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Theranostic Nanoparticles for Imaging and Treating Obesity-Associated Inflammation

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ABSTRACT

Obesity-associated inflammation is a central driver of metabolic dysfunction, contributing to insulin resistance, type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease. This chronic low-grade inflammatory state originates primarily from dysfunctional white adipose tissue and is characterized by immune cell infiltration, cytokine overproduction, oxidative stress, and altered tissue architecture. Early detection and precise intervention remain major challenges due to the diffuse and heterogeneous nature of obesity-related inflammation. Theranostic nanoparticles integrated platforms combining diagnostic imaging and therapeutic functions have emerged as a powerful strategy to address these challenges simultaneously. By enabling real-time visualization of inflamed tissues while delivering targeted anti-inflammatory or metabolic therapies, theranostic nanomaterials offer unprecedented opportunities for precision medicine in obesity. These nanoparticles can be engineered to respond to inflammatory cues, selectively accumulate in inflamed adipose depots, and provide multimodal imaging capabilities such as magnetic resonance imaging, fluorescence imaging, positron emission tomography, or photoacoustic imaging. This review provides a comprehensive overview of the molecular basis of obesity-associated inflammation, principles of theranostic nanoparticle design, and current advances in imaging-guided treatment strategies. We discuss key nanoplatforms, preclinical applications, translational challenges, and future perspectives, highlighting the potential of theranostic nanotechnology to transform the diagnosis and management of obesity-related inflammatory disorders.

Keywords: Theranostic nanoparticles; Obesity-associated inflammation; Adipose tissue imaging; Nanomedicine; Metabolic syndrome

INTRODUCTION

Obesity has become one of the most pervasive global health challenges, with its prevalence rising steadily across all age groups and socioeconomic strata[1-4]. Beyond excessive fat accumulation, obesity is increasingly recognized as a chronic inflammatory disease that drives the development of insulin resistance, type 2 diabetes, cardiovascular disease, and other metabolic complications[5, 6]. This inflammatory state is characterized by persistent activation of innate and adaptive immune pathways, particularly within white adipose tissue, and is a key determinant of disease progression and therapeutic response[7, 8,9-13].

In lean individuals, white adipose tissue functions as a metabolically active endocrine organ that regulates energy storage, lipid metabolism, and insulin sensitivity through the secretion of adipokines[9-11,14-18]. In obesity, however, adipocyte hypertrophy, hypoxia, oxidative stress, and adipocyte death disrupt tissue homeostasis. These changes promote the recruitment and activation of immune cells, particularly pro-inflammatory macrophages, leading to sustained production of cytokines such as tumor necrosis factor-α, interleukin-6, and interleukin-1β. The resulting inflammatory milieu interferes with insulin signaling pathways locally and systemically, contributing to metabolic dysfunction[12,19-23].

A major challenge in managing obesity-associated inflammation is its diffuse, heterogeneous, and often subclinical nature. Conventional diagnostic tools rely largely on systemic biomarkers or indirect imaging methods that lack spatial resolution and specificity for inflamed adipose tissue[13, 14, 24-29]. Similarly, pharmacological interventions are typically administered systemically, resulting in limited tissue specificity, off-target effects, and variable therapeutic efficacy. These limitations underscore the urgent need for technologies that can both detect and treat inflammation with high precision.

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Theranostic nanotechnology offers a compelling solution to this challenge. Theranostic nanoparticles are multifunctional platforms that integrate diagnostic imaging agents and therapeutic payloads within a single nanoscale construct[15-18,30-35]. This dual functionality enables real-time visualization of disease processes while simultaneously delivering targeted therapy. In the context of obesity, theranostic nanoparticles can be engineered to selectively accumulate in inflamed adipose tissue, report inflammatory activity through imaging signals, and release anti-inflammatory or metabolic drugs in a controlled manner.

The application of theranostic nanomedicine to obesity-associated inflammation represents a paradigm shift toward precision and personalized treatment. Imaging-guided therapy allows clinicians to identify inflamed adipose depots, monitor disease progression, assess treatment response, and adjust therapeutic regimens dynamically. Furthermore, the ability to visualize nanoparticle biodistribution and drug release enhances safety and accelerates translational development[15,36-40]. This review focuses on the role of theranostic nanoparticles in imaging and treating obesity-associated inflammation. We discuss the pathophysiological features that enable nanoparticle targeting, design principles of theranostic systems, current imaging modalities, therapeutic strategies, and translational challenges. By integrating diagnostics and therapy, theranostic nanotechnology holds significant promise for improving outcomes in obesity-related inflammatory diseases.

2. Molecular and Cellular Basis of Obesity-Associated Inflammation

Obesity-associated inflammation is driven by complex interactions between adipocytes, immune cells, and metabolic stress signals. As adipose tissue expands, adipocytes experience hypoxia due to insufficient vascularization, leading to activation of hypoxia-inducible factor-1α and pro-inflammatory gene expression[9, 19–21,41-45]. Concurrently, excess nutrient availability induces mitochondrial dysfunction and endoplasmic reticulum stress, resulting in elevated production of reactive oxygen species.

Macrophage infiltration is a defining feature of inflamed adipose tissue. In lean states, adipose tissue macrophages predominantly exhibit an anti-inflammatory M2 phenotype. Obesity induces a phenotypic switch toward pro-inflammatory M1 macrophages, which form crown-like structures around dead or dying adipocytes[22–25,46-48]. These macrophages secrete cytokines and chemokines that amplify inflammation and recruit additional immune cells.

Other immune populations, including neutrophils, T cells, B cells, and mast cells, further contribute to the inflammatory cascade. Proteolytic enzymes, matrix metalloproteinases, and inflammatory lipids are upregulated, promoting extracellular matrix remodeling and tissue fibrosis[26,49-53]. The inflamed adipose microenvironment is also characterized by mild acidosis, elevated oxidative stress, and increased vascular permeability[26,54-58].

These molecular features create distinct pathological signatures that can be exploited by theranostic nanoparticles. Overexpression of macrophage scavenger receptors, integrins, and adhesion molecules provides targets for nanoparticle binding, while oxidative stress and enzymatic activity offer triggers for controlled drug release and imaging signal activation.

3. Design Principles of Theranostic Nanoparticles

Theranostic nanoparticles are designed to integrate diagnostic and therapeutic functions without compromising either component. Their architecture typically consists of a core material that provides imaging contrast, a therapeutic payload, and a surface layer that enables targeting, stability, and biocompatibility[15, 17,59-63].

Imaging components may include magnetic materials for magnetic resonance imaging, radionuclides for positron emission tomography, fluorescent dyes for optical imaging, or plasmonic materials for photoacoustic imaging[27, 28,64-69]. Therapeutic agents can range from small-molecule anti-inflammatory drugs and antioxidants to nucleic acids and biologics.

Targeting strategies are central to theranostic design. Passive targeting exploits enhanced permeability and retention in inflamed tissues, while active targeting involves surface functionalization with ligands that bind receptors expressed on inflamed endothelial cells, macrophages, or adipocytes[28,70-73]. Stimuli-responsive elements enable drug release in response to acidic pH, reactive oxygen species, or enzymatic activity[29,74-78]. Importantly, theranostic nanoparticles must maintain stability during circulation while allowing efficient imaging signal generation and controlled therapeutic release at the target site[30, 31,79-80]. Achieving this balance requires careful optimization of size, surface charge, composition, and degradation kinetics.

4. Imaging Modalities Enabled by Theranostic Nanoparticles

Theranostic nanoparticles provide a powerful platform for the multimodal imaging of obesity-associated inflammation, enabling detailed visualization of inflammatory processes within adipose tissue[32]. Their ability to integrate diagnostic imaging with therapeutic functionality allows for precise detection and monitoring of disease progression as well as treatment response. Among available imaging techniques, magnetic resonance imaging (MRI) plays a central role due to its high spatial resolution, excellent soft tissue contrast, and deep tissue penetration[32]. These features make MRI particularly suitable for visualizing inflamed adipose depots and assessing structural and cellular changes associated with obesity-related inflammation. Iron oxide–based nanoparticles are especially valuable in this context, as they are readily taken up by macrophages, allowing selective imaging of macrophage-rich inflamed adipose tissue and providing indirect insight into immune cell infiltration[33].

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Positron emission tomography (PET) complements MRI by offering exceptional sensitivity and quantitative imaging capability. When nanoparticles are labeled with appropriate radionuclides, PET enables accurate tracking of inflammatory activity and nanoparticle biodistribution in vivo[34, 35]. This quantitative nature allows precise assessment of inflammation severity and therapeutic accumulation, which is essential for evaluating treatment efficacy and disease progression. PET imaging is particularly useful for longitudinal studies and for correlating inflammatory burden with metabolic outcomes.

Fluorescence imaging is widely used in preclinical research due to its simplicity, high sensitivity, and ability to provide real-time visualization of nanoparticle distribution and cellular interactions[36]. Although limited by tissue penetration, it remains a valuable tool for mechanistic studies and early-stage therapeutic evaluation. Photoacoustic imaging further expands the imaging toolbox by combining optical contrast with ultrasound resolution and penetration depth[37]. This hybrid modality enables visualization of vascular remodeling, oxygenation status, and inflammatory changes within adipose tissue, offering complementary functional information.

Importantly, the integration of multiple imaging modalities within a single theranostic nanoparticle enhances diagnostic accuracy and allows cross-validation of inflammatory signals[38, 39]. Such multimodal systems support imaging-guided therapy by enabling dynamic monitoring of treatment responses, facilitating dose optimization, and advancing precision approaches for managing obesity-associated inflammation.

5. Therapeutic Applications of Theranostic Nanoparticles in Obesity

Theranostic nanoparticles represent an emerging and highly promising strategy for the management of obesity-associated inflammation and its metabolic consequences[40]. These multifunctional platforms integrate diagnostic imaging capabilities with therapeutic functions, enabling simultaneous detection, targeted drug delivery, and real-time monitoring of treatment responses. In the context of inflamed adipose tissue, theranostic nanoparticles have been specifically engineered to deliver anti-inflammatory agents directly to pathological sites, thereby minimizing off-target distribution, reducing systemic exposure, and limiting drug-related toxicity[41, 42]. This targeted delivery approach is particularly advantageous in chronic metabolic disorders, where long-term pharmacological interventions often lead to adverse side effects.

By incorporating imaging moieties such as fluorescent dyes, magnetic resonance imaging (MRI) contrast agents, or radionuclides, theranostic nanoparticles provide real-time feedback on biodistribution and target engagement[43]. This imaging capability allows researchers and clinicians to confirm that therapeutic agents are effectively reaching inflamed adipose depots and exerting their intended effects. Such feedback not only enhances treatment precision but also facilitates dose optimization and longitudinal assessment of therapeutic efficacy, which are critical for chronic conditions like obesity and metabolic syndrome[43].

Oxidative stress is a key driver of adipose tissue inflammation and insulin resistance in obesity[44]. In response, antioxidant-loaded theranostic systems have been developed to neutralize excess reactive oxygen species within adipose tissue[45]. These nanoparticles often encapsulate natural or synthetic antioxidants and release them in a controlled manner at inflamed sites. Concurrent imaging enables visualization of oxidative stress reduction, providing a direct link between therapeutic action and physiological outcome. This dual functionality strengthens mechanistic understanding while improving therapeutic reliability[46].

Macrophage-targeted theranostic nanoparticles have also gained significant attention due to the central role of immune cells in adipose inflammation. In obese adipose tissue, pro-inflammatory M1 macrophages dominate and contribute to chronic low-grade inflammation. Nanoparticles functionalized with ligands that recognize macrophage-specific receptors can selectively accumulate in these immune cells[22, 26]. Once internalized, they deliver immunomodulatory agents that reprogram macrophages toward an anti-inflammatory M2 phenotype. Imaging components enable tracking of macrophage targeting and phenotypic shifts, offering valuable insight into immune dynamics within adipose tissue.

Beyond drug delivery, gene-based theranostic approaches provide a powerful means to both visualize and regulate inflammatory gene expression. These systems may incorporate nucleic acids such as siRNA, miRNA, or plasmid DNA alongside imaging probes, allowing simultaneous gene silencing or activation and real-time monitoring of molecular changes[47, 48]. Such strategies enable precise modulation of key inflammatory pathways implicated in obesity-related metabolic dysfunction.

Overall, the integration of imaging and therapy within a single nanoscale platform facilitates early intervention, disease stratification, and personalized treatment planning. Preclinical studies consistently report significant improvements in insulin sensitivity, reduced adipose tissue inflammation, and enhanced metabolic outcomes following theranostic nanoparticle treatment[49]. Collectively, these advances highlight the transformative potential of theranostic nanotechnology in addressing obesity-driven inflammation and paving the way toward more precise, effective, and individualized metabolic therapies.

6. Translational Challenges and Clinical Perspectives

Despite promising advances, clinical translation of theranostic nanoparticles faces significant challenges. Long-term safety, biodegradation, and potential accumulation in off-target organs require thorough evaluation. Manufacturing scalability, reproducibility, and regulatory complexity further complicate development[50, 51].

Inter-individual variability in adipose tissue distribution and inflammatory profiles necessitates personalized design strategies[52]. Additionally, integration of imaging technologies into routine clinical workflows remains a logistical hurdle. Addressing these challenges will require interdisciplinary collaboration, standardized evaluation frameworks, and robust clinical trials.

CONCLUSION

Theranostic nanoparticles represent a powerful and innovative approach for imaging and treating obesity-associated inflammation. By integrating diagnostic and therapeutic functions within a single platform, these systems enable precise detection, targeted intervention, and real-time monitoring of inflammatory processes. Advances in nanomaterial design, targeting strategies, and multimodal imaging have demonstrated significant promise in preclinical models of obesity and metabolic disease. However, successful clinical translation will depend on overcoming challenges related to safety, scalability, and regulatory approval. With continued technological refinement and clinical validation, theranostic nanotechnology has the potential to transform the management of obesity-related inflammation, advancing precision medicine and improving long-term metabolic outcomes.

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