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Nanoparticle-Induced Modulation of Inflammatory Pathways in Obesity: From Mechanistic Understanding to Therapeutic Design

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ABSTRACT

Obesity is characterized by chronic low-grade inflammation that originates primarily in expanding white adipose tissue and propagates to liver, skeletal muscle, vascular endothelium and pancreas, driving insulin resistance and cardiometabolic complications. Hypertrophic adipocytes and infiltrating immune cells, especially adipose tissue macrophages, sustain a network of inflammatory pathways centered on NF-κB, JNK and the NLRP3 inflammasome, with strong crosstalk to autophagy and metabolic signaling. Nanoparticles interact intimately with immune and stromal cells in these tissues, and can either exacerbate or resolve inflammatory stress depending on their composition, size, surface chemistry and cargo. This review summarizes the inflammatory biology of obesity and identifies key signaling nodes that are susceptible to nanoparticle-mediated modulation. We discuss lessons from nanotoxicology, where unintentionally pro-inflammatory nanomaterials highlight crucial design pitfalls, and then focus on rationally engineered anti-inflammatory nanotherapeutics targeting adipose tissue macrophages, adipocytes and systemic metabolic organs. Emerging platforms include drug- and nutraceutical-loaded nanoparticles that reprogram macrophage polarization, silence inflammasome signaling and couple inflammation resolution with adipose browning. Finally, we examine translational challenges regarding safety, targeting, regulation and personalization, and propose design principles for future immunometabolic nanotherapies in obesity.

Keywords: Obesity; Chronic inflammation; Nanoparticles; NLRP3 inflammasome; Macrophage polarization

INTRODUCTION

Obesity is now widely recognized as a state of chronic low-grade inflammation rather than a simple disorder of excess fat storage[1–3]. Hypertrophic white adipose tissue (WAT), particularly in visceral depots, becomes infiltrated by immune cells and remodeled in ways that disturb local and systemic homeostasis. Adipose tissue macrophages (ATMs) are central to this process, often accounting for roughly half of immune cells in obese WAT and acting as major sources of pro-inflammatory cytokines, chemokines and reactive oxygen species[1, 4–6].

In lean states, ATMs and other immune cells support tissue remodeling, angiogenesis and healthy lipolysis, displaying predominantly anti-inflammatory or “M2-like” profiles that secrete IL-10 and maintain insulin sensitivity. With sustained caloric excess, adipocytes enlarge and outgrow their vascular supply, leading to local hypoxia, endoplasmic reticulum stress and cell death[7]. These stressed adipocytes release danger-associated molecular patterns, free fatty acids and adipokines such as leptin and resistin, and they upregulate chemokines including CCL2 that recruit monocytes from the circulation. Recruited monocytes differentiate into pro-inflammatory “M1-like” macrophages that form crown-like structures around dying adipocytes, producing TNF-α, IL-6 and IL-1β, which propagate inflammation and interfere with insulin signaling in adipocytes and distant tissues[1, 8–10].

At the molecular level, several convergent pathways underlie this chronic inflammatory activation. The NF-κB system integrates signals from TNF receptors, Toll-like receptors and advanced glycation products, orchestrating transcription of a broad inflammatory gene program that includes cytokines, adhesion molecules and enzymes. Stress-activated kinases such as JNK respond to nutrient overload, lipotoxicity and endoplasmic reticulum stress, phosphorylating insulin receptor substrates on inhibitory sites and thereby directly linking inflammation to insulin resistance[11–13]. In parallel, the NLRP3 inflammasome acts as a metabolic sensor of excess nutrients and damage signals, regulating caspase-1–dependent maturation of IL-1β and IL-18 in adipose macrophages and, under some conditions, adipocytes themselves[14–16].

The consequences extend beyond adipose depots. In the liver, Kupffer cells and recruited macrophages respond to adipose-derived fatty acids and cytokines, promoting steatosis and steatohepatitis. In skeletal muscle, inflammatory signals impair insulin-stimulated glucose uptake and mitochondrial function[5, 17, 18]. Vascular endothelium exposed to inflammatory cytokines and altered lipoproteins adopts a pro-atherogenic phenotype. Pancreatic islets experience cytokine and lipid stress that can impair β-cell function. This systemic inflammatory state is tightly intertwined with metabolic pathways, such that immune effectors actively regulate energy handling and vice versa [19].

In this immunometabolic landscape, nanomaterials are not neutral bystanders. Nanoparticles (NPs) are avidly sampled by phagocytes, interact with complement and coagulation systems, and can accumulate within adipose tissue, liver and spleen depending on their physicochemical properties[20–22]. Unmodified or poorly designed NPs may activate pattern-recognition receptors, generate oxidative stress and trigger or amplify the same inflammatory pathways that drive obesity complications. Studies on silica and other inorganic nanoparticles, for instance, show activation of NF-κB and MAPK signaling, increased ROS production and pro-inflammatory cytokine release in endothelial and immune cells[23].

Conversely, carefully engineered NPs can leverage these interactions to deliver anti-inflammatory or immunomodulatory cargos with high precision. Adipose-targeted nanomedicines have been proposed that specifically address inflammatory ATMs, adipocytes or both, using passive accumulation in inflamed depots and active targeting ligands[24]. Recent work with drug-loaded polymeric nanoparticles directed to adipose macrophages has shown that local modulation of inflammation can induce browning of WAT, enhance thermogenesis, and improve systemic insulin sensitivity in diet-induced obese mice[24].

Thus, the same features that make NPs powerful delivery vehicles large surface area, tunable interfaces, efficient cellular uptake also make them potent modulators of inflammatory pathways, for better or worse. Understanding obesity-associated inflammatory circuits in detail, and how different NP classes intersect with them, is essential for moving from empirical formulation toward rational therapeutic nanodesign. The next sections delineate key inflammatory nodes in obesity, summarize evidence of NP-induced immune modulation from toxicology and then explore emerging strategies that intentionally harness nanotechnology to resolve, rather than exacerbate, obesity-related inflammation.

2. Inflammatory Signaling Nodes in Obesity as Nanotherapeutic Targets

Several signaling hubs dominate inflammatory responses in obese adipose tissue and provide logical targets for nanoparticle-based modulation. NF-κB is a master transcription factor activated by canonical and non-canonical pathways downstream of TNF receptors, Toll-like receptors, IL-1 receptors and other sensors[25]. Once activated, NF-κB translocates to the nucleus and induces hundreds of genes encoding cytokines, chemokines and adhesion molecules, as well as regulators of apoptosis and metabolism. In adipocytes and ATMs, NF-κB activation sustains TNF-α, IL-6 and MCP-1 production, driving local and systemic insulin resistance[25].

JNK is a stress-activated kinase that responds to saturated fatty acids, ER stress and oxidative stress, and is a key mediator of insulin resistance in liver, muscle, adipose and β-cells. JNK phosphorylates IRS1 on serine residues, suppressing insulin signaling, and influences AP-1 transcriptional activity, thereby modulating inflammatory gene expression. NF-κB and JNK pathways are tightly interconnected; NF-κB–dependent genes can restrain or enhance JNK activation, creating complex feedback loops[26].

The NLRP3 inflammasome has emerged as a crucial instigator of obesity-related inflammation. Nutrient excess, lipotoxicity and adipocyte-derived signals such as ATP and ceramides can prime and activate NLRP3 in ATMs and, under some conditions, adipocytes[27]. Activated NLRP3 assembles with ASC and procaspase-1 to form a complex that processes IL-1β and IL-18 into their mature forms and can trigger pyroptotic cell death. Genetic or pharmacologic NLRP3 blockade reduces adipose inflammation, extracellular matrix remodeling and insulin resistance in preclinical models, underscoring its therapeutic appeal[27]. Other relevant pathways include cGAS–STING and TLR signaling in response to mitochondrial and microbial products, JAK–STAT cascades activated by leptin and interferons, and autophagy–inflammation crosstalk that modulates inflammasome activity and lipid handling[28]. Many of these pathways are engaged at the level of ATMs and stromal cells, which are highly accessible to NPs, and they are influenced by redox state, membrane composition and endolysosomal integrity parameters that NP design can directly impact[28].

Nanotherapeutic strategies therefore, target these nodes via three main approaches: delivering small-molecule inhibitors or natural compounds that block NF-κB, JNK or NLRP3 signaling; delivering nucleic acids that silence key components such as Nlrp3, Casp1 or Tnf; or reprogramming macrophage polarization by combining anti-inflammatory cargos with NP-intrinsic signals that favor M2-like phenotypes[16].

3. Unintended Pro-Inflammatory Effects of Nanoparticles: Lessons from Toxicology

While nanomedicine often focuses on therapeutic benefit, nanotoxicology has revealed that many nanoparticle formulations can themselves activate inflammatory pathways. These insights are highly relevant to obesity, where baseline inflammatory tone is already elevated and additional insults may exacerbate metabolic dysfunction[29].

Inorganic nanoparticles, including various forms of silica, titanium dioxide and some metal oxides, can induce oxidative stress and NF-κB and JNK activation in endothelial cells, macrophages and other immune cells[30]. For example, silica nanoparticles have been shown to trigger ROS production, upregulate adhesion molecules, activate JNK/NF-κB signaling and promote cytokine release, effects that could theoretically worsen vascular and adipose inflammation if similar interactions occur in vivo. Some nanomaterials can also destabilize lysosomes, a known trigger for NLRP3 activation, raising concern that they might potentiate inflammasome signaling in ATMs[30].

Surface properties and protein corona formation are critical determinants. Positively charged or highly hydrophobic surfaces tend to be more cytotoxic and pro-inflammatory, whereas PEGylation or zwitterionic coatings can reduce opsonization and immune activation[31]. The bio–nano interface is further complicated by obesity-associated changes in plasma lipids, proteins and oxidized species, which can alter corona composition and NP behavior compared with lean states[31].

Importantly, toxicological studies often use doses and exposure routes that differ from therapeutic scenarios, but they highlight design pitfalls[31]. Unloaded nanoparticles, or formulations meant for other indications, could inadvertently worsen obesity-related inflammation if repurposed without careful testing in metabolic models. Conversely, understanding which NP features drive inflammasome and NF-κB activation can inform "stealth" designs that minimize these effects, or even "decoy" particles that sequester inflammatory ligands[32]. Thus, before deploying nanoparticles to modulate inflammation therapeutically, it is essential to de-risk their intrinsic immunomodulatory profile, particularly in obese systems. This requires using relevant in vitro models, such as ATMs and adipocytes exposed to obesogenic conditions, and in vivo models of diet-induced obesity, rather than lean animals alone.

4. Nanoparticles Targeting Adipose Tissue Macrophages and Stromal Cells

Adipose-targeting nanomedicines have recently gained prominence as a promising strategy to treat obesity by directly altering adipose tissue biology, including its inflammatory state. Reviews on adipose tissue–targeted nanomedicine emphasize three principal strategies: targeting adipocytes to alter energy balance, targeting ATMs to reduce inflammation and targeting multiple cell types to achieve synergistic effects[33].

One highly visible example is the development of simvastatin-loaded polymeric nanoparticles designed to target inflammatory macrophages in WAT. In diet-induced obese mice, these particles preferentially accumulated in ATMs, reprogrammed them toward an anti-inflammatory, pro-resolving phenotype and induced local WAT browning and thermogenesis, leading to weight loss and improved metabolic parameters[34]. Mechanistically, ATMs exposed to the nanoformulation showed reduced NF-κB activation, lower TNF-α and IL-6 production and increased expression of markers associated with M2-like polarization, such as Arg1 and CD206[34].

Similarly, apigenin-loaded nanoparticles have been reported to reprogram adipose tissue by combining direct anti-inflammatory action with adipocyte browning. In a mouse model of obesity, these nanoparticles reduced macrophage infiltration, suppressed pro-inflammatory cytokines and promoted UCP1 expression and beige adipocyte markers, again resulting in decreased WAT mass and improved insulin sensitivity[35]. Targeting ligands can refine this approach. Peptides recognizing adipose vasculature or ATM markers can be displayed on NP surfaces to enhance uptake by specific cells. Passive targeting also plays a role: the leaky vasculature and altered extracellular matrix in obese WAT can favor extravasation and retention of suitably sized particles. Within adipose tissue, NPs may be preferentially engulfed by ATMs, making them ideal carriers for macrophage-directed therapies, including small-molecule NF-κB or NLRP3 inhibitors and nucleic acids that knock down inflammasome components[36].

Adipocytes themselves can also be direct targets. Lipid-based nanoparticles or nanoemulsions containing anti-inflammatory nutraceuticals, omega-3 fatty acids or PPAR modulators can be taken up by adipocytes and influence gene expression programs controlling adipogenesis, lipolysis and cytokine production. Combining such adipocyte-directed cargos with macrophage-directed agents in a single NP platform is an emerging "two-pronged" strategy now entering preclinical testing[37, 38].

These studies collectively demonstrate that adipose-tropic NPs can be designed not only to suppress inflammation but also to couple inflammation resolution to beneficial remodeling, such as browning and extracellular matrix normalization. Careful tuning of particle properties, ligand selection and cargo combinations will be key to optimizing therapeutic index and minimizing off-target effects.

5. Nanoparticle Modulation of Systemic Metabolic Inflammation

While adipose tissue is a central hub of obesity-associated inflammation, systemic manifestations involve liver, muscle, vasculature and the innate immune system more broadly. Nanoparticles that modulate inflammation in these compartments can indirectly improve adipose function and overall metabolic health[39].

In the liver, Kupffer cells and hepatic stellate cells contribute to non-alcoholic fatty liver disease and steatohepatitis through NF-κB, JNK and NLRP3 activation. Nanoparticles designed to deliver antioxidants, PPAR agonists or NLRP3 inhibitors selectively to hepatic macrophages can dampen inflammatory signaling, reduce steatosis and improve insulin sensitivity. Some of these platforms were originally developed for liver fibrosis or cardiovascular disease but are conceptually applicable to obesity-associated fatty liver[40].

Endothelial inflammation is another important target, as obese individuals often exhibit endothelial dysfunction and accelerated atherosclerosis [41]. Nanomaterials have been explored that deliver anti-NF-κB agents or NO donors to inflamed endothelium, mitigating adhesion molecule expression and leukocyte recruitment. Because systemic low-grade inflammation in obesity primes the endothelium, such strategies might provide dual benefits for vascular and metabolic outcomes[40, 42].

The gut–liver–adipose axis offers additional opportunities. Nanoparticles acting within the intestinal lumen to modulate microbiota composition, reinforce barrier integrity or deliver anti-inflammatory agents can reduce translocation of endotoxin and bacterial products that drive systemic and adipose inflammation[43]. Nanoemulsions containing omega-3 fatty acids, for example, have shown the ability to modulate ATMs and reduce systemic inflammation in obese subjects and preclinical models, suggesting that part of their benefit may arise from combined gut and adipose actions[43].

Finally, nanoparticle-based vaccines and tolerogenic nanocarriers that re-educate the immune system are being investigated in autoimmune and allergic diseases. Analogous platforms could in principle, be adapted to obesity to induce regulatory T cells or other immunosuppressive populations that dampen chronic metabolic inflammation, though this remains speculative[44]. These systemic approaches underscore that nanoparticle-induced modulation of inflammatory pathways in obesity is not confined to adipose tissue, and that coordinated targeting of multiple organs may ultimately be necessary to break self-reinforcing inflammatory–metabolic loops.

6. Translational Challenges: Safety, Targeting Specificity and Regulatory Pathways

Despite promising preclinical results, nanoparticle-based modulation of inflammatory pathways in obesity faces substantial translational barriers. Safety is paramount, particularly because obesity is a chronic condition that may require long-term treatment in otherwise ambulatory individuals. Nanoparticles must avoid cumulative organ toxicity, genotoxicity and immunogenicity, and their effects on reproductive health and development must be assessed carefully[45].

Materials based on biodegradable polymers and lipids are generally preferred, but even ostensibly biocompatible formulations can elicit immune responses or off-target effects, especially when repeatedly administered[46]. Obesity-related alterations in pharmacokinetics, such as expanded adipose volume, fatty liver, and altered macrophage populations, complicate the prediction of NP biodistribution and accumulation[46]. Hence, dosing paradigms optimized in lean animals may not translate directly to obese patients.

Targeting specificity remains a challenge. Many receptors exploited for active targeting, such as scavenger receptors or integrins, are expressed on multiple cell types, raising the possibility of unintended NP uptake in off-target tissues. Passive targeting based on vascular permeability and the “inflamed tissue” phenotype is also imperfect and may differ between visceral and subcutaneous depots or between individuals. The presence of extensive fibrosis in long-standing obesity further alters tissue penetration[47]. Regulatory agencies increasingly treat nanomedicines as complex products requiring detailed physicochemical characterization, robust demonstration of batch-to-batch consistency, and comprehensive nonclinical testing. For anti-obesity nanotherapies, regulators will likely demand evidence not only of weight loss but also of durable improvements in metabolic and inflammatory markers, and reassurance that modulation of immune pathways does not predispose to infection, malignancy or other immunological complications[47].

Economic and equity considerations also loom large. Manufacturing sophisticated targeted NPs at scale is costly, and advanced nanotherapies risk being accessible only to wealthy patients or health systems[48]. Given that obesity disproportionately affects disadvantaged populations, it is ethically important that nanotechnology-based treatments do not widen health disparities. Simplifying NP designs, using widely available materials and integrating nanotherapies into broader public health strategies will be critical for equitable translation.

7. Future Directions: Designing Next-Generation Immunometabolic Nanotherapies

Future nanoparticle-based strategies for obesity are likely to move toward more precise, multi-modal and personalized designs. On the mechanistic side, deeper single-cell and spatial profiling of adipose tissue is revealing diverse macrophage, stromal and vascular subpopulations with distinct inflammatory and metabolic roles. Ligands that selectively target pro-inflammatory macrophage subsets or fibrotic stromal cells could sharpen nanoparticle specificity and reduce off-target effects[49].

At the signaling level, next-generation nanotherapies may combine small-molecule inhibitors, nucleic acids and biologics to simultaneously modulate NF-κB, JNK and NLRP3 inflammasome activity, as well as pathways governing autophagy and mitochondrial health. For example, a single NP might co-deliver an NLRP3 inhibitor, an siRNA against Tnf and a mitochondrial antioxidant to ATMs and adipocytes, thereby addressing multiple layers of inflammatory activation[50].

Theranostic nanoparticles that incorporate imaging agents or responsive probes could enable real-time monitoring of depot-specific accumulation and inflammatory status. In obesity, such theranostics might help identify patients with strongly inflamed visceral depots who are most likely to benefit from anti-inflammatory nanotherapy, or provide feedback on treatment efficacy to guide dose adjustments. Integration with wearable devices and digital metabolic monitoring could further support adaptive regimens [20, 51, 52]. Personalization will also draw on genomics and microbiome profiles. Patients with polymorphisms in inflammasome components or NF-κB regulators, or with specific microbiota signatures, may respond differently to particular nanotherapeutic strategies. As precision medicine frameworks expand in cardiometabolic disease, immunometabolic nanotherapies can be slotted into tailored care pathways rather than deployed generically[53].

Finally, there is growing interest in combining immunomodulatory nanoparticles with established obesity treatments such as GLP-1 receptor agonists, bariatric surgery or lifestyle interventions. In these settings, nanoparticles might stabilize beneficial inflammatory and metabolic changes, reduce rebound weight gain or allow lower dosing of systemic drugs[54].

Realizing this vision will require iterative, hypothesis-driven design that respects both the power and the risks of manipulating inflammation. Close collaboration between immunologists, nanotechnologists, clinicians, regulators and patient communities will be essential to ensure that nanoparticle-induced modulation of inflammatory pathways moves from an intriguing concept to a safe, effective and equitable tool in the fight against obesity.

CONCLUSION

Chronic low-grade inflammation is a defining feature of obesity and a major driver of its metabolic and cardiovascular complications. Nanoparticles are uniquely positioned to modulate this inflammatory milieu: they are avidly taken up by adipose tissue macrophages and other immune cells, can carry potent anti-inflammatory or immunoregulatory cargos and can be engineered to target specific tissues and pathways such as NF-κB, JNK and the NLRP3 inflammasome. Evidence from preclinical models shows that adipose-targeted nanomedicines can reprogram macrophage polarization, suppress pathological inflammasome signaling and couple inflammation resolution to beneficial adipose remodeling and metabolic improvement. At the same time, lessons from nanotoxicology underscore that poorly designed nanoparticles may exacerbate inflammation. The path forward lies in rational nanotherapeutic design grounded in detailed immunometabolic understanding, rigorous safety evaluation and thoughtful integration with existing obesity treatments. If these hurdles can be overcome, nanoparticle-mediated control of inflammatory pathways may become a powerful component of precision obesity therapy.

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