CRISPR/Cas9, the Powerful New Genome-Editing Tool for Putative Therapeutics in Obesity

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Abstract

The molecular technology known as *c*lustered *r*egularly *i*nter*s*paced *p*alindromic *r*epeats (CRISPR)/CRISPR-associated protein (Cas) is revolutionizing the field of medical research and deepening our understanding of numerous biological processes. The attraction of CRISPR/Cas9 lies in its ability to efficiently edit DNA or modulate gene expression in living eukaryotic cells and organisms, a technology that was once considered either too expensive or scientifically risky. CRISPR/Cas9 has been successfully applied in agriculture to develop the next generation of disease-resistant plants. Now, the capability of gene editing has been translated to the biomedical area, focusing on the future of medicine faced with drug-resistant microbes by selectively targeting genes involved in antibiotic resistance, for example, or finding the ultimate strategy for cancer or HIV. In this regard, it was recently demonstrated that an injection of cancer-fighting CRISPR-modified white blood cells in a patient suffering from metastatic lung cancer could lead to promising results. Researchers and bioethicists are debating questions about the regulation of CRISPR/Cas9 that must be addressed. While legal challenges surround the use of this technique for genetically modifying cell lines in humans, we review the basic understanding of CRISPR/Cas9 and discuss how this technology could represent a candidate for treatment of non-communicable diseases in nutrition, such as obesity.

Keywords Diet · Disease · Gene editing · Nutrition · Obesity

Obesity

Obesity is a health issue characterized by abnormal or excessive fat accumulation and increased body mass index (BMI), which is an index of weight to height commonly used to classify obesity. This parameter is defined as a person's weight in kilograms divided by the square of their height in meters (kg/m^2), with obesity classified as a BMI of 30 or greater (Hruby and Hu 2015). Obesity has been shown to cause additional health problems including heart disease, hypertension, type 2 diabetes, and cancer (Hemminki et al. 2011; Laitala et al. 2011), suggesting the importance of the study of this disorder, as well as the development of approaches for its prevention and management.

Obesity has become a worldwide health problem, with increasing prevalence globally over the past few decades. Among the world's population in 2008, for example, 10% of men and 14% of women were obese, compared with 5% of men and 8% of women in 1980 (World Health Organization 2015); in 2012, more than 40 million children under the age of 5 were overweight or obese (World Health Organization 2016).

The etiology of obesity is complex, since it involves a number of factors that interact in ways that are not well understood. Among these variables, socioeconomic status, genetics, cultural aspects, and lifestyle have been reported as critical elements in the genesis of obesity (Barclay et al. 2015; Borghese et al. 2015; Gervasini and Gamero-Villarroel 2015; Mayans 2015; Smith and Ryckman 2015). Despite its multifactorial nature, a general consensus has emerged that obesity is the result of an energy imbalance and the promotion of excessive fat deposition (Herrera and Lindgren 2010; Kuntz and Lampert 2010; Merchant et al. 2009; Singla et al. 2010; Wiwanitkit 2012; World Health Organization 2016). Understanding the role of the above-mentioned factors in the genesis of obesity is further complicated by the impacts that certain food marketing practices and institutionally driven physical activity reductions have in triggering the development of obesity. In this regard, variables such as increased portion sizes in commercially marketed food items, the ubiquitous presence of inexpensive but unhealthy food sources such as fast food, the availability of vending machines with energy-dense items, the promotion of high-fructose corn syrup (HFCS), and the reduction in physical education in schools have been described as interacting to favor to the development of obesity (Bocarsly et al. 2010; Klurfeld et al. 2013; Stanhope et al. 2011). In addition, neurochemical influences have been documented in obesity. For example, diverse compounds such as peptides (ghrelin, orexin, neuropeptide Y, vasoactive intestinal peptide, cholecystokinin), hormones (melanin-concentrating hormone, leptin), and lipids are associated with obesity (Geibel et al. 2014; Igarashi et al. 2015; Liu et al. 2010; Mallipedhi et al. 2015; Monteleone et al. 2016; Steiner et al. 2013; Wali et al. 2014; Warchol et al. 2014; Zhang et al. 2014). Moreover, obese individuals face a "double burden" of disease, since the disease causes additional health problems, including diabetes, hypertension, dyslipidemia, cardiovascular diseases, fatty liver disease, cancer, musculoskeletal disorders, breathing difficulties, risk of fractures, and psychological effects (Mollard et al. 2014; Papakonstantinou et al. 2013; Vucenik and Stains 2012). Thus one can assume that the obese population will eventually experience multiple different health-related issues.

Current Therapeutic Approaches for Managing Obesity

There are several therapeutic alternatives with positive outcomes for managing obesity (Higuera-Hernández et al. 2018; Igel et al. 2017). Among current strategies, pharmacological treatments including canagliflozin and metformin have been described (Arafa et al. 2016; Martinussen et al. 2017; Razavi and Hosseinzadeh 2017; Zimbron et al. 2016). Cognitive behavioral therapy has also shown positive results, while surgical procedures such as sleeve gastrectomy, gastric bypass, gastric banding, and duodenal switch are the most common bariatric approaches aimed at managing obesity (Gero et al. 2017; Hanipah and Schauer 2017; Kaplan 2017; Zimbron et al. 2016). One noninvasive non-pharmacological intervention is exercise (Bruyndonckx et al. 2015; Carter et al. 2015; Glynn et al. 2015). However, it has been demonstrated that many patients are still unable to achieve a clinically meaningful improvement, since their principal motivation is based on a better appearance rather than improving their health status. Thus, novel therapeutic strategies are needed for obesity interventions.

Obesity as Genetic Susceptibility to Weight Gain

More than 200 common genetic variants have been found to be associated with obesity, which has generated research interest in the development of unique, personalized preventive or treatment strategies (Garver et al. 2013; Loos and Janssens 2017; Manco and Dallapiccola 2012; Ng and Bowden 2013). In this regard, it has been described that obesity is due to rare mutations in single genes or chromosomal abnormalities (Chung 2012; Manco and Dallapiccola 2012; Ng and Bowden 2013; Pigeyre et al. 2016; Romieu et al. 2017). In most of the obese population, multifactorial and polygenic variants are likely responsible for the development of this disease. Several large-scale studies have examined the ability of genome-wide association study (GWAS)-identified BMI-associated loci to predict adult obesity (Belsky et al. 2013; Hung et al. 2015; Li et al. 2010; Locke et al. 2015; Peterson et al. 2011; Sandholt et al. 2010; Speliotes et al. 2010). For instance, eight monogenic genes and four polygenic genes (*FTO, PCSK1, MC4R, CTNNBL1*) from GWAS have been associated with obesity, and several loci have been recognized to be involved in Mendelian forms of obesity. An elegant review of this topic is provided by Choquet and Meyre (2011).

Notwithstanding these fascinating findings, the use of existing and novel technologies would allow us to prevent, rather than predict, obesity by gene editing. The importance of identifying obesity-related genes is in the predictive value of such an approach, enabling the initiation of preventive treatment in those patients determined to be at risk. For instance, three risk-prediction models were examined, with each consecutive model including a higher number of BMI-associated loci, which allowed for the assessment of whether adding more loci would improve prediction. By using previous data from the population-based EPIC-Norfolk study, the models aimed to predict obesity compared to normal weight. The fat mass and obesity-associated (*FTO*) locus was the first GWAS-identified obesity locus (Li et al. 2010). More importantly, polymorphisms in the *FTO* gene region in obese

patients have been identified in multiple populations, suggesting that *FTO* would be the first locus unequivocally associated with adiposity (Fawcett and Barroso 2010). We highlight the importance of recognizing that different forms of obesity may result, unlike genetic and non-genetic risk factors (Aarestrup et al. 2016; Loos and Janssens 2017; Whitaker et al. 1997). Thus, separate therapeutic approaches are needed for different forms of obesity with dissimilar origins, such as monogenic early-onset obesity. In this regard, gene editing has been an important method for studying the function of genes, and may offer a promising new perspective in the treatment of obesity.

CRISPR/Cas9 Gene Editing Technology

Streptococcus thermophilus is widely used in the dairy industry for production of yogurt and cheese (Delorme 2008). Scientists at Danisco explored how the bacteria responded to phage attack, a common problem in industrial yogurt making. Interestingly, Barrangou and coworkers (Barrangou et al. 2007) experimentally showed that a new technique acted as an adaptive immune system, since the authors were able to integrate new phage DNA into the new molecular array, allowing them to fight off the next wave of attacking phage. This novel technology, which was given the name "clustered regularly interspaced palindromic repeats (CRISPR)/CRISPR-associated protein (Cas)," enabled editing of parts of the genome by removing, adding, or altering sections of the DNA sequence (Ding et al. 2016; Lander 2016; Ledford 2016; Nelles et al. 2015).

Given this new technique, it is tempting to consider that several illnesses might be treated by gene editing. In fact, researchers in China investigated whether mutations in the β-globin gene could be corrected in human embryos (Liang et al. 2015). Another potential use of the CRISPR/Cas9 system might be the elimination of malaria by gene editing (Gabrieli et al. 2014). The putative medical uses of CRISPR/Cas9 have been reported as well (Harper 2017; Kehler et al. 2017; Pope 2017; Wang et al. 2017; Zulfiqar et al. 2017), including in obesity (Ackermann et al. 2017; Bao et al. 2015; Lu et al. 2017; Xia et al. 2016). However, several ethical issues have been raised concerning the potential use of CRISPR/Cas9 in health issues (Mulvihill et al. 2017). Since CRISPR/Cas9 has been successfully harnessed for genome editing (Cong et al. 2013; Mali et al. 2013), it is critical to consider testing this molecular technology in obesity.

CRISPR/Cas9 as a Promising Tool for Treating Obesity

CRISPR/Cas9 approaches could be utilized to unlock novel insights into obesity research. However, the field has yet to capitalize upon the technology. Although this review provides speculative rather than insightful propositions, CRISPR/Cas9 technology will in time revolutionize our understanding of the genetic mechanisms in several neurobiological functions as well as in pathologies such as obesity, among many others, by investigating CRISPR/Cas9 gene editing in obese experimental models (e.g., Carroll 2016; Heidenreich and Zhang 2015). It will be possible to explore neuromolecular mechanisms associated with obesity that were not possible just a few years ago. Since there are several genes that appear to be associated with obesity, one could assume that even 2–3 years from now, there will be substantial literature showing how the new gene editing technologies have enabled testing of specific hypotheses with regard to treating obesity (Fig. 1).

Claussnitzer et al. (2015) recently reported that CRISPR/Cas9 editing of the rs1421085 T-to-C single-nucleotide variant in adipocytes from patient activated browning expression and restored thermogenesis. Preliminary but significant advances have been achieved using CRISPR/Cas9 technology in fat mass and obesity (Walters et al. 2017). For example, a potential connection has been suggested between the CRISPR/Cas9 fingerprint and obesity based on an existing chemical-gene-disease database (Xia et al. 2016). Along these lines, Roh et al. (2018) have generated the first CRISPR/Cas9-induced leptin and leptin receptor gene knockout mouse model. These experimental animal models have shown phenotypic obesity-related characteristics including enhanced body weight, hyperglycemia, and hepatic steatosis. Although still in the early stages, CRISPR/Cas9 technology may be a critical tool for managing obesity in humans in the near future.

Editing Genes for Obesity…or for Addiction?

Indeed, obesity is a multifactorial and polygenic disease (Loos and Janssens 2017). However, further complexity is introduced in that obesity is linked with compulsive eating behaviors (Moore et al. 2017a). The construct of *food addiction* provides a framework within which to consider the genesis and management of obesity from a different perspective. Current opinions propose that, rather than a metabolic disease, obesity might be the consequence of addictive tendencies toward food (Moore et al., 2017b), and novel theories of obesity as a food addiction issue have been suggested (Hebebrand et al. 2014; Keser et al. 2015; Lerma-Cabrera et al. 2016; Meule et al. 2015; Nolan and Geliebter 2016). Based on several findings, it seems that obesity would promote addiction to palatable and high-calorie food (Leigh and Morris 2018; Mies et al. 2017; Wiss et al. 2017). Whether obesity is the result of food addiction rather than disrupted nutritional processes (ingestion, digestion, absorption, assimilation, digestion, and elimination) requires further study. Moreover, if food addiction is linked to psychological factors, future research should

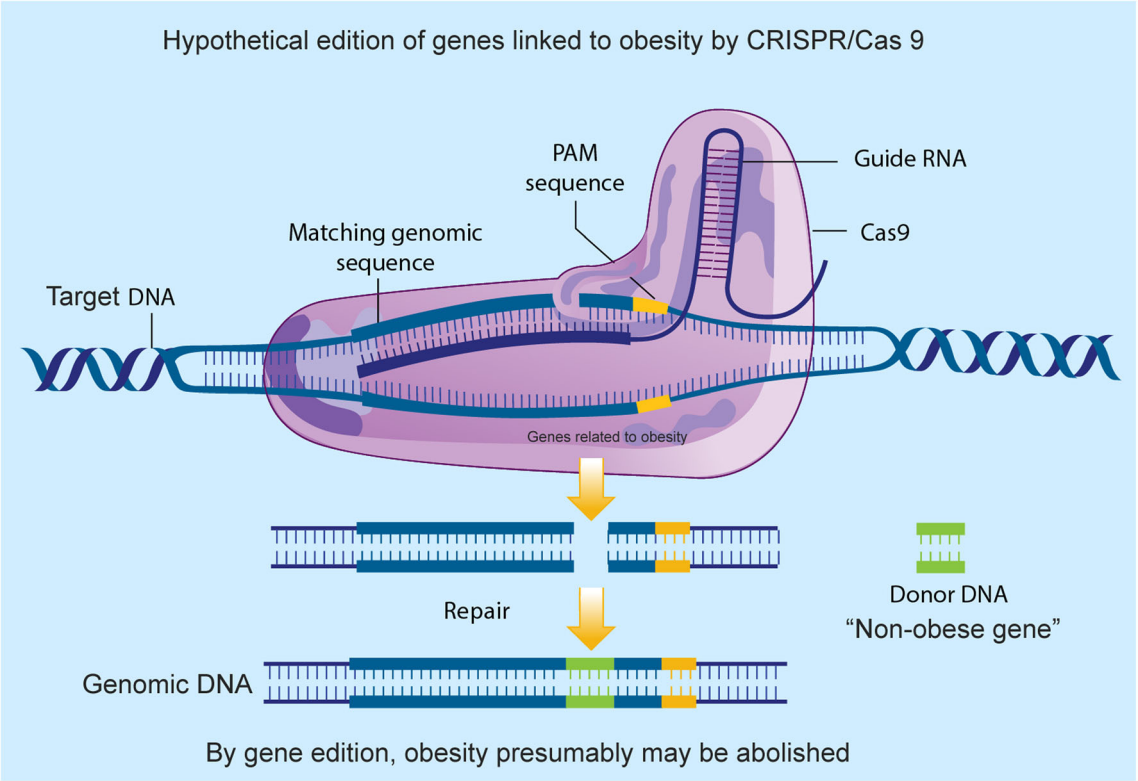

Fig. 1 Proposed use of CRISPR/Cas9 technology for gene editing in obesity. Through molecular manipulation of obesity-related genes, CRISPR7Cas9 may represent a novel therapeutic approach for managing obesity. Experimental genomics-based strategies would include testing CRISPR/Cas9 editing of genes in animal models of diet-induced weight gain

also address the interaction between cognitive/emotional gene activity and obesity. In addition, if gene editing is aimed at treating obesity, we should also target changes in genes associated with addiction (Granholm et al. 2017; Mielenz et al. 2017; Pedram et al. 2017; Rovaris et al. 2017).

Conclusion

Given that the obesity epidemic is a global public health concern, and given the limited effectiveness of standard therapies such as diet or pharmacological treatment, we believe that new and challenging genetic approaches aimed at reducing obesity have great potential in the coming years. Gene editing technologies coupled with knowledge of genes related to obesity will afford new insights into the neurobiology that underlies regulation of body weight and may lead to a breakthrough in the prevention and treatment of obesity.

Despite the fascinating putative use of CRISPR/Cas9 for treating obesity, some limitations should be considered. Obesity is unlike other diseases—for example, compared to metastatic lung cancer. Thus, one methodological challenge would be in identifying a specific target/tissue for obesity. Moreover, even if the mutated gene responsible for obesity were clear, where should transgenic cells edited via CRISPR/Cas9 be put back in the human body to treat obesity? In these contrasting scenarios, additional elements might arise as ethical considerations. For instance, cancer patients could accept transgenic treatment, but perhaps few patients with obesity would favor such treatment. Nevertheless, while the absence of a solid body of evidence regarding the likely use of CRISPR/Cas9 for treating obesity is quite limiting and provides a perception of weakness on the topic, it is precisely within such a limited framework that new perspectives emerge to represent new venues for further studies. Thus, we will assume that in the near future, the generation of empirical evidence derived from CRISPR/Cas9 in obese models will be available.

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