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Review

Immune-mediated animal models of Tourette syndrome

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ABSTRACT

An autoimmune diathesis has been proposed in Tourette syndrome (TS) and related neuropsychiatric disorders such as obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, autism and anorexia nervosa. Environmental triggers including infection and xenobiotics are hypothesized to lead to the production of brain-directed autoantibodies in a subset of genetically susceptible individuals. Although much work has focused on Group A *Streptococcus* (GAS), the role of this common childhood infection remains controversial. Animal model studies based on immune and autoantibody findings in TS have demonstrated immunoglobulin (Ig) deposits and stereotypic movements and related behavioral disturbances reminiscent of TS following exposure to GAS, other activators of host anti-microbial responses, soluble immune mediators and anti-GAS or anti-neuronal antibodies. Demonstration of the ability to recreate these abnormalities through passive transfer of serum IgG from GAS-immunized mice into naïve mice and abrogation of this activity through depletion of IgG has provided compelling evidence in support of the autoimmune hypothesis. Immunologically-based animal models of TS are a potent tool for dissecting the pathogenesis of this serious neuropsychiatric syndrome.

Contents

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1. Introduction

Tourette syndrome (TS), named for the French neurologist Georges Gilles de la Tourette, is a disorder marked by persistent motor and vocal tics, high rates of neuropsychiatric comorbidity (Robertson, 2012), male predominance (Clarke et al., 2012) and a fluctuating course. Although attributed to such colorful factors as demonic possession, hysteria and masturbation (Germiniani et al., 2012; Kushner, 1998), most research is centered on genetic and immunologic mechanisms (Clarke et al., 2012; Singer, 2005). Failure of monogenic or multigenic hypotheses to adequately account for variance in TS susceptibility has led to consideration of environmental influences on genetic vulnerability (Deng et al., 2012; Eldridge and Denckla, 1986). An environmentally-triggered autoimmune diathesis is proposed wherein exposure to infection, xenobiotics or other risk factors leads to the production of brain-directed autoantibodies in a subset of individuals. Here we review the immune findings in TS and examine animal models of TS and their implications for dissecting the pathogenesis of human disease.

1.1. Clinical evidence suggesting immune dysfunction in Tourette syndrome and tic disorders

Immune and infectious factors are implicated in the pathogenesis of TS (Martino et al., 2009a; Murphy et al., 2010a; Singer, 2011) and a wide range of related neuropsychiatric disorders arising in childhood, including obsessive-compulsive disorder (OCD) (Gray and Bloch, 2012; Murphy et al., 2006; Rotge et al., 2010), autism spectrum disorders (ASD) (Fox et al., 2012; Goines and Ashwood, 2012; Harvey and Boksa, 2012; Hollander et al., 1999; Margutti et al., 2006; Needleman and McAllister, 2012), attention-deficit/hyperactivity disorder (AD/HD) (Peterson et al., 2000; Rout et al., 2012; Toto et al., 2012) and anorexia nervosa (Favaro et al., 2011; Henry et al., 1999; Holden and Pakula, 1996; Kam et al., 1994; Sokol, 2000; Sokol et al., 2002). Overlap of a subset of these disorders with the prototypical, infection-related, autoimmune brain disorder, Sydenham chorea (SC), led to the application of the acronym PANDAS, or Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection, to cases wherein illness follows infection with β-hemolytic Group A *Streptococcus* (GAS) (Leonard and Swedo, 2001; Swedo and Grant, 2005; Swedo et al., 1998, 1994, 2010). As one of the diverse clinical manifestations of the post-streptococcal autoimmune disease, rheumatic fever, SC is marked not only by involuntary chorea but also by OCD-like signs (Swedo et al., 1989) emotional lability (Swedo et al., 1993) and other neuropsychiatric features (Swedo et al., 1993). Despite the clinical similarities of PANDAS, TS and SC, and the high rate of response of these conditions to immunomodulatory therapies such as intravenous immunoglobulin (IVIg) (Allen et al., 1995; Müller et al., 1997; Perlmutter et al., 1999), glucocorticoids (Kondo and Kabasawa, 1978) and plasma exchange (Allen et al., 1995; Perlmutter et al., 1999), data supporting a relationship of GAS-induced antibodies specific for epitopes present in basal ganglia (BG) is much stronger for SC than it is for PANDAS or TS (Brilot et al., 2011; Singer et al., 2005a). Whether clinical differences across the disorders contribute to reported variations in autoantibody prevalence and specificity for different targets and/or brain regions is unclear. Anti-CNS antibodies may not always be detected, even in SC, pointing to the potential role of animal models in dissecting the mechanisms involved in autoantibody induction; identifying the determinants of autoantibody specificity, binding characteristics, and ability to gain access to the central nervous system (CNS); and exploring the importance of other immune factors such as cytokines in modifying the course of illness. Animal models also present an opportunity to pursue other mechanistic avenues that may stimulate production of autoantibodies or lead to immune disturbances and to examine how these might affect brain circuitry and behavior.

1.1.1. Clinical profiles and course of illness

The clinical diversity and comorbidity patterns of TS are important both to the recognition of the disorder and to its management (Robertson, 2012). This heterogeneity makes it likely that multiple etiologic pathways are involved in TS pathogenesis, and less probable that all cases of TS are immune or autoimmune in nature. Biomarkers that help distinguish among immune and non-immune TS phenotypes do not yet exist. The initial presentation or exacerbation of TS in close temporal relationship to an infectious insult lends support to an immune or autoantibody-mediated mechanism. The presence of either the clinical features or comorbid diagnoses of OCD, ASD, AD/HD or anorexia nervosa – neuropsychiatric disorders that are part of the PANDAS spectrum and that are also associated with independent evidence of anti-brain antibodies or immune disturbances (Vincenzi et al., 2010) – strengthens the probability that an immune pathway is involved.

Many medical disorders frequently reported in TS are categorized as immunologically-determined illnesses, linked to other classical autoimmune disorders, or have been found to have an increased prevalence of autoantibodies or autoimmunity-associated immunoglobulin (Ig) isotypes. The presence of these disorders and immune-related markers tends to corroborate a generalized increase in vulnerability to immune-mediated disease in TS. Reports of an increased rate of allergic disorders (Chang et al., 2011; Ho et al., 1999) and elevated IgE (Finegold, 1985; Hsieh et al., 2010; Landau et al., 2012) lend support to this concept. A higher frequency of migraine, possibly associated with the presence of antiphospholipid antibodies (Toren et al., 1994), is noted in TS at rates similar to the elevated rates in SC and rheumatic fever (Barabas et al., 1984; Ghosh et al., 2012; Kwak et al., 2003; Teixeira et al., 2005). Patterns of familiality in TS also point toward the existence of an immune subset. A strong family history of autoimmune disorders, including but not limited to rheumatic fever (Hounie et al., 2007; Murphy et al., 2012, 2010b), is often found, along with enrichment of pedigrees for other neuropsychiatric disorders in which autoimmunity has been implicated, such as OCD, ASD and AD/HD (Burd and Kerbeshian, 1988; Debes et al., 2010; Eapen et al., 1997; Hebebrand et al., 1997; Knell and Comings, 1993; Lees et al., 1984; Leonard et al., 1992; Pauls et al., 1995; Sverd, 1991).

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1.1.2. Comorbidity of TS with other immune-mediated neuropsychiatric disorders of childhood

The prevalence of TS is estimated to be 1% worldwide (Robertson, 2012) with overall rates of comorbid neuropsychiatric disorders or psychopathologic features nearing 90% (Cavanna and Termine, 2012; Robertson, 2012). Males are more likely than females to have the disorder (3–4:1 male:female ratio) (Deng et al., 2012; Freeman et al., 2000; Robertson, 2012), and also more likely to bear a comorbid diagnosis (Freeman et al., 2000). OCD and AD/HD are the most common comorbid diagnoses in TS (53% and 38%, respectively, in a large muticenter study of children with TS) (Lebowitz et al., 2012). TS prevalence is also reported to be increased within samples of children with OCD and/or AD/HD, relative to rates in the general population (Leonard et al., 1992; Swedo and Leonard, 1994; Schuler et al., 2012; Yoshimasu et al., 2012). Heritable components are suggested by strong associations of TS and OCD and of OCD and AD/HD within families (Mathews and Grados, 2011). ASD comprise another set of neurodevelopmental conditions associated with heightened risk for a diagnosis of TS that are thought to relate to an immune mechanism. Reported rates of TS diagnoses in children with ASD range from 6.5 to 11% (Baron-Cohen et al., 1999; Canitano and Vivanti, 2007). Conversely, 4.6% of children with TS were found to have a comorbid pervasive developmental disorder in the Tourette Syndrome International Database Consortium Registry, representing a 13-fold increased risk. Rates were highest among TS males, those without a family history of TS or tic disorder, and those with the highest number of overall comorbid conditions (Burd et al., 2009). Approximately 30% of individuals with TS express self-injurious behaviors with or without a comorbid ASD diagnosis (Robertson, 2012). TS males also have a higher rate of childhood-onset schizophrenia than the general population (2.5% vs. 1%) (Kerbeshian and Burd, 2000). Immune and autoimmune pathways are strongly implicated not only in TS, but also in the development of a set of neuropsychiatric disorders – OCD, AD/HD, ASD and schizophrenia – that has frequently been found to cluster with TS (Bessen, 2001; Gimzal et al., 2002; Moore, 1996). The high rates of comorbidity in TS suggests shared genetic and environmental risk factors, overlap in mechanisms of pathogenesis, and a common neuroanatomical substrate (Murphy et al., 2010a; Robertson, 2012; Swedo et al., 2012).

Somatosensory urges prior to expression of tics (Leckman et al., 1993) help to differentiate TS and tic disorders from other movement disorders (Jankovic and Kurlan, 2011) and are likely subserved by different brain circuits than those underlying the motor response of the tic itself (Jackson et al., 2011). Post-mortem and imaging studies suggest that dysfunction in dopaminergic circuitry, most notably the BG, is responsible for the movement component of TS (Jankovic and Kurlan, 2011). In contrast, evidence from fMRI (Bohlhalter et al., 2006) and electrical stimulation (Pugnaghi et al., 2011) studies suggests a central role for paralimbic regions in premonitory somatosensory phenomena, including insular and anterior cingulate cortex, the supplementary motor area and parietal operculum; at the onset of tic enactment, activation patterns shift toward the superior parietal lobule, cerebellum and other sensorimotor regions (Bohlhalter et al., 2006). Immune-based animal models may help answer whether these more subtle but important variations in manifestations across neuropsychiatric diagnoses may be explained by differences in autoantibody specificity or binding patterns. For example, some patients may have antibodies that target insular and cingulate cortex.

1.2. Infectious and/or immune factors in TS

Evidence points increasingly toward a role for infection and immune factors in at least a subset of TS. The majority of immunologic investigations in patients with TS show a strong skew toward risk for the development of autoimmune phenomena and increased inflammatory markers (Martino et al., 2009a). A wide range of viral and bacterial agents has been implicated in the generation of cross-reactive antibodies, hypothesized most commonly to occur through a process of molecular mimicry (Allen et al., 1995; Budman et al., 1997; Ercan et al., 2008; Krause et al., 2010; Martino et al., 2011). In molecular mimicry, similarities between the antigens on the proteins that make up a microorganism and the self-antigens on the proteins of the host allow for the antimicrobial antibodies and T cells generated by the host to also react against self-antigens (i.e., exhibit cross-reactivity; here, to CNS elements); this process is most likely to occur in the context of a loss of the typical protective state of immune tolerance toward self-antigens. As the direct effects of an actual infection in an animal host often differ greatly from those in humans, we restrict our focus here to the microbial agents most commonly implicated in induction of autoimmunity.

1.2.1. Infection

One of the earliest appearances in the literature suggesting a connection between infection and tic disorders came from Laurence Selling in 1929, published as a case series of three boys presenting with tics that were ameliorated upon surgical correction of their sinusitis (Selling, 1929). β-Hemolytic streptococci were cultured from two of the cases. Selling's report included a tightly-reasoned plea to consider medically-based treatments in lieu of psychoanalytic frameworks and strategies in an era when the relationship between infection and SC and encephalitis lethargica were first coming to light. A common theme among the many subsequent reports of infectious triggers in TS that began to surface in the late 1980s was a relationship to GAS infection; the publication of working diagnostic criteria for PANDAS by Swedo in 1998 consolidated the focus on GAS as a model for autoimmune neuropsychiatric disorder (Swedo et al., 1998).

1.2.1.1. Group A Streptococcus. Streptococcal infection has figured prominently among the microbial agents considered as potential TS risk factors. Similarities in some motor manifestations of TS with those of SC, a post-streptococcal autoimmune movement and neuropsychiatric disorder primarily targeting the BG, and the high rate of obsessive-compulsive features in both TS and SC (Murphy et al., 2000; Rapoport et al., 1992; Swedo and Leonard, 1994) led to the suggestion that some cases of TS might also represent sequelae of streptococcal infection. The observation that tics and/or obsessive-compulsive phenomena may follow infection with GAS in the subset of children classified as PANDAS strengthened this idea (Swedo et al., 1998). An association between GAS infections and onset or exacerbations of illness in a subset of individuals with TS, tic disorders and OCD is also supported by numerous case-control (Church et al., 2003; Dale et al., 2004; Kurlan et al., 2008; Leslie et al., 2008; Mell et al., 2005; Rizzo et al., 2006) and prospective (Lin et al., 2010; Martino et al., 2011; Murphy and Pichichero, 2002; Murphy et al., 2004, 2007) investigations. Some longitudinal studies fail to confirm one of the essential criteria for establishing a diagnosis of PANDAS, that of a temporal relationship between new GAS infections and clinical exacerbations (Leckman et al., 2011; Luo et al., 2004; Singer et al., 2008). Although antibiotic prophylaxis against subsequent GAS infections has been shown to reduce exacerbations of OCD and tics (Leonard and Swedo, 2001; Murphy and Pichichero, 2002; Snider et al., 2005), other non-antimicrobial effects (e.g., immunomodulatory, glutamatergic) of some antibiotics must be considered (Culic et al., 2002, 2001; Henry et al., 2008; Tanaka, 2005; Vrancic et al., 2012).

Additional support for a role for GAS in triggering TS came from demonstrations of the presence of high anti-streptococcal antibody titers and of anti-neuronal antibodies targeting the caudate nucleus (Kiessling et al., 1993, 1994) and/or putamen (Kiessling et al., 1994)

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in children with TS and other movement disorders. In some studies, higher levels of anti-neuronal antibodies to putamen (Singer et al., 1998) or the neuron-like HTB-10 neuroblastoma cell line (Singer et al., 1999) were found in TS, but did not correlate with markers of GAS infection, including levels of anti-streptolysin O (ASO) or anti-deoxyribonuclease (DNase) B antibodies. Some studies find ASO and anti-DNase B antibodies to be significantly more common in TS, but not all studies differentiate TS subjects from controls on the basis of anti-streptococcal antibodies (Kiessling et al., 1994). The reported prevalence of ASO antibodies ranges from 29 to 69% in TS to 18 to 52% in healthy controls (Cardona and Orefici, 2001; Kiessling et al., 1993, 1994; Müller et al., 2000; Singer et al., 1998; Murphy et al., 1997; Morshed et al., 2001; Church et al., 2003; Rizzo et al., 2006). The prevalence of antibodies to DNase B ranges from 13 to 85% and from 8 to 59% for TS and controls, respectively (Kiessling et al., 1994; Müller et al., 2000; Singer et al., 1998; Murphy et al., 1997; Morshed et al., 2001). One large, long term, population-based follow up study of children after GAS infection found a strong relationship with behavior and non tic-like motor changes but no association specifically with tics (Murphy et al., 2007). Children with multiple GAS infections in the preceding 12-month period had a 13-fold increased risk for TS as compared with children who did not have multiple GAS infections (Mell et al., 2005). In another case-control study of privately-insured children, streptococcal infection in the preceding 12 months was associated with an increased likelihood of a new diagnosis of OCD or of tic disorder, but not of TS (Leslie et al., 2008). The latter study also found that streptococcal infection in the prior year was associated with a greater likelihood of a diagnosis of AD/HD or of major depressive disorder.

This raised the possibility that other infectious stimuli or environmental factors may serve as inciting factors for autoimmunity. It also indicated that the autoimmune parameters identified in TS may only be a proxy for the actual pathogenic mechanisms involved in disease induction. The failure of other studies to find a temporal relationship of changes in anti-streptococcal or anti-neuronal antibody levels in TS patients with new-onset streptococcal infections (Singer et al., 2008) or to detect a difference between TS and PANDAS subjects as compared with controls in anti-neuronal antibody levels pose further challenges to the explanatory power of the autoimmune hypothesis of TS (Brilot et al., 2011; Morris et al., 2009). Discrepancies in the results across these studies cannot be easily resolved; potential explanations include differences in the specific characteristics, comorbidity and clinical status of study subjects and limitations of the assays employed to detect and quantitate anti-neuronal antibodies. It is possible that even if GAS infection is sufficient or necessary for the triggering of the initial onset of illness, other stimuli, including other infections or physical or psychosocial stressors, may be important. We have yet to understand why certain circulating autoantibodies may become pathogenic in TS, as these are also detected with relatively high frequency in the sera of healthy controls (Levin et al., 2010). Studies in animals afford the opportunity to define the relationship of autoantibody blood level, Ig isotype or subclass and circulating factors that affect BBB compromise to the timing or severity of episodes.

1.2.1.2. Other microbes. Uncertainty regarding the requirement for documented infection with GAS in PANDAS spectrum disorders led to the newly-coined taxonomic category, PANS (Pediatric Acute-onset Neuropsychiatric Syndrome) (Swedo et al., 2012), wherein infection has been removed altogether as a diagnostic criterion and emphasis has been refocused on clinical features consistent with OCD or anorexia, minimizing the importance of tics or other movement disturbances. Other infectious agents, including *Mycoplasma pneumoniae* (Müller et al., 2004, 2000), other intracellular bacteria (Krause et al., 2010), and herpes and other viruses (Allen et al., 1995; Basheer et al., 2007; Budman et al., 1997; Dale et al., 2003; Northam and Singer, 1991; Shanks et al., 1991) have also been proposed to play a role in TS pathogenesis (de Oliveira and Pelajo, 2010). Acute onset movement and psychiatric disorders consisting of tics and obsessive-compulsive or other symptoms of anxiety are described following febrile illnesses of presumed but unknown infectious origin, with delay in the appearance of neuropsychiatric features ranging from a few days to a year (Mink and Kurlan, 2011).

1.2.2. Immune abnormalities

Reports of improvement of TS with immunomodulatory therapies (plasma exchange (Allen et al., 1995; Perlmutter et al., 1999), IVIg (Allen et al., 1995; Müller et al., 1997; Perlmutter et al., 1999), corticosteroids (Kondo and Kabasawa, 1978)) is consistent with an immune-mediated mechanism of pathogenesis. Most of these reports, however, are based on small numbers of subjects selected largely on the basis of clinical features or history of recent infection with GAS or other pathogens, as opposed to laboratory criteria supporting the presence of anti-neuronal antibodies or other immune system disturbances. The risks associated with use of these treatment modalities, particularly in children, make it essential to intensify the search for immune markers predictive of response to these therapies. An increased prevalence of both adaptive and innate immune abnormalities is widely reported in certain TS subsets, including alterations in immune cell number or function, levels of cytokines and chemokines, presence and specificity of autoantibodies, and association with immune response gene mutations, polymorphisms or copy number variations (CNV). Animal studies directed at understanding pathogenesis and treatment response in immunologic subsets of TS provide an opportunity to discover and validate robust immune markers that reliably identify subjects with an immune diathesis who are more likely to benefit from an immunomodulatory therapy.

1.2.2.1. Altered numbers and function of immune cells. A host of abnormalities in immune cell number and function have been reported in patients with TS. These include alterations in T, natural killer (NK) and B lymphocyte subsets. Reports of fewer regulatory T (Treg) cells in patients with moderate to severe TS as compared with age-matched healthy controls (Kawikova et al., 2007) raise the intriguing possibility that vulnerability to autoimmune phenomena in TS may relate to a relative insufficiency of the immune cells dedicated to controlling autoreactive lymphocytes, such as Treg. The finding could be secondary to one of the core neurotransmitter disturbances described in TS, however. Decreased Treg number and function might be accounted for, in part, by the observation that dopamine can downregulate Tregs (Kipnis et al., 2004), given the hypothesized hyperactivity of dopaminergic transmission in the disorder (Singer, 2011). In line with this explanation, higher expression levels of DRD5 dopamine receptor mRNA are reported in peripheral blood lymphocytes of subjects with TS (Ferrari et al., 2008). Studies in animals could be used to assess whether disturbances of dopamine transmission in peripheral immune cell subsets may drive autoantibody production in general, or lead specifically to the generation of antibodies directed against dopamine receptors.

The elevated percentage of $CD19^+$ B cells reported in TS as well as in patients with acute GAS infection or rheumatic fever (Weisz et al., 2004) is also suggestive of a predisposition for generation of autoantibodies (Puccetti, 2007). Augmented expression of CD19 or enhanced signaling along this pathway is associated with higher levels of autoantibody production and with autoimmune disease in both animal models and human studies (Poe et al., 2001; Sato et al., 1997; Tedder et al., 2005). A key regulator of CD19 signaling pathways and thus of autoantibody generation is indoleamine 2,3-dioxygenase (IDO) (Puccetti, 2007), one of two enzymes known to

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activate the kynurenine (tryptophan degradation) pathway. The finding of higher levels of kynurenine pathway metabolites in two TS studies (Dursun et al., 1994; Rickards et al., 1996) and decreased plasma levels of tryptophan in children with TS as well as in their parents (Comings, 1990) suggests that in addition to the higher levels of autoantibody-producing B cells in TS, IDO-mediated potentiation of $CD19^+$ B cell populations may heighten the predisposition toward autoimmune reactions. Another study suggesting increased drive toward autoreactive antibody production in TS reported higher levels of the $CD69^+/CD22^+$ B cell subset associated with antibody production (Moller et al., 2008). Studies in animals models are consistent with a role for kynurenine pathway metabolites in induction of motor tics in TS (Handley and Miskin, 1977) and will be reviewed below. The relationship of immune cell subsets to CNS outcomes has not been examined in detail in animal models of TS.

1.2.2.2. Cytokine and chemokine disturbances. Altered cytokine and chemokine levels have been reported in TS. Levels of the proinflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-12 were found to be increased at baseline as compared with healthy age-matched controls in one study of children and adolescents with TS; levels increased in conjunction with clinical exacerbations (Leckman et al., 2005). In a later study that compared children with TS with and without comorbid OCD, IL-12 levels were only found to be increased in the group that had both TS and OCD and no differences were found in levels of TNF-α (Gabbay et al., 2009). The altered proportions of children with a PANDAS diagnosis in these two studies – 26.8% vs. 6%, respectively – or other differences in study populations may have contributed to differences in cytokine findings. Other studies have found decreases in levels TNF-α as well as in soluble IL-1 receptor antagonist (sIL-1Ra) (Matz et al., 2012). In addition to the peripheral disturbances of immune function reported in several studies, markers of inflammation may be present in the brains of individuals with TS. Heightened expression of the genes coding for the T lymphocyte growth factor, IL-2, and monocyte chemotactic factor-1 (MCP-1), a marker of chronic inflammation, was reported in a post-mortem study of BG from adults patients diagnosed with TS (Morer et al., 2010). Animal model studies pertinent to TS have not generally examined immune cell subsets or their potential relationship to peripheral or central cytokine expression.

1.2.2.3. Immunoglobulin profiles. Elevated IgE levels have been reported in most studies of TS subjects (Finegold, 1985; Hsieh et al., 2010; Landau et al., 2012). One study found that 10 of 15 subjects with TS and atopic disease (67%) had higher levels of IgE (Hsieh et al., 2010), suggesting a potential relationship between higher IgE levels and the presence of allergic disorder. Another study reporting elevated IgE levels in subjects with TS additionally noted elevated levels of IgG4 (Landau et al., 2012), consistent with a possible vulnerability to the development of autoimmune disease (Takahashi et al., 2010). In contrast, one report based on two independent cross-sectional study samples noted that IgE serum levels tended to be decreased in one of the two samples, and also reported decreased levels of IgG3 and a trend toward a decrease in IgM levels (Bos-Veneman et al., 2011). In keeping with Landau et al. (2012), this study found elevated levels of IgG4, bolstering evidence for a drive toward autoimmune disturbance. A trend toward an increase in IgG1 during tic exacerbations was found in a prospective analysis in the same study (Bos-Veneman et al., 2011). IgA dysgammaglobulinemia has been reported in another study of children with TS. Whether these disturbances in Ig isotype and subclasses define a vulnerable phenotype in TS populations is unclear, as is their relationship to the detection or pathogenicity of autoantibodies within each of the different isotypes and subclasses. Studies in autoimmunity-dependent animal models may help elucidate the role of Ig of varying types and specificities in brain and behavioral outcomes.

1.2.2.4. Autoantibodies. Clinical similarity to SC, the prototypical autoantibody-mediated CNS disorder induced by GAS infection, has strengthened consideration that TS, tic disorders and OCD may also be manifestations of a post-streptococcal autoimmune process. In SC, a higher frequency of antibodies directed against BG or other targets is frequently reported, but anti-CNS antibodies are sometimes absent even in this hallmark autoimmune entity (Brilot et al., 2011). The mere presence of anti-CNS antibodies may also be insufficient to determine their pathogenic potential; anti-neuronal antibodies are highly common, even in apparently healthy individuals (Levin et al., 2010; Wendlandt et al., 2001). Whether anti-neuronal antibodies can be detected in subjects with TS and related disorders is a matter of some controversy (Hoekstra et al., 2002; Martino et al., 2009b; Murphy et al., 2010a; Robertson and Stern, 1998; Singer et al., 2008). Although many studies support the presence of anti-CNS IgG autoantibodies in at least a subset of subjects with TS (Cheng et al., 2012; Church et al., 2003; Kiessling et al., 1993, 1994; Laurino et al., 1997; Loiselle et al., 2003; Martino et al., 2011, 2007; Morer et al., 2008; Morshed et al., 2001; Rizzo et al., 2006; Singer et al., 1998, 1999; Wendlandt et al., 2001; Yeh et al., 2012, 2006; Zykov et al., 2009), some studies have found the levels of IgG autoantibodies in TS or PANDAS sera to be indistinguishable from those of controls (Brilot et al., 2011; Kawikova et al., 2010; Kirkman et al., 2008; Morris et al., 2009; Singer et al., 1998, 2005a) and a temporal relationship to documented GAS infection or the presence of anti-GAS antibodies has not always been evident (Kawikova et al., 2010; Loiselle et al., 2003; Martino et al., 2011; Singer et al., 2008, 1998, 1999). One study found lower levels of antibodies against a panel of neuronal targets previously identified in TS and/or OCD, but only in antibodies of the IgA isotype (Kawikova et al., 2010).

In addition to studies evaluating immunoreactivity of patient sera to BG structures or to general brain targets, evidence also exists that the sera of subjects with tics/OCD with or without a PANDAS diagnosis harbor antibodies that target one or more of four glycolytic enzymes in brain: pyruvate kinase M1, aldolase C, neuronal-specific and non-neuronal enolase. Commercial forms of these anti-glycolytic enzyme antibodies had effector function, as demonstrated by their capacity to induce apoptosis in primary rat cerebellar granule cells. The sequences of the human forms of three of these enzymes (pyruvate kinase M1, non-neuronal enolase and neuron-specific enolase) showed high levels of homology (38–49%) with the GAS equivalents of these enzymes (*Streptococcus* pyruvate kinase, *Streptococcus* enolase, *Streptococcus* enolase, respectively). In further support of the presence of similar epitopes in GAS and these glycolytic enzymes, antibodies against pyruvate kinase were also shown to cross-react prominently with GAS proteins, supporting a probable post-streptococcal origin, and anti-streptococcal antibodies reacted with pyruvate kinase at the anticipated 60 kDa molecular weight (Kansy et al., 2006).

Anti-neuronal antibody status appears to be related to TS comorbidity patterns but not to other phenotypic characteristics such as tic type and severity, duration of disease, self-injurious or aggressive behavior or family history of OCD or tics. Martino et al. (2007) demonstrated that comorbidity with AD/HD (but not OCD) was less likely in individuals with TS whose sera exhibited immunoreactivity to one or more three striatal targets commonly reported in TS, with a significant inverse relationship with the frequently demonstrated, 60 kDa BG antigen. Volumes of grey or white matter structures in frontostriatal circuits were the same in adults with TS whether anti-BG antibodies were present or absent (Martino et al., 2008). Closer dissection of the ontogeny of

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autoantibody development in animal models after exposure to relevant immunogens, accompanied by careful delineation of antibody isotype, demonstration of reactivity with the initial immunogen and with autoantigens present in CNS, and delineation of antibody binding patterns in brain circuits relevant to TS and OCD will help to address some of the apparent discrepancies of findings with the autoimmune hypothesis of TS. Detailed examination of behavioral consequences in motor, sensorimotor, and other domains relating to TS and OCD pathogenesis and determination of the potential correlation of these behaviors with the pattern of distribution of autoantibody deposits in key brain regions will provide clarification as to the mechanisms by which autoantibodies may contribute to disease.

1.2.3. Immune response genes

A number of polymorphisms, CNV and mutations of genes with products affecting immune pathways have been reported in TS. Some, such as the strong association of TS with a polymorphism in IL-1RN, the gene encoding for IL-1 receptor antagonist (IL-1Ra), lend support to the idea that cytokines and other immune molecules may contribute to TS pathogenesis separately from the influence of autoantibodies on the disease (Chou et al., 2010). IL-1Ra, a component of the alternative type (M2) macrophage response, appears to influence responses to GAS infection, as these are characterized by a combination of classical (M1) macrophage type responses (associated with secretion of proinflammatory cytokines TNF-a, IL-1 and IL-6) and M2 macrophage activation patterns (Goldmann et al., 2005).

An increase in CNV affecting genes within histamine receptor signaling pathways that have also been shown to be involved in ASD was recently described in TS; in addition, a rare functional mutation has been described in the HDC gene that encodes the rate-limiting enzyme in histamine biosynthesis, L-histidine decarboxylase (Ercan-Sencicek et al., 2010). Although these findings add support to reports of higher rates of allergic phenomena (Chang et al., 2011; Ho et al., 1999) and higher levels of Ig isotypes associated with allergy (IgE) (Bos-Veneman et al., 2011; Finegold, 1985; Hsieh et al., 2010; Landau et al., 2012), not all histamine-related gene findings have been confirmed in other populations (Lei et al., 2012).

1.3. Rationale for the design and evaluation of animal models of immune-mediated TS pathogenesis

Animal models facilitate the evaluation of disease mechanisms and accelerate our ability to appraise the potential of therapeutic strategies. They need not comprehensively represent every aspect of a disorder to derive this validity and value. In TS, gene-environment interplay during critical periods of brain development is thought to play a role in the pathogenesis of the disorder. Some models incorporate genetic polymorphisms or mutations implicated in the development of TS; other models focus on specific environmental factors supported by human epidemiologic or clinical studies.

When the disease in question involves disordered behavior, emotion or cognition, as in the case of TS and other neuropsychiatric illnesses, assessing the suitability of an animal model becomes a more complex endeavor. Superficially similar behaviors may serve different functions across species (Langen et al., 2011b). Functional equivalency is enhanced when a behavior or set of behaviors in animals and humans is dependent on the same or closely-related brain regions or neural circuits, or are regulated by similar neurochemical systems (Swerdlow et al., 1999). In TS, the ability to not only induce repetitive behaviors in an experimental animal but to also relate the occurrence of these behaviors to dysregulated dopamine transmission and corticostriatal circuitry, two abnormalities that are well-established in the TS literature (Leckman et al., 2010; Swerdlow et al., 1999), would lend strength to that animal model. The face validity of an animal model is stronger when the phenotype includes multiple core features of a specific disorder but phenomenologic resemblances need not be comprehensive for a model to be useful.

Disturbances along distinct pathways may lead to the same phenotype; conversely, changes in a single gene may, through pleiotropic effects, contribute to the appearance of multiple phenotypic characteristics when the downstream product of the gene is a participant in more than one pathway (Bucan and Abel, 2002). Stereotyped movements reminiscent of tics may occur spontaneously in conditional knockouts with deletions of the MeCP2 gene that are restricted to GABergic neurons (Chao et al., 2010); the ability to produce stereotypic behaviors through an animal model based on immune manipulations is not necessarily weakened by the occurrence of a similar behavioral outcome in a different model. Experimental systems attempting to reproduce the biologic processes, such as the induction of cross-reactive autoantibodies by exposure to microbial antigens, have strong construct validity. The design of such model systems often presents a challenge as natural infection may not be possible, or may have different consequences, in different species. For similar reasons, studies in mice attempting to model the naturalistic development of post-GAS, brain-directed, autoimmune responses have used GAS or GAS components as immunogen instead of relying on GAS infection.

2. Immune-mediated animal models of TS

Interest in the role of immune processes in the pathogenesis of neuropsychiatric disorders such as TS has accelerated over the past two decades as evidence has grown for the importance of CNS-immune interactions in shaping brain development and function (Bilbo and Schwarz, 2009; Sredni-Kenigsbuch, 2002). Animal models focused on the role of immune disturbances in TS and tic disorder pathogenesis have employed a variety of approaches (Tables 1–3). Some involve disruption of innate immune signaling; others rely on induction of autoantibody and other responses in the adaptive arm of the immune system. These strategies include:

1. peripheral or central injection of cytokines or other immune modulators that alter neuronal function and behavior relevant to TS;
2. immunization with immunogenic components of microbes suspected of inducing cross-reactive autoantibodies; these autoantibodies are hypothesized to target epitopes present in TS-relevant neural circuitry, such as the dopaminergic pathways of cortico-striatal-thalamo-cortical circuits;
3. passive transfer into naïve animals (peripherally or centrally) of sera putatively harboring autoantibodies that bind to epitopes localized on neurons or other resident cells of the CNS (using sera derived either from affected patients or from animals directly immunized with the inciting antigen) and disrupt CNS signaling and behavior;
4. studies in mouse strains or transgenics that spontaneously produce autoantibodies or develop immune abnormalities after exposure to specific environmental stimuli.

2.1. Genetic mouse models of immune-mediated TS

Some mouse strains and transgenic models with altered immune function or sensitivity to the development of autoimmune disease have been shown to demonstrate repetitive behavior patterns. The BTBR T+tf/J (BTBR) mouse strain is an example of a strain that was developed primarily as a model of ASD but

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Table 1
Animal models of Tourette syndrome based on increased brain immune mediators (spontaneous or induced).

Exposure	Controls/comparators	Route of exposure	Species	Strain	Agent of BBB breach	Pathologic findings	Behavior abnormalities	Citation
BTBR T + tf/J (BTBR) mice	C57BL/6J (B6) mice; BTBR × B6 F1 mice	NA[a]	Mouse	BTBR	NA	↑ serum anti-brain antibodies; ↑ IgG and IgE deposits in brain; Brain region-dependent ↑ in IL-1β, IL-6, IL-10, IL-12, IL-18, IL-33 and IFN-γ	↑ self-grooming; ↑ marble burying, bar-biting; ↓ interaction with novel social partner vs. novel object	McFarlane et al. (2008), Heo et al. (2011), Pearson et al. (2011), Amodeo et al. (2012)
IL-2, mid-gestation	Vehicle (PBS)	ip	Mouse	SJL/J	None	[^{125}I] IL-2 injected into mothers crossed the placenta	↑ self-grooming; ↑ rearing; ↓ conditioned eyeblink acquisition	Ponzio et al. (2007)
IL-6, mid-gestation	IL1-α, TNF-α, or IFN-γ, or vehicle (PBS)	ip	Mouse	C57BL/6J	None	↑ expression of α, β and γ crystallin genes in fetal brain	↓ PPI; ↓ latent inhibition	Smith et al. (2007), Garbett et al. (2012)
IL-2; IL-6	IL-1β or vehicle (PBS)	ip	Mouse	Balb/cCR	None	*IL-2*: ↑ DA activity in prefrontal Cx; ↑ NE activity in Hc, HYP; *IL-6*: ↑ DA activity in prefrontal Cx, Hc; ↑ 5-HT activity in prefrontal Cx, Hc	*IL-2*: ↑ digging, rearing; ↑ investigation of novel object; *IL-6*: ↑ digging, rearing; ↑ grooming	Zalcman et al. (1994), Zalcman et al. (1998)
TGF-β1 overexpression (viral vector)	β-galactosidase overexpression (viral vector)	Hc injection, age 2 or 8 weeks	Mouse	C57BL/6J	NA	*Early*: Chronic ↓ TGF-β1 mRNA in Hc; *Adult*: Transient ↓ MCP-1 mRNA in Hc but no persistent changes	*Early*: ↑ self-grooming; ↑ forced swim test immobility; *Adult*: ↓ self-grooming; ↓ forced swim test immobility	Depino et al. (2011)
sIL-2Rα; sIL-2Rβ	sIL-1R1; Vehicle (PBS)	sc	Mouse	Male Balb/cCR	None	*sIL-2Rα*: ↑ c-fos immunoreactivity and sIL-2Rα deposits in STR and motor, infralimbic and cingulate Cx; *sIL-2Rβ*: ↑ c-fos immunoreactivity and sIL-2Rβ deposits in STR and motor, infralimbic, cingulate and prepyriform Cx	*sIL-2Rα*: ↑ rearing, turning; ↑ grooming; ↑ head bobbing, jumping; *sIL-2Rβ*: ↑ rearing, turning; ↑ grooming; ↑ head bobbing, jumping; ↑ horizontal stereotypic and ambulatory movements	Zalcman et al. (2012)
sIL-6Rα	Vehicle/test stress; Uninjected/no test stress	sc	Mouse	Male Balb/cCR	None	↑ sIL-6Rα in STR, motor and infralimbic Cx, ventral nuclei of thalamus; gp130 colocalized with sIL-6Rα in brain	↑ rearing, turning; ↑ head bobbing; ↑ horizontal ambulation; ↑ vertical stereotypic movements	Patel et al. (2012)

Key: 5-HT, serotonin; BBB, blood-brain barrier; Cx, cortex; DA, dopamine; Hc, hippocampus; HYP, hypothalamus; IL, interleukin; ip, intraperitoneal; NE, norepinephrine; PBS, phosphate-buffered saline; PPI, prepulse inhibition; s, soluble; sc, subcutaneous; STR, striatum.

[a] NA, not applicable.

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Table 2
Animal models of Tourette syndrome based on injection of autoantibodies.

Exposure	Controls/comparators	Route of exposure	Species	Strain	Agent of BBB breach	Pathologic findings	Behavior abnormalities	Citation
TS sera or IgG positive for anti-neuronal antibodies ($n = 5$)[a]	Control sera or IgG (low levels of anti-neuronal antibodies) ($n = 5$)	Striatal micro-infusion	Rat	Male Fischer 344	NA[b]	↑ IgG deposits in STR	↑ motor stereotypies; ↑ episodic vocalizations	Hallett et al. (2000)
TS sera with high ($n = 12$) or low ($n = 12$) levels of anti-neural or anti-nuclear antibodies[c]	Control sera with low levels of anti-neural or anti-nuclear antibodies ($n = 12$)	Ventro-lateral striatal micro-infusion	Rat	Male Sprague-Dawley	NA	Not done	TS sera with high levels of anti-neural or anti-nuclear antibodies associated with: ↑ oral stereotypies; ↑ genital grooming	Taylor et al. (2002)
TS ($n = 9$) or PANDAS ($n = 8$) sera immunoreactive with putamen homogenate or synaptosomes, respectively[c]	Controls (unknown anti-neuronal antibody status); Anti-streptococcal M5 type antibody	Ventral or ventro-lateral striatal micro-infusion	Rat	Male Fischer 344	NA	Not done	No change in levels of motor stereotypies or episodic vocalizations	Loiselle et al. (2004)
TS sera with high ($n = 9$; 1 TS only, 3 TS/OCD, 5 TS/OCD/ADHD) or low ($n = 7$; 1 TS/OCD, 4 TS/ADHD, 2 OCD) levels of anti-neuronal antibodies[a]	PBS; Sham surgery only	Ventro-lateral striatal micro-infusion	Rat	Male Sprague-Dawley	NA	Not done	↑ oral stereotypies; ↑ genital grooming	Singer et al. (2005a,b)
SC IgG ($n = 8$)	Control IgG ($n = 8$)	Caudate micro-injection	Rat	Male Wistar	NA	No IgG deposits or change in basal ganglia tyrosine hydroxylase or GAD65/67 immunoreactivity	No differences in rotational behavior in apomorphine and amphetamine behavioral tests	Ben-Pazi et al. (2012)
TS sera ($n = 32$; 19 TS only, 11 TS/ADHD, 2 TS/OCD) immunoreactive with 120 kDa HCN4 (putative autoantigen)	ADHD sera ($n = 47$); Control sera ($n = 14$); Vehicle (PBS)	Striatal micro-infusion	Rat	Male Sprague-Dawley	NA	Anti-HCN4 antibody colocalized with human TS sera in thalamus	↑ stereotypic movements; ↑ tic-like behaviors (especially forepaw grooming)	Yeh et al. (2012)
Pooled IgG from mothers of ASD children, immunoreactive with fetal brain ($n = 7$)	Pooled IgG from mothers of control children, not immunoreactive with fetal brain ($n = 7$)	IV injection, 3 times in first trimester of pregnancy	Macaque	NA	None	Not done	↑ stereotypies and hyperactivity in novel testing contexts	Martin et al. (2008)
Anti-strep IgM mAb	Anti-strep IgG mAb; Anti-KLH mAb; Vehicle (PBS)	sc	Mouse	Male Balb/cCR	None	*Anti-strep IgM mAb*: ↑ IgM deposits in STR, motor Cx; ↑ c-fos immunoreactivity in STR, motor Cx; Fcα/μ receptors colocalized with IgM deposits	*Anti-strep IgM mAb*: ↑ stereotypy scores; ↑ head bobbing, sniffing; ↑ grooming; *Anti-strep IgG mAb*: ↑ ambulation, vertical activity; No stereotypic behaviors; *Anti-KLH IgM mAb*: ↓ activity	Zhang et al. (2012)

Key: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BBB, blood-brain barrier; Cx, cortex; Hc, hippocampus; IV, intravenous; KLH, keyhole limpet hemocyanin; mAb, monoclonal antibody; OCD, obsessive-compulsive disorder; PBS, phosphate-buffered saline; s, soluble; sc, subcutaneous; strep, streptococcal; STR, striatum; TS, Tourette syndrome.

[a] Anti-streptococcal antibody status not reported.

[b] NA, not applicable.

[c] No difference across groups in levels of anti-streptococcal antibodies.

Table 3
Animal models of Tourette syndrome based on immunization with microbial immunogen or mimics.

Exposure	Controls/comparators	Route of exposure	Species	Strain	Agent of BBB breach	Pathologic findings	Behavior abnormalities	Citation
GAS (M6 type) homogenate	Vehicle (PBS)	sc	Mouse	SJL/J	CFA, 1° immunization; IFA, 2° boosts (3-week intervals)	↑ anti-brain antibodies in serum; Brain-reactive GAS-immunized mouse sera were immuno reactive against strep antigens; ↑ IgG deposits in STR, CBLM, lateral HYP, nuclei in thalamus, pons, and brainstem; Presence of serum anti-brain antibodies and IgG deposits immunoreactive against CBLM (deep cerebellar nuclei) correlated with degree of stereotypic behaviors (rearing)	↑ rearing; ↓ coordination; ↓ exploration, social investigation; ↑ submissive behaviors; ↑ defense-escape behaviors; ↑ grooming; ↓ olfactory discrimination learning; ↓ errors and inter-response time in reversal learning and memory task	Hoffman et al. (2004), Yaddanapudi et al. (2010)
Sera from GAS-immunized mice	IgG-depleted GAS sera; PBS mouse sera; IgG-depleted PBS sera	IV injection into tail vein, ip injection of LPS	Mouse	Male SJL/J	LPS	↑ IgG deposits in Hc and periventricular area; IgG depletion prior to injection of GAS-immunized mouse sera decreases binding in brain and abrogates behavioral effects	↑ rearing; ↓ exploration, social investigation; ↑ submissive behaviors; ↑ defense-escape behaviors; ↑ grooming	Yaddanapudi et al. (2010)
GAS (M18 type) cell wall components	Vehicle (PBS)	sc injection of CFA and IFA, ip injection of *B. pertussis*	Rat	Male Lewis	CFA + heat-inactivated mycobacteria + *B. pertussis*, at 1° immunization; IFA, 2° boosts (2-week intervals)	↑ IgG deposits in STR, thalamus and frontal Cx; ↑ DA levels in frontal Cx, entopeduncular nucleus (human globus pallidus equivalent); ↓ glutamate levels in frontal Cx; Sera from strep-immunized mice were immunoreactive with strep antigens, tubulin and DA receptors DRD1 and DRD2; GAS rat sera induced CAM kinase II activity; activation was reduced after IgG depletion of sera	↓ food manipulation capacity; ↓ narrow beam walking (unimpaired wide beam); ↑ induced grooming; ↓ motor abnormalities with DRD2 blocker (haloperidol); ↓ induced grooming with selective serotonin reuptake inhibitor, paroxetine	Brimberg et al. (2012)
Poly I:C (double-stranded RNA viral mimic), mid-gestation	Vehicle (PBS)	ip	Mouse	C57BL/6J; C57BL/6N	None	↓ T regulatory cells; ↑ IL-6 and IL-17 production by $CD4^+$ T cells; Bone marrow transplantation reconstitutes immune system and reverses stereotypic, social and communication deficits	↑ self-grooming; ↑ marble burying; ↑ ultrasonic communication deficits; ↓ sociability; ↓ PPI	Malkova et al. (2012), Hsiao et al. (2012)
Poly I:C (double-stranded RNA viral mimic), late gestation	Vehicle (PBS)	ip	Mouse	C57BL/6J	None	↓ neurogenesis (reduced generation of intermediate progenitor cells, ↓ $Cux1^+$ neurons); ↑ neuronal apoptosis; Barin abnormalities reversed by single dose of non-steroidal anti-inflammatory COX-2 inhibitor, carprofen	↓ early motor coordination; ↓ PPI; ↑ locomotor activity in novel environment; ↓ habituation to novelty; Behavioral deficits reversed by single dose of non-steroidal anti-inflammatory COX-2 inhibitor, carprofen	De Miranda et al. (2010)
LPS, mid-gestation	Vehicle (PBS)		Rat	Wistar	None	↓ DA synthesis in STR; No glial activation evident	↑ repetitive behaviors in male offspring	Kirsten et al. (2012)

Key: BBB, blood-brain barrier; CaM kinase II, calcium/calmodulin-dependent protein kinase II; CBLM, cerebellum; CFA, complete Freund's adjuvant; Cx, cortex; DA, dopamine; GAS, Group A *Streptococcus*; Hc, hippocampus; HYP, hypothalamus; IFA, incomplete Freund's adjuvant; IL, interleukin; ip, intraperitoneal; IV, intravenous; LPS, lipopolysaccharide; poly I:C, polyinosinic:polycytidylic acid; PBS, phosphate-buffered saline; PPI, prepulse inhibition; s, soluble; sc, subcutaneous; STR, striatum; TS, Tourette syndrome.

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that shows features that overlap with the immune and behavioral disturbances described in TS. As compared with C57BL6/J mice and BTBR × C57BL6/J F1 offspring, BTBR mice had increased serum IgG and IgE, similar to some reports in TS, even in the absence of a specific exposure. In addition, BTBR mice had increased anti-brain antibodies of the IgG isotype in serum, consistent with their high levels of IgG-secreting B cells in peripheral blood and of IgG and IgE deposits in brain. Increased stereotypic behaviors have been described in several studies of BTBR mice (Amodeo et al., 2012; Heo et al., 2011; McFarlane et al., 2008; Pearson et al., 2011).

2.2. Exposure to immune molecules that alter CNS function

Since the discovery that the proinflammatory cytokines IL-1β and TNF-α and their receptors were present in brain under healthy conditions (Breder et al., 1988; Plata-Salaman et al., 1988), our understanding of the role that cytokines and other immune molecules play in brain development and function, as well as in pathological states, has grown (Kerr et al., 2005; Maslinska, 2001; Merrill, 1992). Neurons and glial cells are not only able to synthesize different cytokines and chemokines but can also respond to them via a diverse set of cytokine receptors that are expressed on the surface of cells localized in different brain regions. Several immune mediators, including IL-1β, IL-6, TNF-α, and IFN-γ, appear to regulate synaptic transmission, and the receptor for IFN-γ is localized at certain synapses (Habibi et al., 2009). A subset labeled as neuropoietic cytokines plays several key roles in normal brain development, contributing to the proliferation, differentiation and ultimate fate of neural precursor cells; neuronal and glial cell migration and survival; and activity-dependent synaptic plasticity (Stolp, 2012). Chemokines are also important as messengers for the communication of signals between neurons and microglia in health and disease (Biber et al., 2008; Hesselgesser and Horuk, 1999). Polymorphisms that alter the structure and functional capacity of immune molecules, or their receptors, also appear to modify responses to infection, including infection-induced alterations in levels of cytokines and chemokines (Piraino et al., 2012; Vollmer-Conna et al., 2008). Although exposure of animal hosts to immune mediators or microbial mimics such as lipopolysaccharide (LPS) is frequently associated with a robust, acute sickness response- the coordinated set of infection-related adaptive changes characterized by anorexia, social withdrawal, sleepiness or fatigue, cognitive deficits and mood and anxiety disturbances (Dantzer, 2001, 2004; Dantzer et al., 1998; Dantzer and Kelley, 2007)- cytokines and chemokines are associated with a far wider array of dysregulatory effects, consistent with the multifaceted functions that they serve in the CNS. The association of cytokine dysregulation with TS (Cheng et al., 2012; Gabbay et al., 2009; Leckman et al., 2005; Matz et al., 2012; Morer et al., 2010) and other neuropsychiatric syndromes (Ashwood et al., 2008a,b; Chez et al., 2007; Gray and Bloch, 2012; Hickie and Lloyd, 1995; Mittleman et al., 1997) underscore the relevance of animal model studies of the cytokine milieu for delineation of immune mechanisms in TS.

2.2.1. Cytokines and chemokines

Studies in mice demonstrate that acute disruption of cytokines can alter CNS development and lead to persistent behavioral disturbances reminiscent of TS, tic disorder and OCD. IL-2 introduced mid-gestationally to pregnant autoimmune disease-sensitive SJL/J mice was confirmed to cross the placenta and lead to immune and behavioral disturbances in the offspring. IL-2-exposed mouse pups had accelerated T cell development that was skewed toward production of proinflammatory Th1-type cells and abnormalities of the conditioned eyeblink reflex (Ponzio et al., 2007). A single injection of IL-6 at mid-gestation causes deficits in exposed offspring in prepulse inhibition (PPI) (Smith et al., 2007), a test of the sensorimotor gating processes demonstrated to be abnormal in many studies of TS, OCD, ASD and related neuropsychiatric conditions (Swerdlow, 2012). Although mechanisms regulating the passage of maternally-introduced IL-2 and IL-6 across the placenta into the fetal circulation remain unresolved, such studies do not require an additional inflammatory stimulus to result in behavioral disturbances in the offspring. The brains of offspring exposed prenatally to increased levels of either maternal cytokines, the double-stranded mimic of viral infection,known as polyinosinic:polycytidylic acid (poly I:C), or influenza show overlapping alterations in gene expression, suggesting the possibility that the substances injected into pregnant dams or shared mediators that they induce enter fetal brain to affect common pathways (Garbett et al., 2012; Smith et al., 2007).

Different proinflammatory cytokines differentially affect behavior (Zalcman et al., 1998) in a pattern corresponding to the regionally-specific changes these cytokines induce in brain monoamines and the distribution of their cognate cytokine receptors in brain. Intraperitoneal (ip) administration to male BALB/c mice of IL-2, a cytokine produced by peripheral immune cells as well as by resident cells of the CNS that influences release of dopamine (DA) in mesocorticolimbic structures, led not only to higher DA turnover in prefrontal cortex but also to increased norepinephrine (NE) utilization in hippocampus and hypothalamus. IL-6 administration also induced higher levels of serotonin (5-HT) as well as DA activity in hippocampus and prefrontal cortex. IL-1 induced a diverse array of changes in central NE, 5-HT and DA activity across these brain regions (Zalcman et al., 1994). Groups of mice treated with IL-2 or IL-6 both showed more digging and rearing behavior. IL-6-treated mice also demonstrated increased locomotor and grooming behaviors. In contrast, IL-1 administration was associated with markedly decreased levels of ambulatory and non-ambulatory exploration (Zalcman et al., 1998). IL-2-mediated increases in climbing behavior were blocked by SCH 23390, an antagonist of the dopamine D1 receptor (DRD1) and by the DRD2 antagonist, sulpiride, whereas the noncompetitive NMDA receptor antagonist, MK-801, had no effect (Zalcman, 2002). The cytokine specificity of these behavior-activating effects, the regionally-specific monoaminergic changes associated with administration of these different cytokines, and the patterns of response to neuropharmacologic agents may provide a basis for understanding some of the mechanisms contributing to repetitive motor abnormalities in TS.

How peripherally administered cytokines might cross the BBB to alter brain function is controversial (Kowal and Diamond, 2012; Willis, 2012). Peripheral cytokines may enter the CNS at areas of BBB compromise or through active transport mechanisms (Maslinska, 2001). One potential mechanism is that proinflammatory cytokines themselves decrease BBB integrity, thereby facilitating their own entry into the brain. Interleukins such as IL-17A can decrease resistance at the BBB through induction of reactive oxygen species (ROS) and activation of contractile machinery in the endothelial cell barrier in parallel with decreased levels of the tight junction (TJ) protein, occludin. Some data also suggest that whereas IL-2 entry into the brain occurs at a low rate under most circumstances, due to the absence of a blood-to-brain transporter for cytokines and a usually impenetrable BBB, the existence of a saturable brain-to-blood efflux system may also be operative. With high level or chronic IL-2 exposure, saturation of the efflux system may favor accumulation of the cytokine (Banks et al., 2004).

Other immune molecules that have been found to increase self-grooming and other stereotypic behaviors in mice, such as TGF-β1, appear to have differential effects depending on age. Whether this relates to regionally-specific compromise of the microvasculature of the BBB as a function of maturation is not known. Overexpression of TGF-β1 in the dentate gyrus of hippocampus during early

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postnatal development can lead to persistently increased repetitive (self-grooming) behavior and social interaction deficits. TGF-β1 overexpression in adulthood led to opposite effects, albeit transiently (Depino et al., 2011). The impact of age is likely to not only be cytokine-specific, but also brain region-dependent, in keeping with the differential expression of immune molecules and receptors across brain regions and throughout brain development. Astrocytes with foot processes adjacent to the tight junctions of the BBB may respond to inflammatory or toxic stimuli, ROS or other stressors in a regionally-specific manner that results in differential modulation of the permeability of the BBB (Aschner, 1998; Chaudhuri, 2000).

2.2.2. Soluble cytokine receptors

Stereotypic behaviors have also been observed after peripheral administration of soluble cytokine receptors, constituents of normal peripheral circulation that lack the extracellular component of membrane-bound receptors. Soluble cytokine receptors play important roles as regulators of cytokine and lymphocyte activity and are increased in some autoimmune conditions and psychiatric disorders. Balb/c mice receiving single subcutaneous (sc) injections of soluble IL-2 receptors (sIL-2R) α or β showed increased repetitive head bobbing, grooming and rearing/sniffing behaviors as well as other stereotypic behaviors in the vertical and horizontal planes (Zalcman et al., 2012). Effects were most prominent with administration of sIL-2Rβ as compared to sIL-2Rα and behavioral profiles differed slightly for the two sIL-2R subtypes. Effects appeared to be specific for certain soluble cytokine receptors as no effects were observed after injection of type 1 sIL-1R (sIL-1R1).

Marked increases in immunoreactivity to c-fos protein, a marker of CNS activity, were observed in caudate-putamen, nucleus accumbens and in motor, infralimbic and cingulate cortex following sIL-2R α or β administration. Enhanced expression of c-fos in prepyriform cortex (thought to be an extension of primary olfactory cortex) was only observed in sIL-2Rβ treated animals. Regional sIL-2Rα and β brain deposits, as shown by immunofluorescent staining, were distributed in a pattern that paralleled the brain regions with elevated c-fos expression in immunohistochemical studies of the brains of mice treated with either sIL-2Rα or sIL-2Rβ.

Another soluble cytokine receptor that is elevated in some autoimmune and neuropsychiatric disorders, sIL-6R, produces effects similar to those observed with sIL-2R (Zalcman et al., 2012) in BALB/c mice (Patel et al., 2012). Vertical stereotypies and novelty-associated exploratory motor behaviors increased within 80 min of injection of recombinant human sIL-6Rα, a form that is reactive with both human and mouse IL-6; effects were exacerbated when sIL-6Rα administration was followed by the DA uptake inhibitor GBR 12909. Peripherally-administered sIL-6Rα accumulated in cortico-striatal-thalamo-cortical (CSTC) regions – circuitry implicated as the neuroanatomical substrate of motor stereotypies – in a distribution pattern overlapping with but not identical to that observed with administration of sIL-2R (Zalcman et al., 2012). The brain distribution of injected sIL-6R also co-localized with the IL-6 trans-membrane signaling protein gp130 in nucleus accumbens, caudate-putamen, thalamus and motor and infralimbic cortex; the source of this accumulated sIL-6R was able to be unambiguously identified in immunohistochemical experiments as the exogenous recombinant sIL-6Rα as opposed to any endogenous mouse IL-6R that may be found in brain by using anti-human IL-6Rα antibodies that do not detect mouse IL-6R. Expression of gp130 was increased in controls injected with saline and subjected to open field behavioral testing but not in untreated mice, suggesting that IL-6 trans-signaling pathways may be activated in the absence of sIL6R following stressor exposure alone. Whether this change in gp130 expression may have led to some degree of increase in stereotypic movements could not be assessed through these experiments, as the investigators did not subject uninjected controls to novel open field testing. The results suggest that peripheral sIL-6R can act as a neuroimmune messenger, crossing the blood-brain barrier (BBB) to selectively target CSTC circuits rich in IL-6 trans-signaling protein, and inducing repetitive stereotypies. Whether endogenous levels of IL-2, IL-6, or the cytokines associated with soluble receptors can augment or diminish such behavioral effects remains unclear.

2.3. Exposure to antibodies from patients with TS

2.3.1. Direct CNS administration of antibodies

As evidence has accumulated in support of an autoimmune mechanism in the pathogenesis of TS, particularly in the context of GAS infection (Martino et al., 2009b; Murphy et al., 2010a; Shulman, 2009), several animal models have been established to test this hypothesis. The majority of such models have utilized direct administration of anti-neuronal antibodies from patients with TS and related disorders into rodent striatum. By eliminating the need to consider the added dimension pertaining to differences in inflammatory state or other systemic factors that facilitate peripheral antibody entry into brain through induction of BBB compromise, these studies address the more fundamental ("downstream") question of whether patient sera or IgG are capable of affecting striatal function in vivo. Although these models cannot elucidate the factors important to the generation of pathogenic antibodies or examine how circulating antibodies enter brain and bind to their cognate antigens, they do have the potential to delineate the patient phenotypes and antibody characteristics that are most tightly associated with behavioral disturbances reminiscent of TS and/or OCD.

Although most studies selected sera wherein elevated levels of anti-neuronal IgG antibodies were established, selection of TS sera on the basis of GAS infection was more unusual. In the first of these animal model studies, microinfusion of either unfractionated sera from five TS subjects or controls, or IgG extracted from these sera, led to motor stereotypies and episodic vocalizations in male Fischer 344 rats that persisted for days after microinfusions ceased. Although all TS sera were demonstrated to have anti-neuronal antibodies, and levels of these antibodies were shown to be low in control sera, subjects were not characterized with respect to GAS infection status or a diagnosis of PANDAS. The presence of IgG deposits on striatal neurons was confirmed by immunofluorescence assays (Hallett et al., 2000) demonstrating correspondence with brain circuitry implicated in the clinical manifestations of TS (Peterson, 1996). Oral stereotypies were similarly found following infusion of TS sera containing high levels of anti-neural or anti-nuclear antibodies into rat ventrolateral striatum (Taylor et al., 2002). After establishing the identity of a 120 kDa protein target against which TS sera were immunoreactive as hyperpolarization-activated nucleotide channel 4 (HCN4) protein, infusion into rat striatum of antibodies against the HCN4 protein resulted in dose-dependent increases in stereotypic behaviors. Further work on the role of HCN4 in TS pathogenesis is needed to clarify the implications of this finding (Yeh et al., 2012).

The level of antibodies in blood may have no influence on their pathogenicity. In a study that assessed the effects of anti-neuronal antibodies of high and low titers on the capacity to induce stereotypies following infusion into rat ventrolateral striatum, no relationship was found (Singer et al., 2005b). Whether adjustment for total IgG level or examination of other Ig isotypes would have altered results is unclear. Two studies found no effects of anti-neuronal antibody infusion into striatum, although the reasons for failure to detect stereotypies are unclear (Ben-Pazi et al., 2012; Loiselle et al., 2004). Of additional interest, transplantation of rat neural stem cells into rats previously receiving infusions of TS sera into their striatum was associated with reversal of stereotypic behaviors (Liu et al., 2008).

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2.3.2. Peripheral administration of antibodies

Two studies employing peripheral injection strategies for the introduction of antibodies both led to significant effects without the concomitant administration of an agent to breach the BBB. In work in rhesus macaque monkeys, IgG from mothers of children with ASD induced stereotypies and hyperactivity in association with novel, presumably stressful, contexts (Martin et al., 2008). Another study reported repetitive movements in mice injected peripherally with commercial anti-GAS antibodies, but only in association with IgM, and not IgG antibodies. Patterns of c-fos activation closely paralleled striatum and other brain regions subserving stereotypic motor behaviors that are implicated in TS. Although still speculative, the authors found that sites of IgM binding and cell activation colocalized with Fcα/μ receptors in striatum and motor cortex. The investigators postulate that transcellular mechanisms may play a role in facilitating entry of IgM antibodies to brain in the absence of administration of any agent known to compromise BBB integrity (Zhang et al., 2012).

2.4. Infection or immunization with microbial immunogen(s)

Exposure of animal hosts to infection, microbial antigens or mimics of viral or bacterial infection are methods that allow for the induction of autoantibodies or immune factors putatively associated with disease. As hypotheses differ regarding the importance of brain and/or immune system maturation to the development of immune-mediated TS, animal studies vary with respect to the timing of the introduction of the immune-activating stimulus and their anticipated effects on brain development and function. The mechanisms by which different species respond to infection also vary greatly; thus, we focus here on models that expose animals to microbial antigens or to mimics of viral or bacterial pathogens as opposed to those using direct infection with live organisms. These models provide an opportunity for investigators not only to determine the mechanisms involved in triggering CNS-directed autoantibodies that may be relevant to TS; they also permit examination of the processes that are required for peripherally-generated antibodies and immune molecules to cross the BBB to enter the CNS. To date, animal models employing peripheral exposure to microbial antigens have focused on GAS for the generation of anti-brain autoantibodies leading to effects reminiscent of TS.

2.4.1. GAS and autoimmunity

In 2004 we reported CNS-directed autoimmunity and behavioral disturbances after immunization of mice with GAS (Hoffman et al., 2004). To increase the probability of an autoantibody-based, PANDAS-like response, we used the autoimmune disease-susceptible SJL/J mouse strain to establish our experimental model. Immunization with GAS homogenate (M6-type) resulted in behavioral features reminiscent of TS including increased rearing behavior, taken to be a reflection of repetitive or stereotypic behaviors, during open field testing (Hoffman et al., 2004) as well as during a test of social interaction (resident-intruder task) in subsequent experiments (Yaddanapudi et al., 2010). GAS immunization also led to the development of antibodies that were immunoreactive with brain antigens. We observed that rearing behavior was closely correlated with serum levels of anti-GAS and anti-brain antibodies and with the presence of IgG deposits in brain. Other behavioral abnormalities observed in the later study included increased grooming behaviors during social interaction tests and decreased motor coordination in a rotating rod test (Yaddanapudi et al., 2010). The appearance of compulsive grooming in conjunction with a social challenge, but not at baseline, is consistent with the fluctuations of behaviors described in TS, as is the presence of sensorimotor deficit in rotarod testing.

The immunoreactivity of peripheral antibodies in GAS mice targeted cell bodies of neurons within the deep cerebellar nuclei (DCN). The pattern of immunolabeling resembled that observed in the perineuronal nets of DCN (Bertolotto et al., 1996; Brauer et al., 1984; Seeger et al., 1994) in assays using lectins that also bind N-acetyl-beta-D-glucosamine (GlcNac), the dominant epitope of GAS carbohydrate. Prior work by Cunningham and collaborators showed that monoclonal antibodies generated from children with SC target GlCNac, among other GAS epitopes; these antibodies are associated with calcium/calmodulin-dependent protein kinase II (CaM kinase II) activity that is absent from sera obtained during convalescence or from children with GAS-related but non-choreic illnesses (Kirvan et al., 2003). GAS mice harboring sera that bound to DCN in normal SJL mouse brain sections using indirect immunofluorescence also showed increased numbers of IgG deposits in the parenchyma of DCN in their own brain tissues (Hoffman et al., 2004). Other brain regions exhibiting immunoreactivity using sera from GAS mice included the globus pallidus, lateral hypothalamus, and nuclei in the thalamus, pons, tegmentum, periolivary areas and brainstem. Notably, these regions of observed immunoreactivity are implicated in the neuroanatomical circuitry implicated in TS (Leckman et al., 2010) and mediate the behaviors found to be disturbed in this animal model, based on studies with both mice (Langen et al., 2011b) and men (Langen et al., 2011a).

We questioned whether anti-brain antibodies associated with repetitive behaviors and induced by exposure to GAS antigens were more likely to show particular profiles of immunoreactivity against GAS proteins, and whether the identity of the specific epitopes that were bound might help to explain the cross-reactivity of the antibodies. Examination of serum from mice showing immunoreactivity against DCN antigens demonstrated greater heterogeneity in immunoreactivity against GAS M6-type bacterial proteins than sera from mice that did not bind to DCN, but did not exhibit a specific anti-GAS profile. Sera with high levels of immunoreactivity to GAS proteins had higher levels of immunoreactivity to DCN and were most likely to be present in GAS mice in which the highest levels of IgG deposits were demonstrated in their DCN structures; preabsorption with the GAS homogenate used as immunogen removed this immunoreactivity.

GAS-related anti-neuronal antibodies described in human studies have primarily been detected using denaturing techniques that might eliminate conformational structures. Thus, false negative results could have been obtained in conditions wherein the antibodies involved bind only to non-denatured epitopes. Using non-denaturing techniques that preserve conformational epitopes to detect the CNS targets of GAS-induced antibodies in our mouse model, we detected antibodies in GAS mice that cross-reacted to antigens present in the cerebellum of normal SJL mice and had sequence homology with the functionally active, denaturation-sensitive (Sim and Sim, 1981, 1983) thioester bond regions (Isaac and Isenman, 1992) of C4 complement and α-2-macroglobulin. In addition to their role in GAS pathogenesis and host responses (Areschoug et al., 2004; Blom et al., 2004; Thern et al., 1995; Toppel et al., 2003), C4 and α-2-macroglobulin are dysregulated in autoimmune diseases (Borth, 1994; Paul et al., 2002; Samano et al., 2004; Saso et al., 1993; Traustadottir et al., 2002) and are also involved in CNS functions (Barnum, 2002; Mori et al., 1991). Of note, the presence of α-2-macroglobulin in brain is also considered a sensitive indicator of BBB compromise (Garton et al., 1991); thus, studies of these targets in mouse models may add to our understanding of the factors affecting BBB integrity and the entry of peripherally-synthesized, cross-reactive antibodies into brain. The role these targets of cross-reactive, GAS-induced, anti-brain antibodies may play in TS remains to be determined.

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We next sought to fulfill the Witebsky et al. (1957) criteria for evaluating causality in disorders of hypothesized humoral autoimmunity, an adaptation of Koch's postulate about demonstrating microbial causation in animal models (Koch, 1890; Rose and Bona, 1993), whereby antibodies are able to be demonstrated in the human disease, the autoantigen target of these antibodies can be identified, and introduction of the autoantigen induces autoimmune responses and pathologic changes in the experimental animal analogous to those in humans. Transfusion of IgG from GAS-immunized mice into naïve mice reproduces key aspects of the model, including increased rearing behavior and brain IgG deposits; IgG-depletion of GAS-immune serum abrogated these effects (Yaddanapudi et al., 2010). These data provide support for the presence of a pathogenic immunoglobulin of the IgG isotype and a compelling case for GAS-induced humoral autoimmunity as a mediator of brain and behavior disturbances akin to TS. These data provide a rationale for future studies in human neuropsychiatric populations to confirm the relationship of clinical phenotype to candidate biomarkers and CNS targets.

Similar findings were obtained in another model of GAS-induced autoimmune neuropsychiatric disturbance recently developed in the Lewis rat (Brimberg et al., 2012), a strain with a high propensity to develop autoimmune syndromes after exposure to a wide range of antigenic stimuli (Stohr et al., 1999). As in the mouse model developed by our group (Hoffman et al., 2004), experimental immunization with GAS antigens substituted for natural infection. In contrast to our studies, however, Brimberg and colleagues used a cell wall antigen preparation of GAS M type 18 bacteria as the immunogen. Animals exposed to GAS cell wall antigens developed motor and compulsive disturbances consistent with SC, PANDAS and TS, including impaired ability to manipulate food and traverse a narrow beam, and compulsive, induced grooming behaviors. Motor abnormalities were abrogated by the DA receptor type 2 (DR2) blocker, haloperidol, and the compulsive grooming behavior was alleviated by administration of the selective 5HT reuptake inhibitor, paroxetine. IgG deposits were detected in striatum, thalamus and frontal cortex after GAS exposure, largely confined to neurons. No staining was found in the hippocampus or cerebellum of GAS rats. Using HPLC, GAS-immunized rats were found to have increased levels of DA in frontal cortex and in the rat analogue of the internal segment of the globus pallidus in primates, the entopeduncular nucleus; levels of glutamate were also decreased in frontal cortex. The localization of these monoaminergic and glutamatergic disturbances in cortex and BG, when paired with the GAS-induced motor coordination deficits and repetitive behaviors, provides a compelling case for the development of TS-like phenomena in the context of GAS-mediated CNS autoimmunity.

Further work determined that GAS rat sera contained antibodies that were immunoreactive against the GAS cell wall antigen used as immunogen as well as against peptidoglycan-polysaccharide and GlcNAc. Antibodies directed against the cytoskeletal protein, tubulin, and the DA receptors DRD1 and DRD2 were also found using western blot technique. In an important parallel to previous work in children with SC, TS, PANDAS and OCD that showed activation of CaM kinase II signaling in the SK-N-SH catecholamine-secreting neuronal cell line, Brimberg and colleagues demonstrated that GAS rat sera were similarly capable of inducing CaM kinase II activity. The CaM kinase II activity was markedly reduced after depleting IgG from the sera.

Antibodies against DRD1 and DRD2 were detected in sera from children with PANDAS and SC, but not in sera from children with AD/HD or healthy controls. Quantitation of antibody levels by ELISA showed fluctuation of DRD1 and DRD2 immunoreactivity with the course of disease. Whereas immunoreactivity in GAS rats appeared to be against both the long and the short form of DRD2, with bands at both 48 kDa and 51 kDa in western blot, immunoreactivity of human sera against DRD2 appeared only around 51 kDa, suggesting that immunoreactivity of antibodies in children with PANDAS and SC was restricted to the long, primarily postsynaptic isoform of DRD2 (D2L), as opposed to the short form (D2S) of the D2 receptor that operates mainly as a presynaptic autoreceptor (Usiello et al., 2000). The D2S/D2L ratio has been shown to be reduced in association with single nucleotide polymorphisms (SNPs) that regulate alternative splicing of DRD2 pre-mRNA. The SNPs that reduce relative D2S expression are overrepresented in patients with compulsive disorders such as cocaine abuse (Moyer et al., 2011), and have been shown to play a role in DA regulation. Stimulation of D2L in NG108-15 cells stably expressing this splice variant has been shown to activate the nuclear isoform of CaM kinase II (Takeuchi et al., 2002), an effect that was demonstrated with GAS rat sera as well as with sera from children with PANDAS-related tics and OCD and SC. In keeping with this model, serum autoantibodies in GAS-associated tics, OCD and SC that specifically target the D2L form of the receptor may not inhibit the receptor but rather serve to activate it, thereby also activating nuclear CaM kinase II. The reduced rearing behavior observed in D2L receptor-deficient mice (Wang et al., 2000) suggests that activating effects of anti-D2L antibodies in TS and related syndromes would fit more closely with the model.

To facilitate trafficking of cross-reactive antibodies into brain, interruption of the integrity of the BBB appears to be necessary (Kowal and Diamond, 2012). Inflammatory molecules and other substances upregulated during infection, including cytokines, are widely recognized as potential agents of BBB breakdown; however, other factors are known to contribute. Occludin, one of the proteins in the brain microvasculature that makes up the tight junction (TJ) protein complexes and normally helps to restrict the paracellular diffusion of substances from blood into brain, may be altered in structure under conditions of oxidative stress, leading to its movement away from the TJ (Lochhead et al., 2010). Interestingly, the mode of disrupting BBB integrity appears to influence the distribution of IgG deposits and behavioral sequelae. Following complete Freund's adjuvant (CFA) induction of BBB compromise in our primary immunization model, IgG deposits were identified in DCN, globus pallidus, lateral hypothalamus, and in nuclei in the thalamus, pons, tegmentum, periolivary areas and brainstem (Hoffman et al., 2004). In contrast, with the LPS exposure that accompanied the passive transfer of donor GAS serum IgG into naïve mice, IgG deposits were restricted largely to hippocampus and the periventricular area (Yaddanapudi et al., 2010). Administration of CFA with additional heat-killed mycobacteria and separate ip injection of *Bordetella pertussis* were also found to be required in the work by Brimberg et al. (2012) in order to breach the BBB and be able to demonstrate IgG deposits in brain. IgG deposits were largely found confined to neurons in striatum, thalamus and frontal cortex using this mode of compromising the BBB. Work by Diamond and colleagues in an animal model of anti-NMDA receptor antibody-mediated neuropsychiatric systemic lupus erythematosus has confirmed a hippocampal distribution of BBB compromise, inferred from restriction of IgG deposits to hippocampal structures, with use of LPS as an agent to reduce the integrity of the BBB; intriguingly, co-exposure of mice to epinephrine at the time of antibody injection led to IgG deposits in the stress-responsive amygdala (Huerta et al., 2006; Kowal et al., 2006, 2004; Kowal and Diamond, 2012). Note that exposure of the circumventricular organs to antibodies injected into the bloodstream is not restricted by the TJ of the BBB. Given data suggesting that anti-neuronal antibodies are frequent even in the peripheral blood of healthy individuals, dissection of the determinants of autoantibody binding to different regions of brain remains a critical step in understanding TS pathogenesis.

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2.4.2. Other infections

TS-like behavioral disruptions consistent with effects on cortico-striato-thalamo-cortical circuits may occur in the context of other infections, possibly due to generic mechanisms of innate immune activation. Prenatal exposure of pregnant mice to the viral mimic, poly I:C, or injection of IL-6 led to comparable effects on the CNS gene expression and behavior of offspring. Stereotypic behaviors consistent with both the core motor tics of a TS diagnosis as well as the sensorimotor gating deficits (decreased PPI capacity) of the wider range of neuropsychiatric disorders frequently found to be comorbid with TS were identified, along with social interaction disturbances typically linked to ASD (Malkova et al., 2012). Offspring exposed prenatally to poly I:C in this model showed persistent decreases in Treg along with elevated IL-6 and IL-17 production. These immune alterations and the repetitive behaviors were reversed by irradiation and reconstitution of the immune system through transplantation of immunologically normal bone marrow from either prenatally immune challenged or control offspring, suggesting that persistent immune dysregulation may drive specific behavioral anomalies in TS, OCD, ASD and related disorders (Hsiao et al., 2012). Work from our group identified the requirement for toll-like receptor (TLR)3, the innate immune system receptor for poly I:C, in PPI disruption and other behavioral effects of the prenatal immune exposure model as well as the capacity to abrogate the effects of prenatal immune challenge on offspring CNS and behavior by a single administration of the nonsteroidal anti-inflammatory COX-2 inhibitor, carprofen (De Miranda et al., 2010). These data suggest that genetic polymorphisms in TLR or other components of innate immunity, or the use of anti-inflammatory or antipyretic agents, may modify risk for the development of immune-mediated CNS and behavior abnormalities after infection or other immune-stimulating exposures.

Induction of stereotypic motor behaviors does not appear to be limited to prenatal administration of viral mimics, as a single injection of the bacterial mimic, lipopolysaccharide, to pregnant Wistar rats in mid-gestation was also reported to result in repetitive behaviors in male offspring. Reduced DA synthesis in striatum without evidence of glial activation suggests that LPS-induced activation of innate immune pathways during brain development can lead to persistent underactivation of DArgic pathways in the absence of continued inflammation (Kirsten et al., 2012). The behavioral manifestations of the model may change with age (Enayati et al., 2012). Further support for alternate immune pathways for stimulation of stereotypic behaviors is derived from work that shows increased repetitive head shakes in mice following the activation of the kynurenine (tryptophan degradation) pathway by IFN-Y induction of IDO, a rate limiting enzyme in the kynurenine pathway (Gaynor and Handley, 2001).

3. Implications for immune hypotheses of TS and future animal model and clinical research

Studies of immune-mediated phenomena in animal models reveal a wide range of behavioral and brain changes consistent with findings reported in human studies of TS. The majority of the animal models described here that used extra-CNS exposures (either through tail vein or at subcutaneous sites) depended on the inclusion of agents associated with BBB compromise. The exceptions are the rhesus monkey model described by Amaral and coworkers (Martin et al., 2008) and several mouse model studies by Zalcman and colleagues (Patel et al., 2012; Ponzio et al., 2007; Zalcman et al., 1994, 1998, 2012; Zalcman, 2002). Further examination of the means by which antibodies enter CNS across the BBB are required. In light of the high frequency of autoantibodies in the general population, it is hypothesized that pathogenicity may be less related to the levels or specificity of the antibody, and more dependent on factors that modify access to brain tissues and control antibody binding once in brain. Cross-reactive antibodies arising through processes of molecular mimicry are postulated to be less specific for their target than the antibody induced by the original inciting antigen (microbial or other).

Animal models that demonstrate both core and associated TS features may be particularly valuable in sorting out conundrums of diagnosis and psychiatric taxonomy. Although repetitive movements correspond most closely with the motor tics that are part of the current American Psychiatric Association diagnostic criteria for TS (APA, 2000), motor coordination deficits are also highly prevalent in TS (Avanzino et al., 2011; Bloch et al., 2006; Sukhodolsky et al., 2010). The co-occurrence in the two GAS exposure models of behaviors similar to the core diagnostic features (tic-like motor behaviors) of TS with features that are not diagnostic but nonetheless commonly associated with the disorder, such as impaired motor coordination, boosts the face validity of these models. Establishment of a link among the appearance of deficits in these behavior domains, alterations in TS-related neural circuitry, and the presence of regional brain IgG deposits strengthens support for the autoimmune construct. The accelerating rotating rod test requires good sensorimotor coordination and is known to be sensitive to both BG and cerebellar dysfunction (Crawley, 1999). In Rhesus macaque monkeys, neurons of the DCN have been shown to be particularly well suited for the regulation of continuous movements (Soteropoulos and Baker, 2007). For Purkinje cell output to reach the rest of the brain it must be conveyed by neurons of the DCN or vestibular nuclei. DCN neurons may be most critical for maintenance of normal gait patterns (Hurlock et al., 2009). Thus, abnormalities in rearing and performance on the rotating rod are both likely to be dependent on BG and cerebellum. We found a particularly tight correlation of the number and intensity of IgG deposits in DCN with dysregulated rearing behavior. Our identification of IgG deposits in BG and cerebellum in conjunction with behavior deficits thought to be regulated by these regions is consistent with the concept of an autoantibody-mediated process targeting TS circuitry.

Important questions remain regarding the autoimmune hypothesis of TS. Animal models based on exposure to microbial antigens or to autoantibodies implicated in disease may facilitate resolution of these challenging issues. The range of triggers for immune-based TS may extend beyond GAS (PANDAS) to viruses and agents that induce anti-NMDA receptor encephalitides/encephalopathies (including ovarian teratomas). The factors that contribute to vulnerability for the development of immune-mediated TS are likely to include genetic and maturational factors that play an important role in shaping host responses to environmental agents. Differences in heritability and timing of exposure may also help to explain the diversity of CNS outcomes that are proposed to result from these mechanisms. Analyses of immune response genes (HLA, cytokine and cytokine receptor polymorphisms, other) have yielded some candidates, but the search for genetic factors is complicated by the absence of a clear endophenotype that defines a TS subset that is most likely to be linked to an autoimmune CNS mechanism. Genetic factors underlying risk for rheumatic fever and other post-GAS autoimmune syndromes may not be the only ones to consider; some polymorphisms, for example, are more likely to alter risk for infection with intracellular organisms as opposed to infection with GAS. The role of ROS in increasing BBB permeability and the capacity of N-acetyl-cysteine and other antioxidants to strengthen the BBB suggest important overlap in inflammatory and oxidative stress pathways. Their contribution to the pathogenicity of autoantibodies in TS sera deserves closer assessment in experimental models.

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4. Conclusions

Animal model studies in TS demonstrate robust support for a hypothesized autoimmune process. Although models based on GAS provide a compelling parallel with studies of children with tics and/or OCD that meet criteria for PANDAS, it is likely that different microbial and other triggers may also be able to incite and/or exacerbate the disorder. In addition, changes in immune molecules may propagate activity in inflammatory, kynurenine or oxidative stress pathways and regulate autoantibody pathogenicity by influencing the integrity of different regions of the BBB.

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