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Zebrafish as a Model to Study Autism Spectrum Disorder Caused by Environmental Chemicals Exposure

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Autism spectrum disorder (ASD) is a behaviorally defined, neurodevelopmental disorder with increasing reported prevalence worldwide [1,2]. ASD is a serious debilitating mental illness affecting approximately 1-2% of the general population [3-5]. Individuals with ASD display a wide range of symptoms, including difficulty with social interaction and communication skills, restricted activities and interests, and repetitive behavior [6,7]. ASD is a polygenic disorder with multiple genetic determinants and candidate genes [3]. More than 200 autism susceptibility genes have been identified to date, and complex patterns of inheritance, such as oligogenic heterozygosity, appear to contribute to the etiopathgenesis of autism [8]. Although genetics plays a crucial role in ASD, evidence suggests that environmental chemicals are consistently associated with increased risk of ASD [9].

Environmental chemicals exposure, especially during pregnancy, are increasingly being recognized as potential risk factor for ASD, and the possibility that the prenatal environment affects fetal programming is a promising direction for research [10]. Prenatal environment includes maternal use of medication, maternal infection and inflammations, and exposure to various substances such as alcohol and heavy smoking during pregnancy [11]. The contamination of water resources has important repercussions for the environment and human health [12,13]. There are many toxic substances in the water soluble fraction of crude oil (WSF), for example, polycyclic aromatic hydrocarbons, phenol, and heterocyclic compound [14]. Heavy metals, such as lead (Pb) are also important environmental contaminants, which can reach aquatic systems via the effluents of industrial, urban and mining sources [15]. Humans may be exposed to heavy metals via food and water contamination, as well as air pollution caused by industrial emissions [16]. Many cellular processes are affected by expose to mercury and lead and the correct function of central nervous system can be impaired by neurochemical changes [17].

Animal models of brain disorders are an indispensable tool for dissecting the pathogenic mechanisms of brain disorders, and the zebrafish (*Danio rerio*) is emerging as a model organism for the study of neuropharmacology and behavior [18]. Zebrafish have highly conserved neural architecture that facilitates comparisons to other, more commonly used species [19]. This model is widely considered to offer numerous logistical and economic advantages over mammalian models as zebrafish spawn overnight, hatch in 2-3 days post fertilization, develop complex behavior within the first week of life, and reach sexual maturity in 2-3 months [19]. Zebrafish have been proposed as a model of Alzheimer´s disease [20,21], schizophrenia [22], drug abuse [23], and other brain disorders [24,25]. 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 (69% of zebrafish genes have human orthologs meaning that it is frequently possible to study human disease-related genes in fish), and also because of the ease of genetic manipulation, fully characterized genome [24,26-31]. The use of zebrafish to model ASD is supported by several lines of evidence [24]. 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 [3]. Because of the genetic tools developed for the zebrafish, this species is expected to be a useful model organism for ASD. In zebrafish, knock-down met, which has been linked to greater autism risk in humans, impairs cerebellar development and facial motor neuron migration. 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 of zebrafish models [24].

Zebrafish models are fully capable of displaying both hallmark behavioral symptoms of ASD-social deficits and behavioral perseverations, indicating high translational potential of zebrafish models for ASD-related states. In the zebrafish social preference test, a target fish given a choice between staying close to the conspecific area. In other modifications of this model, zebrafish typically spend more time near a group of zebrafish, also showing kin recognition/preference and spending more time during social investigation of novel (unfamiliar) zebrafish [3]. Zebrafish circling behavior can be induced by selected psychotropic drugs, such as glutamatergic antagonists MK-801, PCP or ketamine [32]. Acute exposure of adult zebrafish to substances like ethanol, nicotine, fluoxetine or diazepam results in anxiolytic effects. In addition to alcohol, the effects of drugs of abuse including cocaine, amphetamine, and morphine have also been studied in zebrafish [33]. The disruption of retinoic acid and valproic acid on social responding is pronounced and not likely due to motoric or visual impairment because all zebrafish fled the predator image similarly on the escape/avoidance assay [19]. In the shoaling test, zebrafish spent most of their time swimming in dynamic groups (schools), characterized by short interfish distance, smaller zebrafish group area size/diameter, as well as relative polarizations [3]. Different strains of zebrafish have been found to show differences in response to a zebrafish shoal and predator while undergoing alcohol withdrawal and this is correlated with differences in neurochemical (including dopamine) responses [33,34].

The key clinical features of ASD and related symptoms are social deficits, repetitive behavior, language impairment, cognitive deficits and anxiety, mood, and activity [3]. In our study, isolated and combined WSF/Pb alters the behavioral pattern of fish swimming. WSF significantly increases anxiety and locomotor activity, decreases repetitive behavior in the open field test, and reduces the level of serotonin [35]. Many studies prove that maternal exposure to

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neurotoxic environmental contaminants, such as chlorpyrifos, nickel chloride, and arsenic impair the movement activity of zebrafish larvae [36-38]. However, co-exposure to WSF/Pb decreased behavioral activity and shoaling behavior and increased cycle swimming and edge preference. Significant changes in the expression level of the multiple genes potentially critical for regulating environmental factor induced autism-like behavior are found [35].

Zebrafish xenotransplantation is an emerging technique that can be used to model disease rapidly for the purpose of drug screening, as well as to evaluate and validate candidate drugs identified through other screening methodologies [39]. Human experimental neurobiology is mostly limited to non-invasive and indirect methods of investigation. An animal model gives us the opportunity to study how genetic and environmental factors can lead to the neuropsychiatric disorder by allowing us to manipulate molecules and confirm their role in the disease process [33]. Biological research in autism has attempted to improve our understanding of the neurobiological mechanisms possibly involved in autistic disorder; studies have been conducted in domains as diverse as genetics, neuroanatomy, brain imaging, and neuroimmunology [9]. Rapid progress in ASD gene discovery, integrated with multiple complementary genomic data sets, has identified clear points of convergence in ASD neurobiology [40]. A variety of morphological and functional changes have been demonstrated in the brain of children or adults with ASD [10]. Zebrafish is a viable model system for future exploration of the underlying molecular and cellular mechanisms of autism [33]. Experimental evidence shows that zebrafish display complex affective, social and cognitive responses which are similar to those observed in rodents and humans; however, in the case of a complex multi-faceted brain disorder such as ASD, it is impossible to model them fully in fish [3]. More research is needed to unravel environmental contribution to the genetic etiology of ASD [11]. The environmental modulation of autism-like behavior in zebrafish has not yet been thoroughly investigated, and further studies of environmental effects on zebrafish phenotypes relevant to ASD may be important [3].

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