COMMENTARY

The potential of engineered multifunctional quantum dots for macrophage theranostics

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Macrophages play important roles in tissue repair, inflammation, and the progression of various diseases. Imaging and tracking macrophage cells *in vitro* and *in vivo* can reveal the location and movement of macrophages in tissues and animals, which is critical to understanding macrophage functions in different diseases.[1] Macrophages can generally be divided into the following two phenotypes based on their physiological functions: proinflammatory M1 macrophages and alternatively activated M2 macrophages, both of which are closely related to the development and progression of various diseases. A promising methodology for disease therapy is the modulation of macrophage phenotypes, which can reverse disease states and metabolic processes. Therefore, engineering nanoparticles that combine the advantages of imaging and therapy may offer novel strategies for macrophage theranostics.

THE BASICS OF QUANTUM DOTS

Quantum dots (QDs) are colloidal nanoparticles with diameters ranging from several to dozens of nanometers that exhibit strong and stable fluorescence with high quantum yields and photostability. The photophysical properties of QDs can be easily controlled by changing their size as follows: redshifted absorption and emission accompany increasing size. The enhanced photostability with high brightness enables single-molecule and single-particle tracking using QDs with different emission colors. QDs can be combined with targeting ligands to enable the imaging and tracking of intracellular proteins, ribonucleic acids, and other targets. By preparing near-infrared (NIR) QDs, *in vivo* and tissue imaging become possible, providing valuable information for analyzing disease states and mechanisms. Metal-based QDs have high brightness, stability, and emission tunable to the NIR region, making them ideal for short-term bioimaging in tissues and *in vivo*, but they are generally limited by the toxicity of heavy metals. Carbon and graphene QDs can also be utilized for bioimaging, and they are more promising for *in vivo* applications, especially therapeutic applications, because of their low toxicity.

QUANTUM DOTS FOR MACROPHAGE IMAGING

Since macrophages can take up nanoparticles via phagocytosis, most fluorescent nanoparticles can light up macrophages. To image macrophages with QDs, various methods can be utilized to enhance macrophage specificity.

A general methodology involves modifying QDs with mannose-functionalized polyethylene glycol, which stabilizes QDs in aqueous solutions and enables macrophage targeting. The targeting of mannose-modified QDs can be hindered by preincubation with mannose, resulting in reduced fluorescence in macrophage cells. However, conjugating QDs to macrophage-specific antibodies can enhance their specificity toward macrophage cells for targeted bioimaging and tracking. A specific type of dextran-mimetic QD with near-infrared emission was synthesized and used for imaging macrophage cells in obese rodents.[2] In this study, a dextran-mimetic QD platform was created by combining NIR QDs with low-molecular-weight dextran through a copper-free click reaction. The resulting dextran-mimetic QDs demonstrated exceptional brightness, photostability, and chemical stability. Additionally, their slower diffusion in crowded microenvironments resulted in improved blood circulation and macrophage targeting in obese mice.

Another strategy is the utilization of nanosystems for QD delivery to macrophage cells for enhanced fluorescence imaging. A common liposomal nanosystem was used to encapsulate QDs to generate macrophage-targeted functional QDs, which showed better photochemical stability and enhanced accumulation and retention compared to free QDs.[3] This liposomal QD system achieved targeted macrophage imaging in a rat injured artery with high resolution and specificity in tissues.

QUANTUM DOTS FOR MACROPHAGE POLARIZATION

Quantum dots can impact the activity of macrophage cells, commonly inducing macrophage phenotype transformation, and thus QDs show therapeutic potential. The macrophage reprogramming ability can be ascribed to the composition and structure of QDs; moreover, QDs can act as a drug delivery system to carry macrophage polarization adjuvants. A kind of graphene QD was designed to measure the therapeutic effect of treating intestinal bowel diseases in mice.[4] The graphene QDs exhibited low toxicity *in vivo* and rapid clearance after intraperitoneal injection. Moreover, they could decrease intestinal inflammation by inducing macrophage M2 polarization and regulatory T cell infiltration, revealing its potential for the treatment of colitis by regulating immune cell functions. Another type of carbon QD derived from chlorogenic acid was found to promote cancer cell ferroptosis and immune cell infiltration into solid tumors, which enhanced tumor immunogenicity by activating antitumor immune responses.[5] Thus, this type of carbon QD significantly inhibited tumor growth in hepatoma H22-bearing mice by enhancing tumor infiltration by immune cells, such as T cells, NK cells, and macrophages, to activate immune responses. Overall, these studies demonstrate the potential of QDs as a tool for macrophage polarization and immune cell modulation, opening up new avenues for treating various diseases and enhancing immunotherapeutic efficacy.

THE POTENTIAL OF QUANTUM DOTS IN MACROPHAGE THERANOSTICS

Traditional QDs have great potential in macrophage theranostics due to their optical properties, which enable improved bioimaging *in vitro*, *in vivo*, and *in situ*, making it possible to track different targets at the single-particle level. Quantification in tissues or in cells reveals the heterogeneity of cells and target distribution, which is closely related to the development of a variety of diseases. In this direction, the engineering of NIR QDs, especially NIR two-emissive QDs, can significantly improve the sensitivity and accuracy of tissue and *in vivo* imaging. Moreover, safety issues are a potential limitation of traditional QDs because of their heavy metal or adjuvant compositions. Metal-free QDs thus present improved biocompatibility with diverse functions, which allows their use in long-term *in vivo* applications for bioimaging and disease therapy with minimal safety concerns. A suitable combination of macrophage-targeting ligands, peptides, or polysaccharides with QDs can affect the targeting affinity to macrophages and thus impact the outcome of macrophage theranostics. The development of novel QDs with diverse compositions can improve QD bioactivity, especially for macrophage cells, which have high plasticity. Thus, a promising methodology to design QDs that can modulate macrophage phenotypes is to combine different bioactive small molecules or biomacromolecules. A general strategy might be the use of

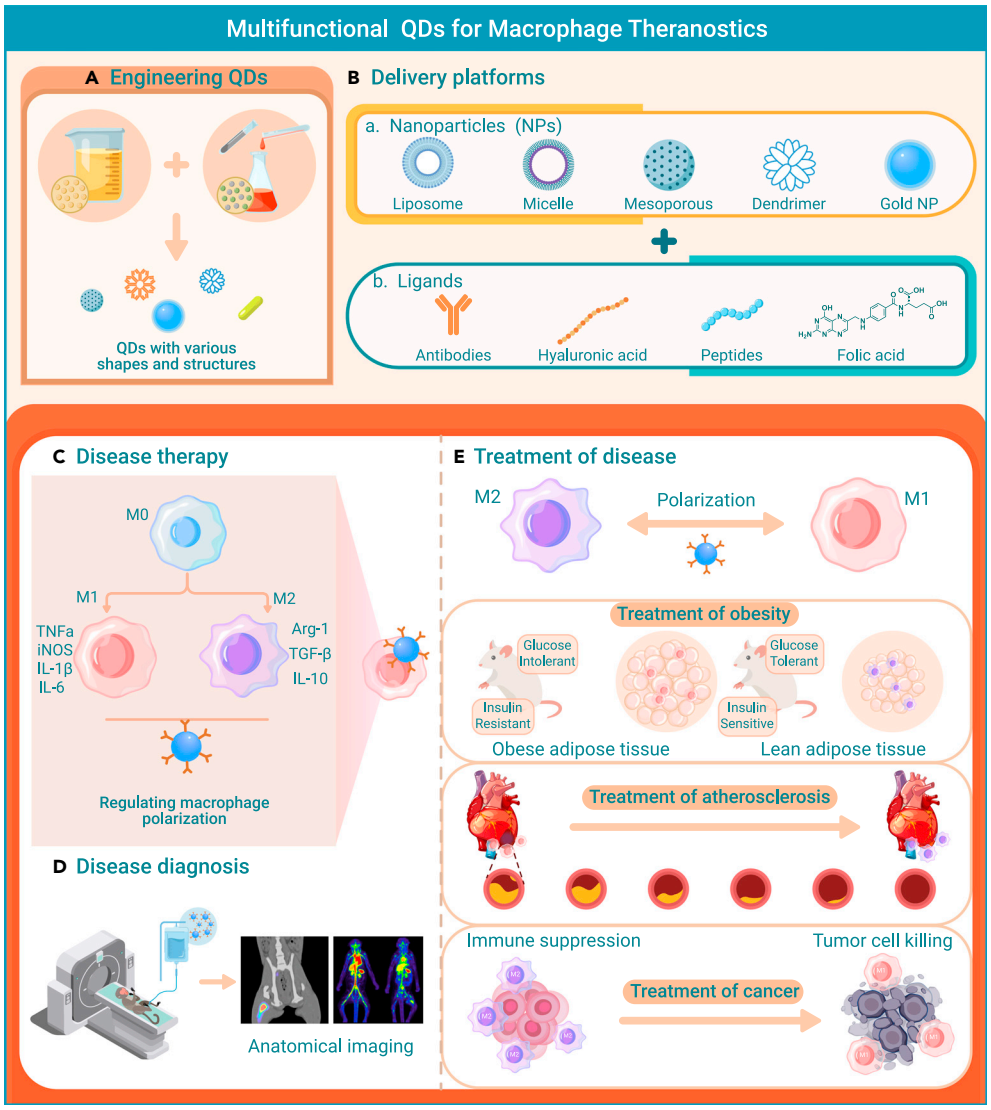

Figure 1. The figure illustrates the preparation of quantum dots for macrophage theranostics Bioactive quantum dots can be fabricated or functionalized via a variety of active ingredients and ligands, which enables targeted macrophage imaging and polarization to M1/M2 phenotypes. The reprogramming of M1 macrophages to M2 macrophages has therapeutic effects in obesity and atherosclerosis, whereas the polarization of M2 macrophages to M1 macrophages promotes tumor immunotherapy.

QDs as a drug delivery system that carries immune adjuvants for macrophage theranostics. Importantly, the biological interface of engineered QDs in organisms needs to be considered when designing multifunctional QDs because of the potential formation of the protein or biomolecule corona *in vivo* to change the targeting or polarization direction of these QDs.

In summary, QDs with intrinsic bright and stable fluorescence emissions are robust tools for the optical imaging of macrophages at multiple scales. In combination with active ingredients, adjuvants, or biopolymers, such multifunctional QDs have promising potential for use in both imaging macrophage cells and modulating macrophage functions, thereby providing novel functions for macrophage theranostics (Figure 1). This novel approach to macrophage theranostics has promising implications for future research and development.

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DECLARATION OF INTERESTS

The authors declare no competing interests.