

Zebrafish as an emerging model for studying complex brain disorders

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The zebrafish (*Danio rerio*) is rapidly becoming a popular model organism in pharmacogenetics and neuropharmacology. Both larval and adult zebrafish are currently used to increase our understanding of brain function, dysfunction, and their genetic and pharmacological modulation. Here we review the developing utility of zebrafish in the analysis of complex brain disorders (including, e.g., depression, autism, psychoses, drug abuse, and cognitive deficits), also covering zebrafish applications towards the goal of modeling major human neuropsychiatric and drug-induced syndromes. We argue that zebrafish models of complex brain disorders and drug-induced conditions are a rapidly emerging critical field in translational neuroscience and pharmacology research.

The zebrafish

A small aquatic vertebrate, the zebrafish (*Danio rerio*), is rapidly becoming a new popular model organism in biomedical research (Figures 1 and 2) [1–5]. Major universities and research centers worldwide have established zebrafish facilities, and the US National Institutes of Health have recently constructed the world's biggest zebrafish center, with the ability to house up to 19 000 tanks and 100 000 fish. The utility of both adult and larval zebrafish in neuroscience has grown markedly in the past decades because it is a vertebrate species with high physiological and genetic homology to humans, and also because of the ease of genetic manipulation and similar central nervous system (CNS) morphology (Boxes 1 and 2, Figure 3A) [1–5]. The zebrafish genome is well characterized and its sequencing has just been completed by the UK Sanger Institute [6], which has further increased interest in this fish as a model organism in neuroscience and pharmacology (Figure 2). Possessing both rapid development and a relatively long lifespan (Box 1), zebrafish are currently used to model various human brain disorders (Table 1). The availability of multiple zebrafish strains (Table 2) is another important aspect of this species,

enabling studies of strain differences in brain function, behavior, and drug responses.

The close parallels between mammalian and zebrafish behavioral paradigms (Figure 3, Table 1) suggest the evolutionarily conserved nature of many behaviors (and deficits of their control) across species, implying face and construct validity of zebrafish models. Zebrafish are also very cost-efficient, easy to breed, and can be housed in large numbers in a relatively small space (Figure 1A, Box 1). Therefore, they may represent an ideal species for medium- and high-throughput screens (HTSs; Figure 2D) for genetic mutations and small molecules [7–10]. Here, we review recent successes and existing challenges in this field, and emphasize the developing utility of zebrafish for translational neuroscience, drug discovery, and the search for novel candidate genes.

Zebrafish models of brain disorders

Numerous behavioral tests (Figure 3 and Table 1) illustrate how various common neurobehavioral disorders can be modeled or studied in zebrafish. Consider depression, one of the most widespread and severely debilitating brain disorders that affects ~20% of the global population at some point during life [11]. Strongly implicated in clinical depression, various genetic factors, environmental stress, and neurochemical disturbances seem to play a similar role in zebrafish phenotypes. For example, *gr-s357* zebrafish with a mutated glucocorticoid receptor gene display aberrant corticoid biofeedback, increased levels of glucocorticoids, and aberrant behaviors (reduced locomotion, impaired habituation, potentiated startle) that resemble phenotypes seen in clinical depression [12]. Interestingly, antidepressants (such as selective serotonin reuptake inhibitors, SSRIs) normalize some of the mutant phenotypes, paralleling known effects of these drugs in modifying glucocorticoid signaling and alleviating stress disorders in human patients, which also confirms the translational relevance of serotonergic modulation of zebrafish stress responses [12,13].

In addition to genetic models, other factors, such as chronic stressors, commonly trigger affective pathogenesis in both clinical and animal studies [14]. For example, the chronic unpredictable stress (CUS) paradigm is a widely used model of experimental stress, in which rodents are subjected to a battery of chronic stressors, such as restraint, crowding, isolation, novelty, temperature

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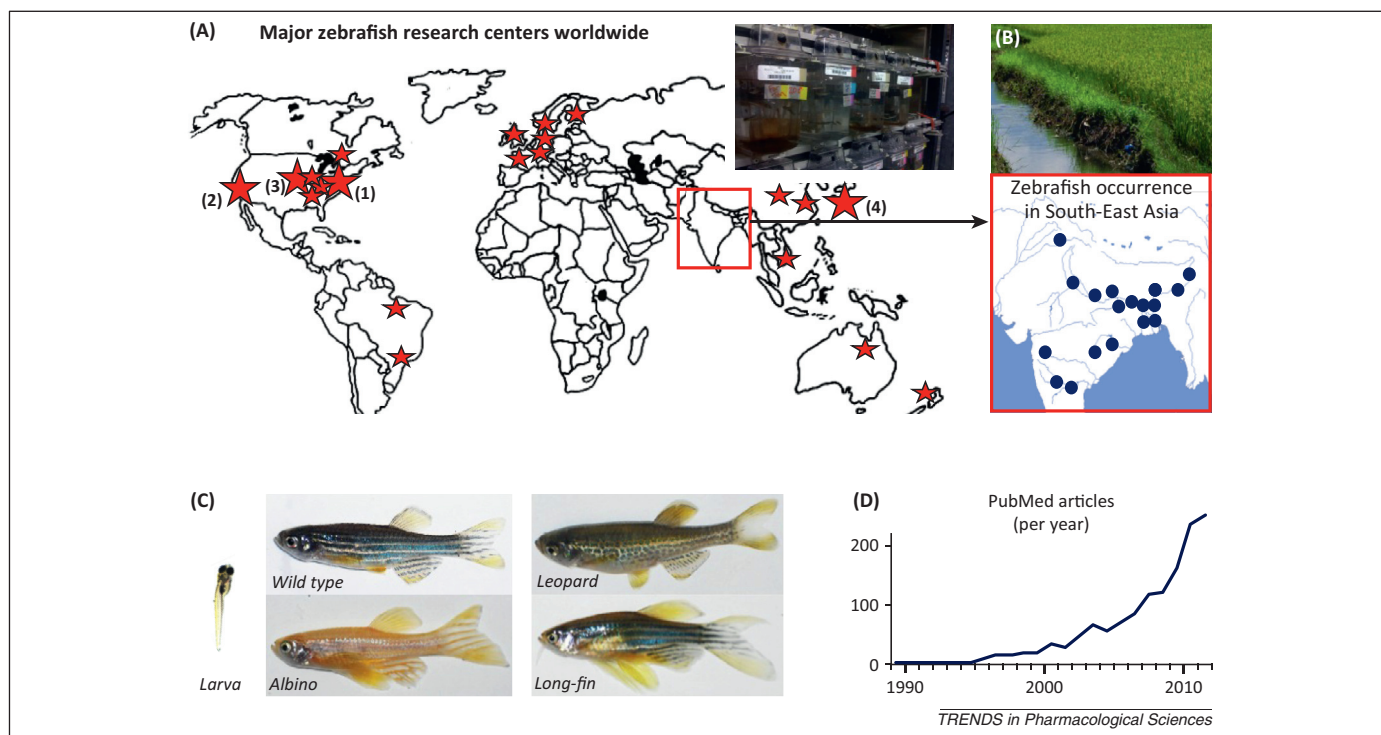


Figure 1. Zebrafish in laboratory research and natural environments. Panel (A) shows major zebrafish research centers established worldwide (red stars), including the National Institutes of Health (1), University of Oregon (2), and Washington University (3) in the USA, and RIKEN Institute (4) in Japan. Inset – a typical rack housing hundreds of zebrafish in a research facility. (B) Typical habitat of zebrafish in the wild (shallow waters, e.g., rice fields) in various regions of Southeast Asia (see [133,134] and Box 1 for details). (C) Larval and adult zebrafish (including several common color variants, also see Table 2 for zebrafish strain information). (D) The growing number of published zebrafish models (assessed in PubMed in September 2013, using terms ‘zebrafish’ and ‘behavior’).

change, light, noise, and/or predator exposure [14]. Recent studies have successfully applied CUS in zebrafish, which affects shoaling, exploration, and anxiety behaviors, as well as alters brain proteome profiles and neurogenesis (the hallmark of affective disorders in rodent models) [15,16]; they also show chronic stress-induced memory deficits and elevated cortisol levels [15,16], paralleling depression-like states in humans and rodents.

Complementing genetic and experimental manipulations, pharmacological models are also widely used in brain research. For example, depression-like behaviors in humans and rodents can be evoked by reserpine, which depletes brain monoamines by irreversibly blocking the vesicular monoamine transporter. The drug induces strong pro-depressant effects in humans, also causing hypoactivity, motor stereotypies, lethargy, and anhedonia in rodents [17]. Reserpine treatment and related neurochemical and behavioral deficits are commonly used as a model of depression in rodents, but can also evoke depression-like behavior in zebrafish (including hypolocomotion and disrupted shoaling, resembling motor retardation and social withdrawal symptoms observed in clinical depression) [17]. Emphasizing the role of monoamine dysregulation in depression, these results also support the developing utility of zebrafish to model complex affective brain disorders.

Autism spectrum disorder (ASD) represents another cluster of serious behavioral deficits, affecting ~1–2% of the general population. Although the prevalence of ASD is lower than depression or anxiety (which affect >10–15% of

the adult population worldwide), autism causes an enormous amount of human suffering, which (if expressed in patient-years; i.e., the number of patients multiplied by the length of time for which the patient suffers from the disease) represents an urgent unmet medical need [18]. In addition to severe behavioral and cognitive impairments, ASD is characterized by high (~90%) heritability, representing one of the most heritable brain disorders in humans [19]. The use of zebrafish to model ASD is supported by several lines of evidence [20]. First, various models relevant to ASD-related social deficits (e.g., social interaction, social preference) have been adapted from rodent studies, and successfully applied to zebrafish paradigms (see examples in Figure 3E, F) [20]. Second, because of the excellent genetic tools developed for the zebrafish (Box 2), this species is expected to be a useful model organism for human disorders with high heritability, which includes ASD [21]. For instance, the human 16p11.2 locus is tightly linked to ASD, and the homologous region in zebrafish spans genes important for brain development [21]. Likewise, the variants of the *MET* gene, which encodes a transmembrane receptor tyrosine kinase of the hepatocyte growth factor/scatter factor (HGF/SF), have been linked to greater autism risk in humans [22,23]. Notably, in zebrafish, *met* genetic knock-down impairs cerebellar development and facial motor neuron migration [24]. Because these genes are important for zebrafish brain development, and ASD is believed to be a disorder of neural development, these findings are probably relevant to ASD pathogenesis, and suggest strong translational relevance

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