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ENDOCYTOSIS, TRAFFICKING AND EXOCYTOSIS OF NANOPARTICLES: A BRIEF REVIEW

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Abstract

Nanoparticles have emerged as promising agents as vehicles for myriad uses varying from drug delivery to gene therapy. The knowledge of their endocytosis, intracellular trafficking and exocytosis becomes crucial for precise modulation of their uptake and retention inside cells which in turn would affect the therapeutic efficacy of the drug carried by them. Intracellular trafficking and exocytosis of nanoparticles are not very well-studied areas in contrast to endocytosis of nanoparticles which has been studied in considerable detail. In this brief review, different pathways of nanoparticle endocytosis, different routes of intracellular trafficking of nanoparticles as well as their exocytosis have been discussed with a focus on recent findings regarding nanoparticle trafficking and exocytosis.

Keywords: Nanoparticles, Endocytosis, Trafficking, Exocytosis.

1. INTRODUCTION

Advancement of nanotechnology has led to development of nano sized particles as vehicles for target specific drug delivery, imaging and gene therapy [1]The taking up of nanoparticles (NPs) by cells has been studied in detail with a focus on various aspects such as constituents , shape , size and surface chemistry [2].

The size of a nanoparticle can range from 5 nm to several hundred nanometers and the nanoparticles can be of various shapes (like spherical or rod shaped) and diverse surface chemistry and this diversity in the surface chemistry can be utilised to target them to particular tissues or organelles. The starting material for production of nanoparticles can be metals (like gold or silver), metal or non- metal oxides as well as various polymers - both biodegradable and non-biodegradable.

Biodegradable nanoparticles are more efficient as a drug delivery system because they possess features of sustained release as well as biocompatibility with different tissue systems. The pathways for uptake of different types of nanoparticles have been studied

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in details and remain comparatively well characterized. The effect of size or surface modifications of nanoparticles in determining the pathway of endocytosis or uptake has also been studied. But intracellular transport or trafficking of NPs remains to be probed in detail. The distribution of NPs inside various subcellular organelles particularly the pathway taken by the NPs inside the cell after they are internalized remain somewhat unclear.

Exocytosis of NPs is similarly an area that needs to be studied in detail. One important fact that has become evident in recent years is that intracellular trafficking, intraorganellar distribution and exocytosis of nanoparticles vary with the nature, size ,surface modifications of the NPs as well as the cell lines that are used.This particular aspect is actually very important and makes it difficult to generalize the whole thing to some extent.But this variation must be kept in mind because successful targetting of NPs or augmentation of the therapeutic effect of the drugs encapsulated inside them depends on sound knowledge of this particular aspect of the NPs under study or NPs of our interest.

Regarding the techniques used to study the NPs, newer methods or techniques are coming up in recent years. Apart from the conventional microscopic techniques, modern techniques are being used to study the intracellular trafficking and localization of NPs as well as exocytosis. Many of these newer techniques are actually based on some improvisation on existing conventional microscopic techniques but some of them are based on different cytometry techniques like flow cytometry and mass cytometry. These techniques have helped overcome various shortcomings of older conventional techniques and also study the above-mentioned aspects in considerable detail.

2. ENDOCYTOSIS OF NANOPARTICLES

Various pathways of endocytosis have been suggested for different types of NPs and the pathway depends on size, charge, constituents and surface modifications of the NPs as well as the type of the cells. Here we briefly discuss different pathways important for nanoparticle endocytosis.

2.1. Clathrin-Mediated Endocytosis

The endocytosis mediated through Clathrin is an important pathway responsible for endocytosis of NPs and involves specialized membrane structures called clathrin coated pits. The vesicles coated with clathrin form in several steps with the help of Adaptor protein called AP2.The alpha adaptin motif of the AP2 binds specific motifs on the cytoplasmic tails of the transmembrane receptors involved in this process. The beta2 subunit of AP2 binds clathrin molecules and intiates the assembly of the polyhedral coat whereas the gamma 2 subunit helps in concentrating the cargo molecules in these pits. Then the clathrin coated pit gets invaginated and its neck gradually gets narrowed and the GTPase called Dynamin promotes the pinching off of the clathrin coated vesicle. The clathrin coat is thereafter disassembled by the help of the chaperone adenosine triphosphatase (ATPase) Hsc70, the J domain protein auxilin and cyclic GMP–dependent kinase and then can be recycled while the vesicle can fuse with similar vesicles or

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endosomes. Endosomes can later on form endolysosomes by fusing with lysosomes thereby causing enzymatic degradation of their contents or alternatively these endosomes can also get recycled [3,4].

Benyettou and co-workers modified AgNPs for the simultaneous delivery of doxorubicin and alendronate in vitro [5]. These nanoparticles entered the endolysosomal system and the drugs were released in the lysosomes owing to the acidic pH and the efficacy obtained was greater than the combined effect of the two drugs administered individually.

2.2. Caveolin-Dependent Endocytosis

Nanoparticles can also be internalised via caveolin-dependent endocytosis [6, 7]. Caveolae, which are flask-shaped vesicles ranging from 50 to 80 nm in diameter, are coated with caveolin protein [8]. As caveolin-based vesicles are generally targetted to Golgi apparatus and Endoplasmic Reticulum (ER) [9], caveolin-dependent endocytosis can be utilised for the purpose of organellar targetting of nanoparticles. Cholesterol, folic acid and albumin can be used as surface ligands to specifically direct the nanoparticles to caveolin-dependent endocytosis pathway [10]. For example, albumin-bound form of paclitaxel got endocytosed by caveolin-dependent endocytosis [11]. Caveolin-dependent endocytosis has been exploited for the delivery of miRNA targetting KRAS [12], as this pathway generally bypasses lysosomal compartment thus making it suitable for delivery of proteins and nucleic acids. Caveolin-dependent endocytosis is also associated with transcellular transport of caveolae known as transcytosis. Transcytosis mediated by caveolin has been studied in a number of cells including endothelial cells [13-16].

2.3. Cholesterol Dependent, Clathrin- and Caveolin-Independent Endocytosis

Various types of cargos as diverse as viruses and toxins are internalized by clathrin and caveolin independent endocytosis. This particular type of endocytosis is nevertheless dependent on cholesterol, and involves specialized structures that are rich in cholesterol and sphingolipids just like lipid rafts- these lipid microdomains with cargo bud into the cell and cholesterol depletion has been found to affect this pathway. A recent study has identified a lipid raft-mediated endocytosis pathway which is instrumental for the uptake of particular cell-penetrating peptides (CPPs) and DNA nanoparticles (DNP) [17, 18].

2.4. Phagocytosis

Phagocytosis is an endocytosis process by which cells of the immune system like neutrophils, macrophages, dendritic cells and B lymphocytes engulf a large particle (0.5 μm or more) with the help of their cell membranes.

Nanoparticles can bind to the membrane receptors of phagocytes so that they can recognize and phagocytose the nanoparticles readily [19, 20]. Following opsonization, the nanoparticles are phagocytosed and finally find their way to phagolysosome where they can be digested [21,22]. Intravenously administered nanoparticles are prone to get opsonized and phagocytosed [23,24] leading to their sequestration in mononuclear phagocyte system (MPS) [25]. Surface modifications are necessary to reduce this opsonization of nanoparticles [26]. Poly (ethylene glycol) (PEG) can be used to coat

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nanoparticle surfaces [27] thus reducing such sequestration, though PEGylation can make nanoparticles more immunogenic.

2.5. Macropinocytosis

Extracellular fluid is ingested by many cells in macropinosomes which are large endocytic structures. Different signals like growth factors stimulate protrusion of plasma membrane in the form of ruffles, a process driven by actin. The ruffles close around extracellular fluid to form macropinosomes which are translocated towards the center of the cell along the microtubules. This process is helpful for bulk nutrient uptake by the cells [28-30].

2.6. Passive Diffusion

Passive diffusion of NPs has also been reported in recent years. In one such study [31], the authors found clathrin and caveolin mediated pathway to be insignificant in uptake of poly (lactic-co-glycolic) acid (PLGA) NPs (200 to 300 nm) in different cancer cell lines and discovered diffusion to be the major pathway in the uptake of these NPs in those cell lines.

3.TRAFFICKING OF NANOPARTICLES

Various microscopy techniques, such as, confocal laser scanning microscopy, super resolution fluorescence microscopy, dark-field microscopy, scanning and transmission electron microscopy, atomic force microscopy,correlative microscopy, photoacoustic microscopy, surface-enhanced Raman scattering- and coherent anti-Stokes Raman scattering- based microscopy techniques have been used to study trafficking of NPs inside cells [32-34].

Recent imaging studies by Vtyurina et al. [35] identified nanoparticle localization in endosomal compartments and lysosome. These authors have also studied the fraction of nanoparticles localized in lysosome which remained constant for the cell types studied by the authors but the lysosome arrival time was highly variable across the cell lines studied by them. The size of the nanoparticles also determines the time taken by nanoparticles to reach lysosomal compartment. A recent study found that smaller (around 50 nm) nanoparticles reach the lysosome earlier suggesting earlier uptake and trafficking compared to larger (around 70 nm) nanoparticles [36].

3.1. Specific Targetting of NPs

Nanoparticles can be modified to target them to specific organelles. Nanoparticles have been targetted to nucleus, Golgi body, ER etc. Nanoparticle entry in the nucleus can be active as well as passive. Smaller nanoparticles (2 to 6 nm diameter) could enter the nucleus while larger nanoparticles (10 to 16 nm diameter) were excluded. Similar size dependent uptake inside nucleus has also been seen in case of gold nanoparticles modified with poly (ethylene glycol) and polyarginine [37]. NLS or nuclear localization sequence has also been shown to be important in localization of NPs inside nucleus as shown with quantum dots [38]. In the passive process of uptake inside the nucleus, diffusion might play a role as only smaller nanoparticles are getting localized inside

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nucleus but in the active process of uptake, the role of proteins like importin might become important. Ran and importin both might play a role in localization of bigger nanoparticles within nucleus and NLS might be important in that process but as the results show, this active process, though helpful for bigger nanoparticles, is not much efficient in its action as the larger nanoparticles are not as efficiently taken up as the smaller ones.

Various modifications can help in localization of NPs inside mitochondria. Triphenyl phosphonium (TPP) group addition increased the localization of NPs inside mitochondria. NPs that are particularly localized to mitochondria can be helpful in the treatment of various diseases related to generation of reactive oxygen species, for example neurodegenerative disorders. Mitochondria Targeted NPs or MitoNANOs have become very exciting area of research in recent times. Other than TPP, trimethyl rhodamine 5-isothiocyanate,7 aminocoumarin, alpha-tocopheryl group, dequalinium etc have also been used to target NPs to mitochondria. Many MitoNANOs work by blockade of Electron Transport Chain, inhibition of anti-apoptotic proteins and promotion of mitochondria-regulated cancer cell death. So MitoNANOs have the potential to be used to target different types of cancer [39].

Golgi body targeting NPs have been prepared by using Retinoic Acid conjugated Chondroitin Sulphate (CS-RA) that accumulate preferentially within the Golgi apparatus [40] and release their Retinoic Acid (RA) in a controlled manner.The chondroitin sulphate moiety in this case helps in localization of these NPs in Golgi body. NPs targeting Golgi body have been used in cancer and various neurodegenerative disorders.

4. EXOCYTOSIS OF NANOPARTICLES

Exocytosis is the process of extrusion of intracellular components contained with membrane bound vesicles out into the extracellular space. This process is crucial in secretion of various biomolecules from cells including hormones and neurotransmitters. Exocytosis can be secretory as well as non-secretory.

Secretory exocytosis can be of two types: conventional secretion and non-conventional secretion. Conventional secretion can be further classified into two types: Constitutive and Regulated [41].

Constitutive secretion is not dependent on any external signal but regulated secretion occurs in response to external signal and change in the intracellular calcium concentration.

Proper receptor functioning is also dependent on exocytosis process as the endosomes have been found to recycle endocytosed receptors back to the cell periphery, a process known as endosomal recycling. [42].

Lysosomal exocytosis is one of the most important routes for extrusion of NPs from cells [43]. Vesicle-mediated exocytosis is much more common than the direct translocation and extrusion of intra-cytoplasmic nanoparticles across the cell membrane [44].

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Polystyrene NPs were shown to accumulate in lysosome and mitochondria in a size and cell line dependent manner.
Lysosomes and microtubules and actin filaments were involved in the exocytosis process according to that study and it suggested that NPs were exocytosed in energy dependent active manner [45].

Similar studies for exocytosis have also been done for other types of nanoparticles like Quantum Dots (QDs). In one such study involving CdSe /ZnS quantum dots, it was found that most QDs entered lysosomes but some of them also entered mitochondria, ER and Golgi body.

The process of exocytosis was an active one and dependent on actin in this case also. Lysosomal exocytosis and ER-Golgi pathway were the main routes for QD exocytosis [46].

A very recent study [47] utilised protein corona fingerprinting to study the exocytosis of iron oxide nanoparticles and revealed lysosomal exocytosis and secretion of extracellular vesicles to be the main exocytosis pathways involved in this case.

Alkylated gold nanoparticles have also been found to be exocytosed by extracellular vesicle secretion [48]. So, it is evident that non-conventional secretion system plays an important role in nanoparticle exocytosis.

As non-conventional secretory pathways are lesser-known areas, the complete picture of the actual pathways of nanoparticle exocytosis remains unclear or a matter of speculation in many cases.

The specific proteins associated with different pathways of exocytosis can be selectively downregulated to identify their role in NP exocytosis and this may in turn give us an idea regarding the exocytosis pathway of that particular type of NPs. The members of the Vesicle-Associated Membrane Protein (VAMP) family can be suitable targets for such experiments.

5. CONCLUSION AND FUTURE PROSPECTS

Nanoparticles can take diverse route inside the cells after being taken up by the cell by any of the endocytic pathways or through passive diffusion and most of the studies till now have shown the endolysosomal pathway to be one of the most important intracellular trafficking routes of NPs, though ER-Golgi pathway is also important and often the NPs are distributed in-between these two major pathways inside the cell.

Some of the NPs also enter the cytoplasm and other subcellular organelles like nucleus, mitochondria etc. and targeting the NPs specifically to particular organelles for different therapeutic purposes by different surface modifications has become one of the important research aspects concerning NPs.

The exocytosis of NPs has been found to be primarily an active process involving lysosomes (lysosomal exocytosis) as well as actin filaments. Some other non-conventional secretory systems have also been found to be relevant in case of NPs.

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Secretion of extracellular vesicles and non-COP II dependent pathways also appear to be involved in NP exocytosis.

Several new techniques are coming up for studying intracellular trafficking and exocytosis of NPs which can be helpful for correctly delineating the subcellular localization of NPs.

These techniques include both microscopic as well as cytometry techniques. Knowledge regarding the intracellular trafficking of NPs can help in the usage of different biomolecules or drugs for subcellular organellar targeting of NPs as well as for inhibition of exocytosis pathway to get increased retention and effect of the drugs encapsulated within the NPs.

Conflict of Interest:

None.

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