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Review

Endocytosis of nanomedicines

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ABSTRACT

Novel nanomaterials are being developed to improve diagnosis and therapy of diseases through effective delivery of drugs, biopharmaceutical molecules and imaging agents to target cells in disease sites. Such diagnostic and therapeutic nanomaterials, also termed "nanomedicines", often require site-specific cellular entry to deliver their payload to sub-cellular locations hidden beneath cell membranes. Nanomedicines can employ multiple pathways for cellular entry, which are currently insufficiently understood. This review, *first*, classifies various mechanisms of endocytosis available to nanomedicines including phagocytosis and pinocytosis through clathrin-dependent and clathrin-independent pathways. *Second*, it describes the current experimental tools to study endocytosis of nanomedicines. *Third*, it provides specific examples from recent literature and our own work on endocytosis of nanomedicines. *Finally*, these examples are used to ascertain 1) the role of particle size, shape, material composition, surface chemistry and/or charge for utilization of a selected pathway(s); 2) the effect of cell type on the processing of nanomedicines; and 3) the effect of nanomaterial-cell interactions on the processes of endocytosis, the fate of the nanomedicines and the resulting cellular responses. This review will be useful to a diverse audience of students and scientists who are interested in understanding endocytosis of nanomedicines.

Contents

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1. Introduction: Cellular entry of nanomedicines

A new era of nanomedicine that uses devices of nanoscale size to address urgent needs for improved diagnosis and therapy of diseases is being etched in the 21st century. Polymeric micelles, quantum dots, liposomes, polymer-drug conjugates, dendrimers, biodegradable nanoparticles, silica nanoparticles, etc. are few examples of nanoparticulate materials researched in laboratories, undergoing preclinical development, or already used in the clinic [1–6]. These nanomaterials, collectively called "nanomedicines", can deliver low molecular mass compounds, proteins and recombinant DNAs to focal areas of disease or to tumors to maximize clinical benefit while limiting untoward side effects. Such nanomedicines are also expected to drastically improve early diagnosis through molecular imaging techniques. A quintessential feature of such modalities is their ability for site-specific delivery, not only to the desired organ, but also to a targeted sub-cellular compartment. Hence, a new paradigm for drug delivery and nanomedicine requires nanomaterials to differentially interact with the surface of their target cells and undergo intracellular trafficking that would lead to determined locations inside cells [7]. Consequently, the interest to intracellular trafficking of nanomaterials has skyrocketed.

A nanoparticle placed in the external milieu of a cell can interact with the exterior of the plasma membrane, which can lead to this nanoparticle entry inside the cell through a process termed "endocytosis" (Fig. 1). Endocytosis involves multiple stages. *First*, the cargo is engulfed in membrane invaginations that are pinched off to form membrane-bound vesicles, also known as endosomes (or phagosomes in case of phagocytosis). Cells contain heterogeneous populations of endosomes equipped with distinct endocytic machinery, which originate at different sites of the cell membrane. *Second*, the endosomes deliver the cargo to various specialized vesicular structures, which enables sorting of cargo towards different destinations. *Finally*, the cargo is delivered to various intracellular compartments, recycled to the extracellular milieu or delivered across cells (a process known as "transcytosis" in polarized cells). Generally, endocytosis can be divided into two broad categories — phagocytosis (the uptake of large particles) and pinocytosis (the uptake of fluids and solutes). Phagocytosis was originally discovered by Ilya Mechnikov as a process by which macrophages engulf particles as large

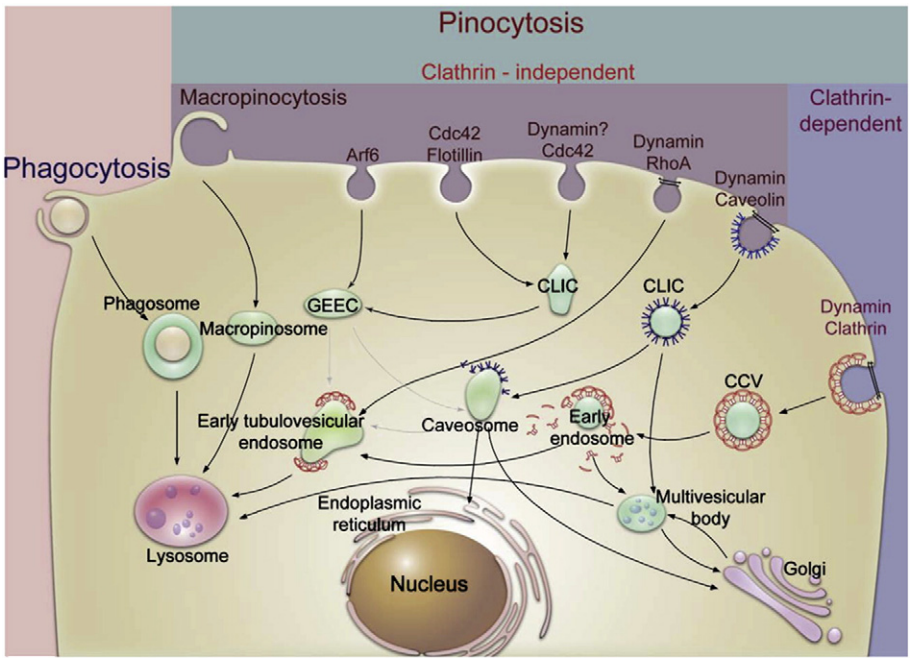

Fig. 1. Different mechanisms of endocytosis. There are multiple pathways for cellular entry of particles and solutes. The picture of endocytosis trafficking is actively researched and evolving [11,12]. In all cases the initial stage of endocytosis proceeds from the plasma membrane portals of cellular entry and involves engulfment of cargo into intracellular vesicles. The second stage often involves sorting of the cargo through endosomes. It is followed by the final stage during which the cargo is delivered to its final destination, recycled to extracellular milieu or delivered across cells (not shown). The figure is a simplified representation of complex trafficking mechanisms and their cross-talks. More details for stages of phagocytosis and CME are presented in Figs. 3 and 5. Abbreviations are: CCV, clathrin coated vesicles, CLIC, clathrin-independent carriers; GEEC, GPI-anchored protein-enriched compartment; GPI, glycophosphatidylinositol, MVB, multivesicular body.