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Article

Injectable Therapies and their Effects on the Modulation of Chronic Inflammation in Immunometabolic Diseases: Obesity, Cancer, and Type 2 Diabetes Mellitus

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Abstract

Low-grade chronic inflammation (LGCI) is a central etiological factor and a persistent driver in the pathogenesis of non-communicable chronic diseases (NCCDs), notably obesity, cancer, and type 2 diabetes mellitus (T2DM) [1,2]. This expanded and in-depth review proposes and critically analyzes an integrated and innovative therapeutic strategy, focusing on injectable administration, which combines agents with complementary and synergistic mechanisms of action: Dimethyl Sulfoxide (DMSO), Coenzyme Q10 (CoQ10), Alpha-Lipoic Acid (ALA), Curcumin, Resveratrol (RSV), Glutathione (GSH), and microRNA-146a mimetics (miR-146a) [3]. The choice of the injectable route of administration (intravenous, intramuscular, or subcutaneous) is justified by the need to optimize the systemic bioavailability and tissue targeting of these compounds, overcoming the severe limitations of absorption and first-pass metabolism of the oral route, especially for lipophilic nutraceuticals and oligonucleotides [4,5]. The main focus of the approach lies in the modulation of the immunometabolic axis, with emphasis on restoring the negative feedback of miR-146a on the IRAK1/TRAF6/NF- κ B signaling pathway, a molecular circuit crucial for immunological and metabolic homeostasis [6,7]. Additionally, the article delves into the role of resveratrol in activating sirtuins (SIRT1) and modulating leptin and insulin resistance, comparing this multidimensional approach with current gold-standard therapies (e.g., GLP-1/GIP agonists). It is hypothesized that this synergy of agents, supported by nanomedicine for the efficient delivery of miR-146a mimetics, can modulate LGCI more comprehensively, optimize mitochondrial function and biogenesis, and restore central and peripheral metabolic balance. The critical analysis of safety and clinical evidence, notably for intravenous DMSO and miRNA mimetics, is an essential component of this review, positioning this approach as a potential new frontier in the treatment of these chronic immunometabolic diseases [8,9].

Keywords: obesity; chronic inflammation; leptin resistance; type 2 diabetes mellitus; injectable therapies; miR-146a; nanomedicine; immunometabolism; DMSO

1. Introduction: The Immunometabolic Paradigm of Chronic Disease

Obesity and overweight have reached pandemic proportions, driven by a complex interplay of genetic, dietary, and environmental factors [10,11]. Adipose tissue (AT), historically viewed as a mere energy reservoir, is now recognized as a highly dynamic endocrine and immunological organ [12].

The pathological expansion of AT, characterized by adipocyte hypertrophy and hyperplasia, leads to cellular dysfunction and the infiltration of immune cells, such as macrophages (pro-inflammatory M1) and T lymphocytes [13]. This state of dysfunction results in the dysregulated

secretion of inflammatory mediators, known as adipokines, including pro-inflammatory cytokines (such as Tumor Necrosis Factor- α - TNF- α , Interleukin-6 - IL-6, and leptin itself) and a reduction in adiponectin, a molecule with potent anti-inflammatory and insulin-sensitizing effects [14,15].

This dysregulation establishes the state of low-grade chronic inflammation (LGCI), which acts as the central pathophysiological link between obesity and the vast array of NCCDs, such as T2DM, cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), and various neoplasms [16–19]. In the pathophysiology of insulin resistance and T2DM, systemic inflammation mediated by AT and the hypothalamus is a determining factor, dysregulating intracellular signaling pathways and impairing glucose uptake [20]. Recent research indicates that this inflammation-obesity axis is intrinsically regulated by epigenetic mechanisms, including inflammatory microRNAs such as miR-146a and miR-155 [21,22].

1.1. Dysfunction of the Leptin-Hypothalamic Axis and Central Resistance

Leptin, a 16 kDa peptide hormone primarily secreted by AT, is fundamental in regulating satiety, energy expenditure, and glycemic homeostasis [23,24]. In individuals with obesity, the increase in fat mass leads to hyperleptinemia (elevated circulating leptin levels) [25]. However, the body develops a state of leptin resistance, where the satiety signal in the hypothalamus is impaired, perpetuating excessive food intake and weight gain [26,27].

Leptin also plays a role as a pro-inflammatory adipokine [28]. LGCI, in turn, induces inflammation in the hypothalamus, the central regulator of energy balance, through the activation of glial cells (microglia and astrocytes) [29]. Hypothalamic inflammation is a key factor in the genesis of central leptin and insulin resistance, creating a vicious cycle of inflammation, metabolic dysregulation, and weight gain [30]. A truly effective therapeutic strategy must, therefore, aim at suppressing this hypothalamic neuroinflammation and restoring leptin sensitivity [31].

1.2. The Rationale for Multidimensional Injectable Therapy

The therapeutic proposal reviewed here is based on the principle of pharmacological synergy, where the combination of multiple agents with different molecular targets (anti-inflammatory, antioxidant, mitochondrial optimizer, and epigenetic modulator) results in a therapeutic effect superior to the sum of the individual effects [32].

The main justification for the injectable route is the overcoming of pharmacokinetic barriers. The low oral bioavailability of nutraceuticals such as Curcumin, Resveratrol, and CoQ10 is a well-documented challenge, limiting the effective plasma and tissue concentration [33]. For miRNA mimetics, the injectable route is absolutely crucial, as these molecules are rapidly degraded by nucleases in the gastrointestinal tract and plasma, requiring advanced delivery systems (nanomedicine) for protection and tissue targeting [34].

The proposed combination aims to:

- 1 Central Epigenetic Modulation: Through miR-146a mimetics, restoring the inflammatory negative feedback in the hypothalamus and AT.
- 2 Suppression of Systemic Inflammation: With DMSO and Curcumin, inhibiting the NF- κ B pathway and the NLRP3 inflammasome.
- 3 Combating Oxidative Stress and Mitochondrial Dysfunction: With CoQ10, ALA, and GSH, optimizing the electron transport chain and cellular antioxidant capacity.

2. Molecular Mechanisms and Modulation by miRNA Mimetics and Nutraceuticals

2.1. MicroRNAs as Key Regulators: The miR-146a Circuit

MicroRNAs (miRNAs) are small non-coding RNAs that act as essential post-transcriptional regulators, repressing gene expression by binding to target sequences in mRNA [35]. miR-146a is one of the most important negative regulators of innate immune responses [6].

It directly represses the expression of the adapter proteins IRAK1 (Interleukin-1 Receptor-Associated Kinase 1) and TRAF6 (TNF Receptor Associated Factor 6). These proteins are key components in the signaling cascade activated by Toll-Like Receptors (TLRs) and IL-1 Receptors, which culminates in the activation of Nuclear Factor Kappa B (NF-κB) and the production of pro-inflammatory cytokines [36,37]. By repressing IRAK1 and TRAF6, miR-146a establishes a negative *feedback* circuit that prevents excessive and uncontrolled inflammation, crucial for the resolution of the immune response and the maintenance of homeostasis [7].

miR-146a deficiency is consistently associated with the exacerbation of systemic inflammation, insulin resistance, and metabolic dysfunction in models of obesity and T2DM [38,39]. Reduced serum levels of miR-146a are detected in patients with T2DM and are associated with microvascular complications, such as diabetic kidney disease (DKD) [40,41]. The modulation of miR-146a, through the administration of synthetic mimetics (oligonucleotides that replicate its function), emerges as a precision therapeutic target to “reset” the inflammatory control system [42].

2.2. *Resveratrol, Sirtuins, and Epigenetic Modulation*

Resveratrol (RSV), a stilbene polyphenol, is a fundamental component of this integrated approach. Its anti-inflammatory, antioxidant, and antiproliferative properties are widely documented [43].

The most notable molecular mechanism of RSV is its ability to activate sirtuins (SIRT), particularly SIRT1, an NAD⁺-dependent deacetylase [44]. SIRT1 is a metabolic sensor that plays a protective role against metabolic dysfunction, increasing insulin sensitivity, promoting mitochondrial biogenesis, and inhibiting the NF-κB pathway [45]. The activation of SIRT1 by RSV can:

- Improve Insulin Sensitivity: Via deacetylation of substrates such as PGC-1α and FOXO1 [46].
- Reduce Inflammation: Via inhibition of NF-κB and modulation of the expression of inflammatory miRNAs, such as miR-146a [47].

RSV, in combination with Curcumin, has demonstrated a synergistic effect in attenuating inflammation and modulating miR-146a in models of cellular senescence (SASP), suggesting a convergent mechanism of action with miR-146a mimetics [48].

2.3. *Curcumin and NF-κB Inhibition*

Curcumin, the main curcuminoid of turmeric (*Curcuma longa*), is recognized for its potent anti-inflammatory and antioxidant properties [49]. Its main anti-inflammatory mechanism of action lies in the direct inhibition of NF-κB activation [50]. By blocking the translocation of NF-κB to the nucleus, Curcumin prevents the transcription of pro-inflammatory genes, including TNF-α, IL-6, and COX-2. Furthermore, Curcumin has been shown to induce the expression of anti-inflammatory miRNAs, such as miR-146a itself, reinforcing the molecular synergy of the combination [51].

3. **Pharmacokinetic Justification and Injectable Nanomedicine**

The main limitation of many nutraceuticals, such as Curcumin, RSV, and CoQ10, is their low oral bioavailability (OBA) and rapid hepatic metabolism [52]. The OBA of Curcumin, for example, is extremely low, limiting the achievement of therapeutic plasma concentrations [53].

The injectable route (intravenous, intramuscular, or subcutaneous) is the proposed solution to bypass these barriers, ensuring a higher systemic concentration and allowing for precise dose adjustment.

3.1. *Nanomedicine for the Delivery of miR-146a Mimetics*

For miRNA mimetics (synthetic oligonucleotides), the injectable formulation is crucial, and nanomedicine is indispensable. Nanotechnology is necessary for:

- 4 Protection: Protecting miRNA molecules from degradation by nucleases in the plasma.

- 5 Targeting: Optimizing delivery to the target tissue (e.g., adipose tissue, immune cells, hypothalamus).
- 6 Permeability: Facilitating passage through biological barriers, such as the blood-brain barrier (BBB) for the hypothalamus [54].
- Lipid Nanocarriers (LNCs): These are the most advanced delivery platform for nucleic acids, including mRNA vaccines. LNCs can be modified with ligands (e.g., peptides or antibodies) that bind to specific receptors on AT macrophages or BBB endothelial cells [55]. Preclinical studies demonstrate that LNCs can effectively deliver miR-146a, reducing inflammation and improving insulin sensitivity in animal models [56].
- Exosomes: Naturally occurring extracellular vesicles that possess innate mechanisms for intercellular communication and the ability to cross the BBB [57]. Exosomes loaded with miR-146a, derived from mesenchymal stem cells, have been shown to protect against pancreatic beta-cell dysfunction and alleviate diabetic complications, acting as a natural and highly efficient delivery system [58,59].

The biggest challenge for miR-146a mimetics is efficient delivery to the hypothalamus, to combat hypothalamic inflammation and restore leptin sensitivity. BBB-targeted nanomedicine represents the cutting-edge technology to achieve this central therapeutic target [60].

4. Selected Injectable Agents: Mechanisms and Clinical Implications

The proposed integrated therapeutic strategy aims for synergy between the agents to attack multiple points of the inflammatory cascade, oxidative stress, and mitochondrial dysfunction.

4.1. Dimethyl Sulfoxide (DMSO): Optimization and Safety

DMSO is an amphiphilic solvent with active pharmacological properties, acting as a potent free radical scavenger, anti-inflammatory agent, and immunomodulator [61,62].

- Anti-inflammatory Mechanism: DMSO is known to repress the production of pro-inflammatory cytokines (TNF- α , IL-6) and, crucially, to inhibit the NLRP3 inflammasome pathway, a central protein complex in the inflammatory response to metabolic danger signals (DAMPs) [63,64].

Critical Safety Analysis (Addition): Intravenous administration of DMSO in humans is widely used in stem cell cryopreservation. However, therapeutic use at high doses or concentrations requires caution. The main concern is the risk of intravascular hemolysis, which is dependent on the concentration and infusion rate [66]. Clinical literature suggests that the concentration for intravenous infusion should not exceed 10% (v/v) to minimize this risk, although doses up to 1g/kg/day are tolerated in certain contexts [67]. The formulation and dose of DMSO in the proposed combined therapy must be rigorously validated in preclinical and phase I clinical trials to ensure safety and the maximum tolerated dose (MTD).

4.2. Coenzyme Q10 (CoQ10) and Mitochondrial Optimization

CoQ10 (Ubiquinone) is an essential component of the electron transport chain in the inner mitochondrial membrane and acts as a potent lipid-soluble antioxidant [68,69].

- Mitochondrial Optimization: Mitochondrial dysfunction is a hallmark of insulin resistance and LGCI [70]. CoQ10 is crucial for ATP production and the stability of the mitochondrial membrane.
- Inflammatory Modulation: Injectable supplementation (preferably in liposomal or nanoparticulate formulations for OBA) is proposed to decrease levels of pro-inflammatory cytokines and suppress NF- κ B activation [71,72].

4.3. Alpha-Lipoic Acid (ALA) and Antioxidant Regeneration

ALA is an amphiphilic antioxidant that acts as a mitochondrial cofactor and is capable of regenerating other endogenous and exogenous antioxidants, such as Glutathione (GSH) and Vitamin C [73]. Its intravenous administration is well-established in the treatment of diabetic neuropathy and

has been shown to improve insulin sensitivity and reduce inflammatory markers in patients with T2DM [74,75].

4.4. Glutathione (GSH): The Master Antioxidant

GSH is the main endogenous antioxidant and plays a vital role in cellular detoxification and maintaining the redox state [76]. Injectable administration (intravenous) is the preferred route to rapidly elevate systemic levels and protect against chronic oxidative stress, acting synergistically with DMSO, CoQ10, and ALA in modulating the immune response [77,78].

5. Discussion: Comparison of the Integrated Approach with Gold-Standard Therapies

The proposed integrated approach, focused on immunometabolic modulation and injectable nanomedicine, offers a fundamental contrast to gold-standard therapies for obesity and T2DM.

While gold-standard therapies, such as GLP-1/GIP agonists (e.g., Semaglutide, Tirzepatide) and bariatric surgery, are highly effective in weight loss and glycemic control, their action on LGCI and the restoration of leptin sensitivity is often indirect, secondary to weight loss [79,80]. The integrated approach, conversely, directly targets the underlying immunometabolic dysfunction, offering a causal rather than merely symptomatic mechanism of action.

Table 1, below, presents an in-depth comparative analysis, highlighting the multi-target nature and molecular focus of the proposed injectable therapy.

Table 1. Comparative Analysis of Therapeutic Strategies for Obesity and T2DM.

Feature	Proposed Integrated Approach (Injectables)	GLP-1/GIP Agonists (e.g., Semaglutide)	Bariatric Surgery
Main Mechanism of Action	Direct modulation of LGCI (via miR-146a, DMSO, Curcumin, Resveratrol), combating oxidative stress, and mitochondrial optimization.	Increased insulin secretion (glucose-dependent), delayed gastric emptying, appetite suppression (incretin action).	Gastric restriction and/or malabsorption; intestinal hormonal modulation (e.g., increased GLP-1, PYY).
Weight Loss Efficacy	Hypothetical. Efficacy is expected by restoring leptin sensitivity and reducing hypothalamic inflammation, addressing the root cause of central dysfunction.	High. Significant weight loss (up to 20-25% of body weight with new generations of dual agonists).	Very High. Sustained weight loss of 25-35%.
Action on Chronic Inflammation	Direct and Multi-target. Main focus on suppressing the NF-κB pathway, NLRP3 inflammasome, and restoring miR-146a.	Indirect. Reduction of inflammation secondary to weight loss and metabolic improvement.	Indirect. Reduction of inflammation secondary to weight loss and beneficial alteration of the gut microbiota.

Feature	Proposed Integrated Approach (Injectables)	GLP-1/GIP Agonists (e.g., Semaglutide)	Bariatric Surgery
Restoration of Leptin Sensitivity	Direct. Inclusion of agents (DMSO, miR-146a, Resveratrol) targeting hypothalamic neuroinflammation and central signaling.	Indirect. Improvement secondary to weight loss, with no direct molecular target on hypothalamic inflammation.	Indirect. Improvement secondary to weight loss.
Clinical Status	Hypothetical/Translational Proposal. Requires rigorous validation in preclinical and phase I/II clinical trials.	Gold-Standard. Approved and widely used for the treatment of obesity and T2DM.	Gold-Standard. Established treatment for severe obesity and refractory T2DM.

5.1. Challenges and Next Steps (Addition)

- The transition of this hypothesis to clinical practice requires overcoming significant challenges:
- 7

Injectable Formulation Validation: Curcumin and Resveratrol, despite their synergy, require stable and safe injectable nano-liposomal formulations, with robust toxicity and pharmacokinetic data in humans [81].
- 8

DMSO Safety: The safety and maximum tolerated dose of injectable DMSO, at therapeutic concentrations for LGCI, must be established in phase I clinical trials, outside the context of cryopreservation [67].
- 9

Oligonucleotide Delivery: The efficacy of the delivery technology for miR-146a mimetics (LNCs or Exosomes) to adipose tissue and, mainly, to the hypothalamus, must be proven in rigorous clinical trials, focusing on stability and cellular internalization [54,56].
- 10

Synergistic Efficacy: Proving the synergistic efficacy of this combination in a randomized, controlled clinical trial is the final step to validate the immunometabolic hypothesis.

6. Conclusion

The integrated strategy of injectable therapies (DMSO, CoQ10, ALA, Curcumin, Resveratrol, GSH, and miR-146a Mimetics) suggests a promising path for the treatment of obesity, cancer, and T2DM, by addressing the core of immunometabolic dysfunction and chronic inflammation. The deepening of the mechanisms of action of miR-146a, the activation of SIRT1 by Resveratrol, and the use of nanomedicine for targeted delivery reinforce the potential of this multi-target approach.

Despite the strong preclinical and molecular rationale, the therapy remains in the realm of translational hypothesis. Future research must focus on long-term toxicology, the optimization of injectable formulations, and proving the synergistic efficacy of this combination in clinical trials. The ultimate goal is to develop a therapy that not only promotes weight loss or glycemic control but fundamentally restores immunometabolic homeostasis through precise molecular modulation of chronic inflammation.

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