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Active transfection of genetic materials using cyclodextrin-anchored nanovectors

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Gene-based therapy is a sophisticated means for the treatment of various complex diseases like AIDS, cancer, *etc.*, as it resolves the genetic malfunction at the source instead of tackling the superficial symptoms. However, the therapeutic, diagnostic, and theranostic potential of gene-based therapeutic actives such as siRNA, mRNA, pDNA, aptamers, *etc.* is hindered by physicochemical as well as physiological barriers in the form of insufficient bioavailability, systemic metabolism, rapid renal clearance, inefficient carrier systems, *etc.* Although advanced carrier systems such as polyplexes, lipoplexes, dendriplexes, hydrogels, polyrotaxanes, *etc.* are employed to overcome such challenges, their structural configuration results in notable cytotoxicity to induce bio-incompatibility. In this context, strategic integration of cyclodextrins subdues the cytotoxicity by virtue of unique architectural characteristics and allows the fabrication of sophisticated systems for delivery of gene-based therapeutics. Inclusion of cyclodextrins offers benefits like enhanced protection of gene-targeted payloads, compact loading, nanoscale carrier dimensions, biostability, *etc.* by forming densely packed cargo systems. Cyclodextrins nullify the active cationic moieties to lower *in vivo* cytotoxicity and improve transfection efficiency across biomembranes. The multi-ligand binding capability of structurally-modulated cyclodextrins avails receptor specificity and gene-targeted therapeutic efficiency. The ability to form reversible covalent linkages allows the fashioning of multi-stimuli responsive supramolecular nanocarriers for a desirable drug release profile. The present review article features cyclodextrins and associated successful applications as the integral components of non-viral nanovectors such as cationic polymers, dendrimers and polyrotaxanes as well as supramolecular assemblies for efficient delivery of RNA-, DNA- and aptamer-based genetic payloads for the achievement of desired treatment outcomes.

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1. Introduction

Gene-based therapy encompasses tremendous potential in the permanent treatment of several complex ailments like cancer, neurological problems, autoimmune diseases, *etc.*, as it delivers genetic therapeutics such as siRNA, miRNA, pDNA, aptamers, *etc.* into the abnormal cells and on-target nuclear components.[1–7] Gene-based therapy is also implemented on stem cells to attain genetically modified therapeutic agents as well as gene delivery systems. Such systems employ intracellular signaling networks to modify molecular and cellular activities, enhancing the wound healing mechanisms of the target tissue in cases of skin regeneration, wound therapy and scar formation.[8,9] However, the interaction between the genetic payload and systemic biofluids compromises the molecular stability of gene therapeutics. This necessitates the fabrication of sophisticated nanovectors configured from viral sources like lentiviruses, poxviruses, adenoviruses, human foamy viruses, *etc.*, as well as non-viral origins such as cationic polymers, lipids, dendriplexes, stimuli-responsive supramolecular assemblies and polyrotaxanes/polypseudorotaxanes.[10,11] As viral vectors elicit significant immunogenic responses and suffer from premature gene expression, an immense focus is placed on the evolution of non-viral vectors for gene delivery.[12] Cyclodextrins (CDs) are biocompatible macromolecules of toroidal architecture, with the ability to host various guest molecules *via* reversible non-covalent interactions for the fabrication of stimuli-responsive delivery systems.[13] The inclusion of CDs in non-viral vectors aids to overcome delivery-associated limitations such as cytotoxicity and offer enhancement in gene transfection efficiency. The dual faces of the CD structure along with less hydrophilic cavities provide ample functional zone for further conjugation with peptides, ligands and genetic cargo to impart targeted and controlled gene delivery systems.[14] CDs also intensify the proton-sponge effect in non-viral nanovectors to elevate the transfection efficiency across the targeted biomembrane.[15] Furthermore, CD-based constructs possess a huge prospect in the development of fluorescent probes, diagnostic

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assemblies as well as theranostic systems to further augment gene-based therapy.

2. Cyclodextrins

CDs are extensively studied in the pharmaceutical industry due to their potentially superior drug delivery characteristics for the treatment of various cardiological illnesses, neurological maladies, oncological disorders, *etc*.[16–20] CDs are cyclic macromolecular oligosaccharides chiefly constructed of six, seven, or eight α-D-glucopyranose units, named α-CD, β-CD and γ-CD, respectively.[21,22] The rings are linked *via* α-1,4-glycosidic linkages to fashion into a toroidal architecture with a relatively more hydrophobic cavity and hydrophilic exterior, a primary face and a secondary face, respectively, as depicted in Fig. 1.[23,24] Such structural features allow the formation of inclusion complexes where CDs encapsulate hydrophobic therapeutics and improve physicochemical properties such as solubility, permeability, stability and bioavailability.[25–28] Different CDs possess different dimensions of the hollow space and the conic configuration provides stability to various biomolecules in physiological media by enclosing the molecules and shielding them from non-specific interactions. The carbohydrate composition along with the multiple hydroxyl groups provides the possibility of further chemical modifications like RVD peptide conjugation, linkage to PEI (polyethyleneimine), PLL (poly(L-lysine)), PAMAM (polyamidoamine), PEG (polyethylene glycol), disulfide linkers, *etc*.[29] CDs are versatile carriers, fashioned into several sophisticated formulations like nanoparticles,[30] nanosponges,[31] stimuli-responsive polymers,[32] dendrimers,[33] hydrogels,[34] *etc.* to achieve an enhancement in therapeutic control. CDs are capable of encapsulating an extensive range of synthetic drugs like doxorubicin (DOX),[35] paclitaxel,[36] camptothecin,[37] levodopa,[38] acyclovir,[39] as well as large-sized herbal actives like curcumin,[40] resveratrol,[41] baicalin,[42] *etc.* The ability of CDs to conjugate with peptides and proteins,[43] nucleic acids,[44] carbohydrates,[45] and steroids[46] to offer flexible therapeutic delivery. The versatile binding potential allows conjugation with receptor ligands for the fabrication of receptor-specific delivery systems. Additionally, the structural incorporation of agents into the CD cavity along with binding to the dual faces of the structure allows multi-drug treatment as well as combinational therapy.[47,48] The ability to form reversible covalent bonds with its guest molecules enables site-specific drug release, a desirable duration of action (>48 h) and a sustained release profile. Moreover, appropriate modulation of the chemical structure imparts the desired *in vitro* and *in vivo* bio-stability in addition to the longer shelf-life of the formulation.[49,50] On the other hand, cyclodextrins classified as generally-recognized-as-safe (GRAS) need to be used carefully as factors such as the number of glucopyranose units, the chemical nature of the substituents, the degree and pattern of chemical substitutions, the HLB value, the applied concentration, the duration of exposure, the presence of serum components, the density of the cells, *etc.* contribute to the hemolytic attributes of the overall drug delivery complex.[51,52] CDs in controlled concentrations and complexed forms such as 2-hydroxypropyl-β-cyclodextrin (HP-β-CD), sulfobutylether-β-cyclodextrin (SBE-β-CD), hydroxypropyl-α-CD (HP-α-CD), *etc.* are extensively reported as safe for use.[53,54] Approved as excellent biomolecules, CDs are globally accepted as pharmaceutical excipients and are extensively explored in modern healthcare as a testament to exceptional biocompatibility, non-immunogenicity, low toxicity and high biological availability.[55–57] This encouraged the scientific community to study their potential as non-viral gene carriers and deliver therapeutic genetic materials such as siRNA, miRNA, mRNA, pDNA, aptamers, *etc.* through different CD-based constructs.

3. Challenges in the delivery of genetics

Several extracellular and intracellular barriers hinder the transportation of genetic material like pDNA, siRNA, miRNA, *etc.* from reaching the site of action and performing gene corrective responsibilities. The epithelial cell membranes, linings along with the extracellular matrix around the cells obstruct the genes from directly accessing target cells. The abundant extracellular nucleases present in the systemic circulation, as well as the extracellular matrix, rapidly deteriorate the free and unprotected genetic material.[58] The phagocytic Kupffer cells in the liver and the macrophages of the spleen eliminate the gene-loaded carriers from the bloodstream *via* renal clearance.[59,60] Additionally, due to the hydrophilic nature of naked genetic material and its anionic charge, almost no intracellular uptake occurs due to the poor interaction with the cellular membrane. The passage of genetic material through the cellular membrane is restricted unless their entry is assisted by the generation of transient holes or through various cell uptake processes like endocytosis, pinocytosis, or phagocytosis.[61,62] On permeation of the biomembrane, the slow and inefficient movement of the naked genetic material across the protein-filled cytoplasmic matrix prompts insignificant gene expression.[63] The genetic therapeutics are further prone to undergo hydrolytic action by hydrolases present in the lumen of intracellular lysosomes. The nuclear envelope represents another hindrance as the double membraned structure embedded with nuclear pore complexes largely regulates the transport across the nuclear membrane and acts as one of the rate-limiting factors in transportation of gene-based therapeutic actives.[64] As a consequence, different types of viral and non-viral vectors are required for gene delivery. Viral vectors provide enhanced transfection efficacy but are immunogenic in nature due to viral origins and the immune responses are suppressed to attain transgenic expression.[12,65] Systemic administration of viral vectors triggers innate as well as adaptive immune responses against the viral components and gene segments, lowering the efficiency of gene payload. Non-viral vectors display insignificant immunogenicity and cytotoxicity, but exhibit low transfection efficiency.[66,67] Such complications in the

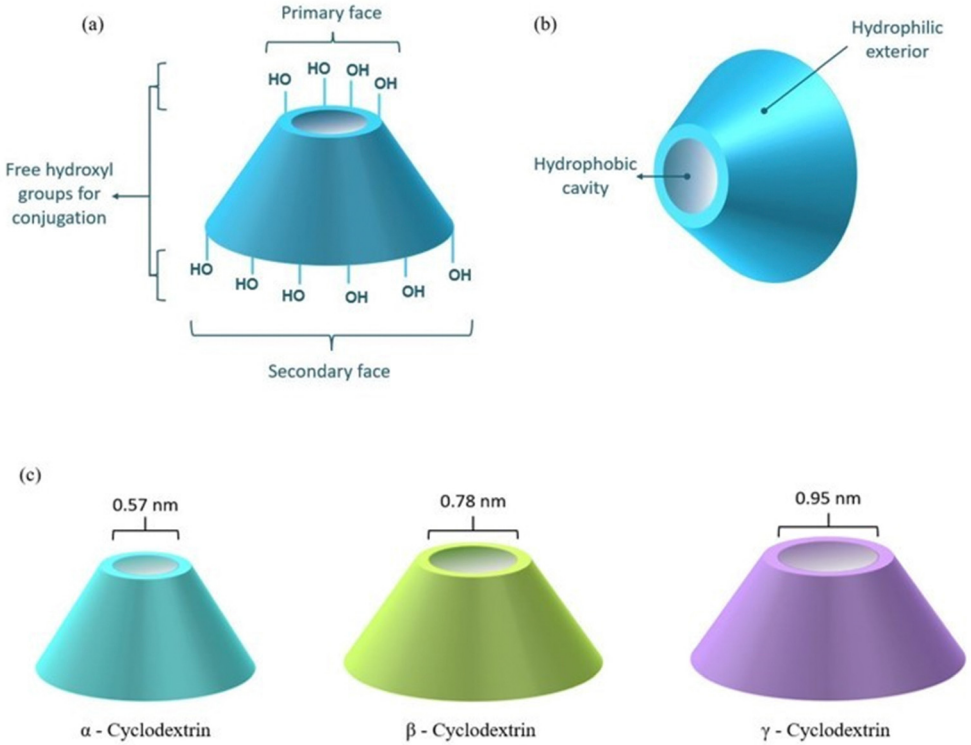

Fig. 1 Toroidal architectures of cyclodextrins: (a) primary and secondary faces of cyclodextrin with free hydroxyl groups for potential structural modification with different groups, (b) the less hydrophilic cavity and hydrophilic exterior of cyclodextrin and (c) the cavity size of different cyclodextrins.

delivery of gene-based therapeutics necessitate the development of capable carrier systems to achieve high *in vivo* stability, sufficient transfection efficiency, and low cytotoxicity, and establish effective gene-based therapy.

4. CD-based nanocarrier systems for gene delivery

CDs are frequently employed as one of the core components in gene delivery systems, where the dual faces of the molecule provide the foundation for the addition of various units like glucuronylglucosyl units, RVD peptides, fluorescent moieties, PAMAM, PEI, PLL, *etc.* CDs enhance permeation of the cargo across biomembranes, potentially preventing the genetic material from non-specific interactions with biological media.[68] Incorporation of CDs in polymers,[69] dendrimers, supramolecular assemblies, *etc.* imparts beneficial characteristics to the entire system by acting as a linker or modular component, hosting small molecules, lowering immunogenicity, permeating biomembranes, *etc.* Although CDs directly interact with the genetic cargo to form 'pure CD-vectors', several other studies reported the linkage between the genetic cargo and different complex systems, where CDs played a crucial role, provided carrier stability and ensured endosomal escape of the delivery design.[70,71]

Cationic polymers are extensively employed in gene delivery as the positively charged amine moieties on the active surface allow electrostatic interactions with negatively charged genetic materials and undergo structural condensation to emerge as gene-loaded polymeric condensates called polyplexes.[72,73] Polyplexes provide safety to the genetic material, possess nanodimensions under 200 nm and offer a desirable storage stability with a zeta potential above 30 mV.[74,75] The osmosis-driven proton sponge effect to disrupt the membranes of endosomal vesicles delivers the cargo into the intracellular spaces. However, real-life applications of cationic polymers are limited due to low efficiency of cellular uptake, non-biodegradability, and low biocompatibility.[76] As depicted in Fig. 2, the structural fabrication of CDs with cationic and anionic/nonionic groups results in the formation of amphiphilic CD-based constructs. The assemblies resemble cationic polymers as they complex with negatively charged genetic materials to directly self-assemble into polyplexes without any significant *in vivo* cytotoxic impact.[77] Gonzales *et al.* reported the premier study of β-CD conjugation with cationic polymers for effective transfection of pDNA in the year 1999.[78]

Cationic dendrimers of PAMAM, PEI, PLL, *etc.* also complex with genetic fragments through terminal amine functional moieties and bind to glycosaminoglycans on the cellular surface for desirable gene transfer. The proton-sponge effect of dendrimers emanating from the hemolytic activity, liposomal membrane-disruptive effect and intracellular distribution, in addition to the superior structural configuration, enhances gene transfer in the target cells.[79] However, the use of dendrimers is hindered due to the direct proportionality between dendrimer generation and cytotoxicity.[80–82] Significant gene

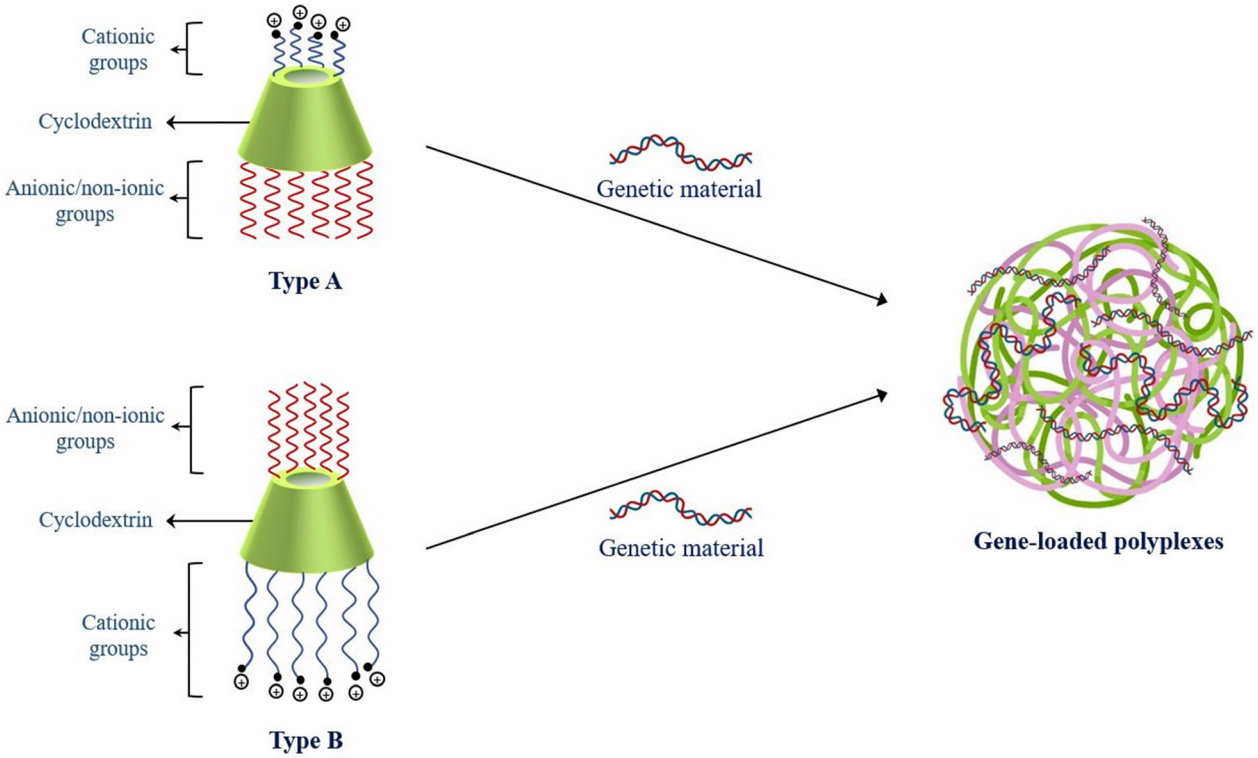

Fig. 2 Amphiphilic cyclodextrin constructs (types A and B) for encapsulation of genetic material and self-assembly into polyplexes.

transfer activity is exhibited by high generation dendrimers, but the cytotoxicity intensifies with the increasing number of primary amine terminal zones. *In vitro* cytotoxicity studies report a tolerable bio-acceptance of lower generation dendrimers, but display a lower transfection efficiency.[83] Moreover, the clinical applications of commercially accepted PEI are challenged due to charge-driven binding with intra- and extracellular components.[84] As reported in a study, the ED_{50} value for linear PEI is 4 mg kg^{-1} in BALB/c mice, severely limiting its usage at higher concentrations.[85] The cytotoxicity was known to be directly tackled by altering the linear PEI with CD carbohydrates.[86,87] The introduction of cationic-modulated CDs to the free amino terminals of dendrimers (Fig. 3) reduces the cytotoxicity and further enhances the delivery characteristics to enable leak-proof encapsulation of even small genetic molecules like siRNA, ligands, and encapsulation of drugs like DOX, sorafenib, *etc*.[88,89]

CDs provide the core for accommodation for a variety of molecules and facilitate host–guest interactions to yield supramolecular assemblies. This forte is employed for the fabrication of gene delivery systems as the dual faces of CDs combine with cationic molecules, polymeric strands, proteins as well as peptidyl ligands and further host different guest molecules like adamantane (AD), azobenzene (Az) and ferrocene (Fc).[90] AD possesses a suitable size and hydrophobicity to form a desirable host–guest interaction within the CD cavity. Modulated AD groups improve the cationic density of the system and greatly improve the transfection efficiency. PEGylation of AD increases the aqueous solubility of polycations and enhances the bioavailability of the supramolecular gene cargo assemblies.[91] Hosting Az and Fc into the CD cavity imparts sensitivity to stimuli such as light, reactive oxygen species (ROS) and intracellular enzymes like glutathione (GSH).[92–97] The stimuli-responsiveness to the cargo systems is provided by CD-supramolecular assemblies and presents site-specific therapeutic release as shown in Fig. 4.

CD-based polyrotaxanes/polypseudorotaxanes are supramolecular constructs where liner polymeric strands thread through the central cavity of multiple CDs and form mechanically interlocked configurations.[98] These configurations are physically flexible in comparison with the traditional polymers and confer additional mechanical stability of the delivery systems. According to the studies, the threading of linear polymers like PEI with CDs reduces their cytotoxic nature and elevates biocompatibility.[99] Additionally, the free mobility of CDs provides efficient grafting of gene-binding cationic elements and improves the stability of gene-loaded assemblies. Furthermore, polypseudorotaxanes based on CDs with cationic polymers are used to design controlled release gene-delivering hydrogels as the shedding rate of CDs from the backbone of linear polymers is dictated by their de-threading rate, and the volume of biological fluids stimulates a sustained gene release profile and a lower dosing frequency.[100,101] In this manner, the incorporation of CDs potentially enables larger therapeutic frameworks with proficient applications in gene-targeted therapy (Table 1).

5. CD-hybrids for RNA delivery

Several studies reported the incorporation of CDs in polyplex structures to obtain sophisticated RNA carriers. Minnaert *et al.*

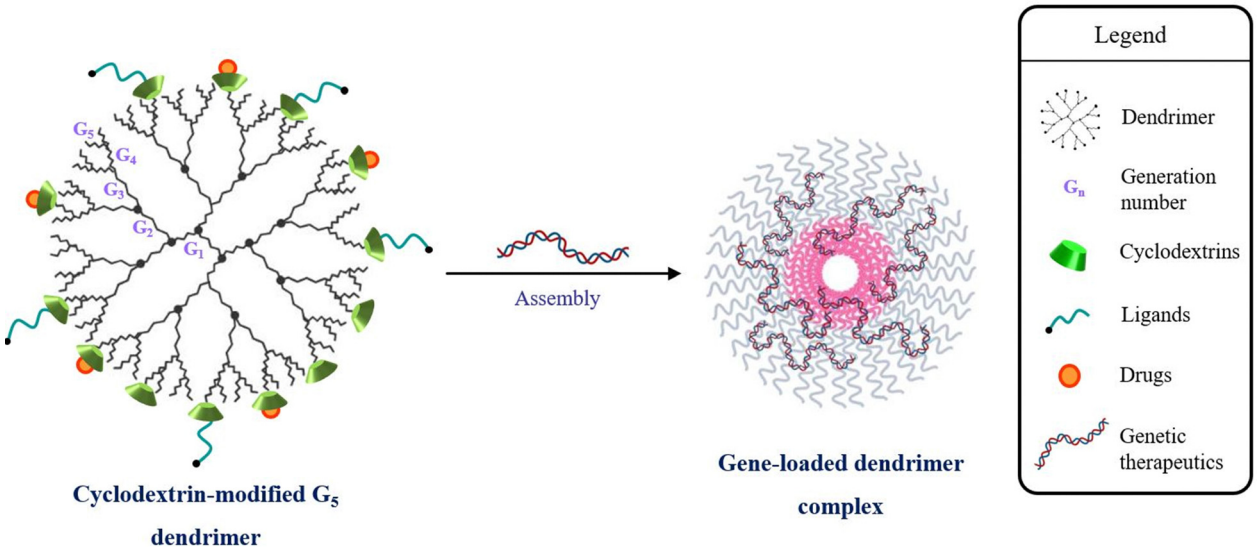

Fig. 3 Cyclodextrin-modified cationic ends of G_5 dendrimers for reduction of cytotoxicity and formation of gene-loaded dendrimer complexes.

designed luciferase siRNA-conjugated CDs (CD-ADM70) to develop a nanoparticulate gene-based therapy system against peritoneal carcinomatosis. The siRNAs were conjugated with thiourea segments present in the polycationic amphiphilic CDs to form positively charged systems and effectively interact with negatively charged cell membranes for subsequent cellular uptake. During bioluminescent studies performed on the SKOV-3 human ovarian cancer cell line, administration of 10 pmol CD-ADM70 caused an 85% reduction in luminosity compared to the control group and suggested the insignificant impact of CD-conjugation on the gene-suppressive activity of siRNA. Furthermore, an enhanced gene silencing ability of CD-ADM70 was reported by SKOV-3 cell line studies as 80% downregulation of luciferase gene was observed in the treatment group. Similarly, nebulized CD-ADM70 demonstrated an ~80% downregulation of luciferase genes, indicating the robust transfection ability and stability of the polyplexes even after exposure to a high-pressure dosing system.[102] Malhotra *et al.* directly conjugated β-CD with the sense strand of siRNAs by a bioreducible disulfide linkage for targeted silencing of overexpressed luciferase and PLK1 genes in cancer cells. Furthermore, ligand systems of adamantyl-conjugated RVD peptides were incorporated into the cavity of siRNA-conjugated CDs to generate polyanionic constructs. The constructs were charge-neutralized using polycationic chitosan to develop ligand-directed CD-siRNA nanoparticles with dimensions of ~100 nm. Cell culture

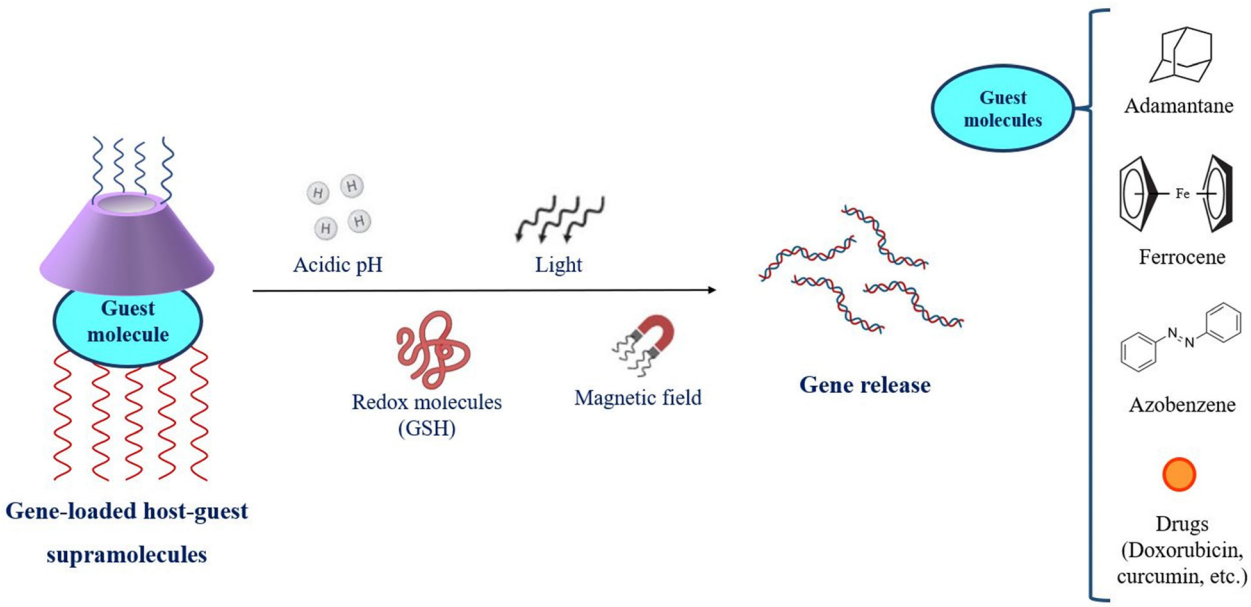

Fig. 4 Stimuli-responsive release of genetic therapeutics from cyclodextrin-based host–guest supramolecular constructs.

Table 1 Advantages of CD-hybrids for genetic delivery

CD-hybrids for the delivery of	Advantages of CD-hybrids over non-CD based systems	Ref.
RNAs	Effective gene silencing and targeted delivery of siRNA-conjugated CDs	102,120
	Enhanced gene knockdown using siRNA-β-CD in comparison with naked siRNA	103
	The siRNA–CD complex delivery system exhibited a consistent 85% reduction in CLTC, CAV1 and PAK1 protein expressions and indicated the ability to block key target endocytic pathways.	104
	Serum stability of the CD-siRNA was observed	108
	Extended protection against enzymatic degradation by nucleases	109
	Stimuli-responsiveness, site-specific release and increased therapeutic effectiveness	111
	Improved loading of the therapeutic cargo	117
DNA	Reduction in the cytotoxicity and immunogenic responses of several vector formulations	123
	Improved gene stability and transfection ability	
	Targeted and safe DNA transportation *in vivo*	125–128
	Stimuli-responsiveness to pH, light, redox and magnetic field is imparted to carriers by CD integration	
	Synergistic therapy	129
	Development of CD-based theranostic systems for effective gene delivery	130
Aptamer	Overcomes the instability and conformation flexibility of the aptamer and provides synergistic profiles	131
	Stimuli responsive release was achieved	132
	Surface engineering with the help of CD molecules with theragnostic applications	133 and 134
	Fabrication of high sensitivity and specificity biosensors	135

studies performed in the U87 human brain cancer cell line reported a 70% reduction of PLK1 gene expression compared to the untreated group, whereas similar studies performed in the DU145 prostate cancer cell line reported a 75% reduction. A luminescent intensity study performed on luciferase-over-expressing PC3-Luc cells reported a luminescence of 1500 units by CD-siRNA-treated cells compared to the 7500 units of scrambled siRNA cells and reflected a gene knockdown effect of 80%.[103] In a related study performed by Manzanares *et al.*, a β-CD-based multivalent amphiphile, AMC6, was conjugated with different siRNAs as transfection vectors to knock down SCR, CLTC, CAV1 and PAK1 protein expressions. The AMC6 structure possesses 28 cationizable centers as the primary ring surface of β-CD was linked to seven tetraethyleneimine linkers, each containing four protonatable nitrogen atoms. This allowed stable interactions with negatively charged siRNAs and rapid self-assembly into nanoparticles with an average size of 110 nm. Fluorescent studies performed on the C6 rat glioma cell line, GL261 rat glioma cell line, U87 human glioblastoma cell line and T98G human glioblastoma cell line revealed a maximum fluorescence of nearly 4000 RFU, 4500 RFU, 5100 RFU and 5000 RFU, respectively, suggesting the effective siRNA transfection ability of the nanoparticles after an incubation time of 8 h. At a strength of 100 nm, the siRNA delivery systems exhibited a consistent 85% reduction in CLTC, CAV1 and PAK1 protein expressions during 72 h cell line studies and indicated the ability to block key target endocytic pathways.[104]

Zhang *et al.* co-delivered siRNA and DOX by the fabrication of nanoparticles from carboxymethyl-β-CD (CM-β-CD) grafted trimethyl chitosan (TMC). Here, carboxymethylation of β-CD improved the solubility as well as hemocompatibility of the siRNA carrier. *In vitro* studies revealed that a 10 mg mL^{-1} formulation induced an insignificant hemolysis of 0.76%. The moiety also underwent dehydration with the amino groups of the TMC chain to form a stable and safe graft polymer. At a strength of 1 mg mL^{-1} siRNA and 10 mg mL^{-1} DOX, the A549 cells exhibited an effective 10% cell viability, indicating the *in vitro* effectiveness of the formulation.[105] Evans *et al.* employed an amphiphilic CD-based vector for the delivery of siRNAs to prostate cancer cells and incorporated a folate-targeted fusogenic peptide, GALA, for ligand-specific uptake of the therapeutic siRNA. The primary face of CD provided the base for lipophilic C_8 chains, whereas the secondary face was linked to cationic groups for conjugation with different siRNA molecules. Insignificant cytotoxicity levels were observed in healthy cells as a 95% survival rate was reported during cell viability studies. Cell culture studies performed on PC3 cancer cells revealed an effectively reduced relative luciferase expression by 75% and suggested a significant uptake of carrier vectors as well as effective gene silencing activity. Similarly, selective mRNA-silencing was also noted as 50% NRP1 and 45% ZEB1 mRNA suppression were reported compared to the 100% expression observed in control groups. Significantly, the treatment of 3D spheroidal tumors with the nanoparticles resulted in lower metastasis, reduced infiltration in the Matrigel layer and formation of compact non-invasive colonies.[106]

Kathleen *et al.* modified CDs with dilysine on their primary face for interaction with siRNA moieties. On self-assembly into nanoparticles, the anionic siRNA was encapsulated within the cationic dilysine–CD assembly for safe and stable gene delivery. CDs also availed host–guest interactions with AD-linked PEG strands modified with anisamide as a tumor-targeting ligand. MTT assays in cancer cell lines reported a cell viability of $>80\%$ 24 h post-transfection, indicating the safety of the CDs. After incubation for 48 h, a relative gene expression of $\sim 75\%$ in the test group compared to 100% in the control group revealed the effectiveness of the system to safely and effectively deliver siRNA to the target cells.[107] Evans *et al.* prepared amphiphilic CDs and further modified them with folate-targeting ligands for assembly into siRNA encapsulated nanoparticles.[108] The charge neutralizing ability of the CD moiety to result in an optimized siRNA carrier was reflected by an 8 h serum stability test as well as cell viability tests in healthy cells. *In vivo* studies performed on male BALB/c mice reported a high $t_{1/2}$ of 14.61 h,

a high AUC of 12.24 ng h mL^{-1} and a low clearance of 2.01 L h^{-1}, further proving the *in vivo* stability as well as activity of the design. Gooding *et al.* modified amphiphilic β-CD derivatives with rabies virus glycoprotein (RVG) for glioblastoma-specific delivery of siRNA. In the presence of siRNA, the modified β-CD molecules self-assembled into nanomicelles with siRNA strands encapsulated between the β-CD layers. *In vitro* analysis revealed extended protection of siRNA for 24 h against the enzymatic degradation by nucleases. Additionally, incubation of the nanomicelles with U87 human glioblastoma cells caused a 27% reduction in endogenous glyceraldehyde 3-phosphate dehydrogenase (GAPDH) mRNA expression, demonstrating a potential improvement in glioblastoma therapy.[109] Chen *et al.* constructed a novel carrier system using CDs for an innovative approach for co-delivery of siRNA, aptamer and the antitumoral drug sorafenib for combined anticancer activity. Patterning RCT-synthesized gene products on amino-CD-modified (amCD) DNA probes promoted the formation of nanoparticles as the positively charged amCDs reshaped the RCT structures *via* electrostatic interactions with RNA strands to form porous nanospheres. The less hydrophilic cavity of CDs further allowed host–guest encapsulation of insoluble sorafenib to treat the tumor tissue and suppress further growth of the tumor. 24-Day *in vivo* studies performed on tumor bearing nude mice reported a tumor volume of 300 mm^3 compared to the volume of 1200 mm^3 in control groups. The tumor xenografts collected from the treatment group showed a depletion in epithelial cell adhesion molecule (EpCAM) expression levels, whereas the phosphorylation of extracellular signal-regulated kinase (ERK) and cRAF was consistently restrained to highlight the effective siRNA transportation and gene silencing activity of the therapeutic system.[110]

A distinctive ability imparted by the application of CDs is the establishment of stimuli-responsive supramolecular delivery of genes due to the ability to form reversible host–guest systems. This property demonstrates great potential in site-specific release and increases the therapeutic effectiveness. Li *et al.* fabricated strands of hyaluronic acid (HA) with α-CDs for conjugation with siRNA, where Az-modified diphenylalanine derivatives (*trans*-G) acted as linkers between CDs and siRNA to achieve *trans*-G/HA-α-CD/siRNA ternary supramolecular nanoassemblies. Photosensitivity was imparted to the system as 365 nm UV irradiation triggered conformational changes in the *trans*-G structure to weaken its α-CD association stability and lead to carrier disassembly for the release of siRNA. As confocal laser fluorescence microscopy confirmed the photo-responsive cellular delivery of siRNA in the A549 human lung adenocarcinoma cell line, GAPDH expression levels lowered by 55%, suggesting effective siRNA delivery and gene-silencing efficiency of the formulation. Further evidence of siRNA activity was provided as abnormal gene expression resulted in a 50% growth inhibition of the tumor cells at a concentration of 80 mM after UV irradiation.[111] Similarly, Zhang *et al.* designed novel photo-responsive supramolecular constructs of CD–AD to suppress firefly luciferase siRNA expression. β-CD hosted amantadine groups conjugated with the photo-sensitive linker phosphoramidite, which was terminally linked to the 5′ end of siRNA. Studies performed on HEK293T cells reported a 6-fold reduction in luciferase expression after a 3 min exposure to UV light. In the absence of β-CD, the gene expression was noted as nearly 96% in the absence of UV light, indicating the introduction of photo-modulation by β-CD incorporation. On employing HA-conjugated CD, the pre-UV exposure leakage was notably reduced with improved cellular delivery and photo-modulated gene-suppression of the endogenous Eg5 gene was also achieved.[112]

Wang *et al.* coated gold nanorods (GNR) with CD-grafted PEI for dual loading of docetaxel (DTX) and siRNA-p65 and achieve a multi-active host–guest-based chemotherapy. Infrared-triggered hyperthermia effectively drove the cytosolic release of siRNA and DTX as displayed by confocal laser scanning microscopy (CLSM) images. Without laser treatment, the internalized siRNA was entrapped within the lysosomes for 12 h, whereas exposure to an IR laser for 3 min promoted siRNA escape to enhance the therapeutic efficiency of the active carrier. *In vivo* studies performed on Wistar rats reported a tumor volume of ~400 mm^3 in the siRNA-loaded formulation compared to the ~1350 mm^3 and 800 mm^3 of PBS- and GNR-treated groups, respectively, indicating the *in vivo* efficiency of siRNA-p65 delivery along with potential therapeutic effectiveness.[113] Xiong *et al.* developed a supramolecular nanoparticulate system for hepatoma-targeted co-delivery of oligoRNA and DOX. Polylysine (PLL) polymer was conjugated to the smaller face of β-CD and DOX was encapsulated within the CD cavity *via* host–guest interaction.[114] The resultant polycationic framework was condensed with oligoRNA to form supramolecular nanoparticles and further coated with HA for CD44-mediated endocytic targeting. pH-responsiveness behaviour was observed during *in vitro* studies as to the formulation as 47.3%, 37.4%, and 31.8% of the drug was released at pH 5.0, 6.5, and 7.4, respectively. CLSM images revealed high fluorescence of free oligoRNA in the cytosol of MHCC-97H cells and HepG2 cells, suggesting successful transportation and pH-responsive release of oligoRNA along with DOX. Similarly, Xiong *et al.* fabricated a pH-responsive supramolecular carrier for synergistic release of miR-122 as well as DOX for targeted hepatic activity.[115] The β-CD-based star copolymer nanoparticles contained a core of polyCD-conjugated PDMAEMA for host–guest interaction with DOX as well as attachment to miRNA. pH-responsiveness was noted as 94% miRNA was released at pH 5.0 compared to 60% at pH 7.2, whereas CD incorporation further delayed DOX release by 6 h due to the decreased drug diffusion from the CD core.

The application of dendrimers to impart benefits is hindered due to challenges like cellular toxicity and low transfection rates into target cells. Arima *et al.* reported a study conjugating β-CD with polyamidoamine dendrimer for an enhanced transfection ability of pDNA in the year 2011.[116] The incorporation of CDs into the dendrimer compensated free amine groups to reduce the cationic charge on the carrier and lower the toxic impact on cells. CDs also facilitate the release of genetic material after endosomes after endocytic uptake, thus overcoming the low transfection efficacy problem. This strategy was employed by Qiu *et al.* as they conjugated

PAMAM dendrimers with β-CD and entrapped gold (Au) nanoparticles in the assembly for enhanced delivery of siRNA. The amine groups of G2 dendrimers interacted with β-CD fractions, which further bonded with two cationic siRNAs, namely B-cell lymphoma 2 (Bcl-2) and vascular endothelial growth factor (VEGF), for silencing the genes in cancer cells. β-CD also improved the therapeutic loading due to tight siRNA compression into the resultant polyplexes. The safety of the CD-dendrimers was confirmed as the MTT cytotoxicity assay on U87MG cell lines reported >80% cellular viability even at a higher drug concentration of 2000 nM. Bcl-2 and VEGF expression studies reported a 25% expression in vector exposed U87MG cells compared to the 100% expression in naked-siRNA exposed cells, indicating the heightened gene transfection of siRNA by the CD-vector system.[117] Similar observations were reported by Hayashi *et al.* as they developed siRNA polyplex delivery with hepatocyte-specific action for anti-amyloidosis therapy.[118] The lactose appended G3 dendrimer was conjugated with α-CD for loading siTTR siRNA. The role of α-CD was established as the carriers without CD displayed low gene silencing activity against the CD-containing polyplexes. In the absence of α-CD, the polyplexes circumvented the high endosomal escape activity to elicit insufficient interactions with phospholipids, resulting in transfection driven solely by the proton sponge effect of the dendrimer. The CD-conjugated dendrimers displayed more safety in the HepG2 cell line as compared to lipofectamine 2000 carriers with a 3-fold increased cell survival rate even at a 100 nM concentration. Furthermore, 50% gene silencing activity reported during *in vivo* studies using BALB/c mice indicated the vital impact of α-CD on the carrier. Modified β-CD groups such as glucuronylglucosyl-β-CD (GUG-β-CD) interact with endosomal membranes to further improve the endosomal escape of the siRNA complex post membrane disruption.[119]

Mohammed *et al.* reported the utility of GUG-β-CD conjugation with G3 dendrimers as siRNA carrier systems. α- and β-CDs were linked to the dendrimers *via* a GUG linker fraction and interacted with siGL3 siRNA to evaluate the gene silencing efficiency *in vitro*. A ~80% suppression of luciferase activity noted after incubation for 23 h indicated the effective delivery of a gene-based therapeutic active, *i.e.*, siRNA, by the CD-modulated system. Fluorescence tests to detect intracellular distribution revealed that a considerable number of assemblies escaped endosomes after uptake, whereas the assemblies released the gene-based therapeutic active in the cytoplasm. A compilation of results suggested enhanced endosomal escape ability and siRNA releasing properties of GUG-β-CD systems.[120] Further, Mohammed *et al.* conjugated a DOX-loaded G3 PAMAM dendrimer with GUG-β-CD for complex formation with siGL2 and siPLK1 siRNAs for effective antitumor therapy. *In vivo* studies performed on BALB/c mice reported a tumor volume of ~375 mm^3 and ~600 mm^3 in the siPLK1- and siGL2-vector groups, respectively, compared to ~650 mm^3 in the control group after 15 days of injection.[121]

Polyrotaxane structures are potential RNA carriers due to their targeted delivery characteristics and gene protective abilities. Gocke *et al.* employed α-CD-threaded polyester polyrotaxanes to deliver GFP siRNA and studied their *in vitro* gene transfection ability. The rotaxane α-CD further provided the base for modification with DMEDA to achieve a stronger linkage with siRNA due to free rotatability and form dense nanoplexes with significant gene loading. The assembly displayed significant biosafety with an 80% cell viability in normal HeLa cells, notably greater than that of the standard transfection agent branched PEI. Gene silencing assays on HeLa cells reported a 50% gene silencing efficiency of the optimized formulation compared to the 100% of the control group, and CLSM images showed macrophage-driven transfection complex internalization within 4 h of the treatment.[122]

6. CD-hybrids for DNA delivery

CDs reduce the cytotoxicity and immunogenic responses of several vector formulations and hence hold immense potential to deliver DNA, just like potential RNA delivery. Elsana *et al.* improved the gene stability and transfection ability of polyplexes using CM-β-CD as the non-viral vector. CM-β-CD enhanced the pDNA condensation as reflected by a 45.20% inclusion rate and provided protection to the pDNA in the DNase I environment even at low concentrations as revealed by gel electrophoresis. The polyplexes significantly transfected the COS 7 and SH-SY5Y cell lines as well as increased the transfection against the commercial transfection reagent TransIT-LT1. In addition to polyplexes, liposomal systems incorporated with CDs also show promise in targeted and safe DNA transportation. Structural integration of less polar CDs results in non-specific interactions with the cell membrane during ingestion by endocytosis rather than sole electrostatic interactions to display an enhancement of gene transfection in liposomal vectors.[123] Elsana *et al.* formulated cationic lipoplexes with the aid of CM-β-CD for efficient condensation of pDNA into stable nanomicelles of dimensions under 160 nm. Gel electrophoretic studies revealed sufficient protection for DNase I enzyme, indicating potential *in vivo* stability with adequate condensation of pDNA into the nanoparticles. A transfection efficiency of above 40% was consistently observed in CD-based groups compared to <30% for the control formulation during *in vitro* studies on Sh-SY-5Y cells. The safety of the formulation reflected by >80% during COS7 cell line studies ensured the non-toxicity of the CD-based formulation.[68] Similarly, Štimac *et al.* merged β-CD into the liposomal design by conjugating the primary rim of CDs with hydrophobic n-dodecyl chains, whereas the secondary rim was linked to hydrophilic oligo(ethylene glycol) substituents. The resultant complex was fused within the phosphatidylcholine moieties of the liposomal vesicles to bind pDNA *via* suitable linkers.[124] Stimuli-responsiveness to pH, light, redox and magnetic field is assigned to carriers by CD integration.

Zhang *et al.* designed a pH-responsive supramolecular polymer by conjugation of the poly(β-CD) (PCD) backbone with poly(glycidyl methacrylate) (PGEA) *via* acetal bonds to generate a cationic PCD-acetal-PGEA carrier assembly. Additionally, β-CD also formed complexes with AD-modified ligands for targeting folate receptors. The resultant supramolecular polymer showed the ability to form polyplexes with both anti-EGFP

siRNA and pcDNA3-Luc plasmid DNA. The gene transfection assay performed on 293T, HeLa and MCF-7 cell lines using pDNA as a reporter gene revealed a noteworthy 50% reduction in luciferase expression.[125] Similar observations were noted on using pEGFP as a reporter gene during cell culture studies and the siRNA knockdown results demonstrated the effectiveness of multifunctional supramolecular gene delivery assembly to deliver siRNA to cancer cells. Photodynamic nanoplatforms of CD-based supramolecules were developed by Wang *et al.* for better control over DNA delivery. By modification of cationic PLL with β-CD, photo-responsiveness was incorporated into the systems as CDs hosted TPP-PEG as a water-soluble photosensitizer for synergistic anticancer activity. The CD-constructs are self-assembled into polyplexes, with β-CD-PLL encapsulating pDNA within its cavity *via* stable electrostatic interactions. CLSM studies performed on HeLa cells reported an intense red fluorescence intensity after 15 min LED exposure compared to the low fluorescence observed before LED exposure, indicating the photo-responsive cleavage of the host–guest molecule to provide a controlled gene delivery.[126]

The redox-responsive trait was incorporated into the DNA delivery system by Sahoo *et al.* by bridging β-CD-scaffolded polycationic clusters with redox-sensitive AD-S-S-AD groups. The resultant construct showed great DNA condensing properties by virtue of its four cationic arms and form polyplexes with a significant DNA payload. The polyplexes also exhibited dense structures with particle sizes below 300 nm due to compact intra-scaffold binding. In the presence of 10 mM GSH mimicking the intracellular concentration scenario, a significant fluorescence intensity of 85 RFI was observed for 4 h, whereas the fluorescence was absent in GSH-deprived concentrations. This confirmed the potential applications of CD for redox-triggered gene release.[127] Magnetic stimuli-responsive CD-based assemblies for gene delivery were developed by Li *et al.* as the superparamagnetic iron oxide nanoparticles (SPIONs) were modified with hydrophobic oleyl chains to specifically stabilize within the less hydrophilic α-CD cavity. The CDs were externally conjugated with cationic OEI to form star cationic polymers for stronger binding with pDNA and form α-CD-OEI-SPIONs/pDNA complexes. Transfection efficiency, reflected by luciferase expression, was greatly enhanced on the application of an external magnetic field as the carriers were rapidly attracted towards the cell membrane and sped up sedimentation to aid in membrane permeation. The *in vitro* studies with exposure to magnetic fields reported a 25% increase in luciferase expression in the MCF-7 cell line. Additionally, the CD-cavities hosted the disulfide-containing Az-terminated branched polymer attached to fluorescent rhodamine groups for a site-triggered fluorescent activity. *In vivo* studies in zebrafish embryos reported insignificant cytotoxicity along with significant gene transfection efficiency.[128] CDs also demonstrate potential for the development of multi-staged inclusion complexes as reported by Ke *et al.* By conjugating Nur77 plasmid-complexed β-CD-PCL-PDMAEMA with DOX-enclosed β-CD-AD strands, synergistic gene therapy was established based on the host–guest complexation of CDs. The dense packing of the construct imparted a smaller and more stable particle size in comparison with PEI-25k. Moreover, due to the higher cationic charge, the complex exhibited a better pDNA binding ability against the standard PEI-25k. With an improved cellular uptake, it proved as a better gene transfection vector in HepG2/MDR1-Bcl2 cells as a consistent luciferase activity of $>10^7$ RLU per mg was reported compared to the variable PEI-25k results. By encapsulating DNA in a self-assembled inclusion complex synthesized by linkage of 2 CD-based polymers and hosting fluorescent probes in the CD cavity, CD-based theranostic systems are developed for gene delivery as well as real-time therapeutic progress.[129] Jiang *et al.* designed targeted and fluorescent traceable supramolecular polyplexes by employing PEGylated CD chains, where the strands interacted with DNA and formed stable genetic complexes for gene therapy, demonstrating the immense scope of CD-based DNA theranostic systems.[130]

7. CD-hybrids for aptamer delivery

Application of CDs as critical components in various formulations also resolves the delivery challenges of instability and conformational flexibility faced during aptamer transportation. Moreover, CDs encapsulate synthetic actives to provide a synergistic treatment profile. Jiang *et al.* conjugated β-CD with circular, bivalent aptamers for stable delivery of saporin protein for its antitumor activity. By linking β-CD to the aptamers *via* linkers, the bivalent genetic material retained high serum stability. β-CD also hosted AD-modulated peptides to introduce antitumor activity as well as enhanced cellular internalization of the system. The resultant suprapolymeric system further encapsulated Au nanoparticles for enhanced cytotoxicity. HeLa cell line studies reported a 3-fold increased fluorescence intensity and a cytotoxicity of ~40% at a concentration of 75 nM, suggesting safe delivery of aptamers and formulation effectiveness, respectively. In addition to stability, CDs are also utilized to strategize stimuli-responsive release of aptamers *via* stimuli-sensitive disulfide linkages.[131] Shen *et al.* fabricated β-CD-dependent pH-activated mesoporous silica nanocarriers (MSNs) for the treatment of breast cancer cells using human epidermal growth factor receptor-2 (HApt) aptamers. After capping the MSN pores with β-CD-SH, the opposite face of CDs was functionalized with the aptamer HApt *via* disulfide bonding. *In vitro* tests confirmed the pH-stimulated aptamer release as the discharge of equivalent DOX revealed an 80% release within 10 h at pH 4.5 compared to 30% at pH 6.4. At a strength of 500 μg mL^{-1}, the nanoassemblies displayed the potent cytotoxicity of HApt aptamers with a cell viability of 45% in HER2-overexpressing SKBR3 breast cancer cell lines to demonstrate the effective separation of aptamers from the β-CD-SH moiety. Surface modification of nanomicelles with aptamers is also made possible by employing conjugated CDs as linker molecules.[132] Li *et al.* conjugated the aptamer AS1411 to the surface of Pluronic F127 nanomicelles using β-CD-linked PELA block copolymers for enhanced tumor-targeting and nucleolin-mediated cellular internalization of the therapeutic system. During the *in vivo* studies performed on MCF-7 tumor-bearing mice, an average signal of 550 units in tumor tissue was

reported compared to the <200 units reported in other vital organs after a dose of 5 mg kg^{-1}. Average fluorescence signals observed during real-time near-IR fluorescence imaging suggested a better tumor targeting potency of CD-associated aptamer-micelles compared to the non-conjugated ones.[133]

8. CD-hybrids for aptamer-based diagnostics

Ultrasensitive sensors and diagnostic tools are driven by the concept of conjugation between CDs and aptamers. Hasanzadeh *et al.* fabricated Au nanoparticles and immobilized DNA-aptamers on the surface using α-CD for the detection of the platelet-derived growth factor-B (PDGF-B) tumor biomarker. The biosensor exhibited a superior sensitivity, a reduced detection limit and high stability for PDGF detection with a linear range of 50 pM–10 nM and an LOD of 50 pM.[134] Wu *et al.* developed a sensitive electrochemical aptamer biosensor for tetracycline determination. The TET aptamer was bound to ferrocene as a signaling section, which was further hosted by the main body of β-CD associated with the Au electrode. In the presence of TET, the aptamer undergoes a configurational change to result in separation from the electrode surface. The accurate detection of tetracyckine in tap water, milk, substrate, etc., enhanced the potential applicability of the HS-βCD-based subject–object recognition technique to develop highly specific and sensitive biosensors was established.[135] On similar lines, He *et al.* also developed a fluorescent assay for the detection of tetracycline using γ-CD as a stabilizer. The triple helix aptamer probe (TAP) formed an inclusion complex with γ-CD *via* a pyrene dimer to form a probe with a low detection limit of 1.6 nM. Target exposure results in structural changes, leading to separation of the signaling probe from the aptamer and generation of pyrene excimer. γ-CD stabilizes the excimer using host–guest inclusion and stabilizes the signaling performance, to remarkably increase the fluorescence intensity. Owing to the stability imparted by γ-CD, the fluorescence is sustained for an extended duration to give an ultrasensitive, stable, specific and efficient biosensor.[136] With the development of α-CD-based polyrotaxanes, Zu *et al.* utilized aptamers for enhanced magnetic resonance imaging (MRI) contrast agents for tumour-targeted imaging. The α-CD axle around the disulfide-modulated PEG thread bestowed the site for modification with lysine dendrons as the connector for gadolinium chelation as well as AS1411 aptamers. The α-CD axle provided free mobility and enabled the modified AS1411 aptamer with suitable rotation as well as slidability. This facilitated the opportunity for greater interaction with surface nucleolins and the achievement of multivalent targeting for faster accumulation and intratumoral retention of contrast for an extended duration at the tumor site. In the tumor microenvironment of high GSH concentration, the biodegradable disulfide linkage undergoes de-threading and results in non-toxic Gd moieties with easier elimination processes. Cellular images of the *in vitro* MCF-7 cancer cell line showed a 5-fold increase in signal intensity compared to the control, whereas *in vivo* MRI studies in tumor bearing mice displayed an evident contrast of 1.5 relative enhancement signal intensity (RESI) after 0.5 h and intensified till 3 RESI till 4 h compared to the consistent 1 RESI of control, indicating the faster accumulation and longer residence time attributed to the α-CD-linked AS1411 aptamer.[137]

9. Future directions for research

CDs, a class of glucose-linked cyclic molecules, are being widely studied for their role in polyplexes and supramolecular polymers for delivering siRNA, pDNA, and gene therapeutics. Ongoing research aims to enhance the efficiency and specificity of gene delivery, with new CD-based polyplexes showing promising results in pre-clinical models. CDs improve the bio-stability, non-toxicity, biodegradability, site-specificity, and systemic solubility of gene vectors. Future research will focus on incorporating CDs for targeted delivery in cancer therapy and regenerative medicine, utilizing surface modifications to improve therapeutic efficacy. Another area of research is the enhanced delivery of therapeutic genes to the brain, as CDs have shown the ability to cross the blood–brain barrier in animal models, suggesting potential for gene-based therapies in neurological disorder.[138–140] CDs are further employed for non-viral neuronal targeting for siRNA delivery, as reported in various experiments.[141–143] The ability of CDs to enhance site-specificity and gene delivery efficiency makes them promising candidates for gene theranostics, combining disease diagnosis and treatment through gene therapy. CDs are complexed with receptor-specific moieties to introduce molecular recognition, further improving the precision of gene-based delivery systems.[109,144–146] CDs are also being explored to enhance the delivery of CRISPR-based therapies, which use guide RNA and Cas enzymes to target and edit specific genes.[147] However, cyclodextrin-based systems are still in early development, and further studies are needed to confirm their safety and efficacy in humans. Research has shown CDs can deliver diagnostic genes, such as imaging reporter genes, to visualize diseases *in vivo* and to enable personalized therapies in the future.[148] CDs are highly sensitive to various molecules, including gases, ions, and biomolecules like proteins, enzymes, lipids, and genes, making them ideal candidates for sensing materials in Internet of Things (IoT) devices. Additionally, they hold potential for low-cost, sensitive diagnostic technology, targeted drug release systems, and future research may focus on IoT-based delivery systems like drug injectors and biomonitoring systems.[149–153] Moreover, CDs are used to develop sensors for specific genetic biomarkers, such as mutations and gene expression changes.[154] While CDs show promise in IoT applications, more research is required to confirm their full potential and safety. In summary, their unique properties make CDs valuable for future gene delivery, personalized medicine, and IoT uses such as sensing, drug delivery, and biomedical monitoring.

10. Conclusion

Advances in gene-based therapy are constrained by delivery challenges and carrier systems. Cyclodextrins (CDs) are versatile macromolecules with multiple conjugation sites for linkers

and genetic payloads. Numerous *in vitro* and *in vivo* studies of CD-integrated nanoparticles show enhanced biomembrane permeation and improved transfection efficiency to enable precise gene delivery. Modified CD systems allow for higher surface conjugation with receptor ligands to enable targeted delivery and reduce adverse effects. Combining CDs with cationic moieties in polyplexes, lipoplexes, dendrimers, and supramolecular constructs lowers biotoxicity and enhances *in vivo* stability. Host–guest interactions, facilitated by covalent linkages with linkers like azobenzene and ferrocene, enable pH-, redox-, light-, and magnetic field-sensitive stimuli-responsive gene release. Additionally, modification of CDs with fluorescent elements enhances probe generation and theranostic assemblies. Given these advantages, CDs are promising for future gene delivery systems and personalized therapies, contributing to real-time monitoring and improved treatment efficacy.

Author contributions

Amey Revdekar: visualization, writing – original draft. Bhagyashree V. Salvi: visualization, writing – original draft. Dr. Pravin Shende: conceptualization, writing – review and editing, supervision.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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