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Review Article

The Zebrafish Model of Diabetes Mellitus: a Re-Appraisal

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Abstract

The objective of this review is to explore multifactorial aspects concerning possible use of zebrafish as a model system for Diabetes Mellitus. For the purpose of this review, bibliographic searches were performed under Pubmed, Medline and Google scholar for articles indexed in these databases ranging from 2000 to 2019. Zebrafish has evolved as a suitable animal model organism for experimental pharmacology is expanding at a great rate to include lifestyle diseases of human. Lifestyle diseases are characterized by conditions which occur in primarily based on the way of living and occupational habits of individuals. Diseases that impact on our daily lifestyle are mainly obesity & diabetes. Nowadays, diabetes and obesity are considered as global epidemics. The prevalence rates of diabetes are increasing day by day in parallel with the rates of obesity. Research is ongoing for surgical and pathological management of obesity and diabetes. For identification and development of effective treatment the use of animal models are important. Zebrafish is poised to present as a unique model for human disease. In this study we discuss the advantages, disadvantages of pathology associated with diabetes & obesity by using zebrafish model. In consideration of these potential shortcomings, it is expected that zebrafish will not replace the classical mammalian test systems anytime soon, but rather complement them as a first step in vertebrate modelling of disease and aid the complex process of drug discovery.

Keywords: *Danio rerio*; Diabetes mellitus; Screening, Type 2 DM

Introduction

The availability of a model predictive animal model of disease is regarded as a cornerstone in the drug discovery and development cycle. Zebrafish is a well-established and powerful model for the study of vertebrate biology. Scientifically zebrafish is known as *Daniorerio* which is belonging to the family Cyprinidae of the order Cypriniformes. Zebrafish is a vertebrate and having a high degree of physiological, anatomical and genetically based similarities to humans. It is reported that the organism shares 70% of the human genotype as also with 84% of genes are known to be associated with human disease [1].

Zebrafish has the capacity to produce hundreds of off springs in a week, they grow at extremely fast rate. Zebrafish has a short reproductive cycle and it is suitable for large scale drug screening. Zebrafish acquire unique characteristics that make this tropical fish a convenient animal model for developmental and genetic studies for the following reasons: this model organism reaches sexual maturity in about 2-3 months, the small size of this model allows for cultivating relatively large numbers in small area, female zebrafish are very fecund and can produce hundreds of eggs on weekly basis, egg fertilization process occurs externally which allows for the production of haploid embryos, the growing embryos are transparent, water soluble drugs are rapidly administered to zebrafish by adding them to water, zebrafish are susceptible to injection [2] and zebrafish are a fully sequenced genome.

Possible role in toxicology and drug discovery

Toxicological studies into zebrafish has only recently emerged for augmenting drug discovery. Drug effects on growth and development have been assessed by gross visual examination of the length and shape of the body segments of *Danio rerio*, the size and morphology of internal organs, including the brain, liver, cardiovascular system, cartilage, notochord, pancreas, intestine, and kidney. In addition, organ function assays have been and continue to be developed, which permit functional assessment of drug effects on the major internal organs in vivo. A large number of Phase I oxidation enzymes (e.g., the cytochrome P-450 family), Phase II conjugationhave been studied [3].

Zebrafish and a diabetes model [4]

Zebrafish is a proper model for studying metabolic dysfunction because they have appropriate organs that involve metabolism including increased adipose tissue, cardiovascular overload, steatosis, and energy homeostasis. The preservation of the structure of the pancreas and glucose homeostasis system make zebrafish convenient to identify novel targets in pancreas related diseases like type I & type II diabetes mellitus. Basic cellular architecture & morphogenesis of zebrafish pancreas is identical with mammalian pancreas which has both exocrine & endocrine compartments. Zebrafish pancreas function has been well-established by some methods which include fasting & postprandial glucose measurements and intra-peritoneal glucose tolerance tests and techniques for islet cell culture and pancreas dissection.

Type 1 diabetes mellitus model

Type 1 Diabetes Mellitus (T1DM) is an autoimmune disease which is caused by destruction of insulin producing pancreatic β-cells. There are 3 methods of β-cells destruction: genetic ablation, chemical-dependent ablation and surgical removal. Chemicalinduced

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Table 1: Summarizes current information of the models of diabetes mellitus using Zebra fish.

Type of model	Disease type	Induced by	Age	Phenotype
Pancreatectomy	T1DM	Physical removal of pancreas	adult	Elevated blood glucose level
Chemical ablation of β cells	T1DM	Intraperitoneal injection of Streptozotocin (STZ)	adult	Hyperglycemia and diabetic complications
Glucose intolerance	T1DM	Alloxan exposure through incubation /IP injection	Larva, adult	β cells necrosis, decreased neuromast number
Glucose immersion	T2DM	Incubation in glucose solution	adult	Hyperglycemia, impaired response to insulin, diabetic retinopathy
Over-nutrition	T2DM & obesity	Over feeding zebra fish with commercial foods	adult	Hyperglycemia, glucose intolerance, insulin resistance

Table 2: Current information of the models of obesity applied using Zebra fish.

Type of model	Induction strategy	Age at induction	Characteristics
High-fat diet	i) Heavy whipping cream	Larvae	Lipid accumulation inter segmental vessels; increased whole larval Triacylglycerol (TAG) & apoliprotein B levels
High-fat diet	ii) chicken egg-yolk	Larvae, juvenile and adult	Hyperlipidemia, increased adipose tissue area & TAG
High-fat diet	iii) corn oil & lard	Adult	Increased body fat
Over-nutrition	Artemia	Adult	increased rate of BMI and hepatosteatosis, hypertriglyceridemia
Over-nutrition & High-fat diet	i) Tetramin & vegetable oil	Juvenile and adult	Increased weight gain & cardiovascular overload
Over-nutrition & High-fat diet	ii) artemia& egg yolk powder	Adult	Increased body weight, adipose tissue mass, adipocyte hypertrophy, Hyperglycemia, hepatosteatosis

diabetes is widely used in zebrafish. In adult zebrafish intraperitoneal injection of Streptozotocin (STZ) is effective at β-cell ablation and causes reduction in insulin levels and there is elevation of fasting blood glucose levels. A total number of 6 administrations of Streptozotocin (STZ) within 4 weeks induces stable diabetic complications and hyperglycemia including nephropathy, retinopathy and impaired fin regeneration. It is the preferred method for modelling type 1 diabetes mellitus.

Type 2 diabetes mellitus model

Type 2 Diabetes Mellitus (T2DM) is characterized by resistance of insulin and β-cell dysfunction. Nutritional and genetic approaches have been used to generate Type 2 Diabetes Mellitus (T2DM) models in zebrafish. The most convenient method for modelling type 1 diabetes mellitus in zebrafish is immersion of zebrafish in glucose solution. Immersing of adult zebrafish into altering glucose concentrations of 0% and 2% every other day for 1 month or chronic exposure to glucose solution of 2% for 14 days induces elevated blood glucose levels, diabetic phenotypes and impaired response to exogenous insulin. Young zebrafish (4-11 months) accommodate to glucose exposure better than older zebrafish (1-3 years) (Table 1).

Zebrafish models for diet-induced obesity [4,5]

The metabolic rate of zebrafish is not regulated by environmental temperature as it is an ectothermic species. Zebrafish have numerous adipose tissue depots and doesn't have Brown Adipocyte Tissue (BAT) depots. At the very first stage, chicken egg yolk solutions, heavy cream are used as a high-fat diet for zebrafish larvae and juveniles .This diet rapidly increases adiposity in zebrafish. Adult zebrafish are also used for obesity models.

Adult fish are routinely fed with 60mg artemia per day for 8 weeks. After overfeeding, they exhibited hypertriglyceridemia, increased the rate of BMI and hepatosteatosis compared to normal zebrafish. Thoroughly zebrafish is a very alluring model system to evaluate the effects of compounds and foods on obesity (Table 2).

The diet-induced obesity approach helps us to understand the disease of systemic obesity and therefore mimicking the common process occurring in humans affected by this same condition has utility in clinical medicine and pharmacology.

What makes zebrafish such a predictive animal model [6-8]

Zebrafish matches all the criteria in the selection process of the animal model that directly related to the final goal. Zebrafish are attractive animal models as they have numerous advantages over other species. The most beneficial features of zebrafish are the presence of a fully sequenced genome, easy manipulation of genome, high rate of productivity, external fertilization, rapid embryonic development, short generation time and transparent embryo. Zebrafish have all the main useful organs involved in the metabolic process which is beneficial to study various human metabolic disorders like diabetes mellitus, obesity, hepatic disease, dyslipidemia, non-alcoholic fatty liver diseases, etc.

Limitations of this model [9-16]

There is dissimilarity of organs like the reproductive system & respiratory system. Thus there is limitation to use zebrafish as a model for reproduction & respiration in humans. On the other hand, the screening of some water-soluble drugs in zebrafish is another limitation as they live in an aquatic habitat. Consequently, zebrafish lack some of the important mammalian organs such as lung, skin, and mammary gland which limits its possible use in mimicking certain groups of human disorders. More generally, the closer the organism is on the evolutionary tree to the humans, the better the predictive value of the animal model. Yet, even nonhuman primates are not entirely predictive for human outcomes in drug development. Thus, the utility of the zebrafish system needs to be carefully validated in the context of drug discovery programs. In consideration of these potential shortcomings, it is expected that zebrafish will not replace the classical mammalian test systems anytime soon, but rather complement them as a first step in vertebrate modelling of disease

and aid the complex process of drug discovery [17,18].

Conclusion

From the aforesaid summary we conclude that the use of adult or larval forms of zebrafish serves as relevant model of considerable potential in fields of developmental biology and medicine. Zebrafish have several convenient features with respect to physiological, developmental and genetic studies including transparent nature of embryo, external fertilization. There are enormous conservation of genetics, physiology and morphology between human and zebrafish makes it an interesting model for various human disorders and development of potential therapies. Advancements of molecular technologies and nanotechnologies also contributes to the use of zebrafish to learn different diseases in humans. In case of toxicology, in addition to the accumulation of genomic and genetic infrastructure will actually provide greater insight into the mechanisms of toxicity of chemicals , as well as aid in new drug discovery for treating human disease. In this review article we emphasized some areas where zebrafish are an attractive model to investigate the processes and mechanisms which are associated with metabolic disorders like diabetes mellitus, obesity, liver-related disease, dyslipidemia, atherosclerosis, and intestinal disease. Recently, Zebrafish have been also used by scientist to develop new therapies for treatment and prophylaxis of various non-communicable human diseases. Zebrafish would contribute significantly to the literature and facilitate the implementation of innovative, cost-effective and comprehensive testing strategies.

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Authors' Contributions

The concept of the study was done by both authors. Sudeshna Sasmal wrote the first draft of the manuscript. Both authors edited the working draft.

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