



Invited Review

Inflammatory profiles in the BTBR mouse: How relevant are they to autism spectrum disorders?

Milo Careaga^{a,b}, Jared Schwartzer^c, Paul Ashwood^{a,b,*}^a Department of Medical Microbiology and Immunology, UC Davis, United States^b The M.I.N.D. Institute, University of California at Davis, CA, United States^c Department of Psychology and Education, Mount Holyoke College, 50 College Street, South Hadley, MA 01075, United States

ARTICLE INFO

Article history:

Received 14 March 2014

Received in revised form 23 May 2014

Accepted 6 June 2014

Available online 14 June 2014

Keywords:

Autism

ASD

BTBR

Mouse

Immune

Inflammation

Model

ABSTRACT

Autism spectrum disorders (ASD) are a group of disorders characterized by core behavioral features including stereotyped interests, repetitive behaviors and impairments in communication and social interaction. In addition, widespread changes in the immune systems of individuals with ASD have been identified, in particular increased evidence of inflammation in the periphery and central nervous system. While the etiology of these disorders remains unclear, it appears that multiple gene and environmental factors are involved. The need for animal models paralleling the behavioral and immunological features of ASD is paramount to better understand the link between immune system dysregulation and behavioral deficits observed in these disorders. As such, the asocial BTBR mouse strain displays both ASD relevant behaviors and persistent immune dysregulation, providing a model system that has and continues to be instructive in understanding the complex nature of ASD.

© 2014 Elsevier Inc. All rights reserved.

1. Introduction

Autism spectrum disorders are a group of neurodevelopmental disorders characterized by restricted interests, repetitive behaviors and impairments in communication and social interaction. Currently 1 in 88 children have been identified as having ASD (CDC, 2012). Despite the high incidence of ASD, the etiology and pathogenesis remain poorly understood. Numerous published findings have identified widespread changes in the immune systems of individuals with ASD both at the systemic and cellular levels (Ashwood et al., 2006). These immune dysfunctions are associated with impairments in core features of ASD as well as aberrant behaviors, decreased adaptability and impaired cognition (Ashwood et al., 2011a,b; Onore et al., 2012).

In individuals with ASD, several lines of evidence point to ongoing inflammation both within the brain (Li et al., 2009; Morgan et al., 2010; Vargas et al., 2005) and in the periphery (Ashwood et al., 2011a; Hashimoto et al., 2011). Work by Vargas et al. demonstrated that in postmortem brains from subjects with ASD there were signs of increased pro-inflammatory cytokines including

interleukin (IL)-1 β , IL-6, IL-12(p40) and TNF α (Vargas et al., 2005). Moreover, microglia from subjects with ASD display a more activated phenotype in postmortem brain (Morgan et al., 2010) and by PET scan (Suzuki et al., 2013). In addition to immune activation within CNS, circulating levels of cytokines exhibit a profile reminiscent of a proinflammatory immune profile with increased IL-1 β , IL-6 and IL-12(p40) production (Ashwood et al., 2011a; Hashimoto et al., 2011; Ricci et al., 2013; Singh, 1996). Increased activation of circulating monocyte cells in the periphery following stimulation with Toll-like receptor (TLR) ligands has also been observed, including changes in gene expression, increased HLA-DR cell surface expression and the release of pro-inflammatory cytokines IL-1 β and IL-6 (Enstrom et al., 2010; Jyonouchi et al., 2008, 2011, 2001). Both the circulating levels of these pro-inflammatory cytokines and the degree of monocyte activation are associated with more impaired behaviors in children with ASD (Ashwood et al., 2011a; Enstrom et al., 2010; Onore et al., 2012). These findings notwithstanding, many of the links between ASD and immune system dysregulation are drawn from associative studies that pose compelling correlations between neurodevelopmental disorders and immune dysfunction. However, limitations in experimental design and the myriad of uncontrolled variability, as a result of ethical boundaries placed on human research, requires the use of animal models to effectively link causality to these patterns of association.

* Corresponding author at: M.I.N.D. Institute, 2805, 50th Street, Sacramento, CA 95817, United States. Tel.: +1 916 703 0405; fax: +1 916 703 0367.

E-mail address: pashwood@ucdavis.edu (P. Ashwood).

Rodent models of human conditions enable scientists to directly test hypotheses generated from evidence drawn from clinical populations. The development of an effective animal model requires extensive investigation into the biological and behavioral pathologies that contribute to the face, construct, and predictive validity of a translational model. These validity measures are crucial for evaluating the relevance of a model for understanding the human condition. For the study of ASD and its associations with immune system dysregulation, researchers have identified a mouse strain, the BTBR mouse, that has strong validity for evaluating the neuro-immunological contributions to ASD-like behaviors.

BTBR mice were derived from an inbred strain carrying the ^a (nonagouti; black and tan) and wildtype T (brachyury) mutations that were crossed with mice with the tufted (*Itpr3^{tf}*) allele (<http://jaxmice.jax.org/strain/002282.html>). As part of the Mouse Phenome Project (MPP), BTBR mice were characterized and found to have neuroanatomical abnormalities such as a hereditary loss of corpus callosum (Wahlsten et al., 2003). However, it was not until work by Moy et al., who characterized the BTBR mice as exhibiting behaviors that had strong face validity to ASD, that the BTBR mouse was brought to the attention of the neurodevelopmental research community (Moy et al., 2007). More recent work by Heo et al. described the immune system of the BTBR mouse as having a number of immunological abnormalities consistent with increased immune activation (Heo et al., 2011). In light of the mounting evidence of immune dysfunction in ASD coupled to the behavioral abnormalities, the BTBR mouse makes for an interesting target to research mechanisms of asocial behaviors as they relate to immune dysfunction (Reviewed in Onore et al., 2012) and may help to better understand the complex nature of ASD.

2. Behavioral phenotype

The BTBR mouse has strong face validity for a range of behavioral deficits that are analogous to those observed in individuals with ASD. Most notably, this mouse is characterized by reductions in sociability and increased repetitive/compulsive behaviors. The low sociability level of the BTBR mouse is most apparent in the three-chamber social approach task. These mice spend equal time approaching and investigating a novel object compared to a novel social stimulus (i.e. novel mouse) (McFarlane et al., 2008), a behavioral response well replicated across numerous laboratories. These reductions in social approach are accompanied by reductions in social motivational processes as BTBR mice fail to form a conditioned place preference for contexts associated with social stimuli (Pearson et al., 2012). While this study suggests that motivation may be a factor contributing to low sociability, the extent to which BTBR mice respond to non-social rewards (e.g. amphetamines, food) remains unknown. Moreover, these deficits in social motivation may reflect dysfunction in the acquisition or retention of social-specific memory cues.

In addition to reduced social approach, the BTBR mouse is characterized by a reduction in the display of a range of species-typical social behaviors. At a juvenile age, BTBR mice spend significantly less time engaging in social interactions including reductions in sniffing and following behaviors compared to the 'typical' C57BL/6J mouse (McFarlane et al., 2008). These reductions in social investigation persist throughout adolescence (Scattoni et al., 2013) and into adulthood (Defensor et al., 2011; Pobbe et al., 2010). Interestingly, when juvenile BTBR mice are reared with more social C57BL/6J mice, the characteristic social deficits are significantly diminished (Yang et al., 2011), highlighting the importance of social peer interactions as a potent influence on social behavior development.

The recently published DSM-5 reformulated the core behavioral domains of ASD by integrating language and communication impairments as a component of social competency, redefining

the deficits as social communication impairments (APA, 2013). This restructuring compels researchers to scrutinize the translational value of mouse behavior as they relate to ASD-like behaviors. For the BTBR mouse, variations in the type and frequency of ultrasonic vocalizations were previously proposed as a model for the language and communication deficits observed in humans (Scattoni et al., 2008; Wohr et al., 2011). However, little is known about the functional significance of mouse vocalizations, particularly in adults, or whether these calls have communicative value. By redefining language deficits in the context of social communication, mouse behaviorists are better suited to explore communication deficits that are more ethologically valid and species specific. For example, although BTBR mice elicit fewer vocalizations, these mice produce calls in response to the presence and/or absence of a female similar to the responses observed in the social C57BL/6J mouse (Yang et al., 2013). Moreover, female BTBR mice are noted to display typical maternal care behaviors (Yang et al., 2007) despite differences in call patterns and number of calls elicited from pups (Scattoni et al., 2008). By examining differences in ultrasonic vocalizations in the context of social behavioral responses, as established by the DSM-5, the translational validity of these differences in vocalization patterns in the BTBR mouse as an analogous model for the communication deficits in humans remains under question. Perhaps more relevant though, are differences in species-typical scent marking behavior in BTBR mice in response to social stimuli. Given that olfactory cues are the predominant sensory modality used for exploring social and environmental stimuli in mice, scent-marking behavior may provide a more robust behavioral measure for identifying deficits in social communication. Interestingly, the BTBR mouse displays fewer scent marking behaviors in response to a social stimulus compared to the more social C57BL/6J mouse, and these reductions are accompanied by fewer vocalizations emitted in response to the scent of female-urine (Roullet et al., 2011; Wohr et al., 2011). Together, reductions in social motivation and social approach along with reduced scent marking and altered vocalizations highlight the strong face validity the BTBR mouse holds for modeling the social communication deficits that are at the core of the ASD diagnosis.

Another core feature of ASD is the presence of repetitive patterns of behavior, restricted interests, and insistence on sameness. The BTBR mouse possesses a range of behavioral traits that model both the repetitive motor patterns and inflexible adherence to routines. The most widely noted motor stereotypy in the BTBR mouse is the excessive time spent engaging in self-grooming behaviors compared to other inbred strains (McFarlane et al., 2008; Pearson et al., 2011; Pobbe et al., 2010). An in-depth analysis of the microstructural components of grooming behavior revealed that the BTBR mouse engages in more frequent and longer durations of all grooming behaviors. Moreover, grooming bouts do not occur in the species-typical cephalo-caudal sequence, underscoring the atypical nature of these stereotypies (Pearson et al., 2011). Another motor stereotypy noted in the BTBR mouse is the increasing frequency of compulsive marble burying observed across several laboratories (Amodeo et al., 2012; Schwartzer et al., 2013). Marble burying behavior is used as an index for perseverative behaviors analogous to the restricted patterns of behavior in ASD (Thomas et al., 2009). Importantly, these motor stereotypies in the BTBR mouse are met with deficits in reversal learning and perseverative behaviors across several cognitive tasks. In the Morris Water Maze, BTBR mice show intact spatial learning similar to the C57BL/6J mouse but fail to show quadrant preference during later reversal learning phases (Moy et al., 2007). Similarly, BTBR mice make significantly more perseverative errors in a modified T-maze task (Guariglia and Chadman, 2013). This lack of reversal learning was further characterized in probabilistic learning tasks when correct choices were only reinforced during 80% of the trials (Amodeo

متن کامل مقاله

دریافت فوری ←

ISIArticles

مرجع مقالات تخصصی ایران

- ✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
- ✓ امکان دانلود نسخه ترجمه شده مقالات
- ✓ پذیرش سفارش ترجمه تخصصی
- ✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
- ✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
- ✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
- ✓ دانلود فوری مقاله پس از پرداخت آنلاین
- ✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات