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Animal models of mental retardation: from gene to cognitive function

Igor Branchi[a,*], Zoë Bichler[b], Joanne Berger-Sweeney[c], Laura Ricceri[d]

[a]*Section of Behavioural Pathophysiology, Laboratorio di Fisiopatologia di Organo e di Sistema, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Roma, Italy*

[b]*FRE 2358 CNRS, Institut de Transgénose, Orléans, France*

[c]*Department of Biological Sciences, Wellesley College, Wellesley, MA 02481, USA*

[d]*Section of Comparative Psychology, Laboratorio di Fisiopatologia di Organo e di Sistema, Istituto Superiore di Sanità, Roma, Italy*

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Abstract

About 2–3% of all children are affected by mental retardation, and genetic conditions rank among the leading causes of mental retardation. Alterations in the information encoded by genes that regulate critical steps of brain development can disrupt the normal course of development, and have profound consequences on mental processes. Genetically modified mouse models have helped to elucidate the contribution of specific gene alterations and gene–environment interactions to the phenotype of several forms of mental retardation. Mouse models of several neurodevelopmental pathologies, such as Down and Rett syndromes and X-linked forms of mental retardation, have been developed. Because behavior is the ultimate output of brain, behavioral phenotyping of these models provides functional information that may not be detectable using molecular, cellular or histological evaluations. In particular, the study of ontogeny of behavior is recommended in mouse models of disorders having a developmental onset. Identifying the role of specific genes in neuropathologies provides a framework in which to understand key stages of human brain development, and provides a target for potential therapeutic intervention.

Keywords: Genetically modified; Neurodevelopmental disorders; Mental retardation; Mouse; Behavior; Development; Neuropathology; Genetic disorders

1. Introduction

Development of the central nervous system (CNS) involves the creation of numerous cell types in precise locations and at precise times, which create neural circuits that subserve sensory, motor, as well as cognitive functions [1,2]. Classically, though simplistically, CNS development is divided into three major stages: neuronal generation (neurogenesis), migration, and differentiation/maturation. Although the subject of debate, maturation of certain regions of neocortex continues likely through the teen years in humans. Aberrations in one or more of these stages lead to alterations in the course of brain development that can have long-term consequences for the integrity of higher cognitive abilities [3,4].

Approximately 2–3% of children are affected by mental retardation (MR). An individual is considered to have MR based on the following three criteria: (i) a significantly subaverage general intellectual functioning, (ii) significant limitations in adaptive functioning in at least two of the following skill areas: communication, selfcare, home living, social/interpersonal skills, use of community resources, selfdirection, functional academic skills, work, leisure, health, and safety, and (iii) the onset of cognitive disabilities must occur before age 18 years [5]. The onset of the disabilities suggests an aberration in the normal course of brain development, particularly in brain regions associated with higher cognitive functions. In one-third of the cases, the etiology of the MR is unknown. In the cases in which the etiology is known, genetic deficits rank among the leading causes [6]. Furthermore, a higher proportion of MR cases in males (25–30% than in females) suggests that an X-linked pattern of inheritance may be an important cause of MR [7]. In fact, X-linked mental retardation (XLMR) represents 5% of total diagnosed MR [8].

Genes regulating proper functioning of the nervous system and development of cognitive functions belong to

* Corresponding author. Tel.: +39-6-499-02039; fax: +39-6-495-7821.
E-mail address: branchi@iss.it (I. Branchi).

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Table 1
A selection of mouse models deficient for genes involved in critical steps of brain development

Gene	Critical step in brain development	Human disorder	Animal model references
*HESX*1	Prosencephalic midline development	Septo-optic dysplasia	[134]
*EMX*2	Specification of the cortex	Schizencephaly	[135]
*ZIC*2, *SHH*	Hemispheric cleavage	Holoprosencephaly	[136,137]
LIS 1, *DOUBLECORTIN*	Ongoing neural migration	Lissencephaly, band eteropia	[105,138]
*MeCP*2	Synaptogenesis (disruption of axon-denditic connections?)	Rett syndrome	[13,79,80]
FMRI	Synaptogenesis (spine abnormalities)	X fragile syndrome	[93–97]
alpha-GDI	Synaptogenesis (impaired neurite extension)	Non-specific mental retardation	[112]

HESX1, homeobox-containing, embrionic stemm cell t-conscription factor [x]1; EMX2, empty spiracles in factor [X]2; ZIC2, zinc finger cerebellar expressed 2; SHH, Sonic Hedgehog; LIS1, Lissencephaly 1; MeCP2, methyl-CpG binding protein 2; FMR1, fragile X mental retardation 1; alpha-GDI, Rab GDP dissociation inhibitor alpha.

highly heterogeneous group, encoding for proteins that play important roles in diverse processes. Alterations in the information these genes encode, or changes in their expression pattern can cause developmental anomalies that have a profound effect on mental processes (Table 1) [9–11]. It is very likely that many of the symptoms seen in human genetic brain disorders are the result of developmental changes [12].

Genetically modified mice are currently the most commonly used approach to investigate the role of a specific genetic alteration and to model pathologies leading to MR [13–18]. It is noteworthy that the information gained by investigating disorders in genetically modified mice is also advancing our knowledge of the role that selected genes play in regulating important aspects of normal cognitive functions.

2. Genetically modified mice: a tool to investigate developmental brain pathologies

The mouse is the most widely used laboratory species to provide insights linking specific genes to biological functions. Its wide use is primarily because among mammals, the mouse is most amenable to genetic manipulations. Furthermore, our extensive knowledge of the genome, physiology and behavior of the mouse makes it possible to interpret the effects of gene manipulations [19–21].

Human brain disorders of suspected genetic origin can be modeled in the mouse using standardized procedures, such as knocking out genes by the homologous recombination technique, or random insertion of wild-type or mutant transgenes. These specific genes (or the lack of specific genes) then induce alterations of protein products that lead downstream to pathological events that mimic the human disorder [19,20]. If the genetically modified mice display symptoms reminiscent of the human disorder, they represent an important tool to study the molecular basis of specific pathologies and test potential therapeutic interventions. Not surprisingly, a considerable effort has been undertaken by many laboratories to develop genetically modified mice that display key features of specific human brain disorders (see the web site of Neuroscience Mutagenesis Facility at Jackson Laboratory, http://www.jax.org/nmf).

With the rapid and dramatic increase in the types of genetically modified mice available [22], it is clear that appropriate phenotyping, including behavioral characterization, is critical [19,23–26]. Behavioral analysis can provide crucial information about the integrity of CNS functions that is not detectable following commonly used molecular, cellular or histological evaluations [12,27]. Most laboratories involved in the testing of genetically modified mice subject adult animals to a battery of behavioral tests that assess motor and sensory, as well cognitive functions. Several learning tests including olfactory-based paradigms (e.g. social transmission of food preferences), which are extremely relevant in macrosmatic mammals such as mice [28], are used to characterize cognitive impairment [29–31].

However, there is still skepticism towards the idea that human cognitive impairment can be modeled in the mouse. This skepticism arises erroneously from the expectation that specific symptoms will have the same physical manifestation across species. However, different species have species-specific behavioral repertoires shaped by their evolutionary history [32]. Thus, modeling of human-like symptoms in animals should be based primarily on an expectation of functional similarity of the displayed behavioral strategy, rather than on one of behavior equivalency. The crucial point is not whether a mouse would show a given cognitive impairment, but rather, how a cognitive impairment would manifest itself in a mouse [23,33]. Ethological studies have provided detailed descriptions of the mouse behavioral repertoire that allow an accurate analysis of its behavioral profile in order to identify deficits in specific behavioral abilities [12,19,20,34].

3. Genetically modified mouse models of neurodevelopmental pathologies

The genetic defects causing neurodevelopmental pathologies have been classified in different categories: