Highlights

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Nanoparticle-based siRNA Delivery System in Intestine Empowers the Obesity Management

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Abstract

We highlighted a poly lactic acid-co-glycolic acid (PLGA)-block-polyethylene glycol (PEG) and chitosan-based nanoparticle system to deliver sterol O-acyltransferase 2 (SOAT2) siRNAs into the small intestines of mice to effectively inhibit lipid uptake and tackle obesity. Intestinal SOAT2 can regulate fatty acid uptake and its inhibition can enhance ubiquitination-based CD36 degradation in the enterocytes. This work demonstrates a potential modulatory function of intestinal SOAT2 on lipid uptake, highlighting the therapeutic effect of targeting intestinal SOAT2 against obesity. It exhibits promising translational relevance in the siRNA therapeutics-based treatment for obesity.

Keywords: nanotechnology; nanoparticle; siRNA therapy; drug delivery system; obesity

Obesity is an epidemic metabolic disorder accompanied by pathological changes such as dyslipidemia, hyperglycemia, and insulin resistance [1], which is often attributed to the excessive intake of high-calorie food and limited physical activity [2]. Therefore, the management of fat intake and harmonizing fatty acid biosynthesis with degradation are crucial principles in preventing obesity development.

Regarding fatty acid absorption in the gastrointestinal tract, therapies targeting the cholesterol transporter in the enterocytes play a key role in controlling cholesterol levels [3]. Although the molecular processes involved in fatty acid uptake in enterocytes: membrane uptake, intracellular transportation, and triglyceride (TG) assembly have been elucidated, no specific inhibitor has so far been proven to effectively prevent obesity by suppressing fatty acid absorption.

Based on physiological and pathological mechanisms, several drugs have been developed for the treatment of obesity, mainly involving appetite inhibition, such as sympathomimetics, serotonin 2C receptor agonists, opioid antagonists, dopamine-norepinephrine reuptake inhibitors, and glucagon-like peptide-1 receptor agonists [4]. However, due to the potential risk of cardiovascular and psychiatric side effects, the use of some has been stopped while others have not yet achieved the expected results [5–7].

Recently, sterol O-acyltransferase 2 (SOAT2), an enzyme that esterifies free cholesterol and fatty acids into cholesteryl esters (CE) was identified [8, 9]. Atherosclerosis development could be prevented by modulating very low-density lipoprotein/chylomicron-

CE synthesis, especially by inhibiting the hepatic SOAT2 [10, 11], and in turn ameliorating insulin resistance in SOAT2 whole knockout mice [12–14]. However, hepatic SOAT2 inhibition would adversely result in higher plasma TGs secondary to the enhanced hepatic secretion of TGs, hinting that intestinal SOAT can be a promising target to modulate the incidence of diet-induced obesity. However, the core issue of positioning special materials, like small interfering RNAs (siRNAs), onto SOAT and ensuring maximal delivery effectiveness has not been well addressed.

Nanoparticles are ideal vehicles for drug loading and delivery. A new epoch of nanocarrier-assisted siRNA therapy has commenced in the U.S. The Food and Drug Administration (FDA) has approved the treatment of hereditary transthyroxine protein-mediated (hATTR) amyloidosis by employing this approach [15–19].

Based on the experience in nanotechnology [20, 21], the authors constructed a novel nanoparticle system comprising chitosan (CS) to deliver Soat2 siRNAs into the intestines (Fig. 1). These nano-formulated Soat2 siRNA/CS-PLGA nanoparticles could be attracted by the negatively charged intestinal mucosa through the positive charge of CS, enabling their retention and facilitating siRNA delivery to the intestinal epithelium. Treatment with these nanoparticles inhibited SOAT2 in enterocytes, which may be adequate to prevent the development of high-fat diet-induced obesity [22]. Furthermore, this work uncovered the underlying mechanism by which

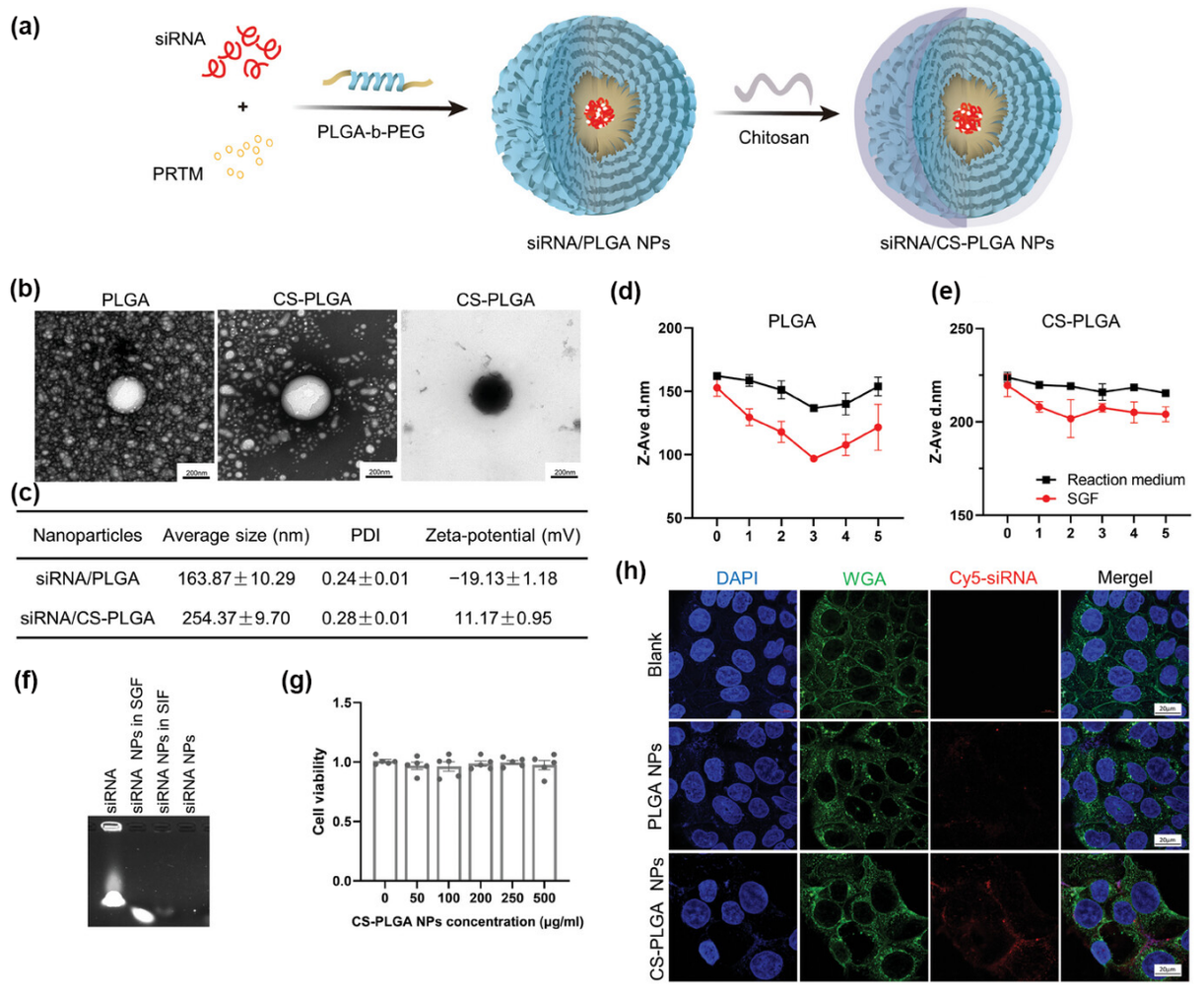

Fig. 1 Preparation and characterization of the siRNA/CS-PLGA nanoparticles system. **(a)** The reaction scheme of nanoparticle synthesis. **(b)** Representative transmission electron microscopy images of PLGA (scale bars: 100 nm) and CS-PLGA nanoparticles (left). **(c)** Zeta potential of PLGA and CS-PLGA nanoparticles. Size distribution of CS-PLGA nanoparticles measured by a Mastersizer Micro. **(d)–(f)** Stability of the CS-PLGA nanoparticles in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) for the times indicated (n = 3/group). **(g)** The viability of cells treated with different concentrations of CS-PLGA nanoparticles. **(h)** Absorption of the Cy5-siRNA by cells post-treatment with PLGA or CS-PLGA nanoparticles. Reproduced with permission from Ref. [22] © 2024 Wiley-VCH.

SOAT2 regulates fat absorption. Inhibition of SOAT2 in the small intestine triggers the degradation of CD36, a fat-transporting protein. This process involves both cellular stress and the recruitment of the E3 ligase RNF5, an enzyme that enhances CD36 degradation. (See the video in the Electronic Supplementary Material).

This strategy is promising with excellent natural characteristics of non-invasiveness, low toxicity, and better patient compliance. Such an intestine-specific approach circumvents the risk of fat accumulation in the liver and thus offers a safer and more focused treatment for obesity. Meanwhile, targeting SOAT2 in the enterocytes may serve a role as "ONE STONE HIT TWO BIRDS" (1 stone: intestine-targeting SOAT2; 2 birds: free fatty acids and cholesterol). We believe that this nanoparticle system represents a breakthrough in obesity management, offering a new solution that tackles both fat metabolism and diet-related weight gain, potentially ushering in a new era of more effective treatments.

Furthermore, as described before, SOAT2 can esterify free cholesterol and fatty acids into CEs in the liver and intestine through targeted inhibition and thus prevent atherosclerosis development. The designing of varied nanoparticle systems is also adapted to deliver relevant siRNAs into cerebral regions targeted by phenotype-specific molecules in brain tissues to treat Alzheimer's disease, which is also a lipid metabolism disorder.

Overall, robust evidence supports the scientific value of nanoparticle systems for small-molecule delivery. However, safe and effective transmission has challenges, which may include immunogenicity, *in vivo* degradation, and even signaling disturbance emanating from the nanoparticle systems themselves. An optimal design must reconsider and overcome these negative factors to the extent possible.

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Not applicable.

Conflict of Interests

The author declares no conflict of interests.

Supporting Information

Supporting information to this article can be found online at https://doi.org/10.26599/NBE.2024.9290110

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