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Cellular uptake and retention of nanoparticles: Insights on particle properties and interaction with cellular components

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ABSTRACT

The utilization of nanomaterials in the biological and medical field is quickly progressing, particularly in areas where traditional diagnostics and treatment approaches have limited success. The success of nanomaterials in medical products such as biomedical implants, wound dressings and drug delivery systems rely upon their effective interaction between the extracellular matrix, cells, and intracellular components. Upon contact with mammalian cells, nanoparticles (NPs) begin to interact with the extracellular matrix, cell membrane, cytoplasmic proteins, nucleus, and other cellular organelles, which result in nanoparticle internalization and subsequent cellular responses. Such responses elicited by the mammalian cells as a result of the cell-nanomaterials interactions, both at the cellular and molecular level, are mainly determined by the morphological, chemical, and surface characteristics of the nanomaterials themselves. This review provides an overview of how such different attributes, such as chemical nature, size, shape, surface charge, topography, stiffness, and functional features of nanomaterials, influence the cell-nanomaterials interactions.

1. Introduction

Owing to the tiny size and large surface area to volume ratio, nanomaterials exhibit different physicochemical features compared to their bulk form. These features are making them attractive for numerous applications, such as fast-moving consumer goods (FMCGs), high-sensitivity nanoscale sensors, high-performance electronics, biomedical implants, and pharmaceutical products [1,2]. Both inorganic (metal or metal oxide nanoparticles, NPs) [3–5] and organic nanomaterials (graphene [6], carbon nanotubes, CNTs [7,8], C60 fullerene [9], carbon quantum dots, QDs [10]) have been used in such applications. Owing to the full range of applications in biomedical and consumer products, it is essential to understand the interactions of nanomaterials with mammalian cells and cellular components [11]. The outcome of various nanotoxicology studies indicates that [12] nanostructures can produce multiple adverse effects in biological systems mainly due to the production of reactive oxygen species (ROS) that results in oxidative stress [13–15]. Nanomaterials can also produce toxic effects on cells by ROS-independent mechanisms [16,17] such as those associated with morphology, size, and zeta potential of nanomaterials [18–20]. Also, the presence of functional groups on nanomaterials and the metal ions released from them can influence the biological system [21]. However, the gap between cytotoxic and therapeutic concentrations of nanomaterials is very narrow, and it may show variation in different types of cells [22]. Thus, a clear understanding of nanomaterials-cell interaction is of prime importance to effectively explore the potential healthcare applications of these tiny particles with no or minimal adverse effects. Although there is plenty of information available in the scientific literature regarding nanomaterials-cellular interactions [23–27], a comprehensive reorganization in an easily understandable form is required.

An appropriate level of interaction between nanomaterials with cells and intracellular organelles is fundamental in various biomedical and drug delivery applications [4,28,29]. To fine-tune the nanomaterial-cell interactions and achieve a desirable outcome [30], multiple methods such as surface functionalization [31–33], surface modification [34], and controlling the physico-mechanical properties [35] were tried [36]. Multiple factors such as the size, shape, net charge, stiffness, the hydrodynamic volume can affect the interactions between nanomaterials

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and cell membranes, their subsequent internalization, and interaction with intracellular components [29,37–40]. A weak interaction between nanomaterials and cell membrane can result in the Brownian collisions of nanomaterials with the cell membrane without facilitating the adhesion of nanomaterials on cell membranes. However, adequate adhesive forces can result in the adhesion of nanomaterials on cell membranes and subsequent internalization by generating a temporary pore in the plasma membrane [41,42]. Such complete internalization of nanomaterials is mainly dependent on the shape, size, and surface functional groups of them [43]. Surface chemistry and stiffness can also play a significant impact on nanomaterial-cell interactions [44]. Apart from internalization, these characteristics can influence the cell viability, phagocytosis, biomolecular signaling, and renal excretion [45]. Despite the cytotoxic effects [46], several inorganic NPs are exploited to destroy pathogenic microorganisms and malignant cells [47,48]. Inorganic nanomaterials are extensively studied for their potential applications in vaccine delivery and immunotherapy [49]. Thus, it is vital to clearly understand both the material characteristics and the doses of nanomaterials to draw a sharp line between the cytotoxic concentration and therapeutic window to use them in clinical settings. This needs substantial advancement in understanding the relevant interactions at nanomaterial-cell interfaces by rigorous research [50]. Understanding the outcome of interactions between nanomaterials with mammalian cells and cellular components, at various levels, could help identify the fundamental requirements for their use in healthcare and FMCG sectors. In this review, we present an overview of multiple properties of nanomaterials that influence their cellular internalization, cytoplasmic transport, interaction with intracellular components, and overall effect on cellular behavior.

2. Factors influencing nanomaterial-cell interactions

There are many factors on a nanomaterial perspective that determine or influence the interaction between nanomaterials and cells/cellular components. Fig. 1 shows the possible characteristics of nanomaterials that influence their interactions with cells. The foremost important factor that influences the nanomaterials-cell interaction is the chemical nature of the nanomaterial itself. Features such as particle size, shape, texture, rigidity, charge, presence of functional groups, and hydrophobicity/hydrophilicity can influence cellular uptake and interaction with cellular components. Many endocytotic routes have been described for nanoparticle internalization into cells (Fig. 2). Clathrin-mediated endocytosis is a significant route of nanoparticle uptake by the cells as the blockade of clathrin-mediated endocytosis has been shown to decrease the cellular uptake of NPs [51]. Studies also indicated that nanoparticle uptake could occur through caveolae-mediated endocytosis as determined by the co-localization with caveolin-1 proteins over internalized NPs found in the caveolae and caveosomes [52]. Caveolin-mediated endocytosis is responsible for the cellular uptake of NPs (20–100 nm), whereas clathrin-mediated endocytosis is mainly responsible for the cellular uptake of submicron particles (100–350 nm) [53].

Phagocytosis and micropinocytosis are the other mechanisms that facilitate nanoparticle internalization [54]. These pathways are mechanistically different and tightly controlled at the molecular level. The path by which NPs enter in cells decides further intracellular

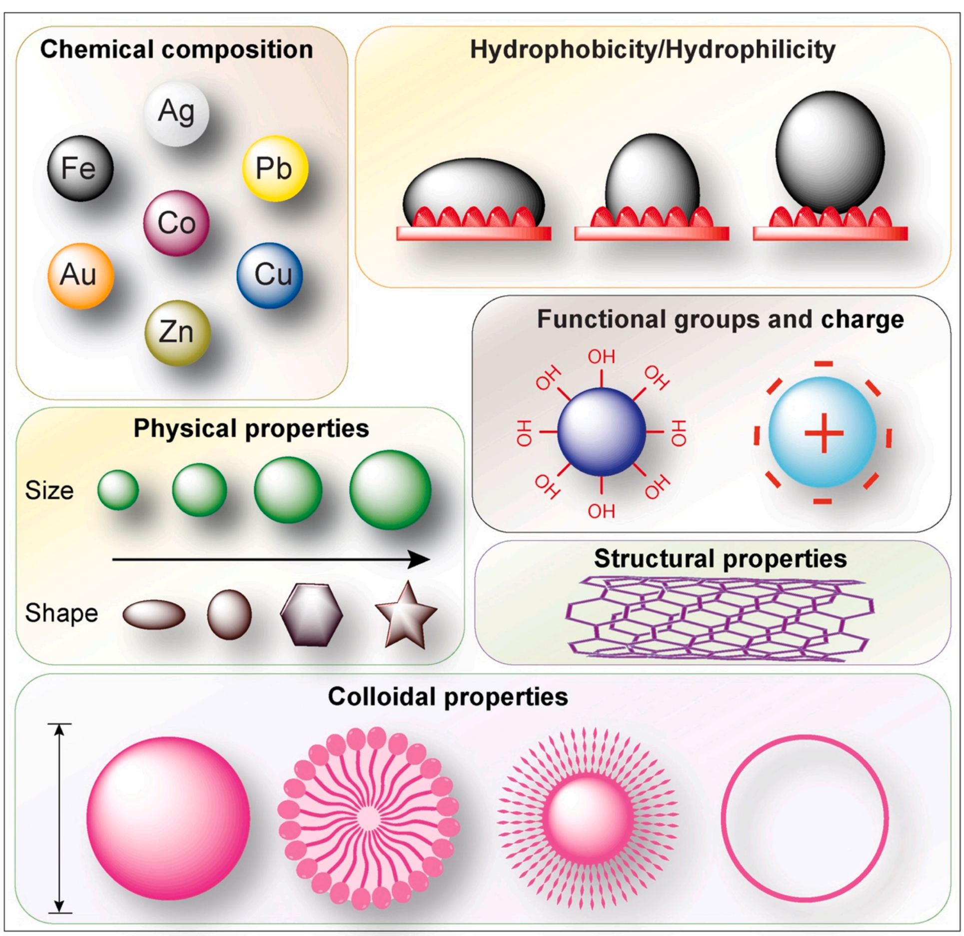

Fig. 1. Schematic representation showing the essential characteristics of nanomaterials that influence cellular uptake and subsequent interaction with cellular components.

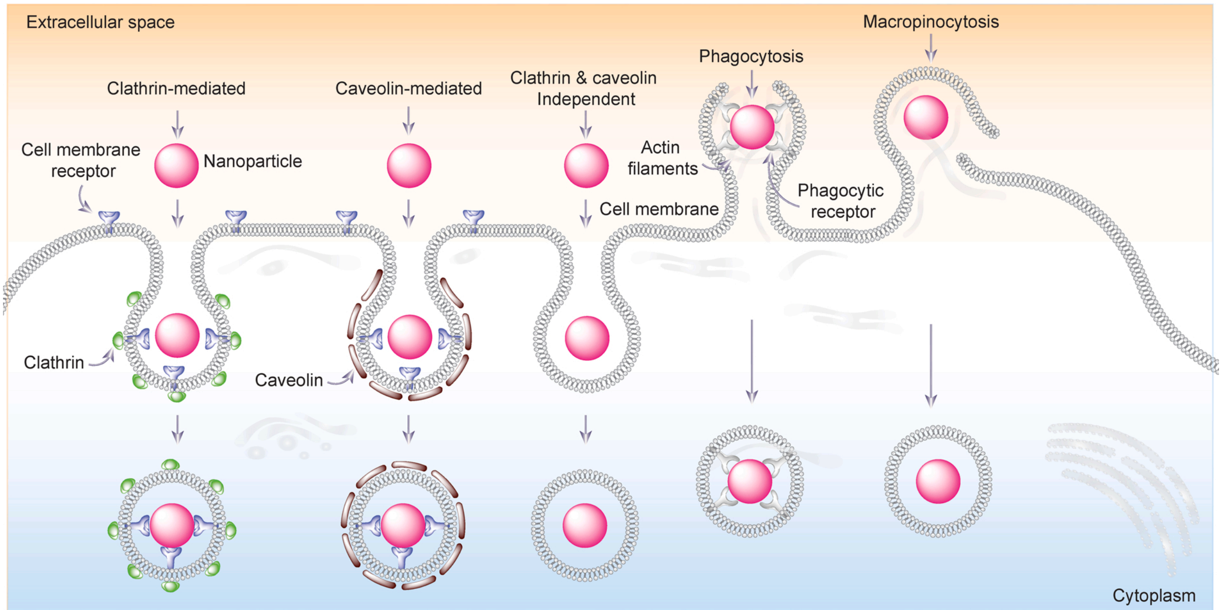

Fig. 2. Schematic representation showing the mechanisms of nanoparticle cellular internalization such as clathrin-mediated; caveolin-mediated; clathrin- and caveolin-independent; phagocytosis and macropinocytosis pathways.

nanoparticle transport and the resultant biological and therapeutic outcome [25]. Regardless of the intended result as desired for the specific application, the interaction of NPs with the target cells can be either advantageous or harmful to the organism as a whole. Upon entering the human or animal body, nanomaterials interact with the serum and extracellular matrix (ECM) proteins and generate a 'protein corona' around them [55]. On the one hand, this corona formation is advantageous as it can prevent the agglomeration of NPs, reduce toxicity, and restrict them from entering the cytoplasm [56]. On the other hand, corona formation may affect the biological (antibacterial activity, antioxidant activity, or ROS generation) and physical (fluorescence, surface plasmon resonance, or magnetic property) properties of the nanomaterial [57]. At the molecular level, ROS generation acts as an essential mechanism by which the nanomaterials induce cellular responses [58]. ROS are double-edged swords as they can help in tissue regeneration at optimum concentration and harm cells by producing DNA and protein damage at higher concentrations [59,60].

The subsequent sections present detailed information regarding various factors that influence the interactions between nanomaterials and cells.

2.1. *Chemistry of nanomaterials*

Chemistry of the base material used for the synthesis of nanomaterials is a significant factor that influences their interactions with the cells and cellular components [61]. NPs synthesized from biopolymers such as chitosan [62] and metal/metal oxide NPs synthesized by biological routes are mostly cell-friendly and bioactive [63]. The beneficial properties of them are attributed to the occurrence of functional groups such as hydroxyl, carboxyl, amino, and acetamido groups [64]. Although not bioactive, NPs based on synthetic biopolymers such as polyvinyl alcohol, polycaprolactone, and polylactic acid are compatible with mammalian cells [65]. The cytotoxicity shown by the nanomaterials is mainly due to the inherent toxicity of the elements used for the synthesis. For instance, since noble metals such as platinum and gold are somewhat compatible with mammalian cells, NPs synthesized from them are harmless despite their size and morphology-associated effects [66–71]. However, nanomaterials based on toxic heavy metals such as cadmium and lead are generally toxic to mammalian cells [72]. Upon interaction with the biological system, nanomaterials can induce either systemic, local, or both toxic responses depending upon the chemical properties.

Moreover, nanomaterials produce functional group dependent cellular responses by either specific (e.g., specific chemical molecules) or non-specific (e.g., presence of simple, functional groups such as –OH, -COOH) surface chemical features. Mainly, specific chemical properties of nanomaterials such as elemental chemistry, presence of specific biochemical molecules, and release of metal ions can play a significant role in the nanomaterials associated with systemic toxic effects. However, local cellular responses such as cell-cell adhesion, cell proliferation, cell-substrate adhesion, and phenotypic changes are dependent on non-specific chemical properties [73,74].

Solubility and ionization of metallic or metal-containing NPs play a significant role in the cellular response and toxicity induced by them at the molecular, cellular, tissue, and systemic level [75]. The dissolution and ionization of nanomaterials mainly rely upon the chemical nature of the NPs in the biological environment [76]. For instance, zinc oxide (ZnO) NPs show higher solubility in aqueous conditions and thus relatively higher cytotoxicity on cells in comparison with less-soluble ones like titanium oxide (TiO_2) NPs [77]. The plausible reason for such a pronounced adverse effect shown by more soluble NPs could be the higher amount of metal ions generated by them in aqueous conditions. It has also been shown that silver and copper ions generated by silver and copper NPs could interact with the cell wall components containing nitrogen, oxygen, or sulfur and damage them [78]. Functionalization with a suitable moiety can modify such characteristics of NPs. For example, when silver NPs were functionalized with citrate groups, they could undergo clathrin-mediated endocytosis, lysosomal dissolution, the subsequent release of a higher amount of silver ions, and resulting toxicity in *Caenorhabditis elegans* [79]. An interesting recent study demonstrated that even minor changes in surface coverage of functional groups would significantly influence the cellular interaction and subcellular distribution of ultrasmall gold NPs [80]. The results of this study indicated that lower surface coverage results in fast cellular communication and strong membrane binding but low cellular uptake.

In contrast, high surface coverage induces slow cellular interaction and low membrane binding but higher cellular internalization. Another example of the effect of materials chemistry of NPs on nanomaterials-cell interactions is the magnetic properties. For instance, a substantial decrease in F-actin remodeling [81,82], disruption of tubulin [83], increased levels of microtubule (MT) acetylation were observed upon treatment with superparamagnetic iron oxide NPs (SPIONs) [84].

Since the inherent chemical properties of the materials employed for the production and surface functionalization of nanomaterials can have a direct effect on their interaction with cells and cellular components [85], the bulk and surface chemistry of them should be carefully assessed before recommending them for biological applications [86].

2.2. Size of nanomaterials

The particle size and size distribution are among the most critical factors that influence cell-nanomaterial interactions. The particle size plays a vital role in the cellular uptake, drug release kinetics, bio-distribution, and toxicity of nanomaterials [40,87]. Unlike micro to large particles, NPs are generally not identified as foreign bodies by the immune system [88,89]. Macrophage engulfment of nanomaterials is also dependent on particle size, and they can only recognize relatively large NPs [90]. Apart from the cellular uptake, the size of the nanomaterials also influences the kinetics of cellular uptake and intracellular distribution [91,92]. To facilitate effective interaction with cells and provide a biological response, nanomaterials should be able to traverse the ECM. Due to the porous mesh-like organization, ECM firmly controls the movement of NPs across it [93]; with the straining properties of ECM mainly reliant on the organization of all their macromolecular

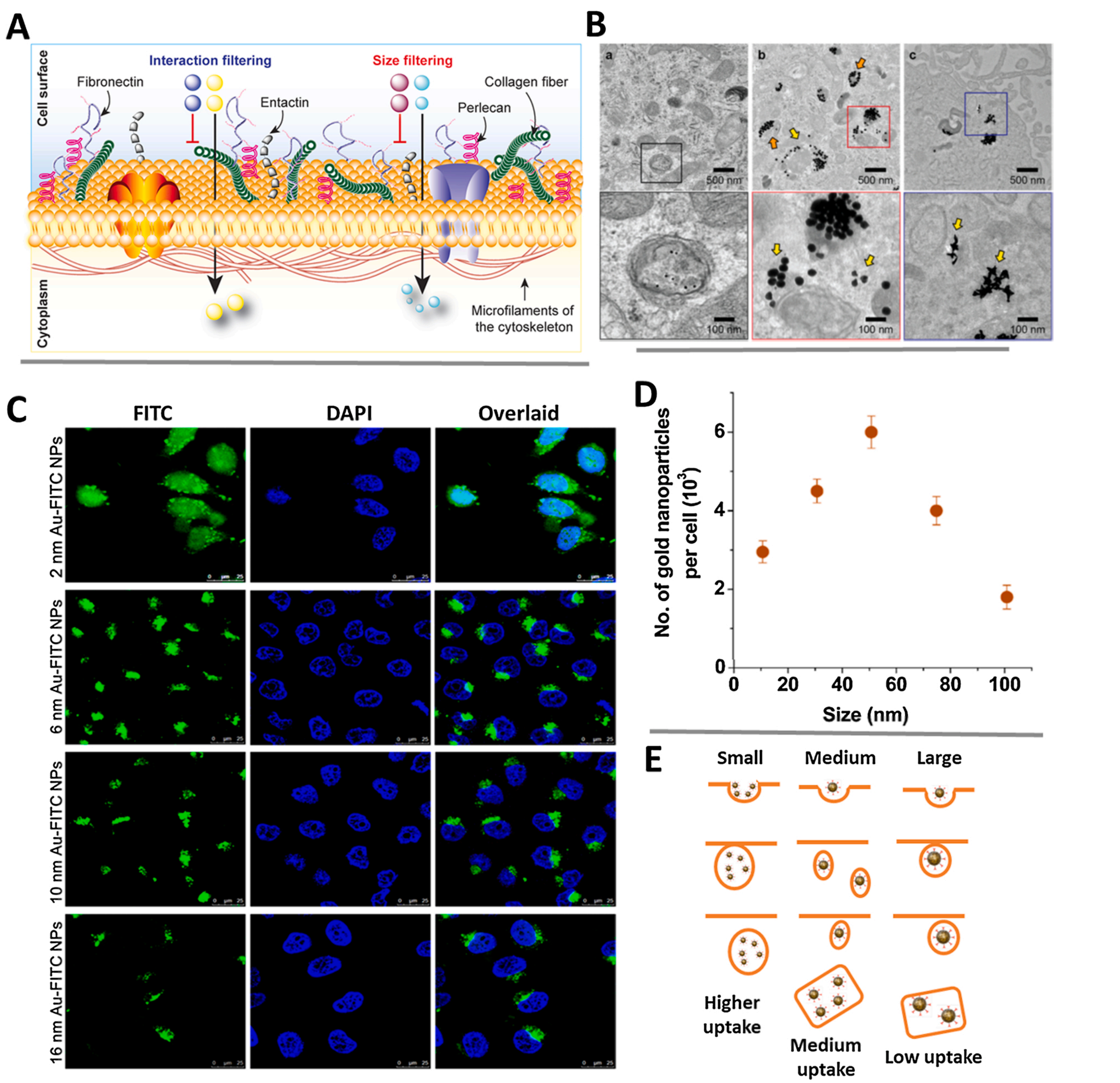

Fig. 3. Effect of nanoparticle size on cellular internalization. A) Schematic showing the size filtering of NPs by ECM. B) TEM micrographs of U87 cells treated with NP-siRNA constructs showing the presence of large particles in cytoplasm. U87 cells were incubated with (a) 13 nm sphere shaped, (b) 50 nm sphere shaped, and (c) 40 nm star shaped constructs for 24 h period. Orange color arrows show locally disrupted membranes of vesicles and yellow color arrows indicate NPs located outside the vesicles. C) Presence of Au-FITC NPs with various particle sizes in MCF-7 breast cancer cells. Au-FITC NPs (green) treated MCF-7S cells, and nuclei were stained by Hoechst 33342 (blue). D) Cells were imaged using confocal microscopy. Difference in cellular internalization of NPs as a function of size. E) Scheme indicating the size-dependent internalization of NPs. Figure A adapted from [94]; Figure B reproduced with permission from [104], Figure C is reproduced from article https://pubs.acs.org/doi/10.1021/nn5008572 [105] with permission from American Chemical society (Further permissions related to the material excerpted should be directed to the ACS), Figure D reproduced with permission from [106].

components: ECM permits the penetration of NPs smaller than its mesh size, whereas larger NPs are restricted (Fig. 3A) [94]. Collagen fibrils of the ECM possess an inter-fibrillar spacing of 20–40 nm, and hence generally allows the transport of slightly smaller NPs [95]. Although there are multiple hurdles in the ECM that hinder the diffusion of nanomaterials, there are several factors that can significantly enhance nanomaterial mobility through the ECM, such as the hydrodynamic diameter and surface charge [96].

After successfully passing the ECM barrier, NPs should be successful in traversing the cell membrane to enter into the cells [88]. The large surface area to volume ratio of small NPs enables their smooth entry into the cells [97]. For instance, smaller fragments of single-walled carbon nanotubes (SWNT) (30 nm) are vigorously internalized by cells more than larger ones (50 nm) [98]. This shows that the effective internalization of nanomaterials happens at an optimal size [87]. Nanomaterial size plays a significant role in determining the mechanism of uptake too. For example, smaller particles pass the cell membrane through clathrin-coated pits, whereas larger ones internalize through the caveolae-mediated process [99]. For instance, in the case of nanotubes, their length plays a crucial role in cellular uptake behavior [100]. Also, the size of nanomaterials has an impact on the cell membrane receptor activation and resulting protein expression [101]. A new study indicated that small mesoporous silica NPs (~100 nm, s-MSN) could adhere to Red Blood Cells (RBCs) without disorganizing the membrane.

In contrast, larger mesoporous silica NPs (~600 nm, l-MSN) produced speculation and subsequent hemolysis [102]. Size-dependent variation in cell membrane-NPs interactions can also be observed in metallic NPs. For instance, 70 nm-sized gold NPs were unable to pass the cell membrane, whereas 20 nm ones were not restricted by the cell membranes [103]. To understand the effect of particle size and shape on gold nanoparticle uptake, Yue et al. visualized the intracellular location of 13 nm and 50 nm nanospheres with transmission electron microscopy (TEM) after 24 h of particles treatment (Fig. 3B) [104]. For those cells incubated with 13 nm nanosphere, almost all the particles were covered by a clear, thin, intact membrane (Fig. 3Ba), suggesting successful vesicular transport of 13 nm nanospheres. However, many of the 50 nm nanospheres were found outside the vesicles (Fig. 3Bb, yellow arrows).

On the other hand, 40 nm star-shaped gold NPs were present in the vesicles as large aggregates or were observed outside of the vesicles (Fig. 3Bc, yellow arrows). Another study examined the application potential of ultrasmall 2 nm NPs as vehicles for nuclear delivery of a triplex-forming oligonucleotide (TFO) that interacts with the c-myc promoter [105]. They used fluorescent dye (FITC) conjugated Au-TIOP NPs for confocal laser scanning microscopy (CLSM). As can be seen in Fig. 3C, only 2 nm Au-FITC NP-treated MCF-7 cells showed green fluorescence (from conjugated FITC) in both nucleus and cytoplasm. Cells treated with relatively larger NPs resulted in a FITC signal in the cytoplasm only. Such results imply that the smaller Au-FITC NPs (2 nm) were capable of entering the cell nucleus, whereas larger Au-FITC NPs (6 - 16 nm) were not. However, among gold NPs sized 14, 50, and 74 nm, 50 nm gold NPs were most efficiently internalized by Hela cells [106] (Fig. 3D). According to the theoretical model proposed by Gao et al., optimal particle size for cellular uptake is decided by the outcome of competition between receptor diffusion kinetics and thermodynamic driving forces [107]. Increased elastic energy coupled with bending of the membrane results in the reduced driving force for membrane wrapping of NPs smaller than the optimal size. Hence, smaller NPs need to flock together to generate enough driving force for successful cellular internalization, as shown in Fig. 3E. This model proposed by Gao et al. also suggests that larger particles accommodate many receptors on the cell surface, which requires the diffusion of receptors over a longer distance during uptake, and this has led to lower internalization of larger particles. Studies using cancer cells also indicated that the presence of functional groups on the surface of NPs could not alter the size-dependent preferential uptake of smaller NPs [43,108]. The size distribution (polydispersity index) of nanostructures is another essential factor to be thoroughly investigated as the cellular responses may vary with the size of the particles. Moreover, agglomeration behavior of NPs can also have an impact on interactions and subsequent cellular response as agglomerated NPs show a much higher size than individual ones [109].

NPs can reach the cell nucleus mainly by two distinct mechanisms: passive diffusion through the nuclear pore complex formation and active transport through the nuclear membrane pore complex. NPs should be very small to pass through the nuclear pore complex passively as the channel width comes between $\sim 6 - 9$ nm [110]. The active transport of NPs is accomplished by the support of a cytoplasmic protein named importins [111]. Nanomaterials having diameters up to 50 nm can reach the nucleus by active transport mechanism [112]. The kinetics of NPs to the nucleus is highly dependent on the size, as evident from the several-fold higher transport of gold NPs (2 nm in size) than 14 nm ones [110].

Similarly, functionalized smaller gold NPs (~2.4 nm) were able to enter the nucleus, while slightly larger ones (5.5–8.2 nm) were circulated in the cytoplasm [113]. Tiny carbon-based nanomaterials can also interact with the cell's nucleus by various mechanisms. In particular, graphene quantum dots (GO-QDs) were able to enter the nucleus due to their small size through DOX/GQD conjugates and deliver drug cargos [114,115].

Although there are several reports regarding the influence of nanoparticle size on NPs-cell interactions, many of such studies did not consider the hydrodynamic diameters (HD). HD is an indication of the apparent size of particles that can be calculated from the diffusional properties of the dynamic hydrated/solvated particle. The hydrodynamic size is an indication of how the particle behaves in a fluid and it indicates the most realistic size of the NPs in cell culture systems or *in vivo* conditions. In addition to microscopic imaging techniques like TEM and atomic force microscopy (AFM), dynamic light scattering (DLS) based particle size measurement can provide information on HD. Studies also indicated that the form of the protein corona formed around NPs could significantly change the size and influence the cellular uptake [116,117]. For instance, a few minutes incubation of magnetite (Fe_3O_4) cores of 25–30 nm in cell culture medium resulted in protein adsorption and a 5-fold increase of the HD [116]. Owing to the importance of self-assembled NPs in various biomedical applications, the size-related effects of such nanostructures on cells need special attention [118–121]. It is interesting to note that self-assembled nanostructures can show pH-dependent HD variation. For instance, self-assembled ultrasmall luminescent gold NPs chitosan assemblies can show ~23.5 nm size at low pH values (pH < 6.5).

In contrast, they transform to swollen larger particles at high pH values (pH 7.4)[122]. Such pH-dependent variation in size can have a significant impact on nanomaterials-cell interaction. Thus, it is vital to thoroughly characterize the NPs in physiological conditions to understand the HD, facilitate cellular uptake, and achieve the desired interaction with intracellular components.

2.3. Shape of nanomaterials

Nanomaterial uptake, distribution, interactions with cellular components, and resulting cellular functions are also influenced by the shape of NPs [40,123]. For instance, elongated nanomaterials generally show higher uptake than spherical ones due to their higher ability to successfully adhere to the cell membranes [124]. Spherical NPs provide less binding sites to interact and comply with the cell membrane because of their curved surface and show relatively less internalization [125,126]. For example, various studies have reported that rod, discoid, cylinder, triangle sharp-shaped, and quasi-ellipsoidal nanostructures were more effectively internalized by cells compared to spherical particles [127,128]. However, disc-shaped NPs showed more effective internalization than rod-shaped ones [129]. Higher cellular uptake was noticed with cylindrical ones than spherical nanostructures [130].

Moreover, nanomaterials with sharp edges can penetrate the cell membranes and successfully internalize. However, a different result was observed when spherical polymer NPs and their deformed quasi-ellipsoidal counterparts with varying ratios of aspect were investigated [131]. Gold NPs with triangular morphology displayed higher uptake than spherical particles in HeLa cells [132]. Among the different morphologies of methyl, polyethylene glycol-functionalized gold NPs, star, rod, and triangular shapes showed the lowest to highest cellular uptake, respectively [133]. However, confocal micrographs of siRNA nano-constructs (NP-siRNA/ Cy5) in U87 cells indicated the relatively insignificant difference in cellular uptake between spherical (13 and 50 nm sizes) and star-shaped NPs (Fig. 4A) [104]. At 24 h incubation, the position of these NPs within U87 cells differed among the three tested ones. In the case of 13 nm sphere shaped ones, most of the NP-siRNA constructs remained entrapped in endosomes with only minor

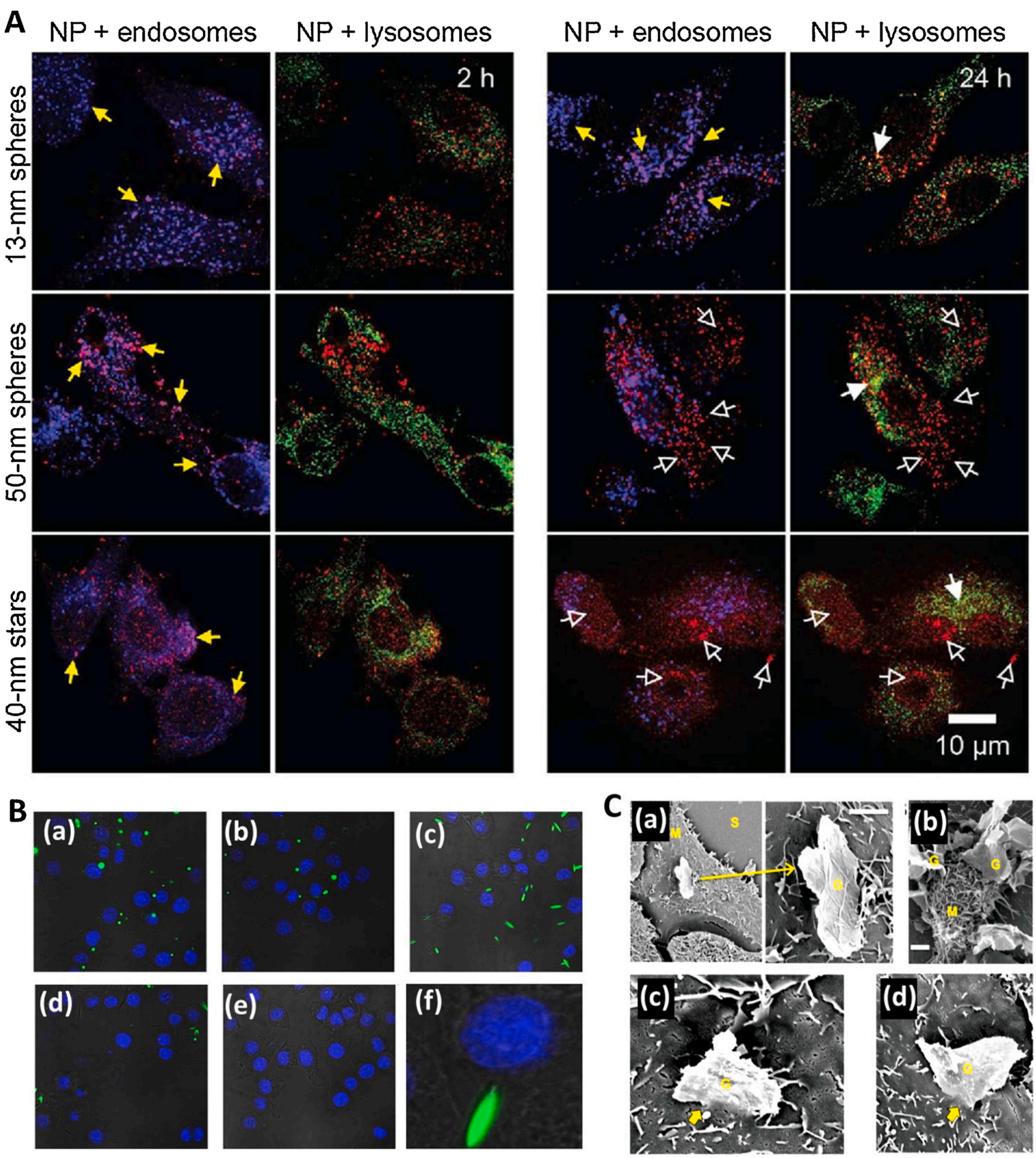

Fig. 4. A) Size- and shape-dependent uptake and subsequent localizations of NP-siRNA constructs in subcellular organelle. Cy5-labeled NP-siRNA constructs (red color) were incubated with U87 cells for 2 h or 24 h, followed by immunostaining of lysosomes and endosomes. Co-localization of constructs with lysosomes are denoted by solid white arrows; co-localizations of constructs with endosomes are denoted by solid yellow arrows; constructs that are neither localized in endosomes nor lysosomes are denoted by hollow white arrows (scale bar is 10 μm). B) Macrophages incubated with green fluorescence PLGA particles: (a) sphere shaped. (b) PEGylated sphere shaped, (c) stretched (elongated), (d) PEGylated stretched (elongated), (e) no particles (control), and (f) internalized stretched particles. C) Cell membrane penetration of graphene sheets. C(a) Corner penetration on the surface of a human lung epithelial cell. C(b) Edge penetration of multiple macrosheets (G) into a macrophage (M). C(c) Edge penetration of graphene sheet in primary human keratinocytes (thick yellow arrow indicates edge entry which was nucleated at a protrusion). C(d) Corner penetration of a graphene sheet in a keratinocyte cell. Figure A reproduced with permission from [104], Figure B reproduced with permission from [134] and Figure C is reproduced with permission from [145].

overlapping lysosomal signals as indicated by solid white arrows. However, most of the spherical nano-constructs with 50 nm diameter showed only slight colocalization along with either endosomes or lysosomes (indicated by hollow white arrows in the figure). Stars shaped NPs (40 nm diameter) showed a comparable trend in intracellular distribution with 50 nm ones. Mathaes et al. performed a detailed investigation to understand the variation of cellular uptake of elongated, non-spherical, and spherical poly(D, L-lactide-co-glycolide) (PLGA) based micro- and NPs [134]. Fluorescent microscopic images indicate that macrophages took up 1.23 ± 0.520 spherical PLGA particles per cell (Fig. 4B). However, stretched particles had a considerably reduced incidence of cellular uptake (0.424 ± 0.210 particles/cell), which was further reduced by PEGylation.

Carbon-based nanomaterials such as fullerenes [135,136] and CNTs [137,138] can penetrate the cell membrane and enter the cells by spontaneous insertion/penetration across the membrane or by endocytosis [139–141]. Studies also indicated that CNTs might pass the cell membrane by exploiting a lipid-mediated process [142], which may include multiples steps such as landing, piercing of the membrane, and subsequent internalization [143,144]. It is also demonstrated that tiny

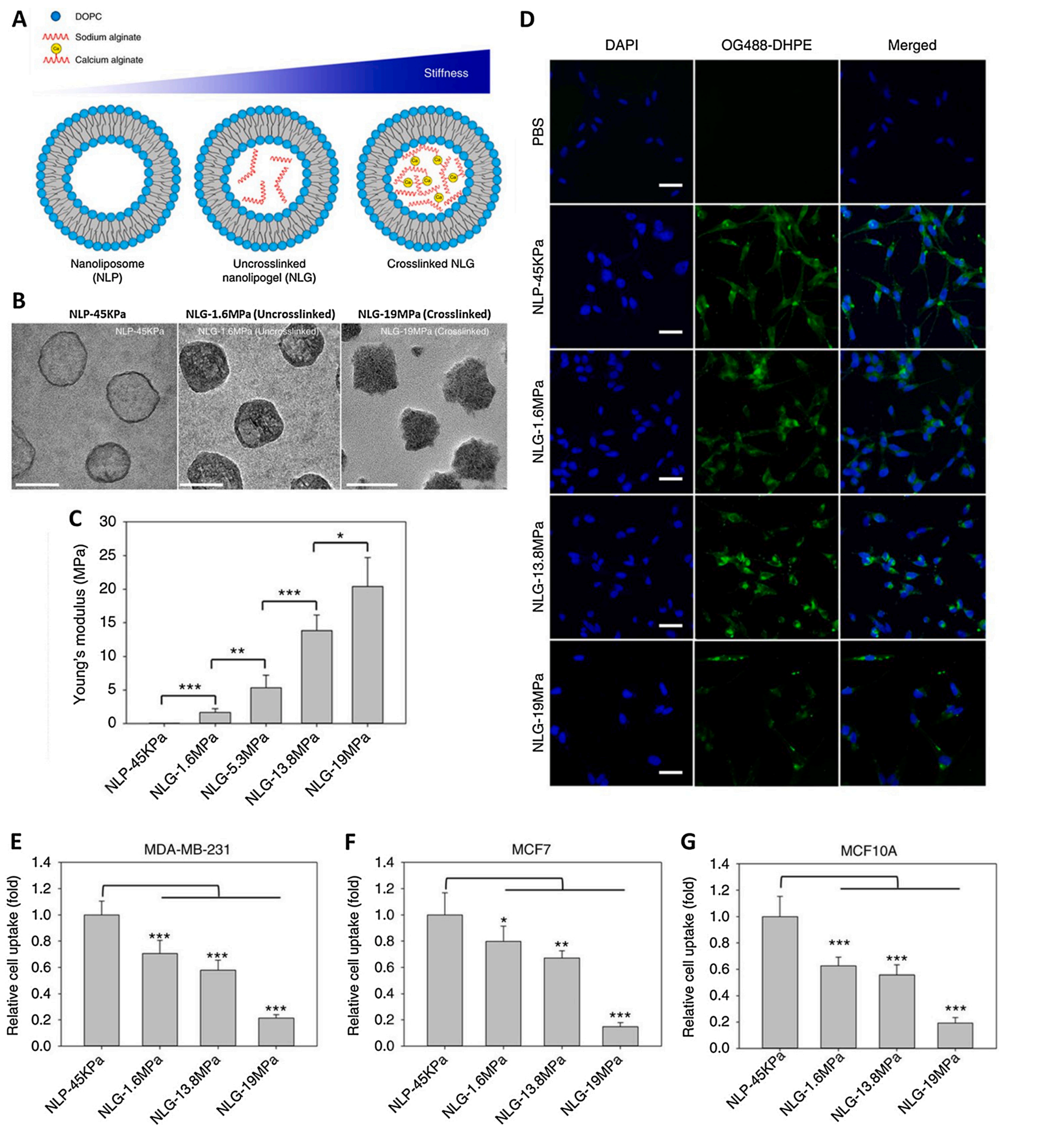

Fig. 5. Influence of nanoparticle stiffness on *in vitro* cellular uptake. A) Scheme showing nanoliposome–hydrogel complex. B) TEM images of NLP with different stiffness properties. Scale bars represent 100 nm. C) The Young's moduli of NLP and NLGs were determined by AFM analysis. D) Fluorescent microscope images showing the cellular internalization of NLP and NLGs with varying elasticity in breast cancer cells (MDA-MB-231). The scale bars are 50 μm. Relative cellular internalization of NLP and NLGs by different cell lines such as MDA-MB-231 (E), MCF7 (F), and MCF10A (G) cells. *** indicates $P < 0.001$. Reproduced with permission from [154].

graphene nanosheets can translocate through lipid bilayers [145]. Uptake of graphene-like materials is typically started at the corners or uneven sides of these nanostructures [145]. Puncturing of the cell membrane initiates at the sharp edges of nanomaterials and propagate along the rest of it (Fig. 4C). Such local piercing minimizes the high energy barrier and helps relatively easy penetration and cellular uptake. However, in contrast to the internalization, the exocytosis of high aspect ratio nanomaterials was found to be lower than that of spherical counterparts [146]. Studies also showed that Fullerenol $C_{60}(OH)_{36}$ can stay in peripheral blood mononuclear cells (PBMCs) without a significant effect on cell survival or the structure of the plasma membrane [147].

2.4. Topography and stiffness of nanomaterials

Nanomaterials-cell interaction and the subsequent cellular responses are influenced by surface topography and stiffness [109,148]. Studies indicated that nanoscale surface features could alter cellular response [149], influence cell adhesion [150] and cell differentiation [151]. Also, matrix stiffness of the nanostructures can alter the nanomaterials-cell interaction and subsequent cellular response [152]. Huang et al. used polyacrylamide (PA) NPs with tunable stiffness as a model substrate to validate the relationship between stiffness and their internalization by mammalian cells [153]. They have demonstrated that a stiffer nanoparticle could undergo higher internalization per cell basis. Guo et al. demonstrated that the *in vitro* cellular internalization and *in vivo* tumor penetration of nanolipogels (NLGs) depends on the elasticity [154]. NGLs with controllable flexibility were spherical and composed of a dense alginate core and a hollow lipid bilayer (Fig. 5A, B). The Young's moduli of the NLGs are given in Fig. 5C. The cellular internalization NLGs were studied in human breast cancer cells (MDA-MB-231 and MCF7) and healthy human mammary epithelial cells (MCF10A). Nanoliposome (NLPs) was used as a control. Representative images show the differential cellular internalization of NLPs and NLGs by MDA-MB-231 cells in Fig. 5D. Cancerous and normal cells showed significantly higher internalization of soft NLGs (Young's modulus <1.6 MPa) compared to elastic ones (Young's modulus >13.8 MPa). NLP-45KPa and NLGs, labeled with Oregon Green 488-1,2-Dihexadecanoyl-sn-Glycero-3-Phosphoethanolamine (OG488-DHPE, a fluorescent lipophilic dye), exhibited diminishing cellular internalization with increasing of the stiffness (Fig. 5E-G). The maximum cellular internalization occurred with NLP-45KPa (modulus, 45 ± 9 kPa) group, which was 80% higher than NLG-19 MPa groups. These findings indicated that the elasticity of nanomaterials could play an essential role in cellular uptake, and it remains a critical design parameter to improve the tumor delivery nanoformulations.

Furthermore, nanofibrous matrices with topographies of the native *in vivo* ECM have been widely used as tissue engineering scaffolds [155, 156]. Nanofibrous scaffolds have been realized using the electrospinning technique [157,158] The individual fiber diameter of such fibrous membranes usually comes below submicron range, which is similar to the nanotopography of native ECM [159]. Various approaches, such as controlling the solvent ratio [160], polymer concentration [161], incorporation of nanofillers [19] and inducing breath figure formation [162] are tried to manipulate fiber diameter and surface topography of nanofibers.

2.5. Surface charge

Nanomaterials-cell interaction, cellular uptake, and the resulting outcome are influenced by the surface charge of nanomaterials [4,163]. The net surface charge of the NPs is usually stated as zeta potential values [164]. ECM remains a net negative charge owing to the presence of glycosaminoglycans (GAGs) chains, which are abundant in negatively charged functional groups. Apart from the size filtering, there is a charge dependent mechanism for NPs trafficking across ECM, namely, interaction filtering [165]. Protein corona formation over the NPs in physiological conditions could change the original surface charge of NPs and the resulting interaction [166]. Mostly, NPs with net positive charge are internalized by cells vigorously than those with net negative charge [167]. This preferential internalization can be due to favorable positive-negative electrostatic interactions, as cell membranes are negatively charged [168]. However, phagocytic cells are reported for the selective uptake of anionic NPs [169]. In an exciting study, high-affinity binding of citrate-coated superparamagnetic iron oxide NPs with cell membranes were hampered when glycosaminoglycan synthesis was blocked [170]. This indicates that the interaction between glycosaminoglycans and the negatively charged NPs played an essential role in the cell membrane binding of NPs. A series of $NaYF_4$: Yb^{3+}, Er^{3+} upconversion NPs (UCNPs) with various morphological features and surface coatings were prepared to understand the effect of surface charge on the extent of cellular uptake. The results of this study highlighted that the cellular uptake was also higher when NPs with higher surface charge were used. The effect of surface charge on the cellular internalization was prominent in small-sized NPs, where several mechanisms were found to have taken part in the cellular internalization such as clathrin- caveolae-mediated endocytosis and physical adhesion-subsequent penetration.

However, in the case of relatively bigger particles, an energy-dependent endocytosis mechanism played a more prominent role. Landgraf et al. investigated the extent of internalization of neutral, positively charged, or negatively charged quantum dots and the Au@MnO particles by confocal laser scanning microscopy [171]. Positively charged quantum dots showed the highest internalization (Fig. 6A). Neutral Au-NH_2@MnO NPs were internalized in a greater magnitude than non-functionalized or NPs that were functionalized at the MnO domain. Hühn et al. studied the influence of charge on the interactions of NPs with components of biological media and subsequent cellular internalization [167]. For this, gold NPs with identical physical properties were modified with amphiphilic polymers to generate NPs with opposite surface charges (negative/positive) [167]. NPs with positive charge were internalized by mammalian cells to a more significant level than those with a negative charge (Fig. 6B). The average fluorescence intensity (I) per cell for NPs versus incubation time for medium #5 (DMEM media), #7 (DMEM media with bovine serum albumin, BSA) and #8 (DMEM media with fetal bovine serum, FBS) (Fig. 6C) showed a higher uptake rate for positively charged ones than for negatively charged ones. This difference was mainly due to the differential interaction of cellular proteins with positively or negatively charged molecules on the NPs. The presence of BSA or FBS in the media inhibited the cellular uptake of both NPs. However, the effect of FBS on the uptake was only marginal in the case of negatively charged NPs. Unlike purified BSA, FBS contains a variety of proteins, and the protein corona formed by them might have contributed towards this difference in cellular uptake [172].

Upon contact with cells, nanomaterials can (i) cause the deformation of lipid membranes resulting in their internalization [173], (ii) disorganize the phospholipids bilayer [174], (iii) generate "holes" in the cell membranes. Nanomaterials with a net positive charge are much more likely to create such membrane distortions than those with net negative and neutral charges. Such holes could result in the leakage of intracellular components and result in cell death. Cationic nanomaterials can provide relatively robust interaction with cell membranes with net negative charge and result in their quick internalization with potential membrane distortions [175]. In contrast, owing to the similar net charge with cell membranes, anionic nanostructures are less harmful. Owing to the net negative charge, cationic NPs are thought to be electrostatically attracted to plasma membranes and subsequently internalized by the cells. Regardless of such theoretical assumptions, experimental research indicated that nanostructures with net negative charges are also able to enter the cells by traversing the negatively charged cell membrane [176]. In contrast to charged nanomaterials, neutral ones show only low affinity with cells and thus result in less internalization [87]. There are

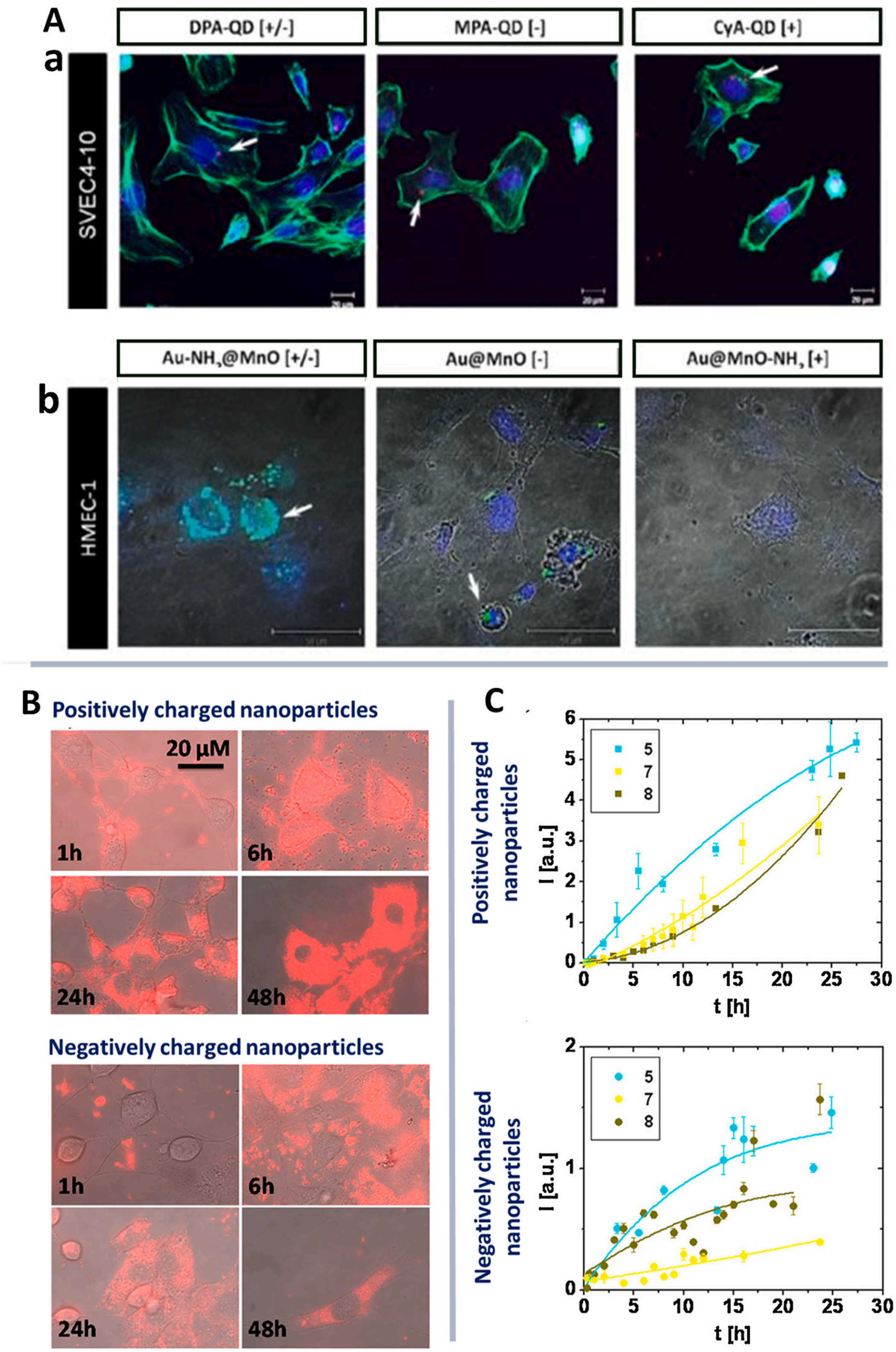

Fig. 6. Effect of surface charge of NPs on cellular internalization. A) Microscopic analysis of NPs internalization after 24 h of incubation showing the charge-dependent internalization of different NPs by endothelial cells : SVEC4-10 cells after incubation with quantum dots (QDs) (A(a)). The QDs are denoted as red, the nucleus in blue and the cell membrane in green (Scale bar is 20 µm). HMEC cells after incubation with Au@MnO NPs denoted as green (A(b)). The nucleus can be seen in blue color. Internalized NPs are denoted by white arrows (Scale bars are 50 µm). B) 3T3 fibroblasts were cultured with charged AuNPs in different culture media. The microscopic images depict the cells at different time points after culturing in medium #8. C) The average fluorescence intensity (I) per cell for NPs versus culture time for media #5 (DMEM media), #7 (DMEM media with bovine serum albumin) and #8 (DMEM media with fetal bovine serum). Figures A is reproduced with Creative Commons Attribution 2.0 (CC-BY-0.2) License from [171]. Figures B and C are reprinted with permission from [167], Copyright (2013) American Chemical Society.

several other factors such as hydrophobicity may also play a significant role in the uptake of charged NPs, and this could be one of the reasons for contrasting results regarding the effect of charge on cellular uptake [169].

Nanomaterials also interact with cytoskeletal proteins depending on their surface charge and result in the modification of the properties of NPs or cytoskeletal proteins. For instance, an increase in zeta potential, and variation in plasmonic properties of silver NPs were observed upon the interaction of citrate-coated silver NPs with cytoskeletal proteins [177,178]. Along with these changes in the properties of NPs, such communications can affect cytoskeletal integrity, as evident from an increase of F-actin expression and the difference in cell polarity [179]. Metallic NPs (e.g. Silver NPs) can sometimes result in the loss of cytoskeleton components such as F-actins and β-tubulins [180]. Studies also show that cationic dendrimers can interact with actin filaments [181] and affect actin polymerization (at 1 μg mL^{-1}). However, at higher concentrations (≥10 μg mL^{-1}), actin polymerization was accelerated. Past research also showed the existence of multiple mechanisms behind the internalization of cationic liposomes, such as those mediated by actin networks or tubulin mediated cytoplasmic transport [182].

Nanomaterials with a net charge can also interact with intracellular organelle like mitochondria. For example, cationic and lipophilic mesoporous silica NPs have shown noticeable interaction with the mitochondrial membrane [183]. Some of the charged nanostructures can enter in cell nuclei and produce genotoxicity. For instance, gold NPs with roughly 1 nm size can enter the nucleus and bind with DNA molecules having a net negative charge [184,185]. Despite the possible harmful effects on DNA, such nucleus targeted NPs are exploited in cancer therapy [186].

2.6. Functional groups of nanomaterials

The presence of various functional groups on the surface of nanomaterials can modify their interactions with cells. Such functional group dependent interactions have relied upon the specific interaction of cell-surface ligands with the surface functional groups present over the nanomaterials. A suitable surface functionalization could allow the nanomaterials to firmly interact with the cell membrane, safe membrane penetration, and cellular uptake. For instance, membrane penetration and subsequent target binding were much higher for oligonucleotide functionalized gold NPs compared to unmodified ones [187]. Similarly, PLGA NPs functionalized with poly-L-lysine have shown superior cell membrane affinity and uptake than blank ones [188].

Functionalization of nanomaterials can reduce the cytotoxicity of them too. Graphene functionalized with carboxyl groups showed less cytotoxicity due to a relatively weak hydrophobic interaction with cell membranes [189]. Cells treated with hydrophilic group functionalized NPs left wrinkles on the cell surface as a hallmark of cellular uptake. Functionalization with ligands such as proteins, peptides, antibodies, small molecules, and nucleic acids can be employed as a robust approach to target nanomaterials to specific cells or intracellular components [190]. Targeting potential of nanomaterial is dependent on the chain length of functionalizing agents too. For instance, such a reduction in the binding affinity with the targeted receptor was highly evident in the case of gold NPs, which were anchored with a high molecular weight polyethylene glycol (PEG) linker between target-specific antibody [191]. Functionalization can inhibit protein corona formation when it comes into contact with serum proteins [191,192]. Owing to the ability to resist protein adoption, nanomaterials can be decorated with PEG to minimize nonspecific membrane interactions.

Moreover, coating with PEG can avoid the agglomeration of NPs [193]. Functionalizing with specific biomolecules such as antibodies to target and facilitate internalization is a critical approach in the field of nanomedicine. For example, Triptorelin (a Luteinizing Hormone-Releasing Hormone (LHRH) agonist) functionalized magnetite NPs showed several-fold higher adhesion to breast cancer cells than to healthy breast cells [194] indicating the massive potential as targeted image contrast agents [195]. A new study showed that biotin incorporation into pullulan acetate self-assembled NPs could enhance the uptake by HepG2 cells [196].

The surface functionalization of NPs with specific agents that have to be delivered in the nucleus is a promising approach [105]. For instance, gold NPs conjugated with a triplex-forming oligonucleotide (TFO) could more effectively decrease the level of c-myc protein expression than free TFO [105]. This indicates the more effective penetration of TFO conjugated NPs in the nucleus than free drug. Moreover, active transportation of nucleolin-specific aptamers labeled gold nanostructures to the nucleus produced substantial variations in the nuclear morphology [197]. This was apparent from the invaginations of nuclear envelope near the internalized nanostructures. Such NPs associated variations in nuclear morphology and greater therapeutic effectiveness are highly encouraging for nuclear-targeted cancer therapy [105,198]. Recent studies also explored the applicability of functionalized NPs to minimize the nuclear damage due to nuclease activity. In a specific study, gold NPs conjugated with a cationic polyelectrolyte, namely poly-diallyldimethylammonium chloride (PDADMAC), presented resistance against DNA degradation [199]. This was achieved by the nanoparticle-DNA interaction and subsequent formation of a nanoparticle- DNA conjugate. Self-assembled carboxymethylated (CM)-curdlan hydrogel NPs showed higher interaction with HepG2 cells when conjugated with lactobionic acid [200]. Such hydrogel NPs are useful for drug delivery applications due to the ligand–receptor-mediated interactions with cancer cells and subsequent controlled release of the loaded drug.

Some studies investigated the cellular internalization of NPs, which are simultaneously functionalized with multiple groups having different surface charges [201]. For instance, Shahabi et al. investigated the cellular internalization of fluorescent silica NPs (FFSNPs) with various ratios of sulfonate and amino groups [201]. These NPs possessed a wide range of zeta potential value. Interestingly, serum proteins adsorbed over these charged NPs neutralized the original surface charges (irrespective of the negativity or positivity) and hindered the agglomeration of them [202]. When serum was not provided in medium, NPs with more positive zeta potential values were accumulated in cells than those with negative zeta potential values. However, in serum-containing medium, negatively charged FFSNPs showed higher uptake by the cells, indicating the importance of sulfonate-functionalized silica NPs in clinical applications where the presence of serum is inevitable. Further, the microscopic analysis was performed to localize FFSNPs in cellular components such as lysosomal structures and actin cytoskeletons. In another study, Mao et al. generated silk fibroin (SF)-based NPs conjugated with polypeptides cyclic pentapeptide cRGDfk and Chlorin e6 (Ce6) [203]. Also, genipin was used to conjugate 5-fluorouracil (5-FU) doped SF-based NPs (NPs). A high level of ROS was observed in the MGC-803 cells upon treatment with the SF-based NPs and photodynamic therapy (PDT). ROS production resulted in higher cell death. The results of *in vivo* experiments indicated that the SF-based NPs had promising tumor targeting potential and the ability to inhibit tumor progression (Fig. 7A). Higher fluorescent intensity by flow cytometry (Fig. 7B) and intracellular fluorescence quantitative analysis (Fig. 7C) indicated the higher cellular uptake of SF-NPs. Overall, such studies suggest that the surface-functionalized NPs have massive potential as drug delivery systems in tumor therapy and could be the potential clinical options shortly.

Functionalized or non-functionalized carbon-based nanomaterials are widely explored in various biomedical applications [204]. Cells exposed to pristine graphene indicated the disorganization of F-actin alignment in mammalian cells [189]. In contrast, functionalized graphene did not produce such an effect on the cytoskeletal proteins. Past research also indicates that N and Cl ligands edge-functionalized graphene QDs improve the nuclear uptake and histone binding in the nuclei [205,206]. Aminated graphene QDs provided higher cleavage and

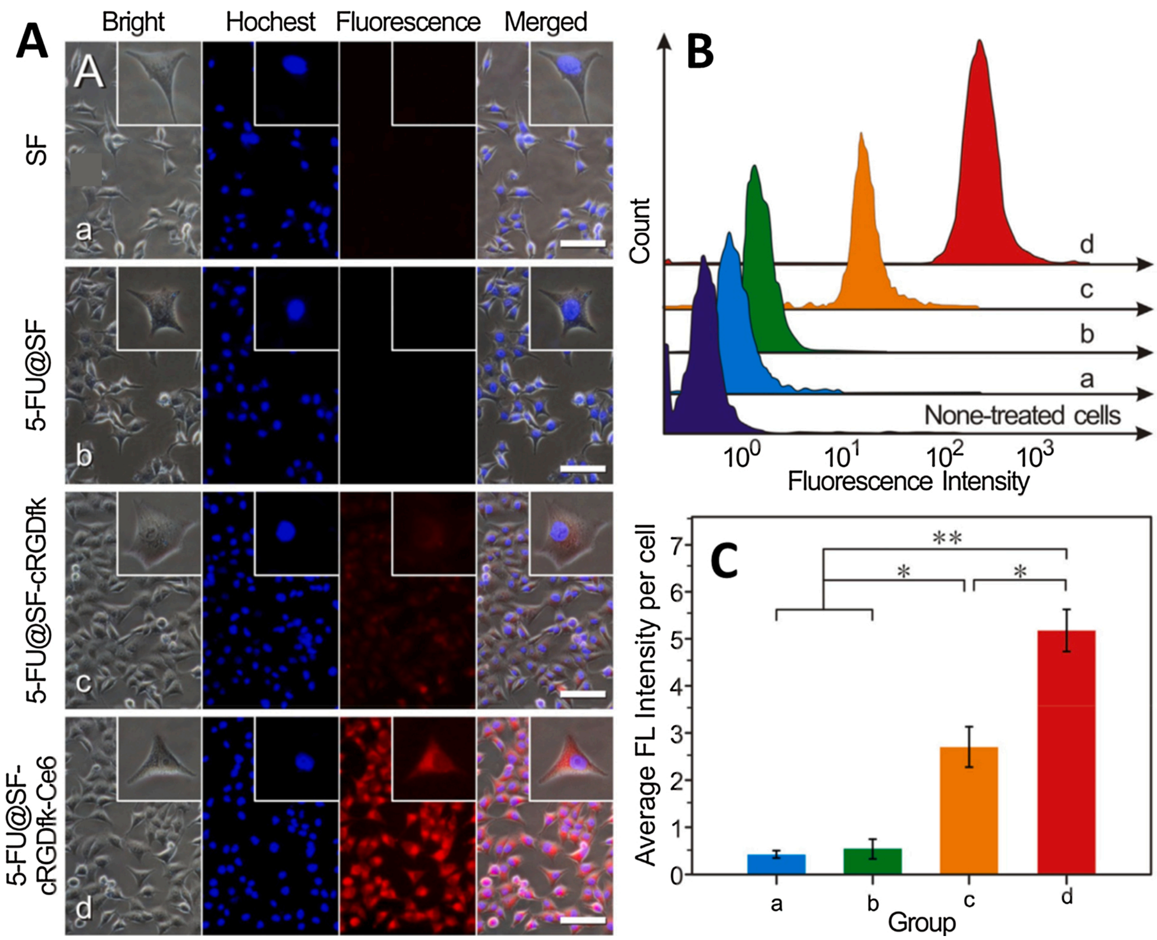

Fig. 7. Effect of surface functional groups on nanoparticle internalization. A) Confocal microscopic images of MGC-803 cells exposed to SF (a), 5-FU@SF (b), 5-FU@SF-cRGDfk (c) and 5-FU@SF-cRGDfk-Ce6 (d) NPs for 4 h. Scale bars are 200 μm. B) The flow cytometric comparison of fluorescence intensity of cellular internalization of various SF-based NPs. C) Quantitative analysis of intracellular fluorescence of MGC-803 cells exposed with various SF-based NPs. (*: $p < 0.05$, **: $p < 0.01$). Figures are reprinted from [203] with permission from Elsevier.

cross-linking of DNA chains in macrophages mediated by H-bonding and π-π stacking [207].

2.7. Hydrophobicity/hydrophilicity of nanomaterials

Interaction between nanomaterials and cells are highly influenced by the hydrophobicity/hydrophilicity of the developed nanomaterials [4,39,40,208]. Interestingly, nanomaterials with hydrophilic surface groups showed an extended circulation period due to the resistance to phagocytosis [209]. Macrophage polarization is also influenced by the hydrophilic/hydrophobic nature of nanomaterial surfaces, as evident from the presence of the anti-inflammatory M2-like state on hydrophilic surfaces [210]. Past research also indicated that cell adhesion and proliferation were higher on surfaces with medium hydrophilicity [211]. Among NPs functionalized with –COOH, -OH or $-NH_2$ functional groups, $-NH_2$ and -OH group functionalized NPs provided significantly higher cytotoxic response than -COOH functionalized ones [212].

Fig. 8 clearly illustrates the alteration in cellular behavior between NPs with varying hydrophilicity. Possible interaction of NPs with hydrophilic or hydrophobic surface functional groups with endothelial cell model membrane is shown in Fig. 8A [213]. Influence of inhibitors on the cellular internalization of carboxyl modified polystyrene (CPS) and plain polystyrene (PS) NPs by mesenchymal stem cells (MSCs) are also investigated [214]. From the results of this study, it is highly evident that dynasore inhibits the internalization of CPS NPs. However, dynasore does not influence the internalization of PS NPs. Results also demonstrated that with the addition of dynasore, internalization of CPS NPs was decreased by 30% compared to the control cells without inhibitor; however, internalization of PS NPs remained the same. These results indicate that the carboxyl groups present on the CPS NPs resulted in the dynamin-dependent endocytosis. Studies also indicated that hydrophobic octane thiol surface modification of zwitterionic luminescent glutathione-coated gold NPs (GS-AuNPs) improved their interaction with the cellular membrane and resulted in higher cellular uptake (Fig. 8B) [215]. Fluorescence microscopic study further demonstrated that hydrophobicity influences endocytic kinetics, as evident from the average number of endosomes in cells that were incubated with NPs at various time points (Fig. 8C-E). As time progressed, several NPs were internalized by cells through the endocytosis mechanism (Fig. 8C). Moreover, the internalization of amphiphilic octanethiol/glutathione coated AuNPs (OG-AuNPs) was considerably fast in the first 2 h of treatment and then reached the maximum amount at 3 h (Fig. 8D) where 42 ± 8 endosomes were observed. In contrast, the internalization process of GS-AuNPs was much slower: after 6 h, there were only 11 ± 3 endosomes observed (Fig. 8E). Hydrophilic sulphonate ligand bearing NPs (MUS), internalized by dendritic cells, provided punctate fluorescence signatures indicating the effective endosomal uptake [216].

Hydrophobic drug carriers are very important in the delivery of water-insoluble therapeutic agents [45,217]. For example, when succinobucol (SCB), a water-insoluble vascular cell adhesion molecule-1 (VCAM-1) inhibitor, was loaded in the self-assembled triblock polymer (poloxamer P188) NPs employing intermolecular hydrophobic interactions, facilitated the effective delivery into target cells [218]. In the case of orally administered NPs, successful epithelial absorption and

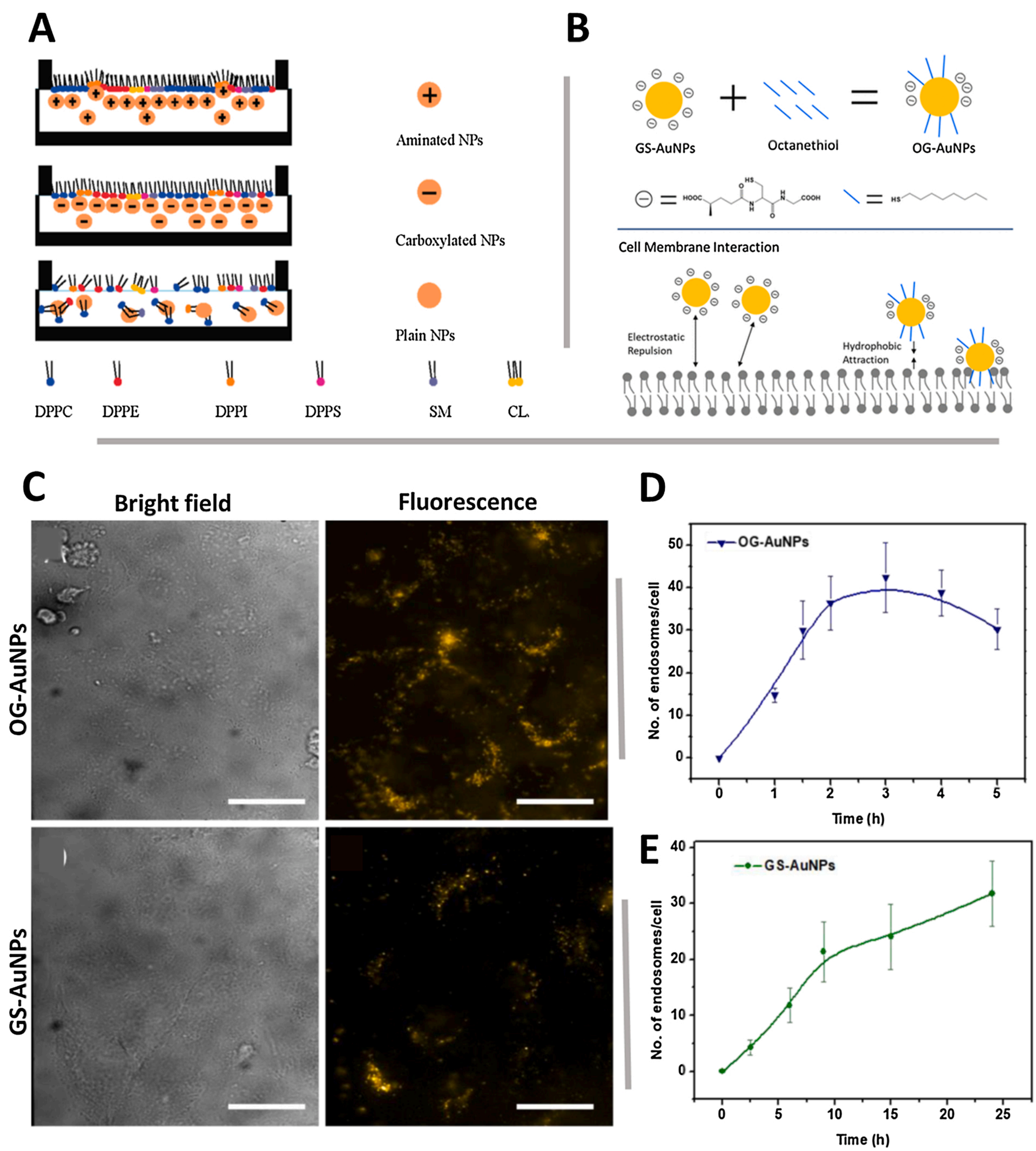

Fig. 8. Surface hydrophobicity or hydrophilicity dependent cellular internalization of NPs. A) Scheme showing the interaction of NPs with hydrophilic/hydrophobic surface groups with endothelial cell model membrane. B) Schematic representation of cellular endocytosis process of AuNPs. C) Bright-field and fluorescent microscopic images of live HeLa cells cultured with OG-AuNPs and GS-AuNPs in MEM at 37 °C for 24 h, Scale bar: 20 μm. Cellular internalization kinetics of OG-AuNPs in 5 h (D) and GS-AuNPs in 24 h (E). Figure A is reprinted with permission from [213], Copyright (2008) American Chemical Society. Figures B, C, D and E are reproduced with permission from 211, Copyright (2018) American Chemical Society.

mucus permeation are also very challenging unless the surface of them are functionalized with specific molecules. For instance, when self-assembled cell-penetrating peptide NPs were coated with a hydrophilic N-(2-hydroxypropyl) methacrylamide copolymer (pHPMA) derivatives, mucus permeation and epithelial absorption were increased [219]. Furthermore, hydrophobically modified glycol chitosan (HGC) self-assembled NPs are reported for the successful delivery of hydrophobized DNA [220]. The HGC NPs provided higher transfection efficiencies compared to naked DNA and a commercially available transfection agent, indicating its application potential in gene delivery.

Thus, hydrophobicity/hydrophilicity of nanomaterials can play a significant role in determining the nanomaterial-cell interactions and influence the outcome of such communications.

3. Future directions

The outcome of nanomaterial-cell interaction, either beneficial or harmful to the cells or the organism as a whole, is greatly dependent on many factors such as chemistry, size, shape, charge, and functionalization of NPs. Several cellular factors also influence the nanoparticle internalization and subsequent interaction with cellular components. For example, nanomaterial internalization is generally difficult when the cells are highly packed [221]. This is a great challenge when NPs are aimed at cancer therapy [222]. Future studies should focus on the interaction of NPs with cells in a tightly packed state both *in vitro* and *in vivo*.

The central nervous system (CNS) targeted nanomedicines are also susceptible to this challenge. The blood brain barrier (BBB), a tight junction between the brain tissue and blood circulation, prevents the entry of foreign materials to the brain [4]. Although there are several reports regarding brain targeted NPs, much focus should be given on the shape, size, particle chemistry, and surface functionality dependent effects of various NPs on tight junction proteins and other BBB components. Transmembrane proteins like claudins and occludin together with the actin cytoskeleton, constitute the principle biomolecular structural elements of BBB [4,223]. Effective crosstalk of ECM components of BBB with nanomaterials performs a major role in the result of the corresponding CNS targeted nanomaterial therapy. Thus, more detailed studies in such interactions may be required to use NPs in brain targeted therapy. Several types of NPs can alter the ECM organization also. For example, NPs can trigger the activation of inflammatory signaling cascades and disorganize the ECM [224]. Specifically, nanomaterial-mediated upregulation of the expression of matrix metalloproteinases (MMPs) can result in damage to ECM components [224]. Thus, a detailed investigation of the effect of various NPs on the expression of various ECM components will be an important area to explore. Some studies indicated that carbon NPs could generate ROS, which can damage ECM components. in mammalian cells [225,226]. Such investigations need to be performed for other commonly used NPs too. Organic-based nanomaterials such as dendrimers and liposomes are highly favorable due to their rapid cellular uptake. However, the attributes of such nanomaterials on the cytoskeleton are not fully analyzed yet.

As a beneficial side of the interaction between nanomaterials and cells, cerium oxide NPs could successfully scavenge the ROS produced by the defective mitochondria and alleviate the damages leading to cell death [227]. Effects of interaction between cellular components and ROS modulation by enzyme mimetic NPs such as cerium oxide [228, 229] and yttrium oxide [230] will be an exciting direction for future research. Detailed investigations on physico-chemical property dependent effects of metallic and metal oxide NPs with the cellular components of both normal and cancer cells can provide insights on the cytotoxicity and clinical application potential for cancer therapy [231]. MDA-MB-231 cells that were incubated with graphene for 24 h, followed by subsequent mitochondria-specific staining and confocal microscopic examination revealed that graphene could interact with the mitochondria [170]. TEM analysis showed that graphene oxide (GO) could also accumulate in mitochondria of mammalian cells [181]. As a widely used material in various industrial applications, a more detailed investigation on the uptake of graphene by skin epithelial, airway cells, and lung epithelial cells and subsequent interaction with intracellular components would be necessary.

Although there are a few studies related to the effect of NPs on the expression of genes relevant to cellular structure and function, understanding the spatio-temporal effects of nanomaterials on gene expression is crucial. For example, cells treated with silver [232] and ZnO [233] NPs can lead to endoplasmic reticulum stress, as apparent from the elevated expression of several stress-related kinases and enzymes. However, detailed studies on the effect of another metal oxide NPs on the expression of such specific genes need to be explored in detail. Golgi apparatus, organelle executing post-translational modifications of nascent proteins, is another vital intracellular structure where nanomaterials can colocalize and produce a pronounced effect. Thus, fully exploring the impact of newly developed nanomaterials aimed for clinical applications on Golgi apparatus should also be a prime focus for researchers in nanomedicine. Inhibition of the function of the Golgi apparatus can also be crucial in some ailments where protein misfolding has a significant role in disease initiation and progression. Although there are several studies in this direction [234–237], the shape, size, texture, and functionalization dependent effect of NPs on the Golgi apparatus at the genomic level can be a future focus of active research.

We hope future studies investigating the application of nanomaterials will give more focus on the potential effects of such nanostructures on various cellular organelles at the molecular and genomic levels. A collective effort from materials scientists, chemists, engineers, toxicologists, and biologists are required to fully understand the possible interaction between nanomaterials and cellular components and explore its outcome.

4. Conclusions

Nanomaterials and their diverse range of interaction with mammalian cells can influence or alter the cellular interactions and which should be carefully examined when considering them in healthcare and FMCG products. The outcome of such interaction between nanomaterials and cells or cellular components can be either advantageous or harmful to the biological system. Several features of nanomaterials such as size, shape/topography, net charge, stiffness/elasticity, functionalization, and hydrophilicity/hydrophobicity can influence their interaction with ECM, cell membrane, cytoskeleton, and other intracellular organelles. Such interactions are crucial factors to be considered when developing nanomaterials for biological applications. Some of the properties of nanomaterials like the release of toxic metal ions, can adversely affect cellular components. However, some other properties of nanomaterials such as shape, size, surface functional groups, and hydrophilicity elicit spatio-temporal favorable outcome in response to the interactions with cellular components. In light of the vast data in the literature, magnitude and the result of such interactions differ between different nanomaterials and different cells, and it is vital to carefully examine them case by case before considering their bench to bedside translation.

Data availability statement

This is a review article and does not contain any raw data.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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