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Review

The endocytosis and intracellular fate of nanomedicines: Implication for rational design

Longfa Kou [a], *Jin Sun* [a,*], *Yinglei Zhai* [b], *Zhonggui He* [a,*]

[a] *School of Pharmacy, Shenyang Pharmaceutical University, Shenyang, China*
[b] *School of Medical Devices, Shenyang Pharmaceutical University, Shenyang, China*

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ABSTRACT

Nanomedicines employ multiple endocytic pathways to enter cells. Their following fate is interesting, but it is not sufficient understood currently. This review introduces the endocytic pathways, presents new technologies to confirm the specific endocytic pathways and discusses factors for pathway selection. In addition, some intriguing implication about nanomedicine design based on endocytosis will also be discussed at the end. This review may provide new thoughts for the design of novel multifunctional nanomedicines.

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1. Introduction

With the continuous development and progress of human society, people are suffering much more modern diseases than before. Tumors, for example, are characterized by heterogeneity and adaptive resistance. Regarding traditional drugs, they work while trafficking in the blood circulation and the concentration at the lesion site determines the therapeutic efficacy of the drugs. Usually, to achieve high concentration at the lesion site, excess drugs are taken. Simultaneously, however, systemic side effects and disorder of other organic or tissular function would appear. It was an inevitable problem for pharmaceutical scientists to solve until nanomedicines emerge. Compared to traditional small molecule drugs, theoretically speaking, nanomedicines can concentrate at certain organs, tissues and even cells, load more drugs to final targets, deliver macromolecules (like proteins and peptides) and minimize side

* *Corresponding authors*. Mailbox 59#, Department of Biopharmaceutics, School of Pharmacy, Shenyang Pharmaceutical University, No. 103 Wenhua Road, Shenyang 110016, China. Tel./fax: +86 24 23986321.
E-mail addresses: sunjin66@21cn.com (J. Sun), hezhonggui@vip.163.com (Z. He).
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effects or toxicity [1]. Scientists see a future in the nanomedicine.

A series of nano-sized preparations, such as liposomes, nanoparticles, polymeric micelles and polymeric-drug conjugates, have been developed in laboratory, and some of them are undertaking preclinical studies. Some successful nano-sized preparations have already emerged in today's pharmaceutical market and shown better clinical performance than traditional drugs [2]. Traditional drugs with small molecule enter cells mainly through the passive diffusion or active transport while nanomedicines come into cells via endocytosis. Endocytosis helps nanomedicines to enter specific cells and accumulate there. Pharmaceutical scientists showed a great interest in this process and spent much time and energy to study, and they have obtained some achievements. The endocytosis pathway has been classified according to the proteins which play a role in the process. Correspondingly, it has been explained that how nanomedicines interact with cytomembrane, enter cells and travel in the cells in different pathways. Even so, there are still many problems that have not been solved. Some pathways are still insufficiently understood, and the functions of some proteins involved in endocytosis are still uncertain, and the factors that affect the pathway for nanomedicines entering cells are not absolutely proven, etc. It is necessary to study further for a better understanding, and the findings may contribute to the emerging of the novel multifunction nanomedicine.

This review summarizes much important advancement about endocytosis mechanisms and the subsequent intracellular fate of nanomedicines. We will focus on the cellular uptake and intracellular route in different type of endocytosis pathways, the tools used to confirm the specific endocytic pathway, and the effect of physicochemical properties of particles and cell types on the selection of the endocytic routes. In addition, some meaningful implications about rational nanomedicine design depending on endocytosis are also introduced in separate paragraphs. The review may provide new thoughts for the design of novel multifunctional nanomedicine and will be helpful to related workers.

2. Endocytic pathways for nanomedicines to enter cells

Endocytosis is the major route for nanomedicines to transport across the membrane (Fig. 1). It is generally classified into phagocytosis and pinocytosis. Phagocytosis was originally discovered in macrophages. Pinocytosis is present in all types of cells in four forms, such as clathrin-dependent endocytosis, caveolae-dependent endocytosis, macropinocytosis, and clathrin- and caveolae-independent endocytosis [3,4].

2.1. *Phagocytosis*

Phagocytosis is a special endocytic pathway predominantly occurred in phagocytes, such as macrophages, neutrophils and monocytes [5]. Relatively, large particles are more likely to take this way. Nanoparticles which adopt this way of entry into cells need to be recognized by the opsonin firstly, such as immunoglobulin (IgG and IgM), complement component (C3, C4, and C5) and blood serum proteins. Thereafter, the

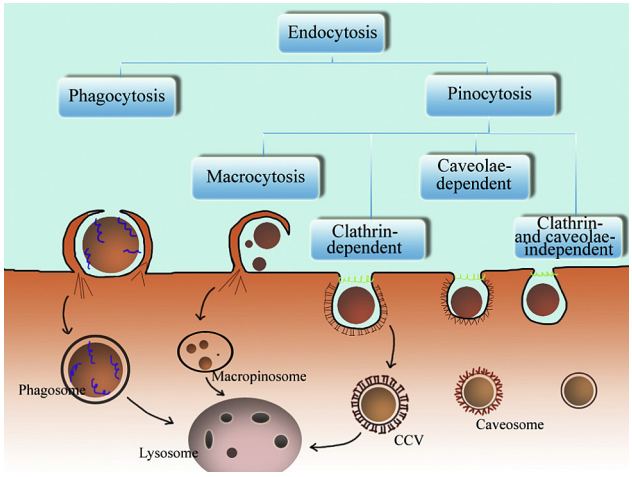

Fig. 1 – Nanoparticles internalization pathways in mammalian cells. The picture briefly shows the classification of endocytic trafficking and different mechanisms of endocytosis. Abbreviation is: CCV, clathrin coated vesicle.

opsonized nanoparticles bind to the cell surface and interact with the receptor, inducing the cup-shaped membrane extension formation. The membrane extensions enclose the nanoparticles and then internalize them, forming the phagosomes which have a diameter of 0.5–10 μm. Finally, the phagosomes move to fuse with lysosomes [5,6]. But the cargo contained in the phagosomes will be destroyed by acidification and enzymolysis in the lysosomes. Therefore, to produce desired effects, nanomedicines must bypass this route to avoid degradation.

2.2. *Pinocytosis*

Pinocytosis is a major route for the cells to drink fluid, solutes and suspensions containing small particles. It is classified to clathrin-dependent endocytosis, caveolae-dependent endocytosis, macropinocytosis and clathrin- and caveolae-independent endocytosis, based on the proteins involved in the pathways [3,4].

2.2.1. *Clathrin-dependent endocytosis*

Clathrin-dependent endocytosis is present in all mammalian cells, occupying an important part in cellar entry. After nanomaterials interact with receptors on the cytomembrane, a kind of cytosolic protein named clathrin-1 polymerizes on the cytosolic side of the plasma where the cargo is internalized [4]. After wrapping the nanoparticles inside, the vesicle is pinched off through the GTPase activity of dynamin, forming a clathrin coated vesicles (CCV) [7]. With energy supplied by actin, CCVs move towards inside the cells, and the route is regulated by the cytoskeleton [8]. The clathrin coat is shed off in the cytosol. Where is the destination of the vesicles? It may be associated with the receptor that nanoparticles' ligands attach to. For example, low-density lipoprotein particles are internalized through LDL receptor and transferred to lysosomes for degradation; while, iron-loaded transferrin is engulfed via transferrin receptor and recycled to the cell

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