

Nanomedicine for obesity treatment

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Obesity, as a chronic condition, has been a serious public health issue over the last decades both in the affluent Western world and developing countries. As reported, the risk of several serious diseases increases with weight gain, including type 2 diabetes, coronary heart disease, cancer, and respiratory diseases. In addition to lifestyle modifications, pharmacotherapy has become an important strategy to control weight gain. However, most of the anti-obesity drugs often show poor outcome for weight-loss and cause severe adverse effects. This review surveys recent advances in nanomedicine as an emerging strategy for obesity treatment with an emphasis on the enhanced therapeutic efficiency and minimized side effects. The insights for future development are also discussed.

drug delivery, nanomedicine, obesity, browning, fat absorption, energy expenditure

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INTRODUCTION

Obesity has been classified as a chronic disease now (World Health Organization, 2014). Usually, people with a body mass index (BMI) above 30 kg m^{-2} are considered obese (Schneider and Mun, 2005). With the increasingly sedentary lifestyles and higher intake of calories in industrialized society, the obese population is rising dramatically in both developed and developing countries (Malik et al., 2013). Right now, obesity is one of the most prevalent health problems all over the world, affecting 15% of the population. The abnormal or excessive fat accumulation leads to a series of co-morbidities such as diabetes, cancer, and cardiovascular diseases (Friedman, 2009).

Obesity is caused by a positive energy balance, while certain factors are involved in this imbalance, including behavioral, environmental, and genetic interactions (Jackson et al., 2015). Careful management of diets and adjustment of lifestyle are important for obesity treatment since pre- and perinatal periods, and it should be lifelong lifestyle changes (Friedman, 2009; Kushner and Ryan, 2014; Wadden et al., 2007). In some severe cases, surgery such as gastric by-pass can restore body weight (Heymsfield and Wadden, 2017). Besides, pharmacotherapy is the focus for obesity treatment over the last decade through either suppression of appetite or inhibition of fat absorption (Mun et al., 2001; Yanovski et al., 1996). However, the commercialization of these anti-obesity drugs is hampered by their serious side effects such as intestinal bleeding or even suicide (George et al., 2014; Kakkar and Dahiya, 2015).

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With the development of nanotechnology (Mura and Couvreur, 2012; Parveen et al., 2012; Sun et al., 2017), the integration of anti-obesity drugs into nanomedicine has exhibited tremendous therapeutic potency for obesity treatment (des Rieux et al., 2013; Hossen et al., 2013). Nanoparticlization provides unique advantages based on different synthetic strategies. For example, nanoparticles with targeting moiety are able to achieve targeted drug delivery to minimize side effects (Yameen et al., 2014; Zhang et al., 2013). The poor water-solubility of anti-obesity drugs can be addressed via nano-encapsulation (Musthaba et al., 2009). In this review, we will summarize the recent advances in the development of nanomedicine for obesity treatment with different mechanisms, including suppression of digestibility and enhancement of energy expenditure (Figure 1). In the end, the challenges and future opportunities will also be discussed.

SUPPRESSION OF ENERGY ABSORPTION

As the imbalance of food intake exceeding energy expenditure is the major cause of obesity (Jackson et al., 2015), appetite suppression and fat absorption inhibition are considered as the most straightforward methods to control body weight. A lot of pharmacological agents have been developed and clinically approved for obesity treatment, such as desoxyephedrine and orlistat (Haslam, 2016; Kang and Park, 2012; Rodgers et al., 2012). However, these drugs are often associated with unacceptable adverse effects including gastric function disorder, steatorrhea, strokes, and kidney injury (Ballinger and Peikin, 2002; Kushner, 2008; Rucker et al., 2007).

Orlistat can inhibit lipase in the intestine to reduce the hydrolysis and subsequent absorption of dietary fat (Ballin-

ger and Peikin, 2002). However, due to the poor water-solubility of orlistat, its bioavailability is very low by oral administration (Ballinger and Peikin, 2002). Nanoemulsion of orlistat has been demonstrated to overcome the high lipophilicity and improve its dissolution and pancreatic lipase inhibition *in vivo* (Sangwai et al., 2014). Another issue for orlistat is its adverse effects in the digestive system (Kolonin et al., 2004). Chen et al. designed a conjugated polymer nanocarrier with the negative-feedback loop to reduce the side effects of orlistat (Chen et al., 2016). In this system, they encapsulated orlistat in nanocarriers using a kind of amphiphilic copolymers with hydrophobic side chains of poly (ϵ -caprolactone) (PCL). Since PCL is also the substrate of lipase, the copolymer side chains gradually degraded in the intestine, leading to the disassembly of nanocarriers and subsequent release of orlistat. The released drug was able to bind to lipase and suppress its enzymatic activity, which in turn slowed down the degradation rate of nanocarriers. An on-demand drug delivery was thus achieved via this negative-feedback loop, which improved the bioavailability of orlistat and minimized its side effects. Instead of small-molecule drug, Kupferschmidt et al. investigated the ability of mesoporous silica particles to reduce body weight (Kupferschmidt et al., 2014). They found the silica particles embedded in food could sequester lipase in the small pores through a lipase-specific interaction, leading to a lower fat absorption. Additionally, some other mechanisms such as bile acid sequestration and a faster passage through the intestine might also contribute to the resulting low energy intake. They further demonstrated that the silica particles with the large pore of 11 nm showed a better effect on weight loss compared to those with small pore size (2 nm).

Appetite suppression is an alternative method to decrease food intake and impact energy homeostasis (Mun et al.,

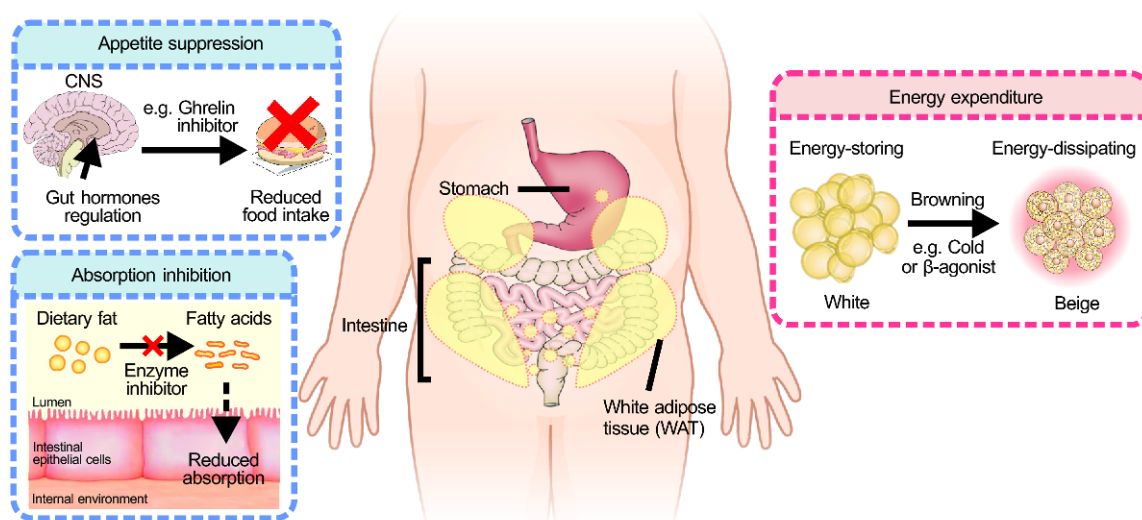


Figure 1 (Color online) Schematic of nanomedicine for obesity treatment with different mechanisms, including suppression of digestibility and enhancement of energy expenditure.

2001). For example, Andrade et al. reported an anti-ghrelin vaccine using virus-like particles for obesity treatment (Andrade et al., 2013). Ghrelin is a gastro-intestinal hormone that stimulates food intake and decreases energy expenditure (Wiedmer et al., 2007). However, the passive delivery of anti-ghrelin antibodies cannot lead to the long-term inhibition of food intake. To address this issue, they immunoconjugated ghrelin with virus proteins to create a vaccine, which was able to trigger an immune response to generate specific anti-ghrelin antibodies. This anti-ghrelin vaccine displayed a significant impact on energy homeostasis in a diet-induced obese (DIO) mouse model.

White adipose tissue (WAT) is used for lipid storage, and white adipocytes contain unilocular lipid droplets (Trayhurn and Beattie, 2001). Inhibition of fat uptake and accumulation in white adipocytes can achieve obesity control. Recently,

Kim and coworkers developed an oligopeptide complex for targeted gene delivery to adipocytes (Won et al., 2014). They designed a short-hairpin RNA to silence fatty-acid-binding protein 4 (shFABP4), which coats lipid droplets in adipocytes (Figure 2). They further constructed shFABP4 with D-form 9-arginine (ATS-9R) to obtain an adipocyte-targeted gene carrier. The selective delivery of shFABP4 to WATs was demonstrated to reduce fat accumulation in adipocytes and consequently inhibit weight gain.

Adipocyte needs a suitable microenvironment to grow (Cao, 2007; Ledoux et al., 2008). Besides lipid deposition, the expansion of WATs requires vascularization (Cao, 2007; Carmeliet and Jain, 2000; Voros et al., 2005). Therefore, antiangiogenic therapy that induced the apoptosis of endothelial cells is able to inhibit the progression of adipocyte hyperplasia and reduce weight gain. A cell death-inducing

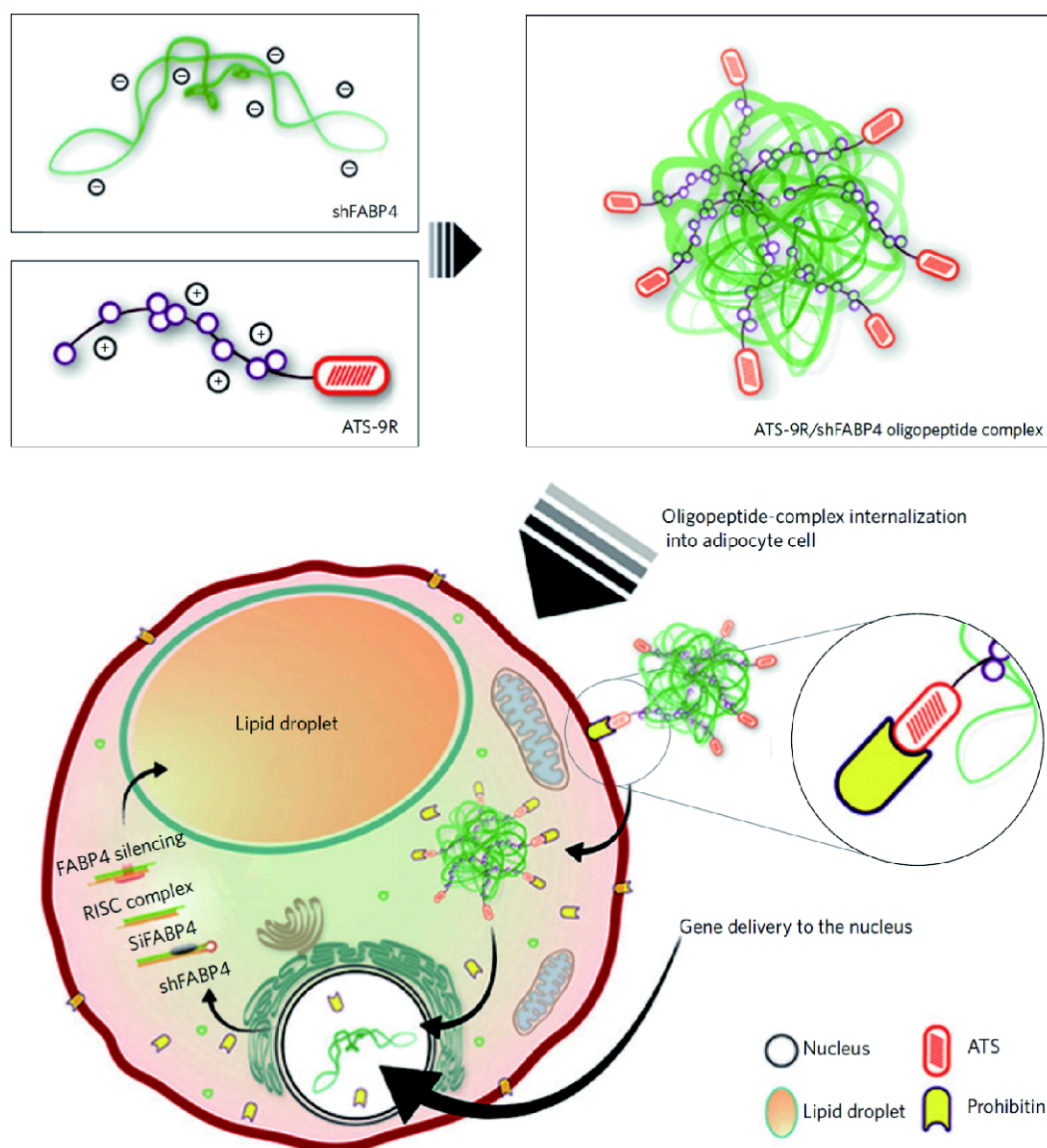


Figure 2 (Color online) Mechanism of the targeted gene delivery to adipocytes by ATS-9R (Figure adapted and modified from Won et al., 2014).

peptide [$D(KLAKLAK)_2$] has been evidenced to promote the death of endothelial cells in adipocyte tissue in obese animals (Barnhart et al., 2011; Kolonin et al., 2004). In order to enhance the accumulation of the antiangiogenic drug in WATs, Harashima and coworkers developed a targeting nanoparticle to deliver their cargo to vascular endothelial cells (Kajimura et al., 2015). A prohibitin-targeting peptide, which can specifically bind to the prohibitin protein on the surface of endothelial cell was modified on the PEG-lipid nanoparticles (Hossen et al., 2010; Hossen et al., 2012). They demonstrated that these nanoparticles were specifically taken up by the adipose vascular endothelial cells through prohibitin-mediated endocytosis and then led to the cell apoptosis. However, the metabolic consequences of this method should be carefully evaluated since the shortage of oxygen supply indeed causes hypoxic stress in adipose tissue, resulting in chronic inflammation and insulin resistance in WATs (Cao, 2013; Harms and Seale, 2013; Voros et al., 2005).

ENHANCEMENT OF ENERGY EXPENDITURE

Unlike WATs, brown adipose tissues (BATs) are formed by a type of adipocytes with enriched mitochondria and vascular

structure, which can transform chemical energy to heat through nonshivering thermogenesis (Harms and Seale, 2013). The “browning” of WATs or activation of BATs to increase energy expenditure capacity has been considered as a promising strategy to combat obesity (Almeida et al., 2014; Jiang et al., 2015). Many thermogenic inducers and the related pathways have been identified recently (Bartelt and Heeren, 2014; Harms and Seale, 2013; Kajimura et al., 2015; Wu et al., 2013). Based on these better understandings, numerous browning agents have been investigated in obesity treatment, while undesired side effects on other organs such as heart and liver are still urgent issues during clinical translation (Harms and Seale, 2013). To address this issue, Langer, Farokhzad and coworkers developed two peptide-functionalized nanoparticle platforms to specifically deliver browning agents to adipose tissue vasculature (Xue et al., 2016). In this system, an endothelial-targeted peptide was modified on the surface of biodegradable poly (lactic-co-glycolic acid)-*b*-poly (ethylene glycol) (PLGA-*b*-PEG) nanoparticles, which promoted their homing capability to adipose blood vessels (Figure 3). They demonstrated that these nanoparticles were able to transport rosiglitazone, a peroxisome proliferator-activated receptor gamma (PPAR- γ) activator, into WATs to stimulate angiogenesis and

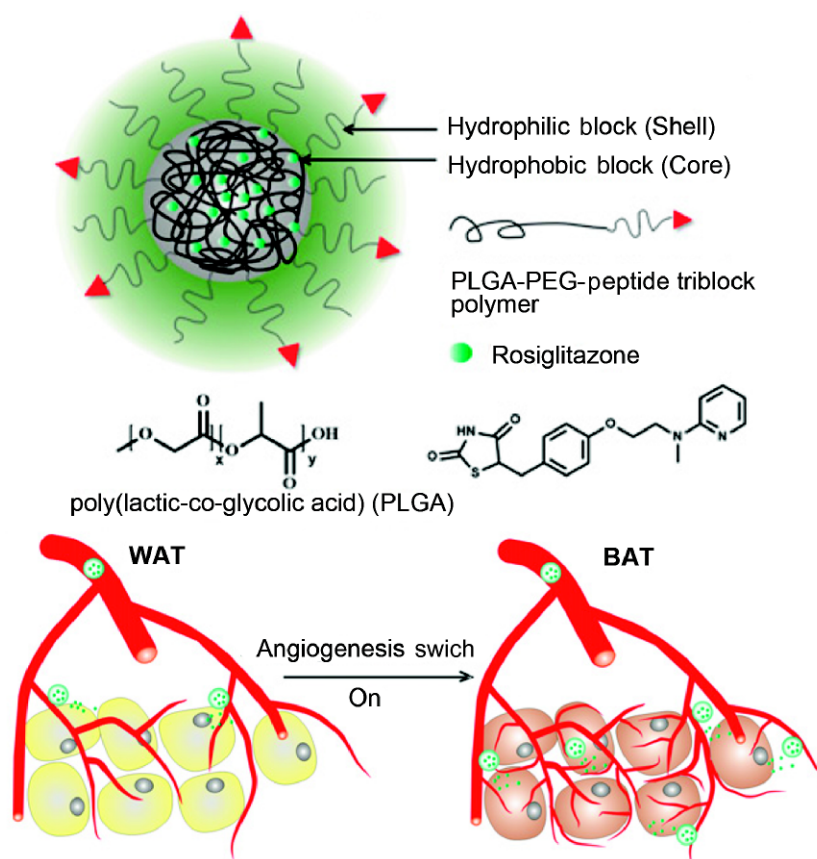


Figure 3 (Color online) Chemical structure of browning agent-loaded nanoparticles and schematic of the WAT browning process through a positive feedback drug delivery system (Figure adapted and modified from Xue et al., 2016).

induce browning via intravenous injection in a DIO mouse model, which further inhibited weight gain.

Marrache and Dhar reported a mitochondria-targeted nanoparticle to deliver anti-obesity drug (Marrache and Dhar, 2012). These nanoparticles were composed of PLGA-*b*-PEG-triphenylphosphonium (TPP) polymer. The PEG shell extends the circulation time of nanoparticles, and TPP could facilitate the internalization into the mitochondrial matrix space to achieve targeted drug delivery. By loading with the mitochondrial decoupler 2,4-dinitrophenol (2,4-DNP), the polymeric nanoparticles were able to reduce lipid accumulation in the adipocytes to manage obesity. However, the over-activation of mitochondria may lead to the excessive generation of reactive oxygen species (ROS), and its possible impairment in non-adipose tissues, such as heart and muscle, should be carefully examined.

Instead of targeted delivery, a localized and sustained release of the browning agent is a promising alternative to facilitate the browning of WATs with minimized side effect. Deng and coworkers locally injected drug-loaded nanoparticles into the inguinal WAT, which allowed localized retention of browning agents and subsequent browning of

this fat depot (Jiang et al., 2017). The local browning improved glucose homeostasis and attenuated weight gain in a DIO mouse model.

Recently, Zhang et al. took the advantage of painless microneedle array patches to directly deliver drugs to the adipose tissue underneath the skin (Figure 4) (Yu et al., 2015; Yu et al., 2017; Zhang et al., 2017a; Zhang et al., 2017b). To achieve a sustained release, they encapsulated browning agents into a glucose-responsive nanoparticle (Bakh et al., 2017; Gu et al., 2013a; Gu et al., 2013b; Lu et al., 2016). Under the physiological glucose condition, a localized acidic environment was generated due to the glucose oxidase-mediated glucose oxidation and then the pH-sensitive nanoparticles gradually degraded to release the drugs within 3 days. *In vivo* studies indicated that the tips of microneedles were exposed to the inguinal adipose tissue after application and *in situ* fluorescent section revealed the model drug was successfully delivered into the adipose tissue. They achieved a ~15% inhibition of weight gain after a four-week treatment. Of note, the inguinal fat pad treated with browning microneedles was significantly smaller compared to the untreated side, confirming the localized release of browning

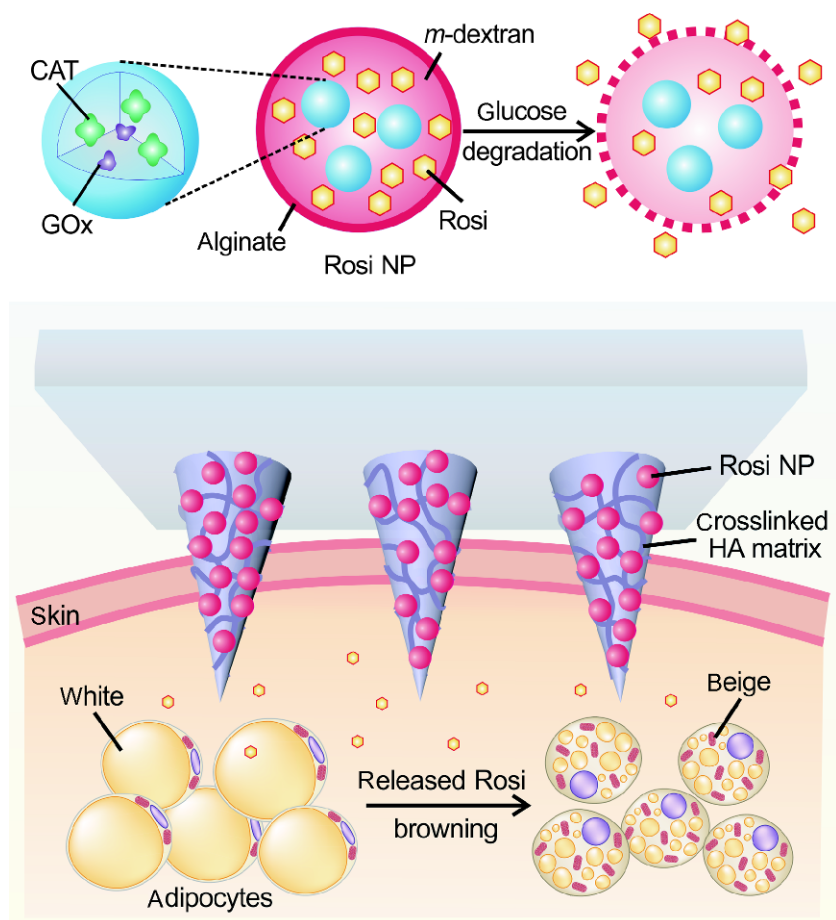


Figure 4 (Color online) Schematic illustration of the browning reagents-loaded transcutaneous MN patch for the brown remodeling of the white fat (Figure adapted and modified from Zhang et al., 2017a).

agents.

CONCLUSION

As summarized above, a large amount of nanomedicine-based strategies have shown promising preclinical activity for weight control via suppression of digestibility or enhancement of energy expenditure. Through different approaches such as oral administration and transdermal delivery, nanocarriers exhibit an efficient and convenient method for body weight control. Despite these advances, the successful clinical trials and further marketization remain challenging by several aspects. First of all, a clear understanding of different critical pathway involved in the regulation of energy homeostasis is required for the design of transformative delivery platforms. For example, the leptin and melanocortin systems have been well investigated in the recent years (Ahima et al., 1996; Sohn et al., 2013), and several agonists are reported to reduce weight gain (Atasoy et al., 2014; Clemmensen et al., 2014; Ghamari-Langroudi et al., 2015). Therefore, it is possible to exploit nanocarriers for these drugs to achieve more effective weight control. Meanwhile, different drug delivery carriers/materials and administration routes may also affect the therapy efficiency. Second, how to reduce the side effects of these nanomedicines remains a barrier for translation. Adipose tissue-targeting groups may be incorporated into nanoparticle-based drug delivery systems to achieve precise therapy (Ma et al., 2016; Thovhogi et al., 2015) but the defects of certain designs must be taken into consideration, such as targeting efficiency and potential immune response. Last but not least, since the weight control requires long-term treatment, a thorough evaluation of the biocompatibility should be carefully performed (Lu et al., 2016).

Compliance and ethics The author(s) declare that they have no conflict of interest.

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