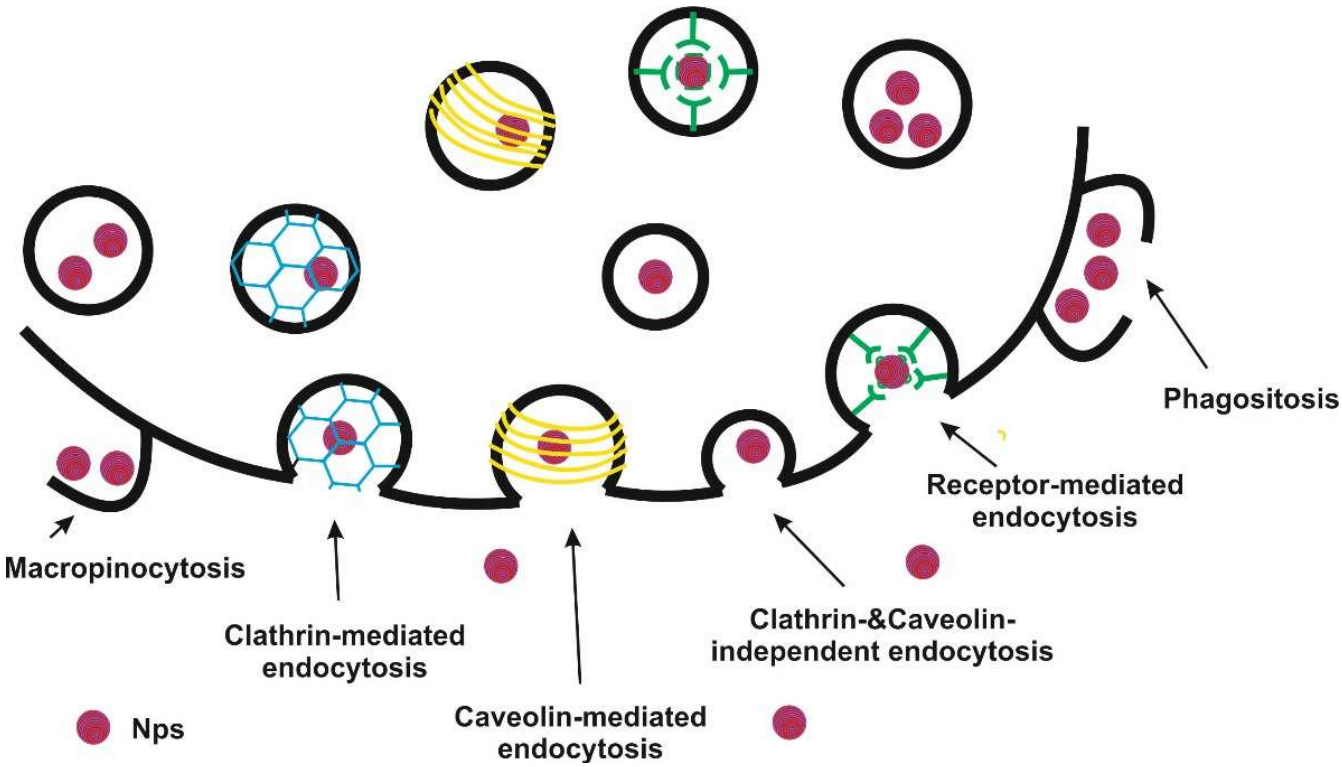

Figure 1. Schematic representation of NPs uptake mechanisms comprising phagocytosis, macropinocytosis, and endocytosis. Endocytosis mechanisms include receptor-mediated endocytosis, clathrin-mediated endocytosis, caveolin-mediated endocytosis, and clathrin-& caveolin-independent endocytosis.

Table 1. Some inhibitors of different uptake mechanisms

Uptake pathway	Inhibitors	Ref.
Macropinocytosis	Amiloride	(27)
Energy-mediated endocytosis	NaN_3	(28)
Caveolin-mediated endocytosis	Nystatin	(29)
Clathrin-mediated endocytosis	Chlorpromazine	(29)
Phagocytosis	Cytochalasin-B	(30)
Pinocytosis	Colchicine	(30)
Clathrin-mediated endocytosis	Dansylcadaverine	(26)
Caveolae-mediated endocytosis	fillipin	(26)

Table 2. Examples of different kinds of Soft/ Hard/ Hybrid NPs.

Different kinds of NPs	Examples
Soft NPs (organic NPs)	NPs of biodegradable polymers such as PLGA, PLA, PGA, PEG, PVAL NPs of non-Biodegradable polymers such as Polyacrylamide polymers Lipidic NPs such as Liposome, NLC, NE, SLN Cyclodextrin-based NPs
Hard NPs (inorganic NPs)	Metal, Metal oxide, Metal hydroxide, Metal carbonates, Magnetic NPs, Quantum dots and Semiconductor NPs such as Gold, silver, copper, ZnO, CuO Metal Salts NPs such as NaYF4, zinc phthalocyanine, LaF3:Ce3+, LuF3:Ce3+, CaF2:Mn2+, CaF2:Eu2+, BaFBr:Eu2+, BaFBr:Mn2+, CaPO4:Mn2+ Silica (SiO2)
Hybrid NPs (organic NPs coated by organic materials)	Silica NPs coated with poly-(L-lysine) and hyaluronic acid Iron oxide NPs coated with polyacrilamide Magnetic NPs covered by chitosan NaYF4 NPs coated with poly(ethylenimine) Gold NPs with PEI coating

Dispersion media can influence ZP and slipping plane shifting. In non-aqueous solvents with dielectric constants greater than 10, there is some ionization similar to polar media. This is while, in solvents with very low dielectric constant value ~ 2, electrostatic interactions are important (40, 41).

There are different mechanisms that particles gain surface charge at aqueous media. These mechanisms include 1) Affinity differences of two phases to electrons 2) Ionization of surface groups 3) Different ion adsorption from electrolyte 4) Different ion dissolution from the surface of the particles 5) Surface anisotropy 6) Isomorph substitution (in clay materials) (39). Surface charge of particles is presented by ZP which is important parameter in 1) Characterization of the biomedical polymers (42), 2) Stability of the colloidal dispersions (In general particles will reach an established dispersion when absolute value of ZP is above ± 30 mV due to the electric repulsion between particles) (43), 3) Electro kinetic transport of particles (44) and blood cells (45), 4) Membrane efficiency (46) and microfluidics (47). As a conclusion measuring ZP is necessary for determination of surface charge. There are some methods for measuring this quantity including Streaming potential (48), Streaming current (49), Micro electrophoresis (50), Electro osmosis (51), Sedimentation potential (52), Light scattering (37) and Electro kinetic sonic amplitude (ESA) technique (53).

CNPs and proton sponge effect

Most of the PCNPs (like NPs containing poly ethylene imine (PEI)) cause an influx of chloride ions into lysosomes to maintain the charge in the constant level; which leads to osmotic swelling and rupture of the lysosomes, well-known as the "proton-sponge" effect. As a result, NPs escape from lysosomal digestion which is sort of non-target localization, thus efficient delivery will be achieved (54). Lysosomal escape is important in

immunotherapy, because it can facilitate cross-presentation of immune responses and cause activation of both $CD4^+$ and $CD8^+$ T cells, simultaneously. Therefore, it can break immune tolerance (55) and tackle intera-cellular pathogens like hepatitis C virus, Mycobacterium tuberculosis and HIV (56). Target site of various drugs such as doxorubicin and cisplatin is the nucleus (57). So, they should flee from lysosomal enzymatic digestion to be delivered into the nucleus successfully. PCNPs show efficient nucleus targeting. Figure 3 illustrates proton sponge effect schematically.

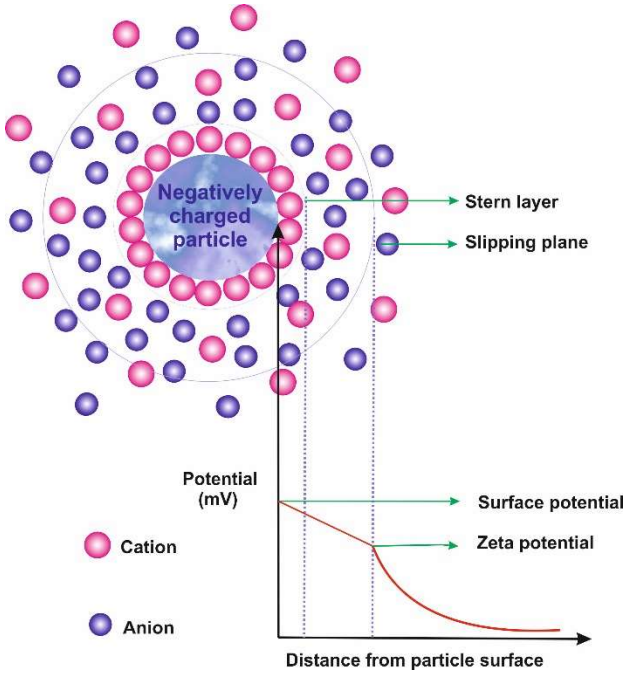

Figure 2. Schematic offering of the electrical double layer containing slipping plane and Zeta Potential (ZP). ZP: the potential differences between slipping plane and bulk solution. Slipping plane: the outer plane of the stationary layer. Stern layer: composed of ions immediately next to the nanomaterial's external face with the opposite charge of CNPs.

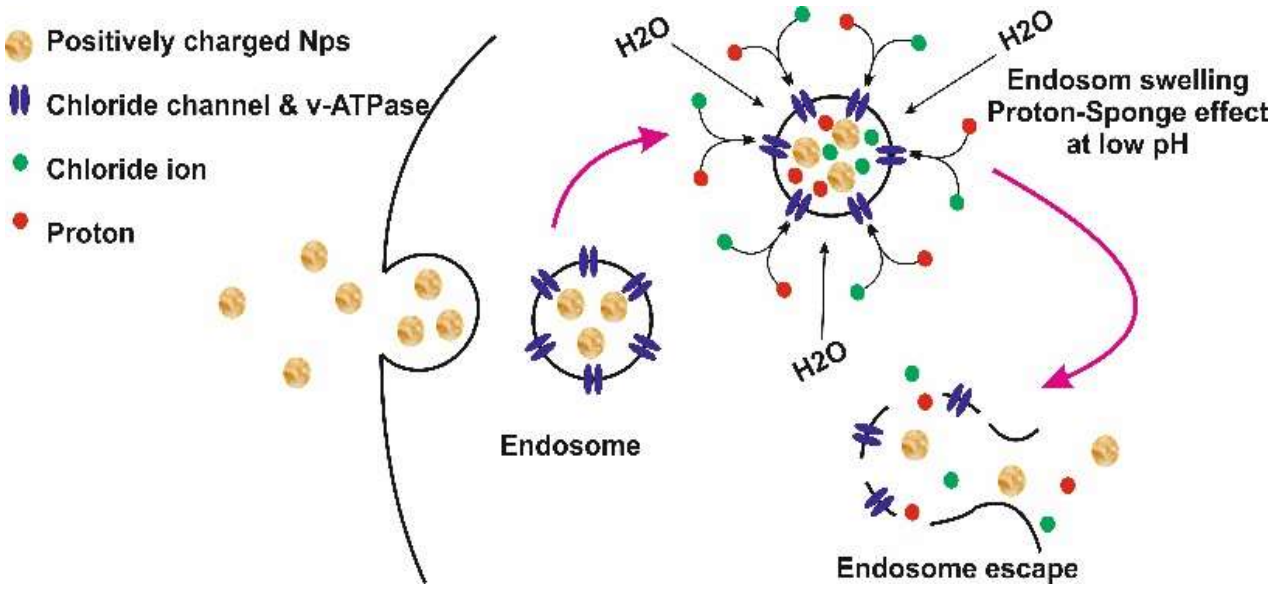

Figure 3. Schematic representation of proton sponge effect. As positively charged particles are taken up by endosome, chloride ions and then protons and water molecules enter the endosome which result in swelling of endosome. Finally, the swelled endosome explodes and the NPs escape from digestion by endosomal enzymes.

Advantages and disadvantages of CNPs in target drug delivery

Hydrophobic NPs and PCNPs show electrostatic adsorption tendency toward anionic proteins in plasma (such as hyaluronic acid and transferrin) (58) hence, they are suitable materials for reticuloendothelial system (RES) clearance. Negatively charged NPs (NCNPs) and hydrophilic ones like PEG-coated particles, escape from protein adsorption and RES clearance; therefore, they have a long time systemic circulation and possess more Enhanced Permeability and Retention (EPR) effect as compared to positive ones (59). Consequently, they are favorable for in vivo experiments as they have more tendencies to accumulate in the tumor site. However, the inefficient cell penetration of NCNPs restricts their final therapeutic performance. PCNPs have advantages as well as proton sponge effect, improved nucleus/cytoplasm delivery and higher cell entrance; but it is worth to note that they show lower blood circulation in higher ZP due to protein binding (60). Moreover, NPs with high cationic charge density show aggregation in microvasculature of some organs such as liver, spleen and especially the lung (61, 62). To overcome disadvantages of charge dependent targeted NCNPs, some strategies have been developed. pH-sensitive NPs are systems presenting negative charge in physiologic pH, but have the positive charge at acidic pH around the tumor cells. Therefore, they show long blood circulation and high cellular uptake. pH-sensitive NPs have both advantages of CNPs and overcome both of their disadvantages (63). Enzyme-degradable surface charge inversion systems have also same characteristics and advantages like pH-sensitive NPs (64). PCNPs have a significant advantage of higher and rapid cellular uptake but the disadvantage of elimination by RES in higher ZP. As a conclusion, particles with lower positive charge have longer blood circulation and higher entrancement to cells. Both CNPs with high positive and negative charge can be taken up by macrophages exhibiting lower blood circulation (65). All the above-mentioned characteristics are summarized in Table 3.

Protein corona and CNPs

For NPs located in blood plasma or other physiologic fluids, layers of proteins surrounding the particles are called “protein corona”. In the first step, the most frequently proteins coat the NPs; but after a while, they will be substituted by proteins with high affinity to NPs surface. This phenomenon is well known as Vroman’s effect (73). The composition of the corona changes over time because there are more than 3700 proteins in blood circulation which are in competition to be adsorbed on the surface of NPs (74). The proteins which are adsorbed tightly on NPs and could not easily be desorbed from their surface are named “hard corona”. “Soft corona” is related to proteins which are adsorbed loosely on NPs surface. Soft corona also interacts with hard corona (weak protein–protein interactions) (75). This model has been suggested by Simberg et al. (76).

Karmali and Simberg have reviewed that apo-lipoproteins as hard corona, could not be coated on inorganic NPs, but usually they are adsorbed on polymeric NPs and liposomes (77, 78). Experimental researches have demonstrated that protein corona load increases by elevation of the NPs’ ZP.

Table 3. Comparison of different NPs properties including cellular internalization speed\extent, RES clearance, protein binding, blood circulation time, proton sponge effect and promise organelle for delivery

Activity	Cationic NPs	Anionic NPs	pH sensitive NPs	Ref.
Cell uptake speed\extent	High	Low	High	(60, 63, 66, 67)
RES clearance	High	Low	Low	(68)
Protein binding	High	Low	Low	(63)
Blood circulation time	Low	High	High	(60, 63, 68)
Proton sponge effect	High	-----	High	(60, 63)
Promise organelle delivery	Nucleuses, Mitochondria, Cytoplasm	Lysosome, Cytoplasm (at low charge)	Nucleuses, Mitochondria,	(60, 67, 69-72)

Proteins with pI <5.5 (such as albumin) are usually adsorbed on PCNPs, while cationic proteins (pI > 5.5) such as IgG, have high affinity to be bound on NCNPs (79, 80). For example, complement (C1q) is adsorbed on anionic liposomes due to electrostatic interaction (81).

Protein corona can be denatured by surface charge of NPs, but it has not seen in the case of neutral NPs (74). Protein corona composition of different NPs with the same charge differs from each other. For instance, the bound proteins on carbon nanotubes are different from that of silica and metal oxide NPs. Carbon nanotubes prefer to adsorb albumin; this is while SiO_2, ZnO, TiO2 NPs show high affinity to other proteins (82). Albumin (pI = 4.7) and fibrinogen (pI = 5.5) are the most abundant proteins which are adsorbed on many types of NPs. Albumin is anionic protein, so it has high affinity to cationic lipoplexes and polyplexes, but it can be bound on poly-anions and hydrophobic surfaces too (77).

In addition to surface charge, the composition of NPs affects the identity of protein corona. Hydrophilic inorganic NPs, polymeric NPs and NPs with hydrophobic properties can be coated by kininogen (pI= 4.9), fetuin A (pI= 4.2-3.5), histidine - rich glycoproteins (histidine pI = 7.59), transferrin (pI= 5.2 to 5.9) and haptoglobin (pI = 5.5-6.2). Materials such as dextran and sugars which contain hydroxyl groups, can bind C3 complement (pI = 6.29) (77). NPs which are coated with dextran have sugar moieties which are cases for binding Mannose-binding lectins (MBLs). Dextran-coated NPs are recognized by antibodies too. Liposomes composed of phosphatidylinositol (PI) show specific interaction with serum mannose-binding protein (MBP) (PI= 5.39). There are compounds participating in soft corona composition (77). PEGylated NPs corona is considered as soft corona, having weak interaction with initial hard corona (83).

Hydrophobic NPs contain more protein corona than hydrophilic ones which increase opsonization of hydrophobic NPs (79). For example, hydrophobic and negatively charged polystyrene NPs possess higher amount of protein corona than hydrophilic polystyrene NPs (84). Hydrophobic NPs have more protein binding sites that is because of forming clusters of the polymer chains which are named "islands" and act as protein binding sites (85). Liposomes composed of long lipid chain adsorb more proteins than liposomes with shorter chain (86). IgG and albumin have high affinity to hydrophobic NPs (87). Proteins of culture media can be adsorbed on PCNPs, change their ZP, and influence cell uptake (88). In summary, surface charge, Size, shape, composition, surface functional groups, and hydrophilicity /hydrophobicity of the NPs affect identity of protein corona.

Importance of ZP in delivery of CNPs into tumor cells trough passive targeting rout

Cancerous tissues can induce angiogenesis. These formed vessels are often leaky without basal membrane resulting in fenestrated endothelial with the pore sizes of 200–2000 nm which let penetration of macromolecules across the tumor cells (89). Furthermore, the lymphatic system has reduced drainage at cancerous tissues because of minimal distances between lymphatic endothelial cells leading to retention of NPs in the tumor microenvironment. This phenomenon is well-known as EPR effect which provides accumulation of NPs (10-200 nm) just around the tumor microenvironment but not around the normal cells (Figure 4). Targeting strategies EPR effect are classified in passive targeting class, although NPs containing target ligands accumulate in tumor tissue using EPR effect as well.

Nonspecific interactions between PCNPs and negative charge of the cell membrane (ZP of MCF-7 cells is -20.32 mV), play a pivotal role in endocytosis of NPs in passive targeting to neoplasm cells. Conversely, there are positive sites on cell membrane that interact specifically with NCNPs and make them to be internalized into cells in the form of clusters. All three cationic (90), anionic (90) and neutral (91) NPs can be taken up by neoplasm and normal cells (92); But PCNPs internalize more rapidly into cancer cells (15, 90, 93). Therefore, uptake of NPs into neoplasm cells is dependent on ZP; but in normal cells, it is not. Cellular entrance of PCNPs of metal oxide (ZP = +20.3 mV) coated with PEG-PEI (30.6 nm); and NCNPs (-10 mV) coated with phosphorylated PEG (11.2 nm), into MDA-MB-231 breast cancer cells showed that PCNPs had higher uptake into MDA-MB-231 cells (90). NCNPs of gold had slightly higher uptake as compared to the neutral ones (17). Since ZP of the cancer cells is negative, the repulsive interaction between NCNPs and negatively charged cell membrane will repel the NPs internalization. Recent studies reported that there are cationic sites on the cell membrane which facilitate fusion of NCNPs with the cells (94).

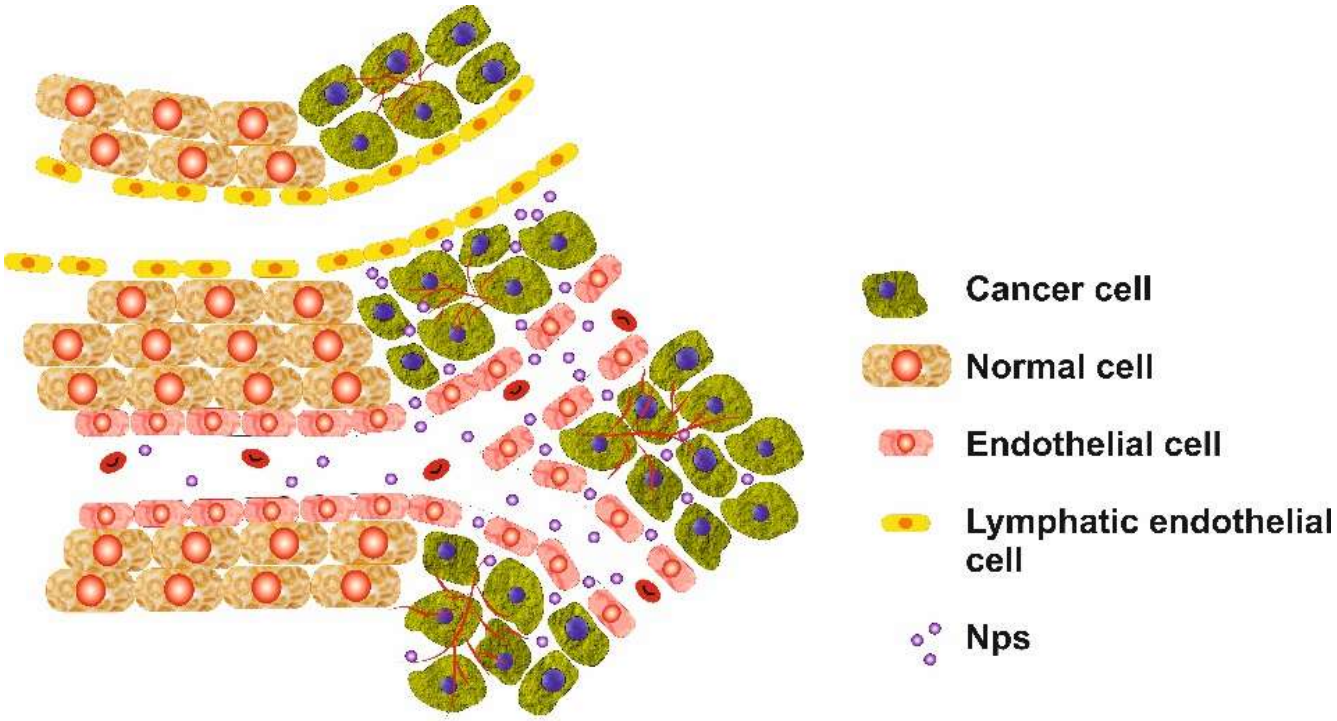

Figure 4. Representation of enhanced permeation and retention of NPs in tumor area known as EPR phenomenon. Blood endothelial cells are leaky at the tumor site, which let penetration of NPs to the tumor milieu. However, the lymphatic endothelial cells are tight at the cancer site, which cause retention of the NPs at cancer site and prevent their departure from the surrounding tumor cells.

Cerium oxide (CeO) NPs with the negative charge of -16.26 mV, have shown higher cellular entrance than PCNPs with +36.60 mV charge. That is for neutralization of cationic NPs by serum proteins in cell culture media. However, there are few positive parts for adsorption of anionic NPs on tumor cells (95).

Wilhelm et al., have reported repulsive interactions between NCNPs and anionic portions on cell membrane (96); so NCNPs form clusters as they bind to positive sites of the cells. In addition, attachment of CNPs on cell membrane lead to reduced charge density and may help adsorption of other free particles (96).

Type of ZP can influence both adsorption of NPs on cell membrane and their entrance into the cells. Adsorption process of all three GNPs with various ZPs is the rate-limiting step, which states the amount of internalized GNPs into SK-BR-3 mammary cancer cells.

PCNPs attach to the anionic cell membrane and cells import them through endocytosis or via another internalizing pathway (97, 98). Meanwhile, cells tend to maintain their original membrane charge (99, 100). As PCNPs attach to the cell surface; rigidity and morphology of the membrane will be changed (21, 97) and fluidity and permeability of the cell membrane will be increased (21). Then, under this condition; PCNPs will be internalized more easily than negative and neutral NPs into the cells. Poly caprolactone NPs with surface charge of +25 mV (due to the localization of drug on NPs surface) and size range of 100-300 nm were used for carrying tamoxifen into estrogen receptor (ER) positive cells of mammary tumor cells (101). Because of positive ZP of tamoxifen-loaded NPs, they were able to enter into the cells through non-specific endocytosis. As described with examples in the passive targeting of NPs to mammary tumor cells, PCNPs have shown to be internalized more rapidly into the cells due to nonspecific interactions with the anionic parts of the cell membrane; whereas, NPs with negative charge were internalized into cells with different mechanisms. NCNPs alter ZP of the cell surface and enter cells in this way. ZP of normal mammary epithelial cells (MCF10A) and mammary tumor epithelial cells (MCF7) were decreased for exposure of negatively charged iron oxide NPs. ZP change

was due to internalizing cationic parts of the cell membrane through endocytosis. So, as shown in the results, NCNPs were internalized by normal cells more quickly than tumor cells. MCF10A normal cells possess ZP of -31.16 mV and are much more negative than MCF-7 cancer cells (-20.32 mV) (102).

It was also shown that vesicles formed in MCF10A cells had bigger average size than those of MCF7 cells, because NPs are filled in the form of clusters in MCF10A vesicles; while, the fractured form of NPs are filled in MCF7 cells vesicles (102). In another study, Vanessa et al., have reported that uptake of iron oxide NPs into Caco-2 human colon cancer cells is increased, when surface charge of these NPs gets more negative. Also, NPs with more negative charge accumulate in larger vesicles. They concluded that non-specific cell uptake and cell interaction are responsible for internalization of highly negative surface charged NPs into cells (26). Arnida et al., have indicated that highly negatively charged GNPs as hard NPs, exhibit more cellular uptake into PC-3 cells, a human prostate cancer cell, than both positive PEGylated GNPs and less negative PEGylated GNPs (103). This phenomenon is due to presence of hydrophilic stealth coating around the PEGylated GNPs which present reduced interactions of NPs with cell membrane and result in reduced cellular uptake (104). In another study, NCNPs composed of Poly (methacrylic acid) and agmatine showed high cell uptake into A2780 ovarian cancer cells (105).

Two kinds of NPs using different polymers (containing cystatin) with the same particle size (250-300 nm) but different ZP were constructed and their cellular uptake into the lysosome of MCF-10A-neoT cells have been investigated (70). PLGA (poly (Dl-lactic-co-glycolic acid) NCNPs (ZP: -22 mV) have shown higher cellular uptake compared to positively charged chitosan NPs (ZP: +36 mV). PLGA NPs exhibited hydrophobic surface properties, whereas chitosan NPs were hydrophilic (70). It is indicated that, NPs with hydrophobic surface show more “aggressive” behavior which make them more suitable for rapid cellular uptake. Also, there are non-specific hydrophobic interactions between NPs and cell surface which lead to endocytosis of hydrophobic NPs (101, 106, 107). Positively charged chitosan NPs did not exhibit inhibitory effect on cathepsin B due to higher hydrophilicity and swelling capacity. In the opposite side, PLGA NPs with negative charge could deliver cystatin to endosomes/lysosomes and inhibited cathepsin B (70).

Surface charge type of NPs determines their internalization mechanisms into cells. Experimental studies showed that all three cationic, anionic and neutral dendrimers were taken up by A549 cells, but with various routes. Cell entrance mechanism of all three dendrimers by A549 cells line (alveolar type II cells) was fluid-phase endocytosis. Cationic and neutral dendrimers were taken up by non-clathrin, non-caveolae mediated mechanism because of electrostatic interactions or non-specific fluid-phase endocytosis mechanism. Anionic dendrimers mainly were taken up by caveolae-mediated endocytosis (108). Clathrin and caveolae pathways are involved in the endo-lysosomal phase (109). Hence as reported, cationic dendrimers were not transferred by lysosomes, but both anionic and neutral dendrimers were localized in the lysosomes (108).

Cell membrane exhibits negative charge, thus cationic dendrimers showed strong adsorption to the cell surface and were rapidly endocytosed. Cationic dendrimers were taken up by adsorptive endocytosis by connecting to the negatively charged proteoglycans. Since neutral dendrimers do not have any net charge; they are presumably endocytosed by non-specific interactions such as hydrophobic and hydrogen bond interactions (110, 111). Similar to the linear macromolecules (112), anionic dendrimers penetrate cells by interacting with the positive sites on the cells.

Zhan-Guo Yue and et al., prepared three kind of Chitosan-Based NPs (215 nm) with different ZP: positive NPs (39.25 mV), negative NPs (-45.84 mV), neutral NPs (0.51 mV); and then they investigated their cellular entrance to A549 cells. They found that: 1) Charge plays a considerable role in cellular entrance. PCNPs promote the speed and amount of NPs absorption. 2) Negative and neutral NPs prefer co-localization with the lysosome, while some of the PCNPs escape from lysosome and show peri-nuclear localization. PCNPs in the smaller size, directly internalize into the nucleus (113). Passive targeting of FITC-Chitosan NPs (194.7 nm, ZP = +35.5 mV) to A549 cells, showed that clathrin-mediated endocytosis was the predominant process of cellular uptake (114).

There are studies showing that culture media can shift uptake mechanism to receptor mediated endocytosis. NPs can adsorb materials from culture media which act like ligands for specific receptors. NPs composed of carboxymethyl dextran and the

most negative charge NPs have shown receptor mediated endocytosis uptake into cells. There are no receptors for carboxymethyl dextran on Caco-2 cells, but presence of protein corona around NCNPs causes cellular uptake by clathrin- and caveolae-dependent pathways (26). In another study, NPs with hydoxylated dextran coat, because of interacting with EGF receptors internalize into cells through clathrin-mediated endocytosis. This pathway is activated by adsorption of ligands from culture media on NPs surface (115). Research demonstrated that Iron oxide NPs adsorb proteins from cell culture media and internalize into cells by receptor mediated-endocytosis like other metal and metal oxide NPs (82, 116). Uptake comparison of different CNPs is summarized in Table 4.

Importance of ZP in gene delivery of CNPs into cancer cells

Gene delivery to tumor site is highly challenging in tumor therapy because of lacking the suitable vector for carrying the desired gene by the intravenous route. Nucleic acids have negative charge; and are better incorporated into positively charged carriers. Some of the NPs containing nucleic acids (122), which are aimed to be delivered to the nucleus, have to penetrate both cytoplasmic and nucleus membranes which both have negative charge. Using PCNPs showing proton sponge effect together with endosomal escape capability will be an added advantage. Resultantly, using PCNPs is a successful approach for gene delivery. In the following, Characteristics of some NPs containing nucleic acid will be explained in detail.

Recently, surface charge effect of oligo-deoxy-nucleotides (ODN) and plasmid DNA with PPI (polypropylenimine) dendrimers and PPI-modified GNPs in cellular uptake by MDA-MB-231 breast cancer cells have been investigated (123). Experimental results showed that ZP is a more important factor in ODN cell internalization rather than particle size.

Table 4. Entrance comparison of the CNPs to neoplasm cells. As a matter of surface charge, PCNPs show higher uptake to the tumor cells compared to neutral and NCNPs; and NCNPs demonstrate more uptake than neutral NPs to these kinds of cells.

NPs composition	Cell line	Average particle size (nm)	Comparison of cellular uptake base on NPs charge (mV)	Ref.
Magnetite NPs	MCF-7	40	+9.4 > -8.3	(15)
Magnetite NPs	HUVEC (normal cell)	40	+9.4 = -8.3	(15)
$MnFe_2O_4$ NPs	MDA-MB-231	30.6 (+NPs) 11.2 (-NPs)	+20.3 > -10	(90)
Gold NPs	SK-BR-3	17.7	+20 > -10 > -4	(17)
Lanthanide-doped upconversion NPs (UCNPs)	MCF-7	87-108	+50.5 > +45.5 > +35.4 > –37.9	(117)
PLGA NPs	lysosome of MCF-10A neoT	250-300	-22 > +36	(70)
ZnO (zinc oxide) NPs	A549	24	+25 > -44.6	(118)
Chitosan-Based NPs	A549	215	+39.25 > -45.84	(113)
Dendrimers	A549	---	Cationic > anionic > neutral	(108)
Cerium oxide (CeO) NPs	A549	3–5 (-NPs) / 8–10 (+NPs)	-16.26 > +36.60	(95)
GMO-chitosan and PLGA-PVA NPs	DU145	201-233	+12.5 > -8 in blank NPs -0.9 > 10 in drug loaded NPs	(119)
Gold NPs	PC-3 cells	30-90	-22 > -18> +24 Non-PEG-NPs > PEG-NPs	(103)
Polymeric NPs	Caco-2	45, 90	+22 > -19	(120)
Mesoporous core-shell silica NPs	Ocar8 cells	74, 125	+24.5 > -31.2	(121)
Polymeric NPs	A2780	5	Cationic > anionic	(105)

GMO : glyceryl monooleate, PLGA: poly(glycolic-lactic) acid

On the other hand, NPs produced with G_1 (+5.6 mV), G_2 (+5.2 mV) and G_3 (+6.5 mV) dendrimers have significantly lowered cellular uptake compared to those produced with G_4 (+12.1 mV) and G_5 (+17.7 mV) dendrimers for the lake of insufficient positive ZP (123). The diameter (and height) of the NPs produced with G2 to G5 dendrimers were 74 nm (17 nm), 98±20 nm (21 nm), 42 nm (14 nm), and 71 nm (20 nm), respectively. GNPs modified G_3 dendrimers (ZP = +34.1 mV), have shown feasible uptake into MDA-MB-231 cells for high positive ZP (123). Gene delivery of acylated chitosan gold NPs (Nac-6-Au) modified with immobilized DNA plasmid into MCF-7 cancer cells is also a charge dependent process. These NPs with the average size of about 15.34 nm and ZP of +20 mV are delivered into MCF-7 cells (124). Low particle size and positive ZP lead to successful penetration of these NPs into cells. Cationic vectors can efficiently condense and protect the gene, so the preferred charge for NPs which are used in gene delivery is positive.

Rajagopal Ramesh et al., designed cationic liposomes (300–325 nm) carrying therapeutic cancer suppressor genes: p53 and FHIT, which are frequently altered in lung cancer. DOTAP-cholesterol is a cationic agent, which was applied in these liposomes. This formation caused their high cellular entrance into human non-small carcinoma cell lines H1299 (p53null/FHIT2) and A549 (p531/FHIT2). They suppressed tumor development in vivo both in local and systemic administration (125).

Gene vector namely FA-SPE-PEG constructed from Folic Acid (FA), Spermine (SPE) (endogenous tetra-amine involved in eukaryotic cell metabolism) and PEG is another NP system with the particle size of 56 nm and ZP of +7.22 mV. This vector showed high loading efficiency and gene protection from degradation by nucleases. Furthermore, these NPs exhibit selective and high entrance towards FR-overexpressed A549 cells. Because of low cationic charge, FA-SPE-PEG NPs showed low cytotoxicity in normal cells (126). PCNPs are also promising vectors for gene delivery in Glioblastoma, Hela, Cos-1 and U 937 cells (88, 127-129). More examples of vectors for gene delivery to different cells are shown in Table 5.

Importance of ZP in targeting of pH sensitive NPs to cancer cells

pH sensitive NPs have charge switchable property when are exposed to different pHs (136). NPs with reversible surface charge can be used as promising carriers of drugs to tumor cells. Their surface charge will be changed to desired positive charge around acidic media of the tumor cells or inside endosomes and lysosomes. These NPs are anionic and repel from the cell membrane, so are engineered to switch positive charge at acidic media. pH-sensitive NPs exhibit positive charge at acidic tumor environment and negative or neutral charge in physiologic pH; for that reason, they pose higher cellular uptake by cancer cells rather than normal cells due to the electrostatic interaction with surface of the negatively charged cell membrane. In some cases, pH-sensitive materials of the NPs are cleaved at the slightly acidic medium of intracellular organelles and result in drug release in intracellular media

Table 5. Some NPs used as gene delivery vector to cancer cells. PCNPs are a promising vector for gene delivery.

NPs	Average diameter (nm)	ZP (mV)	Cell line	Ref.
Dendrimers	71±21	+34.1	MDA-MB-231	(123)
N-acylated chitosan gold NPs	15.34	+20	MCF-7	(124)
Polymeric NPs	60	+30	MCF-7	(130)
Self-cross-linked glycol chitosan NPs	269.8	+7.7	MCF-7/ADR	(131)
Polymeric pH sensitive NPs	94.5	+30	MCF-7	(58)
Reduction-sensitive linear cationic click polymer	150	+10	MCF-7/ADR	(132)
Liposomes containing P53 and FHIT	300-325	positive	H1299, A549	(125)
PEG-NPs	56	+7.22	A549	(126)
Hollow mesoporous silica nanospheres	140	+28	H1299	(133)
Nano lipid carrieras (NLC)	157	+15.9	A549	(134)
Multi-functionalized carbon dots	143.1	+25.7	H460	(135)
Polymeric NPs	10 - 100	+7 - +31	Cos-1	(127)
Polymeric NPs	980	+24	HeLa	(128)
Liposomes	----	positive	A172	(129)
Polycationic peptide NPs	143	+18.58	U 937	(88)

(137). In inflamed cells, the extracellular pH (6.5–7.2) is slightly lower than that of normal cells (pH = 7.4) (138). Involving active targeting moiety (specific ligand-receptor interaction) in drug delivery of pH-sensitive NPs, increases cell entrance efficiency.

For example, morpholino-terminated dendrimers with the average size of 9 nm, show surface charge-tunable property. Their ZP changes from -8 mV at physiologic pH to +14 mV at acidic tumor pH due to the protonation of morpholino group at acidic pH. Finally, their cellular uptake and blood circulation time will be increased and their cytotoxicity will be decreased (66). In another example, neutral charge (-1.91 mV) of the rigid pH-sensitive micellar nano-complex (RPN) containing DOX switches to positive charge (+10 mV) around tumor media; resulting in rapid accumulation of DOX around nucleus area of the MCF-7/ADR cells for the synergistic effect of EPR and lysosomal escape. RPN shows pH-sensitive properties (67). Dual-functional liposomes with pH-responsive Cell-Penetrating Peptide (CPP) and active targeting hyaluronic acid (HA) were prepared for targeting to A549 cancer cells. These NPs (enriched with arginine and histidine) had negative charge (-20 mV) in physiologic pH but they exhibited positive charge (27.45 mV) in acidic pH around the tumor (139).

HA is able to be hydrolyzed by hyaluronidase (HAase) in tumor matrix; in this way, CPPs with the positive charge would be exposed to the tumor media and facilitate effective uptake of NPs into the cancer cells. HA-CPP liposomes exhibit high cellular uptake via EPR effect (140) and for affinity to HA receptors (CD44 and RHAMM) (141, 142). When CPP coated liposomes were internalized into the cells followed by entrance into the endosomes and lysosomes, the imidazole group of histidine in CPP induces proton sponge effect and leads to endosomal/lysosomal escape. In general, cell membrane is negative due to anionic carboxylates, phosphates and sulfates presence on the cell membrane which causes electrostatic interaction with PCNPs (143).

Erlotinib and DOX containing NPs (80 nm) are another examples of pH-sensitive carriers (71). At extracellular acidic pH of tumor, surface ZP of these NPs changes from negative to positive (pH = 7.4: ZP = -38 mV, pH = 6.5: ZP = 4.5 mV, pH = 5.5 and 4.5: ZP = 22 mV) due to the protonation/deprotonation of the amino group of histidine and carboxyl group of hexahydrobenzoic acid (144). This provides stronger positive charge which facilitates cellular uptake via energy-mediated macropinocytosis pathway. Imidazole group of histidine in these NPs, as mentioned before, exhibits proton sponge effect and leads to endosomal escape and cell nucleus entrance (71). Similar results have been reported for different types of pH-sensitive NPs to liver cancer cells (145, 146). Other examples of pH sensitive NPs are summarized in Table 6.

Importance of ZP in overcoming multidrug resistance in cancer cells using CNPs

Multi-Drug Resistance (MDR) is an important problem in chemotherapy of cancer cells expressing ATP binding cassette (ABC) transporters. These are transmembrane proteins with the function of pumping toxins and drugs out of the cells which block the apoptosis pathway (151, 152). P-glycoprotein (P-gp) membrane proteins are encoded by MDR gene family; which is well known as ABC transporters (153). P-gp effluxes hydrophobic and positively charged xenobiotics like DOX and paclitaxel out of the cells; and reduce the chemotherapy efficiency (154-156). D188 (Aspartic acid in the position 188), E353 (Glutamic acid in the position 353), E782, and D997 are residues close to the membrane surface and are located outside the perimeter of the intracellular domain helices of P-gp inside the chamber. These residues have negative charge and show electrostatic interaction with the positively charged drugs (157).

Hence, utilizing NCNPs which are internalized by endocytosis and cover positive charge of the drugs is a useful approach to overcome MDR (158). P-gp among ABC transporters category have same characteristics as well as multi-pass transmembrane portions and using ATP to shuttle materials across the membrane (Figure 6).

P-gp is over-expressed in the malignant tissues of almost 40-50% of mammary neoplasm patients; so that is a promising target which should be considered in nano-system designation (159, 160). To conquest MDR, many researches have been done. One of them is using NPs which internalize into cells via endocytosis (161). NPs with different charges have been used for this purpose.

There are two main approaches to conquest MDR using NPs which are discussed in the following:

Table 6. Some examples of pH-sensitive NPs delivered into cancer cells. These NPs with different compositions have negative charge at physiologic pH and positive charge at tumor microenvironment pH.

NPs composition	Average diameter (nm)	Cell line	ZP at physiologic pH (mV)	ZP at tumor acidic pH (mV)	Ref.
Liposome-cpp-HA	---	A549	-20	+27.45	(139)
Mesoporous silica NPs	80	A549	-38	+22	(71)
Morpholino-terminated dendrimers	9	MCF-7	-8	+14	(66)
Rigid pH-sensitive micellar nano-complex (RPN) containing DOX	50	MCF-7/ADR	-1.91	+10	(67)
PMLA-PEI-DOX-TAT@PEG-DMMA*	108	A549	-16.33	+10.81	(147)
Lipid Polymer Hybrid (LPH) NPs containing DOX	200	MCF-7, and MDA-MB-231 cells	negative	positive	(148)
PLGA-PVA-paclitaxel	195	MCF-7	−31.6	positive	(149)
Smart liposomes	134	A549	-10	+15	(150)
Polymeric NPs	250-2000	HepG2	-15	+13	(145)
Polymeric NPs	210	HepG2, A549	-5.26	positive	(146)

*PMLA: Poly (β-L-malic acid), TAT: Transactivator of transcription, DMMA: Di-methoxy-methamphetamine

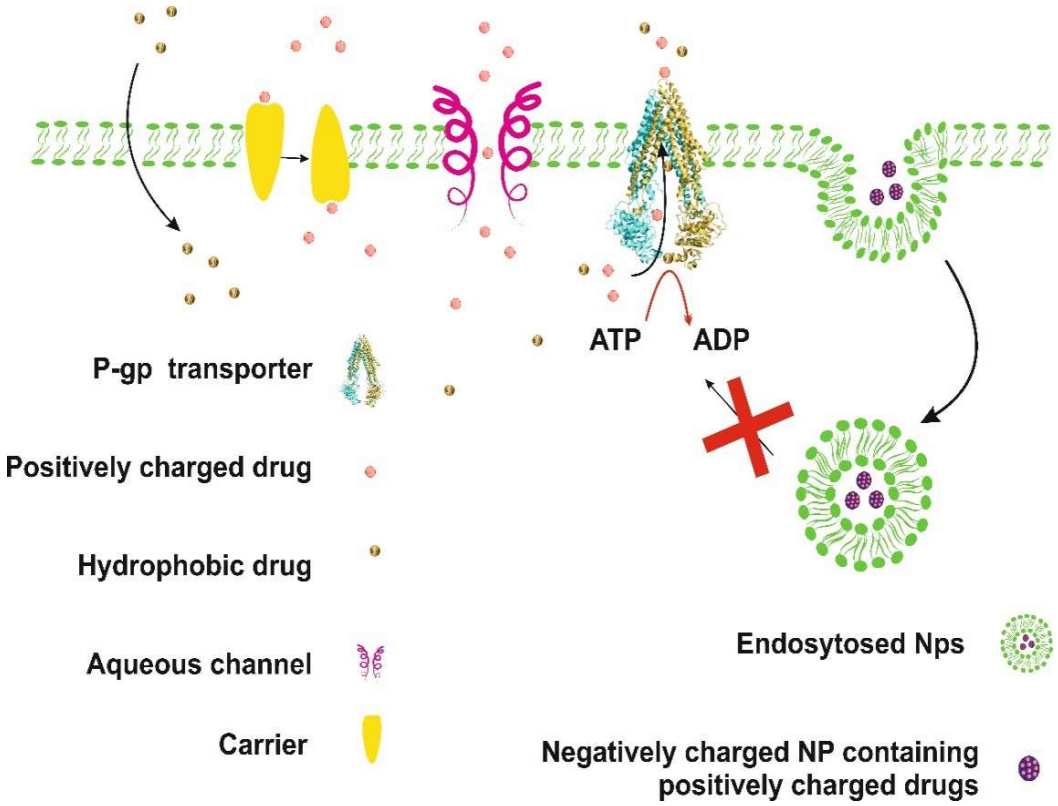

Figure 6. Bypassing P-gp efflux by endocytosed NPs. Cationic and hydrophobic drugs are pumping out of the cells by ABC transporters. Positively charged particles enter cells by aqueous channels and carriers. Hydrophobic drugs inter cells through phospholipid bilayer with simple diffusion. Anionic drugs and endocytosed NPs containing cationic drugs bypass P-gp efflux. (ABC transporter images were adopted from protein data basis (PDB).)

Gene delivery by MDR silencing agents such as siRNA to silence MDR

Nucleic acid delivery in order to silence P-gp encoded gene is one of these strategies. NPs with efficient gene delivery property possess positive charge. For instance, polymeric complex NPs were used to deliver both paclitaxel and survivin in order to overcome paclitaxel resistance in A549 cells. These NPs with the size of 150-180 nm and ZP of +20 mV have shown efficient gene transfer to tumor cells (162). In another example, Polymeric NPs with the average size of 295.3 nm and ZP = +40.8 mV down regulated Stat3 and killed the pulmonary tumor cells effectively (163).

Gene transferring by cationic NPs (+4 mV) to overcome MDR was achieved using liposomes (500 nm). These carriers contain DOX and siRNA which target MRP1 and BCL2 mRNA and then block the pump and non-pump H69AR cellular-resistance, respectively (164). So in this approach, NPs with the positive charge will be applied. PCNPs play two important roles. First, they are the promising vectors for nucleic acids delivery such as siRNA due to attraction between positively charged vectors and the anionic nucleic acid. As a result, this leads to excessive nucleic acid loading and efficient therapy. Moreover, the tendency between anionic cell surface and PCNPs helps them to be internalized into cells via endocytosis and bypassing P-gp efflux (131).

In a recent study by Yin Q. et al., cationic poly amino esters were used for co-delivery of MDR-1 and Survivin-targeting RNA. Polymeric NPs had the average size of 60 nm and ZP of +30 mV. They were composed of polymers, which were administered as a co-delivery system of iMDR-1-shRNA and Survivin-shRNA. The fabricated nano-sized particles caused down-regulation of the P-gp and Survivin expression in MCF-7 cells (130).

Delivering MDR-1 siRNA using self-cross-linked glycol chitosan NPs also was accomplished to dominate MDR. These NPs were composed of Pgp-targeted poly-siRNA (psi-Pgp) and thiolated Glycol Chitosan polymers (tGC). Psi-Pgp-tGC NPs with the average size of 269.8 nm and ZP of +7.7 mV, exhibited high entrance into Adriamycin-resistant MCF-7/ADR cells, resulting in down-regulated P-gp expression (131). Delivery of DOX with psi-Pgp-tGC NPs led to increased cytoplasmic/nuclear DOX accumulation and efficient drug therapy due to overcoming MDR (131).

Polymer coated AuNPs are pH sensitive NPs, which deliver siRNA into MCF-7 cells, in order to gene silencing and reducing MDR1 expression. These NPs were made of PEI (polyethyleneimine), PAH (poly (allylamine hydrochloride)-citraconic anhydride) and AuNP-CS (gold nanoparticle coated with chitosan). The average size of these NPs was 94.5 nm and the ZP was about +30 mV (58). Under the acidic condition, anionic PAH-Cit hydrolyzes and changes to cationic PAH (165). Structure of NPs is destroyed layer by layer, and the siRNA releases to the cytoplasm. Amino groups with the positive charge on PAH induce proton-sponge effect and lead to inhibition of lysosomal ingestion of siRNA. This is a critical step in siRNA delivery for MDR1 silencing (58). MDR1 is P-gp encoding gene; hence, corresponding delivered siRNA should be released in the cytoplasm to silence specific cellular mRNAs.

Gene delivery via reduction of sensitive linear cationic click polymeric NPs to reverse MDR using siRNA to silence the expression of P-gp is also a charge dependent process. These NPs with the average size of 150 nm and ZP of +10 mV have been used as a vector to deliver plasmid iMDR1-pDNA and Adriamycin (ADR) into drug-resistant MCF-7/ADR cells. shRNA expressed by pDNA; targets MDR-1 gene (iMDR1-pDNA), thus reverses MDR. As a result, P-gp expression was suppressed and ADR accumulation and cytotoxicity against MCF-7/ADR cells were enhanced (132).

In conclusion, PNNPs play a critical role in endosomal escape and efficient delivery of siRNA, in order to silence MDR1. This event blocks P-gp and increases the absorption of chemotherapeutic drugs.

Drug delivery by CNPs to overcome MDR and efficient delivery of cationic drugs

As mentioned above, P-gp pumps cationic materials out of the cells. So, overcoming MDR by anionic particles seems to be an effective performance. Negatively charged carriers are mostly used for encapsulation of these materials.

Wei-Ting Huang et al. prepared NPs with different surface modification strategies and different negative charges. These polymeric NPs (with the average particle size of 100 nm and ZP of -3 mV) consisted of amphiphilic carboxymethyl-hexanoyl chitosan (CHC), cisplatin, and the MDR-suppressing Chinese herbal extract: demethoxy-curcumin. They were bio-functionalized by CD133 antibody for enhanced uptake by A549-ON lung cancer stem-like cells (CSC) (166).

DOX and Resveratrol were co-encapsulated in modified PLGA NPs; which were then delivered to MDA-MB-231/ADR cells (DOX-resistant, estrogen receptor negative, mammary adenocarcinoma cell) and MCF-7/ADR cells (DOX-resistant, estrogen receptor positive, mammary adenocarcinoma cell). These NPs inhibited the expression of MDR proteins like P-gp, MRP-1, and BCRP and overcame DOX resistance and also promoted apoptosis through down-regulating the expression of NF-κB and BCL-2. Their average size and ZP were 170 nm and -15.5 mV, respectively (167).

Polymer-lipid hybrid NPs (PLN) with the average size of 290 nm and ZP of -23.1 mV showed cellular uptake via phagocytosis pathway. Uptake of these NPs was evaluated in two Pgp-overexpressing mammary tumor cell lines (a human cell line: MDA435/LCC6/MDR, and a mouse cell line: EMT6/AR1). DOX-PLNs largely accumulated in EMT6/AR1 cells rather than MDA435/LCC6/MDR1 cells, due to the high-level expression of P-gp on EMT6/AR1 cells (30).

Simultaneous delivery of DOX and GG918 (Elacridar) by PLN have also reported to improve the cure of multidrug-resistant mammary malignancy. These NPs with the size range of 187 to 272 nm and ZP of -20 mV had higher uptake into human MDR breast cancer cell line MDA435/LCC6/MDR1 (168). GG918 have MDR reversal activity (169).

EGFR-targeted nano-carriers are used as combination delivery system of Paclitaxel/Lonidamine to treat MDR in human breast tumor cells. These NPs with the average size of 139.6 nm and ZP of -29.6 mV showed high internalization into mammary tumor cells due to EGFR targeting property (170). Lonidamine inhibits the Warburg effect and induces mitochondrial binding of pro-apoptotic Bcl-2 proteins. Paclitaxel stabilizes microtubules and EGFR-peptide targets NP system to EGFR overexpressed MDA-MB-231 cells; as a result, the whole system overcame MDR in these cancer cells (170).

pH-sensitive NPs show a negative charge at physiologic pH and a positive charge at acidic pH around the tumor so they will interact with the negative surface of the cells followed by endocytosis. Rigid pH-sensitive micellar nano-complex (50 nm) containing DOX (Dox\RPN), had ZP of -1.91 mV at physiologic pH and +10 mV at acidic pH (pH = 5.6) around tumor (67). PNNPs with the average size lower than 50 nm have shown passive targeting property and penetrated the tumor through EPR phenomenon. Dox\RPN had a positive core (PLGA) and neutral shell. After internalization into lysosomes of cancer cells; its pH sensitive shell dissociated and the positive core of PLN induced lysosomal escape. Lysosomal escape effect and higher cellular uptake synergistically led to accumulation of Dox\RPN around the nucleus area of MCF-7/ADR cells and prevailed DOX resistance (67).

Importance of ZP in active targeting of NPs into cancer cells

The aim of active targeting is accumulation of NPs in target sites like tumor location and reduction of drug exposure to normal cells. Therefore, the output of therapy will be increased and the adverse effects will be reduced (171). For fabrication of targeted delivery systems, NPs are conjugated to targeting ligands and then they will be destined to special receptors on target cells (172).

In active targeting, there are specific and strong dual interactions between ligand and receptor (173, 174). Furthermore, some receptors have significant surface charge and show electrostatic interactions with ligands which are decorated on NPs surface (175-179). Hence, in targeted delivery, CNPs can be internalized into the cells depending on receptor binding site charge (180, 181). Receptor-mediated endocytosis is the main uptake mechanism of the active targeted NPs.

Charge of ligands and receptors' binding sites can be defined with isoelectric point (pI) (182, 183). Molecules have a positive charge at the pHs lower than pI, and negative charge at pHs higher than pI. At the pH = pI, molecules are neutral. Electrostatic interactions between CNPs decorated by specific ligands with opposite charge of the receptors, lead to attachment of NPs on the cell membrane and their internalization into cells via receptor-mediated endocytosis which is the main uptake mechanism of the active targeted NPs (184, 185). In the following sections, some important receptors and organelles which have attracted attention in targeted delivery of NPs will be explained in this regard.

Targeting of CNPs to cancer cells overexpressing CD44 receptor

CD44 (a type 1 transmembrane glycoprotein) (GenBank accession no. P16070), is the biomarker of tumor stem cells and an overexpression of 4−5 fold, is the early sign of cancer metastasis (186). CD44 can activate signaling pathways such as Rho

GTPases, Ras MAPK and Pi3K/Akt; which are involved in cancer progression (187). The binging site at extracellular domain of CD44 consists of arginine and lysine residues, which possesses a positive charge (175-177).

Hyaluronic acid (HA) is used as targeting agent to CD44 and cells expressing receptor for HA-mediated motility (173, 174). HA is negatively charged molecule that show electrostatic attraction with CD44. NPs containing HA ligand can interact with positively charged aforementioned binging site of CD44 and guide their cellular uptake via receptor-mediated endocytosis (188).

For example, IC87114 loaded polymeric NPs modified by HA with average size of 200 nm and ZP of -10 mV, exhibited higher uptake into MDA-MB-231 with moderate CD44 expression (189). In another study, NPs composed of HA-HPCD/ADA-PEG (HA: hyaluronic acid, HPCD: HP-β-cyclodextrin, ADA: 1-adamantane carboxylic acid) with negative ZP (−14 mV) were delivered into A549 cells successfully (181). These NPs contain hyaluronic acid (HA) as a specific ligand, which is recognized by the CD44 receptor. Carboxyl groups of HA on Dox-loaded NPs are responsible for NPs' negative charge.

Targeting of CNPs to cancer cells overexpressing Folate receptor

Folate receptors (especially FRα (GenBank accession no. P15328)) are one of the common receptors overexpressed on many tumor cells (190, 191). This receptor is found on the cell membrane, in secreted form, in the endosome, in the cytoplasmic vesicles, and in the clathrin-coated vesicles. Folic acid binding site at extracellular domain have a positive charge at pHs below pI (178); pI = 10.8, 8.76. Folate receptor has high tendency to folate and folic acid analogues and conducts receptor-mediated endocytosis. At acidic pH of the endosome, folate receptor triggers a conformational change which strongly reduces its affinity to folates (178, 192-195). Two negatively charged carboxyl groups of Folic acid specifically stick to the positively charged ligand-binding pocket of the receptor. There are negatively charged sites in the extracellular domain of the receptor which are involved in non-specific interactions of the receptor with positively charged parts of the folic acid molecule containing amine groups (178). Hong Yuan et al. have prepared SLNs (d_v = 369.3) containing folate to improve cytotoxicity and cellular uptake by FR mediated endocytosis. These SLNs (ZP = 32) were used to deliver paclitaxel to A549 cells line (196). As another example, MP\Alg–Ccm AuNPs constructed from Curcumin (Ccm) and Methotrexate (MTX) were conjugated to a biopolymer as a stabilizer. These NPs use active targeting pathway to penetrate into MCF-7 cells due to the presence of the "anti-folate" drug, MTX. The NPs' ZP was -25.8 mV and their average size was 187 nm (197). Folate receptor and reduced folate carriers are two systems which are involved in MTX internalization (198). MCF-7 cells have both carriers and MTX exhibits more affinity to reduced folate carriers (199).

Targeting of CNPs to tumor cells' mitochondria

Mitochondria are the primary site of cell apoptosis induction. Hence, targeting them with therapeutic agents such as radiotherapy agents is an important approach in cancer therapy. Recent studies showed that NPs modified with TPP (Tri-Phenyl-Phosphonium) which is the mitochondria targeting domain accumulate extensively in mitochondria (200, 201). Therefore, TPP is the active targeting ligand for delivering modified NPs into the mitochondria. Mitochondria are the most negatively charged organelles in the cells, and since TPP has positive charge; so an electrostatic interaction with mitochondria are established (202). Hence, NPs containing TPP will enter the mitochondria successfully.

In interesting study, three kinds of AuNPs, with negative charge (40 nm, -44 mV), positive charge (45 nm, +53 mV) and positively charged modified by TPP (50 nm, +45 mV) were prepared. Cellular uptake of prepared NPs into MDA-MB-231 cancer cells and MCF-10A normal cells were investigated (203). PCNPs (both positive AuNPs and TPP-Au NPs) enter to MDA-MB-231 cells about two folds more than MCF-10A cells. However, uptake of NCNPs into both cells was the same (203). All three NPs internalized into cells by endocytosis pathway. Negatively charged AuNPs remain in endosomal vesicles but positively charged AuNPs escape from endosome (204, 205) due to the proton sponge effect and were mainly found in the cytosol. TPP-AuNPs indeed accumulate in the mitochondrial intermembrane space of cancer cells due to the presence of TPP targeting agent and positive charge. Since TPP-Au NPs prefer to internalize into cancer cells; normal cells encounter with lower damage (203).

Targeting of CNPs to cancer cells expressing nucleolin receptor

Nucleolin receptor (NR) (GenBank accession no. P19338) is the major nuclear protein seen in the growing eukaryotic normal cells. It can be found in nuclear chromatin and pre-ribosomal particles. NR is overexpressed on most tumor cells, but there is limited expression on the normal cells. Therefore, NPs containing ligands specific for NR have high cytotoxicity on cancer cells than normal cells. This receptor has net negative charge (pI = 4.6) at tumor pH (6.5-7.2). On the other hand, N-terminal domain of this receptor possesses negative charge (179). AS1411 is a DNA aptamer which binds to nucleolin. AS1411 forms a stable G-quadruplex (Guanine) structure, which contributes to specific attachment of the DNA aptamer to the nucleolin (179). Guanine with pKa = 9-10 has the positive charge, that shows electrostatic interaction with the negatively charged domain of the receptor. Accordingly, NPs containing AS1411 will show higher uptake into NR expressing cells.

Polymeric porous silicon NPs modified by methotrexate (MTX) and DNA aptamer named AS1411, have shown increased cellular fusion by NR-positive MDA-MB-231 cells. These NPs internalize into the cells using receptor-mediated endocytosis due to NR interaction with AS1411 and MTX interaction with folate receptor (206).

Targeting of CNPs to cancer cells expressing HER2 receptor

HER2 or Neu, ErbB2 (GenBank accession no. **P04626**) is a membrane tyrosine kinase that is overexpressed in about 20% of breast cancers and in some ovarian and gastric cancers. High multiplication and anti-apoptosis signals are the major drivers of tumor development for this subset of breast tumors. HER2 is not a high-affinity ligand (207). Herceptin (also known as trastuzumab) is a monoclonal antibody against HER2 which targets and inhibits activation of HER2. There are three loops with residues of 557–561, 570–573 and 593–603, which are located at the C-terminal section of domain IV in HER2 structure. Herceptin binds HER2 by these three loops. Interaction between Herceptin and HER2 with first (pI = 8.3) and third (pI = 8.46) loop is essentially charge dependent, while the second loop makes hydrophobic contact with Herceptin (208). Thus, NPs containing Herceptin will have high cellular uptake to HER2 expressing cells.

For example, active targeting to HER2 receptor overexpressing SKBR3 cells using Herceptin modified silica NPs have shown higher cellular entrance. These NPs had the average size of 54 nm and ZP of -44 mV (209).

Targeting of CNPs to cancer cells expressing transferrin receptor

Transferrin receptor (TfR) (GenBank accession no. P02786) is a homo-dimeric type II transmembrane protein, with a small cytoplasmic domain, a single-pass transmembrane portion, and a large extracellular domain (210). With the exception of highly differentiated cells, TfR is present on the surface of many cells but their levels vary greatly. TfR is highly expressed on cells which are active in hemoglobin synthesis, placental tissue, immature erythroid cells, and rapidly dividing cells, both normal and malignant (211). Expression of TfR in tumor cells is greater than normal cells (two- to ten-fold) (212, 213). Hence, NPs containing Tf would show active targeting property.

Iron-transferrin complex is recognized by TfR at physiologic pH. After endocytosis, iron releases from the complex at the acidic pH of endosome and iron-free transferrin tightly binds to the TfR (214). Therefore, Tf can tightly bind to TfR at acidic pH around the tumor.

There are two binding sites on TfR, which bind to N- and C-lobes of Tf. The N-lobe of Tf binds to its binding site on TfR in a nonspecific way; while, C-lobe interacts with the receptor specifically. Leu 619, Arg 623 of helix α1, Arg 629 of helix α2, and Gln 640, Try 643, Arg 646, Phe 650 and Arg 651 of helix α3 are the residues in the helical domain of TfR, which are conducting by the C-lobe of Tf. These portions have a positive charge (pI = 10.84) and establish electrostatic interaction with the negatively charged portion of the Tf C-lope. The residues in the C-lobe positioned close to the helical domain of TfR are His 349, Arg 352, Leu 353, Asp 356, Glu 357, Ser 359, Val 360, Glu 367, Glu 369, Ser 370, and Glu 372 have a negative charge (214) (pI = 3.9). Leu 122, Tyr 123, Trp 124, and Asp 125 of the protease-like domain and Asn 662 and Glu 664 of the helical domain are residues of TfR which are involved in the binding with N-lobe of Tf. These residues have a negative charge (pI = 3.67) which interact electrostatically with the N-lobe of Tf. The residues in the N-lobe positioned close to TfR are Pro 142, Arg 143, Lys 144, and Pro 145 of the N2 domain, and Tyr 71, Leu 72, Ala 73, and Pro 74 of

the N1 domain. These portions have a positive charge (214) (pI = 9.01). Dual interactions between C-lope of the Tf and its binding site on the TfR is specific, and the predominant positively charged patch of the TfR and the negatively charged patch on the C-lobe of the Tf are involved in receptor-ligand connection. Briefly, negatively charged C-lope of Tf interacts specifically with the positively charged portion of TfR, while the positively charged N-lope of Tf interacts non-specifically with the negatively charged portion of TfR (214). Accordingly, NPs containing Tf ligand can be used in active targeting to cells expressing TfR. Dual-functional magnetic NPs with the average size of 184 nm and ZP of -16.7 mV show higher uptake into MCF-7 cells. These NPs transfer Doxorubicin (DOX) and transferrin antibody to MCF-7 cells for treatment and imaging purposes (215). Studying on gene delivery to A549 cells using Tf coated NLC (157.3 ± 4.9 nm, ZP = + 15.9 ±1.9 mV) including plasmid-containing enhanced green fluorescence protein (pEGFP), showed increased cell internalization via receptor-mediated endocytosis (134).

Targeting of CNPs to tumor cells expressing lectin receptor

Targeting of endogenous ligands with different carbohydrate moieties such as mannose, galactose, fructose, and lactose are mediated by Lectin receptors (216). These receptors are over-expressed on macrophages of the brain, splenic, alveolar, peritoneal, and macrophages of liver endothelial as well as Kupffer cells (217-219). Extracellular binding sites of lectin receptor are approximately neutral and a little anionic at acidic pH (pI = 5, 6.52). Hence, electrostatic interactions are less important in active targeting to this receptor.

For example, Gemcitabine loaded mannosylated solid lipid NPs (GmcH-M-SLNs), with the size of 228.8±5.42 nm and ZP of 7.71±0.87 mV showed high cellular uptake by A549 cells due to the lectin receptor-mediated endocytosis (185). Schematic representation of receptors and desired charged NPs are shown in Figure 5. More examples of NPs used in targeted delivery to pulmonary tumor cells are indicated in Table 7.

Table 7. Examples of CNPs used in active targeting goals. Some overexpressed receptors on tumor cells have electrostatic connection with the decorated ligands on NPs.

NPs	Drug/gene/active agent	Particle size (nm)	ZP (mV)	Cell line	Receptor/ organelle	Ligand	Ref
Functional NPs	Chondroitin sulfate	123	-23.9	HCT116 MCF-7	CD44	HA	(180)
PLGA-PEG NPs	IC87114	200	-10	MDA-MB-231	CD44	HA	(189)
HPCD/ADA-PEG NPs	DOX	100	-14	A549	CD44	HA	(181)
PLGA-soya lecithin Micelleus polymer	MTX	114.6	-0.97	MDA-MB-231	Folate	MTX	(220)
TPGS	MTX	374	-11.7	MCF-7	Folate	MTX and folate	(221)
Alg-Gold NPs	MTX	187	-25.8	MCF-7	Folate	MTX	(197)
Gold NPs	NO	50	+45	MDA-MB-231	mitochondria	TPP	(203)
PEI	MTX	245	+40	MDA-MB-231	Nucleolin Folate	DNA aptamer, AS1411	(206)
Human serum albumin	Trastuzumab -modified P12	277	--36.5	BT-474, SK-BR-3	HER2	Oligo-nucleotide	(222)
Silica NPs	DOX, Herceptin iron oxide	155.2	-18.6	SK-BR-3	HER2	Herceptin	(69)
PLGA NPs	PE38KDEL	124	+12	BT-474 cells	HER2	Herceptin	(223)
PLGA NPs	Mutlin-3a	220	-7.8	MCF-7	Transferrin	Transferrin	(224)
Magnetic NPs	DOX	184	-16.7	MCF-7	Transferrin	Transferrin	(215)

SLN	DOX	239	+6.2	A549	Lectin	Galactose	(225)
SLN	Gemcitabine	228.8	+7.71	A549	Lectin	Mannose	(185)
NLC	Plasmid	157	+15.9	A549	Transferrin	Transferrin	(134)

PEI: polyethylenimine, PLGA: poly (DL-lactic-*co*-glycolic acid), PEG: poly (ethylene glycol), HPCD: HP-β-cyclodextrin, ADA: 1-adamantane carboxylic acid, TPGS: D-α-tocopheryl polyethylene glycol 1000 succinate, Alg: Alginate, TPP: Tri-Phenyl-Phosphonium, Herceptin: Humanized monoclonal antibody (Trastosumab), PE38KDEL: A model protein toxin.

CONCLUSION

Surface charge plays an important role in cellular uptake. ZP consideration can dominantly guide researchers using active and passive targeting methods to enhance therapeutic output and cell entrance. In passive targeting, PCNPs show higher cellular entrance. In active targeting, interactions between ligand and receptor are more important. Moreover, in gene delivery; PCNPs show higher cellular uptake as well. ZP is also important in designing NPs to conquest MDR. To target mitochondria, PCNPs are the promising vehicles. Using NCNPs for lysosomal delivery seems rational; whereas, PCNPs are suitable for lysosomal escape. NPs with pH-sensitive behavior have negative charge at physiologic pH and positive charge at acidic pH around the cancer cells, so these NPs have longer blood circulation and higher cellular uptake in target site.

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ABBREVIATIONS

ABC: ATP binding cassette
ADA: 1-Adamantane Carboxylic Acid
Alg: Alginate
CeO: Cerium Oxide
CHC: Carboxymethyl-Hexanoyl Chitosan
CNPs: Charged Nano-Particles
CSC: Cancer Stem-like Cells
EPR: Enhanced Permeability and Retention
ER: Estrogen Receptor
FA: Folic Acid
HAase: Hyaluronidase
HPCD: HP-β-cyclodextrin
MDR: Multi Drug Resistance
NCNPs: Negatively Charged Nano-Particles
NPs: Nano-Particles
ODN: Oligo-Deoxy-Nucleotides
PCNPs: Positively Charged Nano-Particles
PEG: poly (ethylene glycol)
PEI: polyethylenimine
PLGA: poly (DL-lactic-*co*-glycolic acid)
PLN: Polymer-lipid hybrid Nano-Particles,
PPI: Poly Propylene Imine
RES: Reticulo Endothelial System
SPE: Spermine
TfR: Transferrin Receptor
TPGS: D-α-Tocopheryl Polyethylene Glycol 1000 Succinate
TPP: Tri-Phenyl-Phosphonium
ZP: Zeta Potential

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