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Views on Developing New Animal Models to Study Depression

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Over one half-century ago several classes of medications, discovered by serendipity, were introduced for the treatment of depression. These medications revolutionized our approach to mood disorders and helped launch the modern era of psychiatry. However, our progress since those serendipitous discoveries has been rather disappointing. We still do not understand with absolute certainty how those medications produce their desired clinical effects. We have not introduced newer medications with fundamentally different mechanisms-of-action. We have not identified the genetic and neurobiological mechanisms underlying depression, nor do we understand the mechanisms by which nongenetic factors influence these disorders. We have only a rudimentary understanding of the circuits in the brain responsible for the normal regulation of mood and affect and of those circuits that function abnormally in mood disorders. In approaching these gaps in our knowledge, development of animal models is urgently needed.

Zebrafish are emerging as a promising model organism for experimental studies of depression. However, even though zebrafish are rapidly becoming a popular model in the field of biological psychiatry, their application as a robust translational model is still very much in its infancy. Nevertheless, the strength of zebrafish phenotypes makes this species an exceptional animal for investigating experimental, genetic, and pharmacological models of neurobehavioral disorders, such as depression. As a result of the past three decades of intensive investigation with zebrafish, this species has become geneticists' favorite model organisms. The accumulated genetic knowledge about, and the genetic methods specifically developed for the zebrafish now make this species particularly attractive for several research fields. One of these fields is behavioral neuroscience. Zebrafish models strike an optimal balance between system complexity and practical simplicity. Zebrafish are complex organisms with brain anatomy, neurophysiology, and molecular characteristics (e.g., nucleotide sequence of its genes) very similar to those of other vertebrates including mammals. Furthermore, they are small, easy and cheap to maintain in the laboratory, and have been highly amenable to high-throughput screening (e.g., forward genetic or drug screens). The latter is particularly noteworthy for the purposes of unraveling the genetic, and in general the biological, mechanisms of complex brain functions and the disorders of these functions. High-throughput screens may have the ability to identify a significant proportion of the potentially large number of molecular players involved in these functions.There have been many studies devoted to the analysis of the biological mechanisms of depression, and a considerable amount of effort has been invested in the development of pharmacological treatments. For preclinical research, most of these studies used rodents. Since a large amount of data has been accumulated on rodent species, it may seem logical to think that building upon this well-laid foundation is the only way to proceed. The abandonment of rodent research is certainly not likely or recommended; however, utilization of another vertebrate, zebrafish, appears to be a fruitful direction to pursue.

It is challenging to predict how beneficial zebrafish may become in modeling and analysis of the biological mechanisms of human depression. At this juncture, however, it seems that the main components necessary for such research to be successful in the future already exist. While only distantly related to humans, the zebrafish has already proven its translational relevance. But perhaps the most important advantage of this species as a laboratory tool may be best described with one word: numbers. Complex biological phenomena are associated with large numbers of mechanisms. These may be discovered using broad screens, genetic, or pharmacological tools. Zebrafish have been shown to be ideal for large scale screens due to several of its features, but principally to the fact that a large amount of these fish can be produced fast and can be maintained and now tested efficiently in the laboratory. Given the complexity of the mechanisms of depression, one may assume the need to identify a large number of molecular players, i.e., genes and their protein products and the biochemical interactions between the proteins. It can be argued that this complexity may be best tackled, at least initially, using large scale screens for mutations and drugs. These screens are the key to the identification of potential targets and leads that may subsequently be followed up on by more targeted hypothesis driven analyses. It is important to note that I am not advocating the screening approach as the only possible or only potentially fruitful one. There are a large number of unknown mechanisms waiting to be discovered and their discovery may be significantly facilitated by "blind", i.e., unbiased, screening applications. This is exactly where zebrafish have a major advantage over other laboratory organisms. It is imperative that additional novel behavioral endpoints and observational methodologies, such as automated video-tracking systems, strengthen the utility of zebrafish for use as an animal model for depression research. Using biomolecular markers, such as gene expression, immunohistochemistry etc., to parallel zebrafish physiology with behavioral data gives us another essential research direction. Lastly, expanding the area of zebrafish research by including cross-domain modeling, for example drug withdrawal/depression, as is currently done in my laboratory, may well lead to new translational models using a combination of both larval and adult zebrafish.

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