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Review Article

Zebrafish models of autism spectrum disorder

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ABSTRACT

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by motor, social and cognitive deficits that develop early during childhood. The pathogenesis of ASD is not well characterized and involves a multifaceted interaction between genetic, neurobiological and environmental factors. Animal (experimental) models possess evolutionarily conserved behaviors and molecular pathways that are highly relevant for studying ASD. The zebrafish (*Danio rerio*) is a relatively new animal model with promise for understanding the pathogenesis of complex brain disorders and discovering novel treatments. As a highly social and genetically tractable organism, zebrafish have recently been applied to model a variety of deficits relevant to ASD. Here, we discuss the developing utility of zebrafish models of ASD, as well as current behavioral, toxicological and genetic models of ASD, and future directions of research in this field.

Contents

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1. Introduction

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental disorder with early-onset social, motor and cognitive deficits, including impaired social communication, sensory hypersensitivity, repeated actions and/or restricted interests ((A.P.A., 2013). The severity of ASD varies from mild to severe, dramatically interfering with the quality of life (A.P.A., 2013). The estimated prevalence of ASD is around 1.0–2.6% globally, depending on the diagnostic criteria (Elsabbagh et al., 2012; Rice et al., 2012). ASD also shows prominent gender bias, as males are more frequently affected than females, suggesting possible roles of gender differences in the disease etiology (Kogan et al., 2009).

Although ASD is also one of the most heritable brain disorders (Crawley, 2012), as shown by family and twin studies (Bailey et al., 1995; Rutter, 2000; Steffenburg et al., 1989), it is also highly polygenic. For example, >500 genes identified to date can explain nearly 20% of ASD cases (Geschwind, 2011). In addition to genetic factors, various environmental factors also present ASD risks, including exposure to drugs and toxins, viral infections, and pre- and post-natal immune dysfunctions (Chaste and Leboyer, 2012). Furthermore, the pathology of autism involves abnormal connectivity of circuits that process complex sensory (e.g., social) information, including not only the limbic-related affective circuits, but also those involved in processing language, communication, and the interplay between perception and movement (Gotts et al., 2012). Although the variability of symptoms and causes of ASD presents interesting challenges to animal modeling (Stewart et al., 2014b), this direction of research is critically important. Complementing the rich rodent literature on ASD models (Gaugler et al., 2014; Moy et al., 2014; Schmeisser, 2015; Wurzman et al., 2014), here we outline the possibilities offered by zebrafish (*Danio rerio*) as a novel promising model organism in this field.

2. Zebrafish as a model organism for brain pathogenesis

In social neurobiology, zebrafish are rapidly emerging as a new powerful model between in-vitro studies and mammalian in-vivo research (Kalueff et al., 2014a; Sison and Gerlai, 2010; Stewart et al., 2014c). Zebrafish are highly prolific and low-cost, develop rapidly, and demonstrate robust behavioral phenotypes that appear early in life and continue through adulthood (Kalueff et al., 2013). Larval zebrafish display relatively simple, well-defined and stereotyped sensorimotor behaviors with accessible and characterized circuitry, thereby providing a vertebrate system amenable to large-scale forward genetic and chemical screening (Kalueff et al., 2013; Wolman et al., 2011). Transparency of larvae and some strains of adult zebrafish (e.g., casper) establishes this species as a powerful optogenetic model highly amenable to ASD research (Del Bene and Wyart, 2012; Portugues et al., 2013).

Sociality is an essential component of zebrafish behavior (Engeszer et al., 2007), as they express strong preferences towards conspecifics (Saverino and Gerlai, 2008), live in mixed-gender groups (shoals) with structured dominance hierarchies (Abril-de-Abreu et al., 2015a), discriminate kin and familiar individuals (Gerlach and Lysiak, 2006; Hinz et al., 2013) and exhibit behavioral flexibility according to their social experience (e.g., the winner and loser effect) (Oliveira et al., 2011). Social behaviors are established early during zebrafish ontogenesis, as the first signs of shoaling appear at the 6th day post-fertilization (dpf) (Mahabir et al., 2013). During the first 21 dpf, zebrafish establish strong social preferences, based on visual stimuli from their conspecifics (Dreosti et al., 2015). The first month of zebrafish development is also marked with a rapid increase of shoal cohesion, which then proceeds gradually until the third month (Buske and Gerlai, 2011b). Importantly, zebrafish rely heavily on vision, and their attention is mainly concentrated on visual images of conspecifics (Neri, 2012). Disturbances in zebrafish sociality are easily observable and further increase the value of this species in modeling brain disorders involving deficits in social behavior, including ASD (Kalueff et al., 2014b; Stewart et al., 2014b).

Zebrafish models of ASD are also empowered by significant background genetic and developmental information. For example, recent sequencing of the zebrafish genome (Howe et al., 2013) revealed prominent similarity to human, with approximately 71% of human genes having at least one zebrafish ortholog (Amores et al., 2011; Postlethwait et al., 2000). Our analyses of 858 human ASD-associated genes currently listed in the Simons Foundation Autism Research Initiative (SFARI) database, show that approximately 62% of these genes have zebrafish orthologs (Supplementary Table 1S online). The ancient teleost whole-genome duplication event resulted in approximately 2900 pairs of duplicate genes (Alsop and Vijayan, 2009; Meyer and Schartl, 1999), allowing (unlike rodent models) for the investigation of knockouts with only one gene in a pair (Musa et al., 2001). Moreover, zebrafish developmental and brain ablation studies facilitate the identification of neural structures that are functionally analogous to the structures of interest for social neuroscience and ASD pathogenesis. For instance, the mammalian amygdala, which is implicated in avoidance learning, is homologous to the medial pallium in zebrafish (Norton et al., 2011; von Trotha et al., 2014). While zebrafish lack midbrain dopaminergic populations (e.g., the substantia nigra and ventral tegmental area) (Panula et al., 2010), they display behaviors classically attributed to these areas that are highly sensitive to dopaminergic pharmacological modulation (Panula et al., 2006). Note, however, that neuroanatomical comparisons with mammals are not always straightforward for zebrafish, partly due to the development of the “everted telencephalon”, in which dorsal telencephalon (pallium) grows and folds around the subpallium - unlike mammals, that develop an “invaginated telencephalon” (Folgueira et al., 2012).

Zebrafish are also highly suitable for pharmacological studies, especially given simple methods of drug administration (Collier et al., 2014; Kalueff et al., 2014a), such as water immersion, enabling the drug to diffuse through the gill into the bloodstream (Goldsmith, 2004). Moreover, until 8 dpf, the blood-brain barrier of zebrafish remains imperfect, allowing for improved penetration of various drugs into the zebrafish CNS (Fleming et al., 2013). Thus, the signaling pathways of early zebrafish larvae are quite amenable to pharmacological manipulations. However, to address concerns of drug solubility and pharmacodynamic modeling, drugs may also be administered orally (Kulkarni et al., 2014) or intraperitoneally (Parker et al., 2012), and be further complemented with measuring the drug concentration directly in brain tissue (e.g., by mass-spectrometry). Finally, several features of zebrafish neuroendocrine and neurotransmitter systems further increase their translational value. Most notably, like humans, zebrafish release cortisol as a stress hormone (Canavello et al., 2011; Yeh et al., 2013), which is advantageous over rodent models that release corticosterone (Stewart et al., 2012). Likewise, the zebrafish hypothalamic-pituitary-interrenal (HPI) axis is highly homologous to the human hypothalamus-pituitary-adrenal (HPA) axis (Alsop and Vijayan, 2009). At the same time, zebrafish show undetectable levels of non-neural histamine (Eriksson et al.,

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