Review Article

The role of zebrafish in Huntington's disease: a review on therapeutics aspect.

Abstract

Treatment and effective therapies of most of the neurodegenerative disease ~~is~~ are not available due to ~~the~~ social and economic factors which makes it incurable. Huntington's disease is one of such disease.

Huntington's disease is an inherited condition which leads to progressive degeneration of ~~the~~ nerve cells cause cognitive, behavioral, and psychiatric symptoms. Discovery of zebrafish has filled the gap between in vitro and in vivo assays and makes the study of neuroscience easy with less complications. Zebrafish model has become a recent topic to focus on, as ~~it is~~ its utility in the study of neurological disease and role in improving ~~the~~ screening methods makes the treatment and therapies more productive. Zebrafish hold many advanced functional genomics like ~~the~~ human disease, the understanding of genetics, neurodegenerative disease and disorders and the discovery of therapeutics??. Zebrafish assess the mutant gene, etiology of human's disease, it is role in the disease progression and allows the identification of relevant treatment for the same?. This review highlights the role of the zebrafish in the Huntington's disease and the therapeutic aspect.

Keywords: Huntington's disease, zebrafish, neuroscience, neurodegenerative disease, therapeutics.

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Introduction

~~Zebrafish, *Danio rerio* has been proved to be a vertebrate model for the study of neurodegenerative disease, developmental biology, and gene function (1).~~ Huntington's disease is an autosomal dominant monogenic neurodegenerative disease which means that one person needs only one copy of ~~the~~ defective gene to develop ~~the~~ disorder that occurs due to the mutation in Htt gene. Mutation in Htt gene or Huntingtin gene encodes abnormal trinucleotide that leads to glutamine (CAG) expansion at the Htt protein amino terminal. A decline in the Huntingtin cause abnormality in the normal pathogenesis (2). Zebrafish is a tropical freshwater fish which is obtain from the eastern's India ganga river. Zebrafish, *Danio rerio* has been proved to be a vertebrate model for the study of neurodegenerative disease, developmental biology, and gene function (1).

The unique feature about the zebrafish is that it has all the main organs for metabolism (3). Popularity of zebrafish ~~is~~ are not only that they are vertebrate, but they are more evolutionary alike to humans than invertebrates (2,4). Many studies revealed that ~~the~~ in the zebrafish, Htt gene has 70% similarity with the human protein (2,5). Huntington's disease is one of the nine degenerative diseases characterized by the progressive deficit, mood alterations, involuntary movements, ~~and~~ weight loss (even with the adequate dietary intake) ~~also show~~and psychological symptoms (6,7). Huntington's disease like the most neurodegenerative disease is incurable and ~~it is~~ fatal after 15-20 years of onset because ~~it is~~its pathology evidence the gradual and progressive death of medium

spiny gamma-amino butyric acid (GABA) neurons of the striatum and selective death of the neurons found in the deep cerebral cortex (6). Even though the loss of function of Htt did not lead to neurodegeneration, miss-expression of polyQ dilated Htt fragment aim protein aggregate and neuronal death. Since due Due to all these reasons aside of the symptomatic treatment to manage the movements abnormalities no drugs are accessible and obtainable that can steady down the progression of Huntington disease (8). Usually, the onset of symptoms occurs in the middle age between 30-50 years but ad rarely symptoms start before the age of 20 years which leads to behavior abnormality and deceleration in cognitive function which shows difficulty in learning; this condition is well known as juvenile Huntington Disease, JHD(9,10). Symptoms of juvenile Huntington disease includes difficulty in walking, speaking, rigidity that occurs due to gene mutation in short arm of chromosome number-4 (11). Diagnosis of Huntington disease is based in on the clinical signs and symptoms of the patient and their hereditary history as it is hereditary. The non-pharmacological therapy therapies for Huntington's disease includes genetic counselling, psychotherapeutic support and palliative care are also dissertated. Although CNS disease and disorders has have ineffective therapy therapies by the pharmacological treatment. by pridopidine have has shown to be effective (12). Now with the advancing technology degenerative disorder and CNS disorder like Alzheimer's disease, Huntington disease, amyotrophic lateral sclerosis (ALS), Parkinson, schizophrenia are studied using zebrafish because these disorder add up a global burden on society in tern if economic loss and human sufferings which established the need of Zebrafish as an emerging model for the discovery of natural drug products and functional genomics (2,13).

Role of zebrafish in Huntington disease-

Over the past many?? decades's. animal models, especially nice and rats are widely used to study many Human human related disease but recently studies using aquatic fish have become popular

due to cost effectiveness and simplicity(14). Since the population ages there is an urgency for the effective therapies for the treatment of neurodegenerative disease (4). Fir studying neuropharmacology, brain function, dysfunction, and pharmacogenetics. of both the adult and larval Zebrafish are used. The foremost reason if of using zebrafish is that the CNS (stand for?)of zebrafish is suitable to mimic the human neurological disease (2,15,16). Zebrafish can produce enormous number of externally fertilized transparent eggs which develops rapidly this helps in drug screening and behavioral testing by apply simple methods of gene expressions. The small size embryo and larvae is also an advantage of using zebrafish (2,5,17,18).

The CNS of zebrafish is divided into forebrain, mid brain, hindbrain and . ascending and descending spinal cord all thiswhich like the human beings and other vertebrates which highlights that the pathological conditions can be easily identified, examined, and validated (2). Zebrafish models elucidate mutational analysis i.e., the loss as well as the gain of the Huntington's disease mechanism and the role of zebrafish in neurodegeneration disease including Huntington's disease is established. This elucidates the potential treatment for the same. Therapeutically Integrated biological model of zebrafish helps in the research oh natural drug like product using chromatography techniques which requires only microgram quantity oh sample components. The requirements of just microgram quantity to initiate drug discoveryand functional genomics proved out to an advantage of zebrafish for HD in comparison to other vertebrates. The evolutionary lineage begins with the similarity of HD cDNA with the Zebrafish. This cDNAcodes for a protein product if 3121 amino acid which is very much identical to human beings(2,5).

Another advantage of zebrafish in Huntington's disease is its simplicity and effectiveness of manipulating gene expression and rapidly validate the pathological mutation of human gene variant(2). Zebrafish is an absolute viable model if of vertebrate to study the causes of

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neurodevelopmental autism(19). In a study Huntington's like Zebrafish was created by mRNA of the N-terminal with dissimilar length polyQ linked to a GFP fusion protein (4).

Use of Zebrafish in drug discovery-

This review focus to evaluate the feasibility of therapeutic aspect of zebrafish in the Huntington's disease for the natural drug discovery and studying of the impact if drugs in the CNS. A study revealed that the deficiency if the Huntington's gene i.e., Htt in zebrafish may lead to hypochromic blood because of the decreased hemoglobin production, although the supply of the iron in the blood cell us adequate(4). Drugs with known effect shows the similar effect in the zebrafish as they show in humans (Ref). Another study identified the PG E2 through zebrafish based molecular screening. This shows the similar action in both the mammalian and zebrafish hematopoietic stem cell homeostasis (20). Apart from these similar effects. it have been shown for to have many (?) compounds, including chemotherapeutics, narcotics, Antianti-angiogenic, lipid metabolism, anticoagulants, and cardiac cycle(21). Compounds which enhance the regeneration and repair in nervous system have also been identified in zebrafish (21,22,23,24). The use of zebrafish and nanotechnology for the therapeutic optimization in neurodegenerative context has not appraised. But this method helps in the close monitoring if pharmacokinetics specially bio distribution of Nano medicine to the target drug delivery system and hence identification if the therapeutic efficacy (21). Morpholino knockdown if zf-IT 15 cause different morphological abnormalities including pericardial oedema, thin yolk, small head and CNS necrosis, these similar effects have also been observed in the mutant zebrafish strain (25).

Conclusion and future prospects-

The aim of this review as to study is to show that zebrafish model is an adequate system fir this finding of therapeutic treatment of Huntington disease. Because of so much similarity between the zebrafish and Huntington's disease, it helps in determining the outcome of reduced Htt gene expression. Zebrafish modelling give a new direction in the molecular biology including the area of

natural drug discovery, drug optimization, Nano medicine and regeneration medicine. Furthermore, the development attributes of zebrafish push the researchers to understand the etiology and the pathogenesis of the disease and hence it makes the way to find the optimal treatment for the disease and disorders. Thus , this makes the zebrafish a suitable organism to evaluate the therapeutic aspect of the drugs for neural development and neurological disorder. So, the zebrafish model is reported as an early screening tool for neurological disorders.

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