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Effects of Intracellular Process on the Therapeutic Activation of Nanomedicine

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Abstract

In this article, we review the endocytosis ways of nanoscale materials and how they work. Surrounded by FBS in culture medium, the special nanomedicines, entering into lysosome via endosome or autophagosome, are degraded by many kinds of enzymes, and are finally snagged. During this process, they are interacting with lysosome membrane, hence the lysosome membrane changes in permeation. With a weak damage extent of lysosome, the nanoparticles escape the damage effect of lysosome, and interact with other organelles (for example mitochondria, proteins), resulting in their defeature and being swallowed by autophagosomes. Now that lysosomes are damaged, the autophagosomes won't be digested by lysosomes. With accumulation of endosomes, the cancer cells accelerate the aging process or apoptosis. If lysosomes are strongly destabilized, the cathepsin B/D will interact with caspase family, causing necrosis or apoptosis of cancer cells. So we recognise that the lysosome is key for cancer cell death.

Keywords: Nanomedicine; Endocytosis; Autophage; Lysosome; Apoptosis; Necrosis

Abbreviations: FBS: Fetal Calf Serum; EEA: 1early-Endosomal Autoantigen; TFR: Transferrin Receptor; LDLR: Low-Density Lipoprotein Receptor; EGFR: Epidermal Growth Factor Receptor; LDL: Low-Density Lipoprotein; LMP: Lysosomes Membranous Permeabilization; GTP: Guanosine Triphosphate; CCVs: Clathrin-Coated Vesicles; EE: Early Endosomes; Rab: Argeting GTPase; PI(3)K: phosphatidylinositol-3-OH kinase; GEF: Guanine Nucleotide Exchange; UVRAGUV: Radiation Resistance-Associated Gene Protein; VPS: Vacuolar Protein Sorting; HOPS: Homotypic Fusion And Vacuole Protein Sorting; CORVET: Class C Core Vacuole/Endosome Tethering; ATG: Autophagy Protein; SNARE: Soluble N-ethylmaleimide Sensitive Fusion Proteins Attachment Protein Receptor; Stx17: syntaxin 17; SNAP-29: Synaptosomal-Associated Protein 29; VAMP8: Vesicle-Associated Membrane Protein 8; VMP1: Vacuole Membrane Protein 1; UBL: Ubiquitin-Like; LC3: Protein Light Chain 3; PE: phosphatidylethanolamine; TGN: golgi; ER: Endoplasmic Reticulum; MPR: Mannose-6-Phosphate Receptor; AP1: Adaptor Protein-1; Mcl-1: Myeloid Cell Leukemia-1; XIAP: x-Linked Inhibitor Of Apoptosis Protein; SK-1: Sphingosine Kinase-1; TNF: Tumor Necrosis Factor; NF-κB: Nuclear Factor Kappa-Light-Chain-Enhancer Of Activated B cells; MOMP: Mitochondrial Outer Membrane Permeabilization; RIP: Receptor-Interacting Protein; TRADD: Tumor Necrosis Factor Receptor Type 1-Associated DEATH Domain Protein; TRAF2: TNF-Receptor-Associated Factor 2; NIK: nF-κB Inducing Kinase; IKK: IκB kinase; IkB: Inhibitor of κB; MLKL: Mixed Lineage Kinase Domain-Like Protein; RHIM: Interaction Motif; E1: Ubiquitin-Activating Enzyme; E2: Ubiquitin -Conjugating Enzyme; E3: ubiquitin – Ligaseenzyme

Introduction

Tumor microenvironment is a complex system which includes a spectrum of nutrients and their carriers, receptor–ligand complexes, fluid, solutes, lipids, membrane proteins, extracellular–matrix components, cell-debris, bacteria, viruses, etc. In another word, they include peptides, signal peptides, signaling molecules, toxins, metabolites, amino acids, oligopeptides, vitamins, ionic compounds (K^+ Na^+ Ca^{2+} and so on). Cell membrane is a dynamic system, which is combined with phospholipids, glycoproteins and many different receptor proteins, so that it can make different stress responses to the changing surroundings in real-time. Many papers confirmed that ions enter the cytoplasm through membrane ion channels or by freely diffusion. Since most nanoparticles are large polar molecules that cannot pass through cell membrane or the hydrophobic plasma, they are carried into the cell by membrane bound vesicles, which are derived from the invagination and pinching-off of pieces of the plasma membrane, this energy-consuming process is termed as endocytosis [1,2]. Different sized particles come into cells in different endocytosis ways. The compounds as large as 1 um, such as bacterium and virus get into cells by phagocytosis,; Some molecules use macropinocytosis way as predominant entry portal into cells, which forms a vesicle (0.5-5 μm in diameter) filled with a large volume of extracellular fluid and molecules; And the entry route of 100 nm nanoparticles is clathrin-independent or caveolin-mediated endocytosis. All of them need to consume energy. After the endocyto-viscles form, they fuse with the initial endosomes that come from Golgi and produces ER, to form early endosomes that are filled with Rab5-GTPase、early-endosomal autoantigen (EEA1) and phosphorylaed-Vps34 [3]. At the same time, the related member proteins of endocyto-viscles return to the plasmid member via recycling endosomes, such as the transferrin receptor (TFR) or low-density lipoprotein receptor (LDLR), whereas the cargo

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is destined for degradation. Epidermal growth factor receptor (EGFR) or low-density lipoprotein (LDL) is transferred to late endosomes and, ultimately, to lysosomes [4]. Endocytosed cargo is obtained by sorting, processing, recycling, storing, activating, silencing, and degrading incoming substances and receptors, and endosomes are responsible for regulation and fine-tuning of numerous pathways in the cells [5].

The early endosomes fuse with each other, mediated by the member protein Rab7-GTPase, instead of Rab5-GTPase, to develop into large endosomes. The large endosomes walk along with microtubes, from cytoplasmic edge to core, meanwhile the pH drops from 7.0 to 5.0, at this term they are named as late endosomes or mature endosomes; The late endosomes fuse with early lysosomes, then the hydrolytic enzymes are activated by dephosphorylation to degrade endsomal contents.

Two major proteolytic systems contribute to the continuous removal of intracellular components: the ubiquitin/proteasome system and the autophagic/lysosomal system. The ubiquitin/proteasome system is the most important extralysosomal degradative pathway, playing a major role in the maintenance of cellular homeostasis, protein quality control, and in the regulation of essential intracellular processes such as cell cycle progression, cell division, transcription and signaling. The decreased proteasome activity is a consequence of the accumulation of damaged intracellular products in aged cells [6]. The autophagic/lysosomal system is another important extralysosomal degradative pathway, playing an important role in the treatment of damaged organelles. The term 'autophagy' embraces several different mechanisms: microautophagy, macroautophagy and chaperone-mediated autophagy, all of which are involved in the lysosomal degradation of cellular components of autophagosomes, which ultimately fuse with the lysosomal compartments and give rise to the degradation of the sequestered materials. Autophagy plays a cytoprotective role against cell death under environments in which the availability of oxygen and nutrients is poor. Moreover, autophagy protects cancer cells against drug-induced apoptosis in experimental models of tumors.

Lysosomes are Golgi elements to form a single membrane bound degradative vacuole, then fuse with late endosomes to form early lysosomes [7]. Lysosomes are membranous bags of hydrolytic enzymes used for the controlled intracellular digestion of macromolecules. They contain about 40 types of hydrolytic enzymes, including proteases, nucleases, glycosidases, lipases, phospholipases, phosphatases, and sulfatases. A complete breakdown of the organelle with release of high concentrations of lysosomal enzymes into the cytosol results in unregulated necrosis, whereas partial, selective permeabilization triggers apoptosis. LMP can lead to both apoptosis and necrosis, depending on the extent of LMP; Necrosis appears to be the dominant pathway of death in the setting of massive LMP, whereas partial LMP drives apoptotic cell death [8].

Endocytosis ways of nanoparticles

Nanoparticles are defined as particles with a size between 1 nm and 100 nm. As a new technology, nanomedicine is acting an important role in curing cancers. Cancer cells live in a harsh environment that contains all kinds of particles, important nutrients, toxins, effector molecules (growth factors, hormones, antibodies), enzymes, and pathogens.

The plasma membrane is a dynamic structure, which includes lipids, phospholipid bilayers, glycoproteins, and all kinds of receptors, with the function to segregate the chemically distinct intracellular milieu (the cytoplasm) from the extracellular environment by regulating and coordinating the entry and exit of small and large molecules. Endocytosis is a fundamental internalized process of eukaryotic cells interacting with nanoparticles via deformated membrane and membrane-bound carriers [9]. However, endocytosis is an energy-dependent process, which is related to the nanoparticles' sizes, surface chemistry (charge), surface topology, shapes and so on [10,11]. Essential small molecules, such as amino acids, sugars and ions, can traverse the plasma membrane through the activation of integral membrane protein pumps or channels, while macromolecules and particles are internalized into transport vesicles derived from the plasma membrane by endocytosis [1]. The process of uptaking molecules into the intracellular endocytic system is called receptor-mediated endocytosis. Signal transduction processes connect the recognition of environmental information to the appropriate cellular response. Plasma membrane receptors transfer the extracellular stimuli to the interior of cells and initiate signaling cascades that finally result in a physiological response [12,13]. The review reported that endocytosis encompasses four diverse mechanisms: endocytisis-phagocytosis, micropinocytosis, clathrin-independent endocytosis, and caveolin-mediated endocytosis [14].

Phagocytosis is direct for 1um particles, for instance, bacteria, virus. Phagocytosis is the process by which cells bind and internalize particulate matters larger than around 0.75 μm in diameter, such as small-sized dust particles, cell debris, micro-organisms and even apoptotic cells, which only occurs in specialized cells. This process involves the uptake of membrane areas larger than that uptaken by clathrin-mediated endocytosis and caveolae pathway.

Macropinocytosis, a form of bulk uptake of fluid and solid cargo into cytoplasmic vacuoles, namely macropinosomes, usually occurs from highly ruffled regions of the plasma membrane. Macropinocytosis is the invagination of the cell membrane to form a pocket, which then pinches off into the cell to form a vesicle (0.5-5 μm in diameter) filled with a large volume of extracellular fluid and molecules. The filling of the pocket occurs in a non-specific manner. The vesicle then travels into the cytosol and fuses with other vesicles such as endosomes and lysosomes [15].

Clathrin-mediated endocytosis mediate the small vesicles about 100 nm in diameter. First, nanoparticles interact with the plasma membranes, membranes are shaped into vesicle by cytoplasmic coats which then dissociate upon GTP hydrolysis. The ligands-proteins interact with receptors [16] and the membranes invaginate to form clathrin-coated vesicles which have a morphologically characteristic coat made up of a complex of proteins that are mainly associated with the cytosolic protein clathrin. Clathrin-coated vesicles (CCVs) are found in virtually all cells and form domains on the plasma membrane termed clathrin-coated pits. The coated pits can concentrate large extracellular molecules that have different receptors responsible for the receptor-mediated endocytosis of ligands, e.g. low density lipoproteins, transferrins, growth factors, antibodies and many other substances.

Caveolin-mediated endocytosis is fit for small particles (approx. 50-80 nm in size). Caveolae are small flask-shaped pits in the membrane that resemble the shape of a cave (hence the name caveolae). The most commonly reported caveolae are non-clathrin-coated plasma membrane buds, which exist on the surface of many but not all cell types. For instance, they can constitute up to a third of the plasma membrane area of the cells of some tissues, being especially abundant in smooth muscle, type I pneumocytes, fibroblasts, adipocytes, and endothelial cells [15]. They consist of the cholesterol-binding protein

caveolin (Vip21) with a bilayer enriched in cholesterol and glycolipids. Uptake of extracellular molecules is also believed to be specifically mediated via receptors in caveolae. They can not only form remarkably stable membrane domains at the plasma membrane but also function as carriers in exocytic and endocytic pathways. The apparently diverse functions of caveolae, including mechanosensing and lipid regulation, might be linked to their ability to respond to plasma membrane changes, a property that is dependent on their specialized lipid composition and biophysical properties [17].

Particles enter cells by receptor-mediated endocytosis, a coupled process by which selected extracellular proteins or peptides are first bound to specific cell surface receptors and then rapidly internalized by the cells to form different endocytic vacuole [18]. During recycling, vacuole contents and membrane components can be sorted from one another; more fusion events occur with other endocytic vacuoles, lysosomes, or Golgi apparatus [19] (Figure1).

Nanoparticles and endosomes

In previous part, we focus on the endosomes with several classical endocytic pathways, while in this part we talk about the biogenesis of these organelles, highlighting their dynamic inter conversion, maturation and also the generation of heterogenous subdomains on their surfaces. Endosomes are commonly divided into early endosomes (EE), recycling endosomes, and late endosomes [13]. In fact early endosomes are comprised of two distinct populations: a dynamic population that is highly mobile on microtubules and matures rapidly toward late endosomes and a static population that matures much more slowly. This pre-early endosome sorting process begins at clathrin-coated vesicles, depends on microtubule-dependent motility, and appears to involve endocytic adaptors [20]. Small GTP binding proteins of the rab family (rab4, rab5, rab7, rab9, rab11and rab24) are localized to the cytoplasmic surface of compartments of the central vacuolar system and show to be important for plasma membrane internalization, early endosomes fusion, and early endosomes classification (including: recycling endosomes and late endosomes) [21,22]. These small GTPases (Rab endosomal proteins) play important roles in the regulation of various stages of endosomal trafficking.

Rab4, Rab5, and Rab11 are localized to early endocytic organelles where they regulate distinct events in the transferrin receptor pathway. Rab4 has been shown to be involved in the regulation of recycling from the EE and, in particular, TFN receptor (TFR) recycling. Rab5 is important in the homotypic fusion between EE as well as in controlling the transport to the early endosomal compartment. Rab11, on the other hand, has been demonstrated to function in transport through the recycling compartment. In addition, it seems to be also necessary for budding of vesicles from the plasma membrane and has been suggested to regulate transport beyond EE [22,23].

Three major populations were observed: one that contains only Rab5, second with Rab4 and Rab5, and third containing Rab4 and Rab11 [24]. Rab5a regulates the internalization of molecules via clathrin coated vesicles and their subsequent delivery to early endosomes [25]. Rab4 is suggested to be the counterpart of rab5 on the recycling route, regulating membrane traffic leading from early endosomes back to the plasma membrane [26,27]. Rab4 and rab11 are involved in the regulation of recycling back to the plasma membrane [22]. Then the early endosomes fuse with each other to form big endosomes that require phosphatidylinositol-3-OH kinase (PI(3)K) activity as well as the Rab5-GTPase [28]. In early endosomes, Rab5–GTP interacts with multiple effectors, including the tethering factor EEA1 and the phosphoinositide 3-kinase Vps34, thus generating endosomal domains involved in fusion and maturation. These processes lead to a maturation of the early endosomes to the late endosomes [29]. As a direct Rab5 effector, the identification of EEA1 provides a molecular link between PI(3)K and Rab5, and its restricted distribution to early

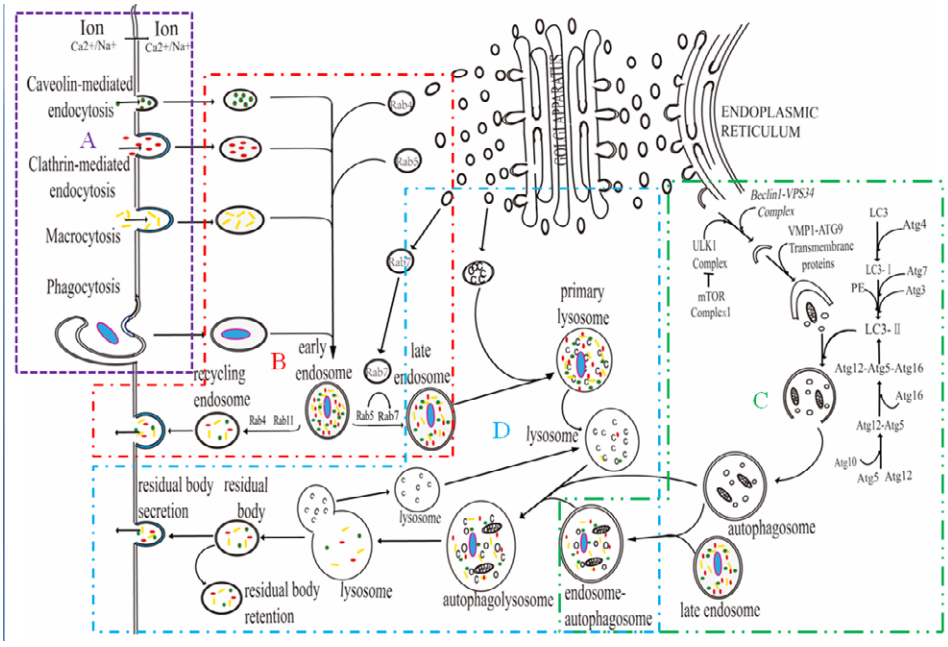

Figure 1: The detail process of cellular uptaking (A), the relations between nanoparticulates and endosome B, autophasgosome (C) and lysome (D).

endosomes indicates that EEA1 may confer directionality to Rab5-dependent endocytic transport [30].

Rab7, Rab9, and Rab24 are localized to late endocytic organelles where they target different organelles. Rab9, a key regulatory component in the recycling of mannose-6phosphate receptors from endosomes to the trans-Golgi network [31], has been shown to regulate transport from late endosomes to the trans-Golgi network [23,32,33]. Rab24 is partially associated with the endoplasmic reticulum [34]. Rab7 also have been shown to be associated with late endosomes [35]. Rab7 mediates transport from late endosome to lysosome in mammalian cells [36].

The small GTPases Rab5 and Rab7 are key determinants of early and late endosomes. As an established GEF for Rab7, the class C VPS/HOPS complex interacts with Rab5 and is required for Rab5-to-Rab7 conversion [37]. The level of Rab5 dynamically fluctuates on early endosomes which form into a network by fusion and fission events in time, so the degradated cargo concentrates become fewer, and larger endosomes form progressively and migrate from the cell periphery to the center where Rab5 is rapidly replaced by Rab7. Rab conversion depends on the ability of Rab5 to hydrolyze GTP [37]. How GTP-hydrolysis of rab bound GTP is related to the role of these proteins in endocytosis is not yet known, but quick progress is being made towards this goal through the identification of proteins regulating the activity of these rab proteins [23]. The activation and recruitment of the small GTPase Rab7 to early endosome is a critical step for early to late endosome maturation, a process that requires the class III phosphatidylinositol 3-kinase(PI3KC3) and GTPase regulators. We demonstrate that Rubicon sequesters UVRAG from C-VPS/HOPS. Activated GTP-bound Rab7 competes for Rubicon binding and releases UVRAG to associate with C-VPS/HOPS, which in turn promotes further loading of Rab7 with GTP. This feed-forward loop ensures rapid amplification of GTP-bound Rab7 and consequent stimulation of endosome maturation [38] (Figure 1).

Nanoparticle and Autophagy

Autophagy is a lysosome-based degradative pathway which plays an essential role in maintaining cellular homeostasis [39]. Autophagosomes are engulfed by double-membrane vesicles. The autophagy embraces three different mechanisms: microautophagy, macroautophagy and chaperone-mediated autophagy, all of which are involved in the lysosomal degradation of cellular components by autophagosomes, which ultimately fuse with the lysosomal compartment and cause the degradation of the sequestered materials [40,41]. The autophagy-related process is dynamic, which can be broken down into four discrete steps for the purpose of discussion: induction, autophagosome formation, autophagolysosome formation, and delivery and degradation of the autophagic body [42,43]. Autophagy is induced as a response to both extracellular stress conditions (nutrient deprivation, hypoxia, and oxidative stress) and intracellular stress conditions (endoplasmic reticulum stress, accumulation of damaged organelles, and aggregation of proteins), so it has a cytoprotective role against cell death in environments in which the availability of oxygen and nutrients is poor [44]. The core autophagy pathway starts with the formation of an isolation membrane (also called a phagophore), most often at the contact sites between mitochondria and the endoplasmic reticulum. However, plasma membranes or other cytoplasmic organelles, including the Golgi, the endoplasmic reticulum and the Mitochondria, may constitute additional membrane sources for the generation of autophagosomes [45-47]. Once the phagophore has been formed, the membrane structure expands to sequester materials to form autophagosome [48]. The autophagy-related genes and their products are named as ATG and Atg, respectively [49]. Several SNARE-like proteins mediate fusion between autophagosomes and lysosomes. For example, the hairpin-type tail-anchored SNARE-like syntaxin 17 is targeted to autophagosomes for fusion with endosomes/lysosomes. Stx17 localizes to the outer membrane of completed autophagosomes rather than the isolation membrane. For this reason, the lysosome does not fuse with the isolation membrane. Stx17 interacts with SNAP-29 and the endosomal/lysosomal SNARE VAMP8. Depletion of Stx17 causes accumulation of autophagosomes without degradation [50,51]. A related report showed that a Beclin1-binding autophagic tumour suppressor, UVRAG, interacts with the class C Vps complex, a key component of the endosomal fusion machinery. This interaction stimulates Rab7 GTPase activity and autophagosome fusion with late endosomes/lysosomes, as well as various lysosomal enzymes that hydrolyse proteins, lipids and nucleic acids at a low optimum pH 4.0 [51], thereby enhancing delivery and degradation of autophagic cargo. Autophagosome/endosome maturation is mediated by the UVRAG-class-C-Vps complex, while autophagosome formation is mediated by UVRAG–Beclin1. This result indicates that UVRAG functions as a multivalent trafficking effector that regulates not only two important steps of autophagy — autophagosome formation and maturation — but also endosomal fusion, which concomitantly promotes transport of autophagic and endocytic cargo to the degradative compartments [54].

Autophagy involves the spatially and temporarily coordinated activation of multiple molecular components, including the ULK1 (UN-51-like kinase1) – FIP200 (FAK family kinase-interacting protein of 200 kDa)–ATG13–ATG101 complex, which is functionally coupled to the negative autophagy regulator, mTOR complex 1, and initiates autophagy; the lipid kinase vacuolar protein sorting 34 (VPS34)–Beclin 1 complex is usually inactivated by anti-apoptotic proteins from the BCL-2 family and by other signalling compounds, but when activated, it drives the nucleation of the isolation membrane. Two transmembrane proteins, ATG9 and vacuole membrane protein 1 (VMP1), which recycle among the Golgi, endosomes and autophagosomes, probably participates in the recruitment of lipids to the isolation membrane [51,52]. There are two ubiquitin-like (UBL) protein conjugation systems, ATG12 and protein light chain 3 (LC3), between whom involves one protease (ATG4, which cleaves LC3 at its carboxyl terminus), the E1-like enzyme ATG7 (common to both conjugation systems), the E2-like enzymes ATG10 (ATG12 system), and ATG3 (LC3 system), which together catalyse the covalent conjugation of ATG12 to ATG5 (which together with ATG16 forms the E3-like ligase of LC3) and that of phosphatidylethanolamine (PE) to LC3. So LC3 remains associated with autophagosomes and autolysosomes, facilitating their identification [51-53] (Figure1).

Nanoparticles and Lysosome

Lysosomes are single-lipid bilayer membrane secretory storage vesicles which bring many kinds of digestive enzymes that break down various molecules. Lysosomes contain about 40 types of hydrolytic enzymes including proteases, lipases, glycosidases, nucleases, phosphatases, phospholipases and sulfatases that are synthesized in ER[55], then transported to Golgi, these acid hydrolases are tagged with mannose-6-phosphate in the cis-Golgi, and subsequently bind to MPRs in the TGN [56,57]. Then the Golgi secretory storage vesicles bound hydrolases are first delivered to late endosomes, where they dissociate from the receptors as a result of the acidic lumenal pH; this allows the receptors to recycle back to the TGN and the

hydrolases continue onwards to lysosomes [56]. Lysosomes usually exert their maximal enzymatic activity at low pH (pH 4.5-5.0) . The acidic milieu of lysosomes is maintained by a vacuolar ATPase that pumps protons from the cytosol into the lysosomal lumen [58]. The lysosomal membrane is protected from the acidic hydrolases by lysosomespecific expression of membrane proteins such as Lamp-1 and Lamp-2 [59]. They are subdivided in three subgroups according to the amino acid of their active site that confers catalytic activity: cysteine (cathepsins B, C, F, H, K, L, N, O, S, T, U, W and X), aspartyl (cathepsins D and E) and serine cathepsins (cathepsins A and G) [60]. Clathrin, its heterotetrameric adaptor AP1 (adaptor protein-1) and the monomeric adaptors known as GGAs (Golgi-localized, γ-ear-containing, ADP ribosylation factor-binding proteins) are required for MPR trafficking from the TGN to endosomes [56]. Lysosomal degradation of endogenous proteins occurs primarily through autophagic mechanisms. Being Golgi elements, lysosomes form a single membrane bound degradative vacuole [61]. Lysosomes are cytoplasmic membrane-enclosed organelles that contain hydrolytic enzymes and that control the intracellular turnover of macromolecules. For optimal activity, they require an acidic environment, just as it is, the lysosome provides an acidic environment by maintaining a pH of about 5 in its interior. In this way, the contents of the cytosol are doubly protected against attack by the cell's own digestive system. The membrane of the lysosome normally keeps the digestive enzymes out of the cytosol, even if they should leak out, they can do little damage at the cytosolic pH of about 7.4, like all other intracellular organelles. The lysosome not only contains a unique collection of enzymes, but also has a unique surrounding membrane. Transport proteins in this membrane allow the final products of the digestion of macromolecules, such as amino acids, sugars, and nucleotides, to be transported to the cytosol, from where they can be either excreted or reutilized by the cells. An H + pump in the lysosomal membrane utilizes the energy of ATP hydrolysis to pump H + into the lysosome, thereby maintaining the lumen at its acidic pH. Most of the lysosomal membrane proteins are unusually highly glycosylated, which is thought to help protect them from the lysosomal proteases in the lumen.

Proteins and lipids are transported through the endolysosomal system of eukaryotic cells, depending on multiple fusion and fission events. Here, we focus on the mechanism of membrane fusion at endosomes, vacuoles and lysosomes, and in particular on the role of the two homologous tethering complexes called CORVET and HOPS. CORVET is a Rab5 effector complex, whereas HOPS can bind efficiently to late endosomes and lysosomes through Rab7. Once activated, Rab7–GTP interacts with HOPS to mediate fusion with lysosomes [62]. The lysosome is considered the terminal point in the endocytic pathway, as molecules are delivered to the lysosome for degradation (Figure 1).

Lysosome and Cancer Cell Death

Lysosomes are intracytoplasmic organelles defined by an acidic milieu (pH around 4.5-5.0) and surrounded by a single membrane, which are present in the cytoplasm of all cell types in mammals except red blood cells [60]. A complete breakdown of the organelle with release of high concentrations of lysosomal enzymes into the cytosol results in necrosis, whereas partial, selective permeabilization triggers apoptosis. By simulating LMP, the released cathepsin B is actived in the cytosol, and the activated cathepsin B can cleave many caspase targets and target anti-apoptotic proteins, including Mcl-1 and XIAP, as well as caspase-2 [62,63]. Cathepsin B can activate trypsinogen and other zymogens during the early course of pancreatitis and thus playing a central role in the pathogenesis of pancreatitis [64]. Besides, cathepsin B could contribute to DNA damage or TNFα-induced apoptosis in tumor cells by inducing directly or indirectly loss of sphingosine kinase-1(SK-1) [65]. Tumor necrosis factor (TNF) is a pleiotropic molecule with a crucial role in cellular stress and inflammation during infection, tissue damage, and cancer. TNF-α can induce apoptosis by activating caspase-8 and caspase -10, but can also inhibit apoptosis via NF-κB, which induces the expression of anti-apoptotic genes such as Bcl-2. So, cathepsin B has been described as an essential mediator in TNFα-mediated apoptosis [65,66]. For instance, hepatocytes from cathepsin B knockout mice are relatively resistant to TNF-α-induced apoptosis [67], for cathepsin B participates in TNF-α-induced, caspase-independent cell death of WEHI-S cells [68]. Ceramide generated by the lysosomal sphingomyelinase can trigger the proteolytic autoactivation of cathepsin D [69]. A single lysosomal hydrolase, cathepsin D, is sufficient to trigger MOMP. The first report showed that cytosolic cathepsin D could trigger mitochondrial outer-membrane permeabilization. The release of cathepsin D from lysosomes reportedly precedes the release of cytochrome c from mitochondria [70]. On the other hand, some data suggest that lysosomal destabilization and cathepsins might trigger cell death via novel, MMP-independent pathways, e.g., via direct cathepsin effects on the nucleus [71,72].

The receptor-interacting protein (RIP) family of serine-threonine kinases (RIP1, RIP2, RIP3, and RIP4) are important regulators of cellular stress that trigger pro-survival and inflammatory responses through the activation of NF-κB, as well as pro-apoptotic pathways [73]. RIP1 contains a death domain responsible for interaction with the death domain receptor Fas and recruitment to TNF-R1 through interaction with TRADD [74]. TRADD recruits TRAF2 to the TNF-R1 complex. RIP also interacts with TNF-receptor-associated factor 2 (TRAF2). Then the aggregated TRAF2 interacts with NIK and activates NIK. In turn, NIK would activate IKK, and the activated IKK phosphorylates IkB. The phosphorylated IkB will be rapidly degraded after ubiquitination. Finally, NF-kB is trans-located [75,76]. Overexpression of RIP1 induces both NF-κB activation and apoptosis. Caspase-8-dependent cleavage of the RIP1 death domain can trigger the apoptotic activity of RIP1 [77]. TNF-R promotes apoptosis via the adaptor proteins TRADD/ FADD and the activation of caspase-8. Interaction of TNF-α with TNF-R may activate the NF-κB pathway via NIK/IKK. The activation of NF-κB induces the expression of pro-survival genes including Bcl-2 and FLIP, the latter can directly inhibit the activation of caspase-8. The receptor-interacting serine-threonine kinase 3(RIP3) acts as the determinant for cellular necrosis in response to TNF-α family of death-inducing cytokines [78]. RIP3 is a key signaling molecule in the programmed necrosis (necroptosis) pathway [79,80]. RIP3 was originally found to interact with RIP and the TNF receptor complex, inducing apoptosis and activation of NF-κB [81,82]. So, it has been shown that the association between RIP1 and RIP3 is a key component of a signaling pathway, resulting in programmed necrosis, or necroptosis, a necrotic-like cell death induced by TNF in the presence of caspase inhibitors. MLKL is phosphorylated by RIP3 at the threonine 357 and serine 358 residues, and these phosphorylation events are critical for necrosis [83]. During the necrosis induction process, RIP3 binds to the kinase RIP1 (RIPK1) through their respective RIP homotypic interaction motif (RHIM) domains. Therefore, the RIPK1 inhibitor necrostatin-1 can prevent the RIP1/RIP3 interaction and block necrosis [78,84]. Importantly, caspase-8 is able to cleave RIP1 and RIP3, effectively terminating necrosis [77,85]. Thus, for necrosis to ensue, the inhibitory effect of caspase-8 must be overcomed either by caspase inhibitors or by a substantial elevation of RIP3 levels, which occurs during tissue damage [83,86] (Figure 2).

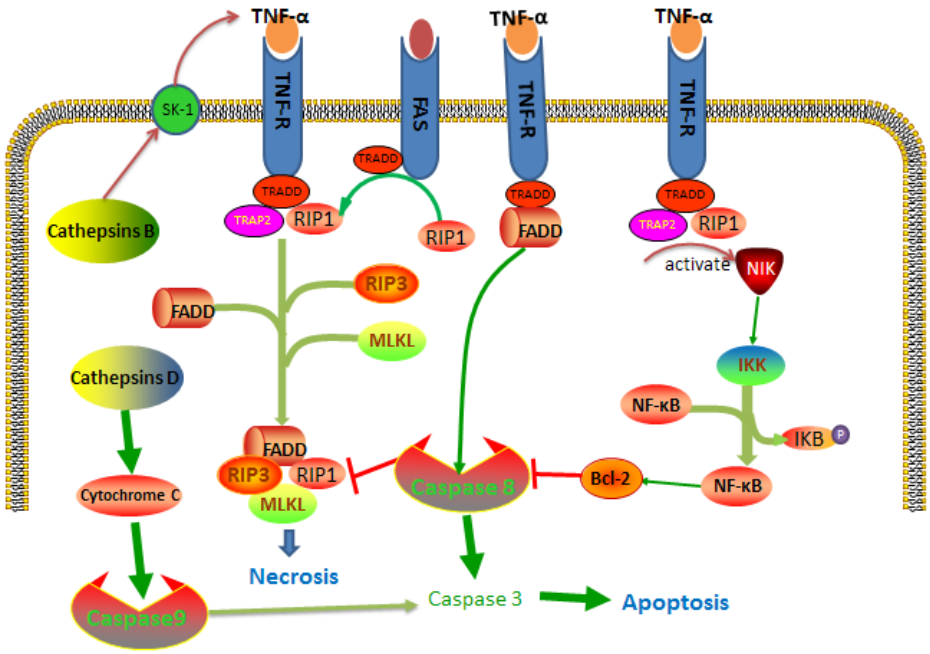

Figure 2: The detail mechanism describing the relations between nanoparticles and necrosis and apoptosis.

Some reports reveal that AuNRs enter the lysosome through endocytosis and AuNRs can be taken into cells by endocytosis in a size-dependent manner. The internalized AuNRs eventually accumulate in lysosomes and cause impairment of lysosome degradation capacity through alkalinization of lysosomal pH. Lysosomal membrane permeabilized by AuNRs, and escape from the lysosomes. But the escaped AuNRs are recycled back into the lysosomal system through cytoprotective autophagy in normal cell. Escaped AuNRs can induce autophagosome accumulation for the destroy of lysosome. autophagosome accumulation results from blockade of autophagy flux, and enhances the likelihood of cell death [87,88] The most important cause is that Lysosomal membrane permeabilization (LMP) causes the release of cathepsins and other hydrolases from the lysosomal lumen to the cytosol. LMP is a potentially lethal event because the ectopic presence of lysosomal proteases in the cytosol causes digestion of vital proteins and the activation of additional hydrolases including caspases. LMP causes the proteolytic activation of Bid (which is cleaved by the two lysosomal cathepsins B and D), which then induces MOMP , resulting in cytochrome c release ,decreasing mitochondrial membrane potential and increasing reactive oxygen species level that enhances apoptosome-dependent caspase activation [89]. With a high level LMP, Cathepsin B inactive TNF-a, and TNF-R collect Rip1 via the adaptor proteins TRADD/ FADD, then the RIP1-RIP3 complex forming,the necrosis program is actived,for example, in a streptococcus pneumoniae meningitis rodent model, cathepsin B inhibitor treatment greatly improved the clinical course of the infection and reduced brain inflammation and inflammatory Interleukin-1beta (IL1-beta) and tumor necrosis factor-alpha (TNF-alpha)[90]. Additionally, the mechanism is useful for regulating the cancer therapeutic index of nanomedicne [91-95].

Conclusions

Nanomedicines, whose particle sizes are about 100nm, get into cytoplasmid by clathrin-independent pathways. The special nanomedicine particles could destroy the lysosomes membrane to different degrees of damage, then the autophagic cargo comes into the cytoplasm, subsequent apoptosis and necrosis are morphologically distinct. Cathepsin B and cathepsin D play an important role in the cancer cell death. Cathepsin D can trigger permeabilization of mitochondrial outer-membrane, and precedes the release of cytochrome c from mitochondria, thus facilitating apoptosis of cancer cells. Cathepsin B can activate TNF-α , which in turn activates the NF-κB and inhibits the activation of caspase-8. So with the amount of RIP1-RIP3 complex increases, more cancer cells necrosis take place.

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