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A Collection Of Novel Techniques to Study Diabetes and Obesity

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Editorial

Diabetes and obesity have emerged as major public health burdens and raise the risk of neurological dysfunction, leading to cognitive impairment in patients[1]. As a result of the alarming rate of increase in these diseases, research efforts to combat these health challenges are growing. This methods collection brings together a wide range of techniques that are used to study diabetes and obesity, along with the associated cognitive impairment, in a variety of model systems.

The zebrafish is an attractive model to study diabetes because the expression and function of the genes that are involved in pancreas development are highly conserved in this organism when compared to mammalian systems[2,3,4,5,6]. Diabetes mellitus and hyperglycemia can be induced in zebrafish using invasive and non-invasive mechanisms and by developing mutant strains[7,8,9,10,11]. McCarthy et al. introduce a novel, non-invasive method to induce hyperglycemia in zebrafish using an alternate immersion protocol[12]. In this method, adult zebrafish are placed in a sugar solution for 24 h and then in water for 24 h to mimic the rise and fall of blood sugar in diabetes. They demonstrate that this process not only successfully induces hyperglycemia but also leads to the complications related to altered glucose homeostasis. Once established, this method could be successfully used to mimic the hyperglycemic condition in adult zebrafish.

Uncontrolled hyperglycemia can lead to an array of complications affecting every organ in the body. Changes in memory and/or cognitive impairment are among the concerning effects of uncontrolled hyperglycemia in patients with elevated blood glucose. As zebrafish have successfully been used in studies testing the effects of altered glucose homeostasis[13], this organism should now be used in behavioral studies as well. In their second article, Rowe et al. demonstrate a method to use zebrafish in behavioral studies[14] using a modified three-chambered apparatus designed to monitor social interactions in the mouse[15]. The zebrafish demonstrate acquired memory in about 8 weeks of training. However, the hyperglycemic fish demonstrate cognitive deficits after 4 weeks of treatment to induce hyperglycemia using an alternate immersion protocol[12]. This method provides a way to use zebrafish in behavioral studies that will be useful not only in the field of diabetes but also in other fields related to age-related, genetic, and other neurodegenerative diseases that lead to cognitive impairment.

Along with the ongoing research on the disease etiology and its effects, the field needs novel molecular avenues to generate functional β-cells for therapeutic interventions. However, the successful production of β-cells, either by *in vitro* culture or by the stimulation of *in vivo* regeneration, has been limited. Memon and Abdelalim describe a method of differentiating human pluripotent stem cells (hPSCs) into PDX1- (pancreatic and duodenal homeobox 1) and NKX6.1 (NKX6 homeobox 1)-expressing pancreatic progenitor cells[16]. The expression of these two transcription factors in progenitors reduces the occurrence of non-functional endocrine cells in cultures and results in functional, insulin-producing, glucose-responsive β-cells[17]. The scalable generation of PDX1 and NKX6.1 co-expressing progenitors has the potential to generate a functional pool of insulin-secreting β-cells for transplantation therapy as well as for disease modeling.

Obesity is a complex metabolic disorder caused by abnormal adipogenesis. Due to the increased need for human adipocytes to model the disease conditions and the limitations of collecting samples from human donors, the *in vitro* generation of adipocytes is in great demand. Aghadi et al. describe a protocol to produce mesenchymal stem cells (MSCs) from embryoid bodies derived from induced pluripotent stem cells (iPSCs) using all-*trans* retinoic acid[18]. The resulting MSCs show rapid proliferation and successful differentiation into adipocytes. They also establish a method to increase the differentiated adipocyte pool by sorting the cells tagged with Nile red, a lipophilic dye[18]. Taken together, they successfully produced cultures enriched in a pure population of mature adipocytes that will help researchers to study adipocyte-associated metabolic disorders with ease.

There are two major problems in the field of obesity research: the inability of cultured cell lines such as 3T3-L1 to reflect the cellular heterogeneity of the adipose depot[19,20], and the low yield of preadipocytes from the tissue collected from adult mice[21,22]. The cells collected from adult mice can reflect the cellular heterogeneity but contain mostly fully matured adipocytes and fewer preadipocytes[21,22]. Saez et al. answer both problems by describing a method for isolating white and brown preadipocytes from newborn mice[23]. These cells show high proliferative capacity and differentiation potential into mature adipocytes compared to the preadipocytes collected from adult mice. Their article is an effective resource to model the complexity of obesity using white and brown preadipocytes that can be differentiated into fully mature adipocytes.

Weight management is an important clinical issue. Long-term lifestyle changes, anti-obesity drugs, and exercise regimes all play important parts in this process. However, the loss of motivation due to the challenges in maintaining long-term lifestyle modifications, the expense of anti-obesity drugs, and the increased incidence of eating disorders have led the scientific community to explore natural remedies[24]. Pérez Gutiérrez and Arrioja explore the potential of two plants, *Syzygium aromaticum* (clove) *and Cuminum cyminum* (cumin)[25], as natural resources of anti-obesity compounds. The active phytochemical contents are extracted using ultrasound in an ethanol:water (50:50) solution and administered to C57BL6/J mice fed a high-fat diet. This represents an obesity model. The outcomes include improvements in various obesity parameters such as the regulation of lipid profiles (cholesterol and triglycerides) and reductions in food intake, weight gain, adipose tissue weight, and liver weight. This proposed method takes 5 weeks compared to the traditional 16 week regime and has the potential to test and identify new phytochemicals for their possible use in weight management.

This methods collection provides novel ways to use zebrafish in behavioral studies, to induce a hyperglycemic condition in this model organism, and to generate progenitor cells that lead to the production of insulin-producing, glucose-responsive β-cells. The collection also focuses on obesity and introduces methods to successfully produce adipocytes from iPSCs, to collect preadipocytes from newborn mice, and to isolate phytochemicals to test their potential in treating obesity. Taken together, this collection targets a broad group of researchers in the field of diabetes and obesity and provides a novel toolkit to illuminate previously unexplored areas in diabetes and obesity research.

Disclosures

The author has nothing to disclose.

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