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ORIGINAL PAPERS

Zebrafish as an Animal Model for Albinism Disorders

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Abstract. *Zebrafish (Danio rerio) is a relevant model for studying many diseases, including the melanocyte-related disorders. In this review of melanocyte literature, we discuss current knowledge about different forms of albinism and the potential of the zebrafish model to find new mechanisms and treatments. Melanin is produced in a process called melanogenesis. This, if altered, leads to diseases such as albinism. Albinism causes an increased risk of skin cancer. Zebrafish are used to study pigment disorders, due to their high fecundity, visible development of melanin in melanophores (melanocytes in mammals) from 24 h post-fertilization, and preserved melanogenesis pathways. In this case, we looked for developmental pathways in zebrafish melanophores and mammalian melanocytes. In addition, we summarized advances in understanding pigment cell disease and evidence supporting the potent potential of using zebrafish to better understand the management of albinism.*

Keywords: Albinism, zebrafish, melanocytes, melanin.

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Introduction

Melanin is a natural pigment, often black but also brown, yellow and red, it is a heterogeneous polymer of phenolic or indolic nature with different functions, structures and presentations. The main functions of melanin are camouflage, protection against ionising radiation, energy recovery and visual perception. Melanogenesis refers to the synthesis of melanin that takes place in the melanosome, it is synthesised by melanocytes, which are specialised dentritic cells from the neural crest, it gives rise to two types of melanin: brown black eumelanin and yellow-red pheomelanin [1.2.3].

Albinism is a genetic disorder characterised by hypopigmentation and ocular abnormalities and occurs in 3 forms: oculo-cutaneous, ocular and syndromic (Hermansky-Pudlak syndrome, Chediak-Higashi syndrome). [4]

The use of animal models is an advantage for the study of albinism, especially the zebrafish, because of its high fertility compared to other animals,

and the genes that control melanogenesis are conserved in zebrafish (melanophore), so zebrafish mutants are used to understand the mechanisms of melanophore development (melanocytes in humans).[5]

Background and history

The zebrafish (Danio rerio) is a small species of freshwater fish native to the Ganges River on the Indian subcontinent and is now valued as a model organism to study many aspects of biological processes. This is due to their size, easy breeding methods, acceptable genetics and fecund breeding patterns [6].

As vertebrates, zebrafish have many advantages over other genetically tractable model invertebrate systems for the study of human development and disease. Zebrafish have a diploid genome with 25 paired chromosomes, with a DNA content about one-third that of humans. Zebrafish are now highly cost-effective for an experimental system suitable for the genetic, cellular, and molecular mechanisms underlying human development and disease [7].

Genetics

Several databases have organized zebrafish genomes very well, including the National Center for Biotechnology Information [8], Zebrafish Information Network (ZFIN) [9], University of California Santa Cruz, and Zebrafish Genome Initiative at Children's Hospital Boston [10], and Ensembl at the Sanger Institute, which recently launched the tenth complete zebrafish genome construction [11]. About 72% of human genes have at least one orthodox evident in the zebrafish genome. Zebrafish have proven useful in advanced genetic studies.

Albinism

Albinism can be defined by the reduction or absence of melanin. Broadly speaking, Albinism can be classified into three types: (1) syndromic albinism due to mutations affecting the lysosome – Cancers 2022, 14, 1752 6 out of 15 related organelles (LRO) and various systems in the body that rely on the biogenesis and correct function of LRO; (2) nonsyndromic albinism with symptoms limited to pigment loss and defects arising from pigment loss; (3) albinism-related disorders resulting from loss of pigment-producing genes due to large chromosomal deletions, such as Prader-Willi syndrome and Angelman syndrome.

Albino mutants characterized in zebrafish

Albinism is defined as a congenital disorder characterized by the complete or partial absence of melanin pigment in the eyes, hair, and skin [12.13.14]. Generally, albinism disorders comprise a number of heterogeneous subtypes that

are all caused by a defect in melanin synthesis, Oculocutaneous albinism affects the eyes, skin, and hair, while ocular albinism affects only the eyes. Visual defects can be caused by both forms which include photophobia, nystagmus, amblyopia, strabismus and astigmatism. [15.16]

Morphologically, these defects can occur in the eye, where unpigmented RPE leads to foveal hypoplasia and, frequently, light-induced retinal damage, because lack of melanin allows stray light to spread to the eye. At the same time, the optic nerve can be underdeveloped and may not project properly to the brain.

Albinism subtypes are caused by mutations in G protein 143 (OA1), tyrosinase (OCA1a and b), OCA2/p (OCA2), tyrosinase protein 1 (OCA3), and membrane/protein AIM1/SLC45A2 associated transporter (OCA4), although recent work has also sought to attribute the albinism subtypes OCA5 (gene unknown), OCA6 (SLC24A5/NCKX5), and OCA7 (C10orf11) [17,18,19]. In addition, there are syndromic forms of albinisms that include symptoms that reduce or eliminate pigmentation, such as Chediak-Higashi syndrome and Hermansky-Pudlak syndrome [20]. Zebrafish mutants exist for albinism subtypes and have been used to study melanin biosynthesis and lysosomal storage.

Albinism in zebrafish

There are albinism mutants of zebrafish, including those with tyr mutation (OCA1), which is characterised by visual impairment, oca2/p mutation (OCA2), which has a reduction in pigmentation, slc24a5 mutation (OCA6), which is characterised by lack of pigmentation and tyrosinase activation, and a c10orf11 mutation (OCA7).

A zebrafish with a mutation in hps5 is a model for Hermansky-Pudlak syndrome, which is characterised by hypopigmentation, reduction in the number, size and maturity of melanosomes, and clumps of ectopic melanosomes in the retina and choroid. Hypopigmentation, frequent developmental delay, neurological disorders, blood abnormalities and immunodeficiency are the hallmarks of Griscelli syndrome, and the zebrafish mlpha mutant is helping to understand the syndrome [21]. The study of albino zebrafish shows that they have a weak visual behavioral response in dark or light conditions or to low contrast stimulation [22].

The Oca2 mutant zebrafish have a high sensitivity to cisplatin, making Oca2 a model for studying the efficacy of chemotherapy in the treatment of melanoma [23].

The role of zebrafish albinism models in finding new treatments for associated diseases

Certain albinism disorders are dangerous for patients, as may be the case with HPS10 [24,25]. Animal models provide the means to study disease progression and rare disease outcomes. For example, recessive homozygous zebrafish have

mutations in ap3d1 (hps10), and fish do not survive the last two weeks of life [26,27]. This expectation is quite different from Mocha mice, most of which survive to adulthood even as homozygotes [28].

In addition, zebrafish research can complement research in mice. For example, new albinism genes can be discovered quickly in zebrafish because of the rate at which genetic knockouts can be performed in large numbers. Then the promising genes can be studied more closely in a mouse model. In addition, biomarkers of disease outcomes can help monitor disease progression, but the biomarkers available to predict mortality in HPS are quite limited. Zebrafish models are better models to study premature death in HPS patients and will be useful in developing these biomarkers [29].

Conclusions

The genetic similarity of melanogenesis and melanophore genes, the availability of current OCA and HPS models of zebrafish, and the ability to generate new ones through genetic engineering make zebrafish with albinism very attractive models for understanding not only albinism disorders, but also other skin pigmentation disorders, or various diseases associated with albinism.

Hereditary diseases as varied as albinism have been modeled and characterized in zebrafish, whose diurnal color vision is a good facsimile of human vision. Zebrafish offer a wide range of experimental advantages. For example, gene duplication in zebrafish allows the effects of RLBP1 on the visual cycles of rods and cones to be studied exclusively in RPE or Muller glia, and simple immersion in glucose solution provides an effective model for diabetic retinopathy. The visual acuity of zebrafish is much lower than that of humans; However, their advantages in modeling retinal diseases come from the powerful genetic, cellular, and imaging technologies available.

Finally, zebrafish can be used to identify compounds that can temper retinal disease, thereby providing insights into the development of therapeutic compounds clinically relevant to human visual impairment, leading to partial resolution of some symptoms for albinism.

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