Advanced Progress of Nano-Based Delivery System for Bioimaging

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Abstract. Nanotechnology has been developing with the development of technology and has made great progress especially in the field of the development of biomedical engineering nanoparticles. Biological imaging plays an important role in medical research. Through biological imaging technology, researchers can intuitively observe the structural and functional changes of organisms at the microscopic level, so as to understand the mechanism of life activities. However, the current biological imaging technology, especially the traditional radioactive material imaging method, has problems such as potential safety hazards and poor imaging effect, which limits its wide application in clinical and scientific research. To address these challenges, research has turned to the field of nanotechnology to explore its potential advantages in bioimaging. Nanotechnology has unique physical and chemical properties. Nano-based bioimaging methods not only improve imaging resolution and sensitivity but also enhance biocompatibility and reduce potential hazards to organisms. This article details the application of various types of nanotechnology, such as liposomes, nanoparticles, and quantum dots, in biological imaging and the remarkable results achieved. These nano-imaging technologies not only realize the fine imaging of cells, tissues and even the whole organism, but also provide strong support for early diagnosis and precision treatment of diseases. This review introduces the applications and effects of different types of nanotechnology in bioimaging, explores the challenges and prospects of nanotechnology in bioimaging, and reveals the current development of bioimaging technology based on nanotechnology..

Keywords: Nano-based; nanoparticles; delivery system; bioimaging.

1. Introduction

Bioimaging plays an important part in the recent development of bioscience and medical research. It not only helps scientists to directly observe the complex physiological processes in living organisms but also provides strong support for early diagnosis and treatment of disease and the development of new medicine. However, with the deepening of biomedical research, the existing biological imaging technology has gradually exposed its limitations and cannot satisfy the growing research needs. Therefore, new technologies are urgently needed to fill this gap. This article aims to discuss the current challenges of bioimaging technology and propose the application prospects and revolutionary changes brought by nanotechnology in the field of bioimaging. By introducing the latest advances in nanotechnology-based bioimaging technology, this article aims to demonstrate the great potential of this emerging field in promoting life science research and medical diagnosis.

Bioimaging technology, serving as a core tool in contemporary biomedical research, goes without saying in terms of its significance. From microscopic observations at the cellular level to macroscopic monitoring of live animals, biological imaging technology has unveiled the mysteries of life phenomena. Nevertheless, existing biological imaging techniques, such as computed tomography (CT), fluorescence imaging, and magnetic resonance imaging (MRI), all have their respective advantages but also numerous limitations [1]. Specifically, for radioactive substance imaging such as X-ray, although it is widely applied in fields like tumor detection, its potential radioactive hazards and the instability of imaging effects have always been the key factors restricting its further development [2]. Hence, developing safer, more effective, and more operationally facile biological imaging techniques has emerged as an important demand in current research.

The advent of nanotechnology has introduced a new era in the field of bioimaging. Nanotechnology combines nanoscale science, technology, and engineering, with nanoparticles in the size scale of 1 to 100 nm [1]. These nanoparticles have unique physicochemical properties, such as magnetism and optical properties, that show great potential application in bioimaging [3]. Nano-based bioimaging enhances imaging resolution and sensitivity, facilitates precise labeling and tracking of specific biomolecules through surface modification and functional design [3-4]. More importantly, the metabolic process of nanomaterials *in vivo* is relatively controllable. By precisely regulating the physical and chemical properties of nanomaterials, they can reduce the toxicity and side effects to organisms, ensure their safe application in vivo, greatly reduce the potential harm to organisms, and make bioimaging safer and more effective [5]. Consequently, nanotechnology-based bioimaging technology represents a significant advancement in the field.

In summary, the purpose of this paper is to introduce the current development of nanotechnology-based bioimaging technology and its latest research progress. Through an in-depth analysis of the unique advantages of nanotechnology, this paper tries to show the remarkable achievements and broad prospects of nanotechnology in the field of biological imaging. With the continuous progress of nanotechnology and the growing demand for bioimaging, we have reason to believe that bioimaging technology based on nanotechnology will play a more important role in life science research and medical diagnosis in the future.

2. Nano-Based Delivery System

According to American Society for Testing Materia (ASTM) standards, nanoparticles are the target particles with lengths between 1 and 100 nanometers [5]. Based on nanotechnology, in the nano-based delivery system, nanocarrier can be applied to bioimaging [6]. Nanocarrier is a kind of nanoscale microscopic entity, with achieving high resolution and high sensitivity imaging through a specific mechanism. Nano-based delivery systems denote the system that employs carrier materials at the nanoscale (typically within the range of 1-100 nanometers) to effectively convey active molecules such as drugs, genes, and contrast agents to specific sites or within cells in the biological body [7-8]. These nanocarriers can not only safeguard the active molecules they carry from degradation in the biological environment but also achieve targeted delivery and controlled-release through specific mechanisms, thereby enhancing therapeutic effects and reducing toxic and side effects.

Nanocarriers that can be used in bioimaging are various. They have their unique physical and chemical properties to adapt to different bioimaging requirements. The following are some specific nanocarrier types **(Fig.1.)**:

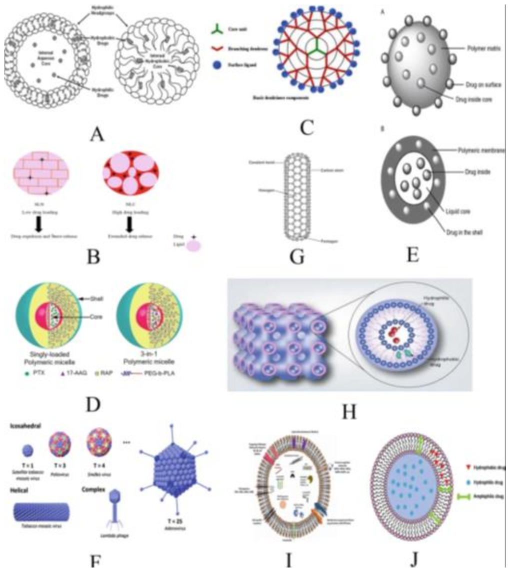

Fig.1. Schematic representation of the structure of varied nanocarriers [6]

2.1. Liposomes

Liposomes are tiny capsules composed of a bilayer of phospholipids. Their properties and applications can be changed by changing lipid composition and surface modification. Liposomes have good biocompatibility and degradability, and are able to encapsulate a variety of drugs and imaging agents. Liposomes are primarily utilized as carrier systems in biological imaging, typically incorporating fluorescent dyes or radioisotopes to facilitate the visualization of cells, tissues, or organs [6, 9]. Through specific binding to surface proteins or antibodies, liposomes efficiently deliver the imaging agents into the organism for precise targeting and visualization of desired tissues or cells [9]. This advanced imaging technology possesses notable characteristics such as exceptional resolution, sensitivity, and specificity, thereby providing crucial support for disease diagnosis and treatment. In addition, liposomes can also be used in areas such as drug delivery and gene therapy [6].

2.2. Polymeric Nanoparticles (PNPs)

PNPs can be synthesized from natural or synthetic materials and exhibit a wide range of structures and characteristics [6]. Various techniques, including emulsification, nanoprecipitation, ion gels, and microfluidics, can be employed to obtain diverse end products. These biodegradable, water-soluble particles possess excellent storage stability and are considered optimal materials for drug delivery applications. Moreover, their surfaces can be easily modified to target specific tissues for the delivery of drugs, proteins, and genetic materials. Through surface modification, polymeric nanoparticles can carry specific imaging agents, such as fluorescent dyes or radioisotopes, to achieve biological imaging. In tumor imaging, polymeric nanoparticles can encapsulate contrast agents and target tumor tissues, improving the sensitivity and specificity of imaging [6].

2.3. Metallic Nanoparticles(MNPs)

MNPs contain metallic elements such as gold (Au), silver (Ag), copper (Cu), iron (Fe), Hybrid metal (bimetallic), and other metals. They have unique catalytic, optical, electrical, and magnetic properties [3]. Because of their relatively free surface electrons, metallic nanoparticles contain unique electronic and optical properties [3]. Therefore, these properties make MNPs an excellent choice for the in vivo imaging of a variety of diseases such as cancer.

2.4. Metal Oxide Nanoparticles (MONPs)

The unique biocompatibility, optical properties, electrical properties, magnetic properties, imaging properties, and targeted delivery properties of MONPs make them highly promising for biomedical applications, especially for imaging in biological delivery [3].

The imaging mechanisms of metal oxide nanoparticles exhibit diversity, contingent upon their species and surface modifications [3]. For instance, due to their favorable magnetic properties, iron oxide nanoparticles find extensive application in MRI imaging. When exposed to an external magnetic field, detectable changes in magnetic moments can be induced by iron oxide nanoparticles, facilitating the visualization of specific tissues or cells within living organisms. Furthermore, metal oxide nanoparticles such as zinc oxide and titanium dioxide can be harnessed for fluorescence or photoacoustic imaging by exploiting their quantum size effect or photocatalytic properties [1, 3-4].

In order to achieve precise imaging of metal oxide nanoparticles within organisms, scientists employ surface modification technology to conjugate them with specific recognition molecules like antibodies, peptides, and small molecule ligands. This enables the targeted delivery of nanoparticles towards particular cells, tissues or biomarkers. Such a targeting strategy not only enhances the specificity of imaging but also reduces non-specific background signal interference thereby improving accuracy and sensitivity [3, 6].

2.5. Magnetic Metallic Nanoparticles (MagNPs)

MagNPs are often composed of NiNP, CoNP, FeNP and their oxide NPs [3]. MagNPs not only have the unique properties of nanomaterials, such as small particle size and good biocompatibility, but also have magnetic responsiveness and super-paramagneties [3]. The application of MagNPs in diagnostic techniques, such as magnetic resonance imaging (MRI), can be utilized as contrast agents to enhance the sensitivity and resolution of imaging [1, 3-4].

2.6. Quantun Dot (QD)

Semiconductor nanoparticles, which means quantum dots, have influenced various research fields to a large extent. QD have unique optoelectronic properties, which makes them well-suited for being utilized as optical probes in bioimaging and biosensing applications [10]. Furthermore, their luminescence properties can be modulated by adjusting their size and composition [10]. QD are commonly used in biological imaging for single-photon or multi-photon fluorescence imaging, which can achieve high-resolution imaging of cells, tissues or organs. In addition, quantum dots can be used in fields such as biosensing and disease diagnosis [10].

3. Basic Operating Principle of Nano-Based Delivery System for Bioimaging

The fundamental working principle of nano-based delivery systems in biological imaging primarily relies on the utilization of imaging probes or contrast agents carried by nanocarriers. These imaging probes or contrast agents interact with target molecules or structures within organisms through specific physical or chemical mechanisms, resulting in the production of detectable signals such as fluorescence and magnetic resonance signals. Nanoparticles, serving as carrier platforms, not only protect imaging probes or contrast agents from degradation and interference caused by the biological environment but also enable precise imaging of target molecules or structures through mechanisms like targeted delivery and controlled release.

Specifically, the nano-delivery system facilitates bioimaging through the following steps: The first step is to load of an imaging probe or contrast agent. A stable nanocomplex is formed when loading an imaging probe or contrast agent into a nanocarrier. Secondly, the important and specific step is targeted delivery. Interaction between targeting groups on the surface of the nanocarrier and specific cells or tissues within an organism enables targeted delivery of imaging probes or contrast agents. Then, it will be the generation of Imaging signal. At the designated site, interaction between biomolecules/structures and the loaded imaging probe/contrast agent leads to detectable signal production. Finally, the step is signal detection and analysis. Optical, magnetic resonance, and other types of imaging equipment are employed to capture and amplify these signals which are then processed using image processing techniques for obtaining information regarding target molecules/structures within the body.

4. Applications of Nano-Based Delivery Systems of Contrast Agent in Bioimaging

Nanoparticles applied as contrast agents in bioimaging have provided enhanced capabilities of visualization and diagnosis for various imaging ways, such as fluorescence imaging, Computed Tomography Imaging (CT), Magnetic Resonance Imaging (MRI), and ultrasonic Imaging [1, 4].

4.1. Fluorescence imaging

Fluorescence imaging utilizes nanomaterials to process imaging with the property of emitting fluorescence under light excitation at a specific wavelength [1, 4].

Fluorescence imaging nanocarriers encompass QDs, MNPs (such as gold and silver nanoparticles), and organic fluorescent dye-labeled nanoparticles [1, 4, 10]. QDs exhibit exceptional performance in fluorescence imaging due to their size-dependent fluorescence emission characteristics, high optical stability, and resistance to photobleaching [10]. MNPs possess remarkable surface plasmon resonance properties that make them suitable for various biological imaging techniques [1, 3-4]. Additionally, there are near-infrared fluorescent dye-labeled nanoparticles available. For instance, with the implementation of small animal in vivo illumination systems (IVIS), leveraging fluorescence imaging in the near-infrared (NIR) spectrum, the routine validation of biodistribution and targeted delivery of drug nanocarriers has become a standard practice [11].

4.2. Magentic Resonance Imaging (MRI)

MRI use nanoparticles as contrast agents to significantly improve the sensitivity and resolution of imaging, providing effective measures for early diagnosis and treatment of diseases. Furthermore, MRI utilizes the unique properties of nanomaterials in magnetic fields, such as the paramagnetism- or superparamagnetism-of magnetic nanoparticles, to enhance MRI signals [1, 3-4].

Magnetic nanoparticles, especially those classified as superparamagnetic, such as iron oxide nanoparticles, have attracted considerable interest in the field of MRI due to their remarkable ability to enhance magnetic resonance contrast, favorable biocompatibility, and capability for magnetic targeting. A notable example is Ferumoxytol, a new formulation of iron oxide nanoparticles that has received FDA approval for clinical use [12]. These nanoparticles can be absorbed by cells through phagocytosis, which enhances MRI signals and aids in the imaging and tracking of various cell types, including stem cells [12].

4.3. Computed Tomography Imaging (CT)

CT utilize X-ray to scan organisms, obtain the sectional imaging through computer reconstruction. Some metallic nanoparticles with properties of high X-ray attenuation can be utilized as contrast agents, such as AuNPs [1, 3-4]. These nanoparticles improve the absorption of X-rays, so that they enhance the contrast of CT images. They facilitate high-resolution visualization of intricate blood vessel networks, neoplastic tumors, and intricate anatomical structures, achieving unparalleled sensitivity and specificity through CT.

Rare-earth element nanoparticles also have high X-ray absorption ability and low toxicity [5]. For example, the $Yb(OH)CO_3$ nanoparticle contrast agent has a good distribution and metabolism in mice, and has obvious advantages for tissue imaging.

4.4. Positron Emission Tomography (PET)

PET imaging is a radioactive tracer-based nuclear [1]. Nanoparticles, functioning as carriers, can load molecules or drugs labeled with radioactive isotopes and be transported through the bloodstream to specific tissues or organs within the human body. For instance, Radioactive-labeled metal nanoparticles can be employed as PET imaging contrast agents through carrying radioactive isotopes. During the PET scanning process, these radioactive isotopes decay and release positrons [1, 3-4]. These positrons combine with electrons in the body to form annihilation radiation, emitting two gamma rays in opposite directions. Through the capture of these gamma rays by detectors, it is feasible to reconstruct the radioactive distribution image within the body, thereby enabling the imaging of the target tissue or organ [13].

4.5. Ultrasonic Imaging

Ultrasonic imaging is a non-invasive imaging method, that can be utilized to molecular level visualize biological processes [1, 4]. Nano-based delivery systems of contrast agents in ultrasonic imaging represent a significant advancement in the field of medical imaging. These systems leverage the unique properties of nanomaterials to enhance the delivery, targeting, and imaging capabilities of contrast agents, thereby improving the accuracy and sensitivity of ultrasonic imaging.

Nanomaterials, such as metal nanoparticles or nanocomposites, can be used as contrast agents in ultrasonic imaging [1, 3-4]. Their high surface-to-volume ratio and small size allow for better interaction with ultrasound waves, resulting in enhanced imaging resolution and sensitivity. These nanomaterials can be tailored to have specific physical and chemical properties that optimize their performance as contrast agents, such as improved stability, reduced aggregation, and enhanced targeting capabilities.

4.6. Multimodal imaging

Multimodal imaging combines the advantages and improved disadvantages of varied imaging modalities in accurately characterizing biological tissues. In this case, multimodal imaging improves sensitivity and imaging accuracy, accompanied by guidance and monitoring of treatment [3].

Through design and modification, nanoparticles can be designed with multiple imaging modalities at the same time. For example, some nanoparticles can be used simultaneously for multiple imaging techniques such as magnetic resonance imaging (MRI), fluorescence imaging, and computed tomography (CT) to provide comprehensive disease information. Multimodal imaging combined with the use of nanoparticles can achieve accurate localization, qualitative and quantitative analysis of the lesion tissue, thereby improving the accuracy of diagnosis.

5. Specific applications of nanoparticles in medical imaging

5.1. Tumor detection and diagnosis

The application of nanoparticles in the diagnosis and imaging of tumors primarily benefits from their characteristics such as small size, high specific surface area, and facile modification. These properties allow nanoparticles to act as novel contrast agents and drug carriers, exerting significant roles in targeted therapy, molecular imaging, and early diagnosis [14].

MNPs, such as gold and silver, have unique optical properties, including surface plasmon resonance effects, that enable them to emit intense fluorescence or scattered light under specific lighting conditions. These intrinsic properties make metal nanoparticles excellent for optical imaging applications. In addition, metal nanoparticles can be tuned to achieve targeted identification of cancer cells, resulting in precise imaging of tumor cells [1, 3-4, 14].

QDs exhibit size-dependent optical properties, allowing for adjustable luminescence wavelengths by manipulating their sizes. This characteristic confers a significant advantage to quantum dots in the field of multicolor imaging and biomarkers. Additionally, QDs possess excellent photostability and resistance to bleaching, ensuring a stable fluorescence signal throughout prolonged imaging sessions [4, 10, 14].

5.2. Angiography

The utilization of nano-delivery systems in angiography primarily involves harnessing the unique properties of nanotechnology to enhance imaging effectiveness and improve diagnostic precision. These systems effectively package contrast agents or other imaging molecules by utilizing the distinctive physicochemical characteristics of nanoparticles, including their small size effect and surface effect. This allows for stable transportation and targeted release of contrast agents within the body, facilitating enhanced blood vessel imaging.

Bio-nano delivery systems employ nanoparticles encapsulated in cell membranes, such as platelets and red blood cells, to enhance the stability and targeting of nanoparticles in blood vessels by taking advantage of the specific targeting capabilities and biocompatibility of these cell membranes. For example, some studies have successfully achieved targeted imaging of atherosclerotic plaques using platelet membrane-modified polylactic acid glycolic acid (PLGA) nanoparticles encapsulated contrast agents [15].

5.3. Infection and Inflammation Diagnosis and Imaging

Nanoparticles are widely used in the diagnosis and imaging of infection and inflammation.

5.3.1 Infection Diagnosis and Imaging

Some nanoparticles can be used for bacterial detection and identification. For example, MNPs are often used for sample preparation and bacterial isolation and detection due to their excellent magnetic properties, low cost and analytical versatility. For example, a variety of bacterial pathogens can be isolated and detected in microcentrifuge tubes using lectin-functionalized silver-coated MNPs and optically active antibody-coated silver-coated NPs. AuNPs can enhance the sensitivity of immune-PCR (IPCR) to detect bacterial antigens. By binding to DNA, AuNPs can further improve the sensitivity of IPCR to achieve accurate detection of bacterial pathogens [1, 3-4, 16].

Moreover, Some specific nanoparticles can be used for virus detection and identification. For instance, Au-silver hybrid nanoparticles combine the properties of gold nanorods and silver nanoparticles and can be used for virus detection and photoacoustic imaging. By monitoring the release of silver ions and changes in photoacoustic signals, real-time monitoring and treatment of viral infection can be achieved.

5.3.2 Inflammation Diagnosis and Imaging

In near-infrared two-region fluorescence imaging, quantum dots (QDs) and other nano-fluorescent contrast agents have long excitation wavelengths and higher brightness, which are suitable for high-definition fluorescence imaging in vivo. For example, NIR-II fluorescent contrast agents such as Ag_2S quantum dots can be used for accurate imaging of bacterial inflammation, which provides strong support for the diagnosis and treatment of inflammation [10].

5.3.3 Comprehensive application

Nanoparticle-based biosensors have high sensitivity and stability and can be used to detect biological signals in the body, such as metabolites, biomolecules or microorganisms. In the diagnosis of inflammation, nanoparticle biosensors can detect inflammation-related biomarkers, such as cytokines and chemokines, and provide important information for the diagnosis of inflammation.

6. Challenge and Outlook

Nano-based delivery systems have emerged as a revolutionary approach in the field of bioimaging, offering unprecedented precision and sensitivity in visualizing biological processes and structures. These systems leverage the unique properties of nanoparticles, such as their small size, high surface-to-volume ratio, and the ability to be functionalized with various ligands, to deliver imaging agents directly to target tissues or cells. However, There all still many challenges in the nano-based delivery system. Nano-based delivery systems face challenges related to biocompatibility and safety [4-5]. Nanoparticles can interact with biological systems in unpredictable ways, leading to potential toxicity and immune responses. Ensuring the safety of these systems is crucial for their clinical translation. Maintaining the stability and longevity of nano-based delivery systems in vivo is another challenge. Nanoparticles can be degraded or cleared by the body’s clearance mechanisms, reducing their effectiveness over time. Developing strategies to enhance the stability and longevity of these systems is essential for their sustained use in bioimaging.

At the same time, as nanoparticles continue to show their great potential in various fields, especially in medicine, future bioimaging research efforts will further exploit the multiple capabilities and special properties of these nanomaterials. The development of new nanomaterials with enhanced properties, such as higher stability, better biocompatibility, and stronger imaging signals, will drive the advancement of nano-based delivery systems for bioimaging. These innovative nanomaterials will enable more precise and sensitive imaging of biological processes. Personalized Medicine will be more researched. with the increasing focus on personalized medicine, nano-based delivery systems will play a crucial role in tailoring imaging and treatment strategies to individual patients. By targeting specific biomarkers or genetic signatures, these systems will enable more personalized and effective care.

7. Conclusion

In this article, the application of various bioimaging systems for biological delivery based on the formation of different nanoparticles, which is the application of various biological imaging such as CT, MRI and PET to various specific nanoparticles have been discussed. In conclusion, this thesis first highlighted the importance of bioimaging in modern medical research, which provides us with a key means of in-depth observation of the structure and function of organisms. Subsequently, the unique advantages of nanotechnology in the field of bioimaging are discussed in detail, including but not limited to high resolution, high sensitivity and good biocompatibility. By introducing several mainstream nanoimaging technologies, such as quantum dot imaging, optical imaging, and nanoparticle-based magnetic resonance imaging, this article further reveals the great potential of nanotechnology in specific medical applications such as cancer diagnosis, vascular imaging, and infection and inflammation imaging. These examples not only prove the feasibility of nanotechnology in the field of biological imaging, but also predict its broad development prospects.

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