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Zebrafish (*Danio rerio*) as a Model for Research On the Pathogenesis of Obesity and Its Treatments

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Abstract

Obesity is a complex epidemic which continues to be prevalent around the world. With escalating concerns due to the life-threatening complications such as type 2 diabetes, liver disease, cardiovascular morbidities and certain cancers. The research on the pathogenesis and its treatments or prevention methods has been carried on for decades. To represent the human conditions of obesity, mostly rodents have been used as a model. Though the use of rodents helped obtain a considerable amount of information, utilizing them as models requires a relatively higher cost, staff, and equipments. Certain limitations to the rodent models have also been found, and as result, zebrafish *(Danio rerio)* emerged as an alternative. Zebrafish are attractive models not only for their short intervals between generations and reproduction but also for the similarities pertaining to structure and hormones. In this review, we highlight research on zebrafish models utilized for investigating the complex and unclear pathogenesis of obesity.

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Introduction

Since obesity was categorized as a worldwide epidemic, increased awareness led to continued efforts for prevention. Despite the development of various measures, obesity has become more prevalent among both developing and developed countries. As of 2016, 39% of the adult population worldwide have been found to be obese, and the obesity rate has increased three folds since 1975 [1]. This increasing trend creates great concern as it impairs human health by directly leading to morbidity, especially that of associated diseases. Some complications include prediabetes, type 2 diabetes, coronary artery disease, sleep apnea, cancer, and liver disease [2]. Though, the pathogenesis of obesity is unclear due to the complexity affected by genetic, environmental, medical and sociocultural factors [3].

Several animal models that can mimic human health conditions have been used to investigate the pathogenesis methods of obesity treatment. Especially rodents were widely used for clinical studies regarding the association between diet (lipid intake) and obesity [4]. Though results from such research have served as standards for decades, employing rodents require large living space, meticulous handling when it comes to collecting embryos or applying substances [5]. Due to these problems, the need for more economic and precise models led to increasing interest in zebrafish (*Danio rerio*) for experimental use.

Zebrafish are teleost fish that belong to the Cyprinidae family. They are distinguished as small sized species, with adults reaching up to 4-5 cm [6]. Females are capable of spawning every 2-3 days, each containing approximately 200 eggs that can reach sexual maturity after 2-3 months [7]. Due to short generation time, rapid production, and small size, there is a constant supply of offspring and approximately 100 mature zebrafish can dwell in a tank of 8-12 L [8]. Along with advantages pertaining to fecundity rate, lower space and maintenance cost is required. These characteristics make the Zebrafish a favorable model for toxicological, biomedical, and developmental research.

Obesity

Obesity results from the imbalance between energy intake, energy expenditure, and energy storage. By consuming carbohydrates, protein, fat, and alcohol, energy is absorbed by the human body. Energy is expended when the body is at rest (Resting Metabolic Rate), ingests consumed food (Thermic effect of Food), and through physical movement [9]. An intricate physiological and hormonal mechanism which involves organs of the digestive system, skeletal system, and endocrine system maintains this balance.

One main trait of obesity pertains to adipose tissues that store energy in the form of fat. Adipose tissues grow through two mechanisms: hypertrophy and hyperplasia. Hypertrophy is the increase of cell size, whereas hyperplasia is the increase of cell number. When an excessive influx of nutrients takes place, adipose tissues go through either hyperplasia or hypertrophy while saving the energy in adipocytes (fat cells) as neutral lipids. When energy intake exceeds energy expenditure levels, weight gain occurs and thus obesity is stimulated.

Another characteristic of obesity is associated to hormonal responses and peptides. Agouti-Related Protein (AgRP) is anorexigenic protein that stimulates nutrient intake, while decreased levels of AgRP lead to elevated metabolic rates [10]. Adiponectin is another hormone produced by adipocytes that regulates glucose levels and fatty acid oxidation [11,12]. It plays a substantial role in energy metabolism and decreased levels of total adiponectin is displayed in obesity whereas increased levels are shown when weight loss occurs [13].

Since obesity occurs with the involvement of various hormones, genes, and organ systems, and different environmental, genetic, and sociocultural factors can affect the mechanism the pathogenesis is not only induced by the consumption of excessive calories. A more in expensive and accurate model replacing rodents that can handle the complex nature of human obesity is in demand.

Zebrafish as a Model of Obesity

Zebrafish are structurally analogous with humans to the extent that worms and flies cannot follow in terms of energy metabolism [14].

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Especially adipocytes, fat cells, show similar traits to those found in the human body. To detect lipids and investigate the process of adipostat, the establishment of methods such as imaging and visualizing (i.g. nile red staining) have been conveniently used in such research. Using the Nile Red staining and electron microscopy, a lipid droplet in mature zebrafish adipocytes was spotted, which can also be seen in white adipocytes (WA) of mammals [15]. Zebrafish adipocytes are also capable of performing the same roles of those in the human body and respond to same hormonal signals such as glucagon and insulin [16]. Whether zebrafish adipocytes can controls to red lipid levels in response to weight loss was proved through a certain period of starvation - 4 days of starvation resulted in size decrease of all fat depots and 7 days of starvation led to absolute depletion [17]. When returned to normal feeding, neutral lipid appeared in the same depots that stored lipid before starvation [17].

Zebrafish also show similarities to mammals when considering obesity associated hormones. The expression of Agouti- related protein (AgRP) is detected in two forms: AgRP1 and AgRP2 which are orexigenic factors [18]. Research shows that zebrafish AgRP cDNA produced proteins that were 36% identical to those found in humans and 40% matched exactly to those of mice [19]. Furthermore, it has been established that excessive levels of AgRP within transgenic zebrafish can lead to the expression of obesity phenotypes and greater appetite [20]. These subjects displayed an increase in body mass, total triglyceride level, and internal adipose accumulation, thus making zebrafish an appropriate model for adipostat related studies [20]. Adiponectin was also found to be prevalent in the brain of a mature zebrafish as Adipor1, Adipor2, and Adipor3 [21].

Because of these shared characteristics, zebrafish models can be and have been employed as obesity models in various directions. Different foods were tested on their effects on body fat. Exposure to green tea extracts led to a decline in the visceral fat tissue volume of zebrafish [22]. The anti-obesity properties of red seaweed *(Palmaria mollis)* was also investigated using diet-induced obese (DIO) zebrafish and showed decreased visceral adiposity [23]. Campari Tomato was found to regulate body weight increase and lipid droplets in the liver of DIO zebrafish [24]. Several biochemical experiments and drug screening tests have been conducted too. To find an alternative appetite modulator that can replace Rimonabant, which is known for its side effects such as anxiety and suicidal thoughts, a large-scale experiment on zebrafish larvae was organized to find 500 substances that inhibited or stimulated appetite [25].

These cases show how zebrafish can be further applied to the study of obesity in terms of finding treatments, anti-obesity drugs, or even food supplements along with the biological mechanisms controlling appetite and lipid storage. Because it's structural, physiological, and genetic similarities to the human body, the use of zebrafish models in biomedical research is untapped. Further research on epidemics other than obesity could be carried out to determine the mechanisms of certain disorders and potential therapies.

Competing Interests

The authors declare that they have no competing interests.

References

1. WHO (2018) Obesity and Overweight.
2. Mitchell NS, Catenacci VA, Wyatt HR, Hill JO (2011) Obesity: overview of anepidemic. Psychiatr Clin North Am 34: 717-732.
3. Gadde KM, Martin CK, Berthoud HR, Heymsfield SB (2017) Obesity: Pathophysiology and Management. J Am CollCardiol 71:69-84.
4. Bray GA, Paeratakul S, Popkin BM (2004) Dietary fat and obesity: a review of animal, clinical and epidemiological studies. Physiol Behav 83: 549-555.
5. Simonetti RB, Marques LS, Streit DP, Oberst ER (2015) Zebrafish (Danio rerio): The Future of Animal Modelin Biomedical Research. J Fish Sci 9: 039-045.
6. Spence, R, Gerlach G, Lawrence C, Smith C (2008) The behavior and ecology of the zebrafish Danio rerio. Biol Rev Camb Philos Soc 83: 13-34.
7. Gerlai R, Lahav M, Guo S, Rosenthal A (2000) Drinks like a fish: zebrafish (Danio rerio) as a behavior genetic model to study alcohol effects. Pharmacol Biochem Behav 67: 773-782.
8. Saleem S, Kannan RR (2018) Zebrafish: an emerging real-time model system to study Alzheimer's disease and neurospecific drug discovery. Cell Death Disc 4: 45.
9. Hill JO, Wyatt HR, Peters JC (2012) Energy Balance and Obesity. Circulation 126: 126-132.
10. Ilnytska O, Argyropoulos G (2008) The role of the Agouti-Related Protein in energy balance regulation. Cell Mol Life Sci 65: 2721-2731.
11. Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, et al. (1996) cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1). Biochem Biophys Res Commun 221: 286-289.
12. Díez JJ, Iglesias P (2003) The role of the novel adipocyte-derived hormone adiponectin in human disease. Eur J Endocrinol 148: 293-300.
13. deRosa A, Ludovica MM, Capasso M (2013) Adiponectin oligomers as potential indicators of adipose tissue improvement in obese subjects. Eur J Endocrinol 169: 37-43.
14. Schlegel A, Stainier DY (2007) Lessons from "lower" organisms: what worms, flies, and zebrafish can teach us about human energy metabolism. PLoS Genet 3: 2027-2040.
15. Napolitano L (1963) The Differentiation of White Adipose Cells. An Electron Microscope Study. J Cell Biol 18: 663-679.
16. Albalat A, Gutiérrez J, Navarro I (2005) Regulation of lipolysis in isolated adipocytes of rainbow trout (Oncorhynchus mykiss): the role of insulin and glucagon. Comp Biochem Physiol MolIntegr Physiol 142:347-354.
17. Flynn EJ, Trent CM, Rawls JF (2009) Ontogeny and nutritional control of adipogenesis in zebrafish (Danio rerio). J Lipid Res 50:1641-1652.
18. Jeong I, Kim E, Kim S, Kim HK, Lee DW, et al. (2018) mRNA expression and metabolic regulation of npy and agrp1/2 in the zebrafish brain. Neurosci Lett 668: 73-79.
19. Song Y, Golling G, Thacker TL, Cone RD (2003) Agouti-related protein (AGRP) is conserved and regulated by metabolic state in the zebrafish, Danio rerio. Endocrine 22: 257-265.
20. Song Y, Cone RD (2007) Creation of a genetic model of obesity in a teleost. FASEB J 21: 2042-2049.
21. Rastegar S, Parimisetty A, Cassam Sulliman N, Narra SS, Weber S, et al. (2019) Expression of adiponectin receptors in the brain of adult zebrafish and mouse: Links with neurogenic niches and brain repair. J Comp Neurol 527: 2317-2333.
22. Hasumura T, Shimada Y, Kuroyanagi J, Nishimura Y, Meguro S, et al. (2012) Green tea extract suppresses adiposity and affects the expression of lipid metabolism genes in diet-induced obese zebrafish. Nutr Metab 9: 73-80.
23. Nakayama H, Shimada Y, Zang L, Terasawa M, Nishiura K, et al. (2018) Novel Anti-Obesity Properties of Palmari mollisin Zebrafish and Mouse Models. Nutrients 10: 1401-1417.
24. Tainaka T, Shimada Y, Kuroyanagi J, Zang L, Oka T, et al. (2011) Transcriptome analysis of anti-fatty liver action by Campari tomato using zebrafish diet-induced obesity model. Nut Metab 8: 88-99.
25. Jordi J, Guggiana-Nilo D, Bolton AD, Parabha S, Ballotti K, Herrera K, Randall TP (2018) High-throughput screening for selective appetite modulators: Amulti behavioral and translational drug discovery strategy. Sci Adv 4: 1966-1981.