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 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 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.

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.

The unique feature about the zebrafish is that it has all the main organs for metabolism (3). Popularity of zebrafish is not only that they are vertebrate, but they are more evolutionary alike to humans than invertebrates (2,4). Many studies revealed that the in 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 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 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 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 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 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 the clinical signs and symptoms of the patient and their history as it is hereditary. The non-pharmacological therapy for Huntington's disease includes genetic counselling, psychotherapeutic support and palliative care are also dissertated. Although CNS disease and disorders has ineffective therapy the pharmacological treatment by pridopidine have 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 productsand functional genomics (2,13).

Role of zebrafish in Huntington disease-

Over the past many decade's animal models especially nice and rats are widely used to study many 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 using zebrafish is that the CNS 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 this 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 discovery and 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 cDNA codes 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 vertebrate to study the causes of neurodevelopmental autism(19). In a study Huntington's like Zebrafish was created by mRNA of the N-terminal with dissimilarlength 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 becauseof 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. 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 have been shown for compounds including chemotherapeutics, narcotics, Anti-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. Zebrafishmodelling 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.

Reference-

1. Xi Y, Noble S, Ekkeí M. Modeling neuíodegeneíation in zebíafish. Cuíí Neuíol Neuíosci Rep. 2011 Jun;11(3):274-82. doi: 10.1007/s11910-011-0182-2. PMID: 21271309; PMCID:PMC3075402
2. Pitchai A, Rajaíetinam RK, Fíeeman JL. Zebíafish as an Emeíging Model foí Bioassay-Guided Natuíal Píoduct Díug Discoveíy foí Neuíological Disoídeís. Medicines (Basel). 2019 May 30;6(2):61. doi: 10.3390/medicines6020061. PMID: 31151179; PMCID: PMC6631710.
3. https://www.otago.axnz>zebíafish
4. Best JD, Aldeíton WK. Zebíafish: An in vivo model foí the study of neuíological diseases. Neuíopsychiatí Dis Ɩ'íeat. 2008 Jun;4(3):567-76. doi: 10.2147/ndt.s2056. PMID: 18830398; PMCID: PMC2526373.
5. Kabashi E, Bíustein E, Champagne N, Díapeau P. Zebíafish models foí the functional genomics of neuíogenetic disoídeís. Biochim Biophys Acta. 2011 Maí;1812(3):335-45. doi: 10.1016/j.bbadis.2010.09.011. Epub 2010 Sep 29. PMID: 20887784.
6. Henshall TL, Tucker B, Lumsden AL, Nornes S, Lardelli MT, Richards RI. Selective neuronal requirement for huntingtin in the developing zebrafish. Hum Mol Genet. 2009 Dec 15;18(24):4830-42. doi: 10.1093/hmg/ddp455. Epub 2009 Sep 29. PMID: 19797250; PMCID: PMC2778375.
7. Lumsden AL, Henshall TL, Dayan S, Lardelli MT, Richards RI. Huntingtin-deficient zebrafish exhibit defects in iron utilization and development. Hum Mol Genet. 2007 Aug15;16(16):1905-20. doi: 10.1093/hmg/ddm138. Epub 2007 Jun 13. PMID: 17567778.Guo S.
8. Using zebrafish to assess the impact of drugs on neural development and function. Expert Opin Drug Discov. 2009 Jul 1;4(7):715-726. doi: 10.1517/17460440902988464. PMID: 19774094; PMCID: PMC2747263.
9. Walker FO. Huntington's disease. Lancet. 2007 Jan 20;369(9557):218-28. doi: 10.1016/S0140-6736(07)60111-1. PMID: 17240289.
10. Roos RA. Huntington's disease: a clinical review. Orphanet J Rare Dis. 2010 Dec 20;5:40.doi: 10.1186/1750-1172-5-40. PMID: 21171977; PMCID: PMC3022767.
11. Aubeeluck A, Brewer H. Huntington's disease. Part 2: treatment and management issues in juvenile HD. Br J Nurs. ("Huntington's disease. Part 2: treatment and management ...") 2008 Feb 28-Mar 12;17(4):260-3. doi: 10.12968/bjon.2008.17.4.28715. PMID: 18414272.
12. Shannon KM, Fraint A. Therapeutic advances in Huntington's Disease. Mov Disord. 2015 Sep 15;30(11):1539-46. doi: 10.1002/mds.26331. Epub 2015 Jul 30. PMID: 26226924.
13. Taylor J.P., Hardy J., Fischbeck K.H. Toxic proteins in neurodegenerative disease. Science. 2002;296:1991–1996. doi: 10.1126/science.1067122. [PubMed] [CrossRef] [Google Scholar]
14. Saluja D, Jhanji R, Kaushal S, Verma B, Sharma N, Singh R, Agrawal S, Yadav M, Kumar A, Singh C, Singh A. Importance of Zebrafish as an Efficient Research Model for the Screening of Novel Therapeutics in Neurological Disorders. CNS Neurol Disord Drug Targets. 2021;20(2):145-157. doi: 10.2174/1871527319666201207211927. PMID:33290204.
15. Bandmann O., Burton E.A. Genetic zebrafish models of neurodegenerative diseases. Neurobiol. Dis. 2010;40:58–65. doi: 10.1016/j.nbd.2010.05.017.
16. Bai Q., Burton E.A. Zebrafish models of Tauopathy HHS Public Access. Biochim. Biophys. Acta. 2011;1812:353–363. doi: 10.1016/j.bbadis.2010.09.004.
17. Clarke A.R. Transgenesis Techniques: Principles and Protocols. Springer;

Berlin,Germany: 2003. p. 561. [Google Scholar]

18. Hruscha A., Krawitz P., Rechenberg A., Heinrich V., Hecht J., Haass C., Schmid B. "Efficient CRISPR/Cas9 genome editing with low off-target effects in zebrafish." ("Efficient CRISPR/Cas9 genome editing with low off-target ...") Development. 2013;140:4982–4987. doi: 10.1242/dev.099085. [PubMed] [CrossRef] [Google Scholar]
19. Tropepe V, Sive HL. Can zebrafish be used as a model to study the neurodevelopmental causes of autism? Genes Brain Behav. 2003 Oct;2(5):268-81. doi: 10.1034/j.1601- 183x.2003.00038.x. PMID: 14606692.
20. Guo S. Using zebrafish to assess the impact of drugs on neural development and function. Expert Opin Drug Discov. 2009 Jul 1;4(7):715-726. doi: 10.1517/17460440902988464. PMID: 19774094; PMCID: PMC2747263.
21. White DT, Saxena MT, Mumm JS. "Let's get small (and smaller): Combining zebrafish and nanomedicine to advance neuroregenerative therapeutics." ("Let's get small (and smaller): Combining zebrafish and ...") Adv Drug Deliv Rev. 2019 Aug;148:344-359. doi: 10.1016/j.addr.2019.01.011. Epub 2019 Feb 12. PMID: 30769046; PMCID: PMC6937731.
22. Goessling W, North TE, Repairing quite swimmingly: advances in regenerative medicine using zebrafish, Dis. Model. ("Wolfram Goessling | Harvard Catalyst Profiles | Harvard ...") Mech 7 (2014) 769–776, 10.1242/dmm.016352. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
23. Barreiro-Iglesias A, Mysiak KS, Scott AL, Reimer MM, Yang Y, Becker CG, Becker T, Serotonin promotes development and regeneration of spinal motor neurons in zebrafish, Cell Rep 13 (2015) 924–932, 10.1016/j.celrep.2015.09.050. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
24. White DT, Senguptra S, Saxena MT, Xu Q, Hanes J, Ding D, Ji H, Mumm JS, Immunomodulation-accelerated neuronal regeneration following selective rod photoreceptor cell ablation in the zebrafish retina, Proc. Natl. Acad. Sci 114 (2017) E3719–E3728, 10.1073/pnas.1617721114. [PMC free article] [PubMed] [CrossRef] [Google Scholar]