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Review article

Dysregulated brain immunity and neurotrophin signaling in Rett syndrome and autism spectrum disorders ☆

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ABSTRACT

Rett syndrome is a neurodevelopmental disorder, which occurs in about 1:15,000 females and presents with neurologic and communication defects. It is transmitted as an X-linked dominant linked to mutations of the methyl-CpG-binding protein (MeCP2), a gene transcription suppressor, but its definitive pathogenesis is unknown thus hindering development of effective treatments. Almost half of children with Rett syndrome also have behavioral symptoms consistent with those of autism spectrum disorders (ASDs). PubMed was searched (2005–2014) using the terms: allergy, atopy, brain, brain-derived neurotrophic factor (BDNF), corticotropin-releasing hormone (CRH), cytokines, gene mutations, inflammation, mast cells (MCs), microglia, mitochondria, neurotensin (NT), neurotrophins, seizures, stress, and treatment. There are a number of intriguing differences and similarities between Rett syndrome and ASDs. Rett syndrome occurs in females, while ASDs more often in males, and the former has neurologic disabilities unlike ASDs. There is evidence of dysregulated immune system early in life in both conditions. Lack of microglial phagocytosis and decreased levels of BDNF appear to distinguish Rett syndrome from ASDs, in which there is instead microglia activation and/or proliferation and possibly defective BDNF signaling. Moreover, brain mast cell (MC) activation and focal inflammation may be more prominent in ASDs than Rett syndrome. The flavonoid luteolin blocks microglia and MC activation, provides BDNF-like activity, reverses Rett phenotype in mouse models, and has a significant benefit in children with ASDs. Appropriate formulations of luteolin or other natural molecules may be useful in the treatment of Rett syndrome.

Contents

Abbreviations: ASD, autism spectrum disorders; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; CRH, corticotropin-releasing hormone; IL, interleukin; MCs, mast cells; MCAS, mast cell activation syndrome; mt, mitochondria; NT, neurotensin; TNF, tumor necrosis factor.

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1. Introduction

Rett syndrome is a neurodevelopmental condition affecting about 1 per 15,000 females and is characterized by neurologic defects, mental retardation and seizures (Neul et al., 2010; Castro et al., 2013). Even though children with Rett syndrome show severe impairment in language and movement, they still make eye contact. About half of children with Rett syndrome also exhibit symptoms consistent with those of autism spectrum disorders (ASDs), also a neurodevelopmental condition. which affects almost 1/68 children but characterized by deficits in communication and sociability (Fombonne, 2009; Kogan et al., 2009; Volkmar et al., 2009).

In Rett syndrome over 2/3 of cases have been linked to specific sporadic de novo mutations (Matijevic et al., 2009; Matsuishi et al., 2011; Banerjee et al., 2012) affecting the gene for the methyl-CpG-binding protein (MeCP2), which is a general transcriptional repressor (Nguyen et al., 2012; Qiu et al., 2012; Ku et al., 2013; Na et al., 2013). In contrast, many gene mutations are associated with higher risk of ASD, but only explain a small percentage of cases (Weiss et al., 2009; Aldinger et al., 2011; Hallmayer et al., 2011; Williams, 2012).

DNA methylation at the C5 position of the cytokine residue of GpG dinucleotides generally leads to gene silencing (Feng and Fan, 2009), especially in the hypothalamus (Chahrour et al., 2008). Some papers have reported specific neuronal gene defects using MeCP2 null mice (Urdinguio et al., 2008), such as abnormal "axonal guidance" (Degano et al., 2009). Loss of MeCP2 also resulted in decreased production of biogenic amines (Samaco et al., 2009). However, it is still not known how the loss of the MeCP2 protein leads to the neurologic or other symptoms (Blackman et al., 2012).

Patients with Rett syndrome often have seizures, but those with ASDs have a number of other comorbidities including allergies, gastrointestinal symptoms and seizures (Bauman, 2010). There is new evidence that epigenetic regulation contributes significantly to neurodevelopmental and neurodegenerative diseases, Rett syndrome and those with ASDs (Herbert, 2010; Lilja et al., 2013; Rangasamy et al., 2013). We compare and contrast the clinical and pathological findings in Rett syndrome and ASDs (Table 1).

2. Methods

PubMed was searched since 1995 for papers reporting on Rett syndrome and/or ASD and any one of the following terms: allergy, atopy, brain-derived neurotrophic factor (BDNF), corticotropin-releasing hormone (CRH), cytokines, flavonoids, gene mutation, inflammation, mast cells (MCs), mitochondria, neurotensin (NT), phenotype, seizures, stress, subtype, treatment, and therapy. Papers were chosen for relevance, human data, and use of English language. Papers were excluded if they were published as "hypotheses" or if they were repetitive by the same authors.

Table 1
Differences and similarities between Rett syndrome and ASDs.

Characteristics	Rett syndrome	ASDs
Present in females	+	
More common in males		+
Neurologic symptoms	+	−
Behavioral symptoms	±	+
Eye contact	+	−
Decreased microglia phagocytosis	+	−
Microglia activation/proliferation	−	+
Neurotrophins (BDNF)	↓	↑ but defective signaling
MeCP2 mutation	+	−
Mitochondrial dysfunction	±	+
Brain autoantibodies	±	+
Brain inflammation	±	+
Seizures	+	±
Allergies/food intolerance	−	+
Gastrointestinal symptoms	−	+

3. Microglia and neurotrophins

A number of papers have reported altered microglial function in Rett syndrome (Maezawa et al., 2011; Derecki et al., 2012; Tsai, 2012; Zachariah et al., 2012; Derecki et al., 2013). In fact, neuron-only expression of normal MeCP2 was not sufficient to reverse the Rett phenotype in mice; instead brain-wide expression was needed suggesting the importance of glia cells, astrocytes or some other brain cell type (Guy et al., 2007; varez-Saavedra et al., 2007). For instance, astrocytes from Rett syndrome patients can spread MeCP2 deficiency (Maezawa et al., 2009). Correction of MeCP2 deficiency in myeloid cells of *MeCP2*-null mice was sufficient to correct most symptoms associated with Rett phenotype, but strangely only if phagocytic activity of microglia was intact (Derecki et al., 2013). There is also increased glia neurodensity in Rett syndrome suggesting inflammatory astrocytosis (Armstrong, 2005). Microglial–MC interactions are considered important in neuroinflammatory diseases (Skaper et al., 2012). Interestingly, the MC-derived protease tryptase induced microglia activation (S. Zhang et al., 2012).

A neuroinflammatory process (Zimmerman et al., 2005), as evidenced by strong activation of microglia and astroglia, along with increased expression of MCP-1 and tumor necrosis factor (TNF)-α, had been reported in ASDs (Vargas et al., 2005), and has since been confirmed. However, "atypical wiring" may be more important than active inflammatory process (Rodriguez and Kern, 2011; Morgan et al., 2012).

Lack of brain-derived neurotrophic factor (BDNF) has been implicated in many neuropsychiatric diseases (Autry and Monteggia, 2012), including Rett syndrome (Li and Pozzo-Miller, 2014). A number of papers have reported reduced blood and cerebrospinal fluid (CSF) levels of BDNF in patients with Rett syndrome (Katz, 2014), and in a mouse model of Rett syndrome (Schaevitz et al., 2010). In fact, loss of MeCP2 has been correlated with reduced levels of neurotrophic factors including BDNF (Abuhatzira et al., 2007). In contrast, BDNF has been largely found to be elevated in patients with ASDs (Nishimura et al., 2007; Sadakata et al., 2012; Ricci et al., 2013), but this increase may be the result of defective signaling (Correia et al., 2010).

4. Autoimmunity

Increasing reports suggest that Rett syndrome and ASDs may have some aspects of immune dysfunction (Derecki et al., 2010). ASDs in particular have been considered having an autoimmune (Ashwood and Van de Water, 2004; Gesundheit et al., 2013; Theoharides et al., 2013) and having some neuroimmune component (Theoharides et al., 2009). MeCP2 has been shown to be an autoantigen associated with increased susceptibility to systemic lupus erethymatosus (Webb et al., 2009). Autoantibodies against the brain have been reported in the serum of Rett syndrome patients (Klushnik et al., 2001). In the case of ASDs, 30% of patients had elevated antibody levels directed against the cerebellum (Wills et al., 2009; Rossi et al., 2011; Braunschweig and Van de Water, 2012). The Autism Phenome Project reported that 42% of 3 year old children with ASDs had plasma antibodies against

GABAergic cerebellar neuron proteins (Rossi et al., 2011). The Autism Genetic Resource Exchange reported 8.8% prevalence of anti-brain of antibodies in the mothers of these families, 53% of whom also had have also the presence of anti-nuclear autoantibodies and also had autoimmune diseases such as rheumatoid arthritis and systemic lupus (Brimberg et al., 2013). A large study conducted in Italy with autistic children (n = 355), their unaffected siblings (n = 142) and their mothers (n = 333) reported that the presence of anti-brain antibodies in neither the patient nor the mother did not indicate increased risk of autism; however, the presence of 45 kDa and 62 kDa were correlated with autism severity (Piras et al., 2014). Another study reported increased levels of anti-phospholipid antibodies in patients with ASDs and the levels were evidently associated with more impaired behaviors as reported by parents (Careaga et al., 2013). Finally, a recent paper described the existence of autoantibodies against human neuronal progenitor cells suggesting an impaired tolerance to neural antigens in ASDs (Mazur-Kolecka et al., 2014).

One paper described that the only statistically significant correlation with the presence of brain autoantibodies in patients with ASDs was with allergic symptoms (Mostafa and Al-Ayadhi, 2013).

5. Allergies and food intolerance

One large epidemiological study reported a strong correlation between eczema and both attention deficit hyperactivity disorder (ADHD) and ASDs (Yaghmaie et al., 2013). Many patients with ASDs suffer from food allergies (Jyonouchi, 2010) and "allergic-like" symptoms (Angelidou et al., 2011), suggesting MC activation (Theoharides et al., 2012a; A. Theoharides, 2013; T.C. Theoharides, 2013). Moreover, children with mastocytosis, a spectrum of diseases characterized by increased number of activated MCs, who present with allergies, hyperactivity and difficulty focusing ("brain fog") (Akin et al., 2010; Petra et al., 2014), appear to have a 5-fold higher chance of developing ASDs (1/10 children) than the general population (1/68 children) (Theoharides, 2009). In fact, mastocytosis patients have unusually frequent neurologic (Smith et al., 2011) and psychiatric (Moura et al., 2014) symptoms.

MCs participate in allergies, innate and acquired immunity (Rottem and Mekori, 2005; Galli et al., 2008), as well as in inflammation (Theoharides et al., 2010a). They are also responsible for eliciting neutrophil infiltration that promotes autoimmunity (Walker et al., 2012). MCs are considered the "immune gate to the brain" and their richest source is the hypothalamus and cerebellum (Theoharides, 1990). MC-derived IL-6 and TGFβ are also critical for the development of Th-17 cells (Nakae et al., 2007; Suurmond et al., 2011) primarily responsible for autoimmunity and MCs secrete IL-17, themselves (Nakae et al., 2007). Brain MCs produce TNF and they are the only cell type that stores pre-formed TNF in secretory granules from which it can be released rapidly (B. Zhang et al., 2012b).

Surprisingly MCs could also have immunoregulatory actions (Voehringer, 2013) possibly because of their ability to secrete specific mediators selectively without degranulation (Theoharides et al., 2007). The state of MC activation could also be determined by other molecules, such as IL-33, which augments the ability of substance P (SP) to stimulate release of VEGF (Theoharides et al., 2010b), while CRH augments the ability of NT to release VEGF from MCs (Donelan et al., 2006).

6. Focal brain inflammation

Neuropsychiatric disorders have been characterized by brain gene clusters associated with increased inflammation and mitochondrial defects (Theoharides et al., 2011). Lymphocyte function has been reported to be affected in Rett syndrome (Delgado et al., 2006). TNF levels were increased in the CSF (Zimmerman et al., 2005; Li et al., 2009) and IL-6 expression was elevated in the brains of patients with ASDs (Li et al., 2009). Maternal immune activation (MIA) in mice led to increased IL-6 (Dahlgren et al., 2006; Smith et al., 2007) and contributed to immune dysregulation and behaviors in the offspring that were reminiscent of autism (Hsiao et al., 2012). Interestingly, mastocytosis patients have high serum IL-6 levels (Theoharides et al., 2002) and MCs can release IL-6 selectively (Kandere-Grzybowska et al., 2003). Substances originating in the gut or the brain can trigger MCs to release mediators that could disrupt the blood–brain barrier (BBB) (Theoharides and Doyle, 2008) and cause "focal encephalitis" in specific brain areas, thus contributing to the pathogenesis of ASDs (Theoharides et al., 2008; A. Theoharides, 2013; T.C. Theoharides, 2013).

Patients with ASDs are prone to stress (Gillott and Standen, 2007) and prenatal stress has been linked to increased risk of ASDs (Beversdorf et al., 2005; Ronald et al., 2010). Stress activates brain MCs leading to BBB disruption (Esposito et al., 2002) that contributes to brain inflammation, as amply documented in multiple sclerosis (MS) (Karagkouni et al., 2013). CRH and NT, secreted under stress, synergistically stimulate MCs, leading to secretion of VEGF (Cao et al., 2005), increase vascular permeability (Donelan et al., 2006) and lead to BBB disruption (Theoharides and Konstantinidou, 2007). NT is a brain peptide (also found in the gut) involved in inflammation (Mustain et al., 2011). NT is neurotoxic (Ghanizadeh, 2010) and can facilitate *N*-methyl-D-aspartate (NMDA)-induced excitation of cortical neurons (Antonelli et al., 2004). NT also induces expression of CRH receptor-1 (CRHR-1) (B. Zhang et al., 2012a), activation of which by CRH increases allergic stimulation of human MCs (Asadi and Theoharides, 2012).

We first reported that NT is increased in the serum of 3-year old children with autism (Angelidou et al., 2010). We also recently reported that both NT and CRH are increased in the serum of children (6–12 years old) with ASDs (Tsilioni et al., 2014). It is, therefore, of interest that high serum CRH and CRH-receptor-positive MCs were reported in a mastocytosis patient whose symptoms worsened with stress (Theoharides et al., in press).

Rett syndrome has been linked to brain mitochondrial abnormalities that have also been reported in about 30% of patients with ASD (Rossignol and Frye, 2012). Mitochondrial dysfunction has been connected to oxidative stress and inflammation in ASDs (Rossignol and Frye, 2014). ATP and mitochondrial DNA could contribute to the pathogenesis ASDs through stimulation of different processes. We showed that MC activation leads to mitochondrial translocation to the cell surface (Zhang et al., 2011) and secretion of mitochondrial ATP and DNA (Zhang et al., 2012a). These extracellular mitochondrial components augmented MC activation and allergies (Asadi and Theoharides, 2012) because they are mistaken by the body as "innate pathogens" and induce a strong auto-inflammatory response (Theoharides, 2013). In fact, mtDNA was reported to be directly neurotoxic and alter behavior in mice (Lauritzen et al., 2010). MCs express Toll-like receptors (TLR) including TLR9 that can be activated by bacterial and viral DNA sequences, leading to the release of different cytokines that allow MCs to participate in immunity against bacteria (Abraham and St John, 2010). Extracellular ATP has been proposed to act as a universal "alarm" signal released from cells under stress and capable of affecting neighboring cells (Corriden and Insel, 2010). We showed that mitochondrial DNA was high in serum of young autistic children (Zhang et al., 2010).

One would have to invoke that inflammation occurs perinatally in different brain regions (Angelidou et al., 2012) (Fig. 1). Mast cells are located perivascularly at the BBB especially in the cerebellum and hypothalamus close to microglia and nerve endings. Absence of MeCP2 and reduced BDNF levels could lead to Rett syndrome. Instead, MC–microglia activation and focal brain inflammation could contribute to ASDs, while MC–cell activation and T cell recruitment could contribute to the pathogenesis of MS. Nevertheless, T cells may have a regulatory role in the central nervous system(CNS) (Walsh et al., 2014b) as they may benefit injured CNS tissues (Walsh et al., 2014a).

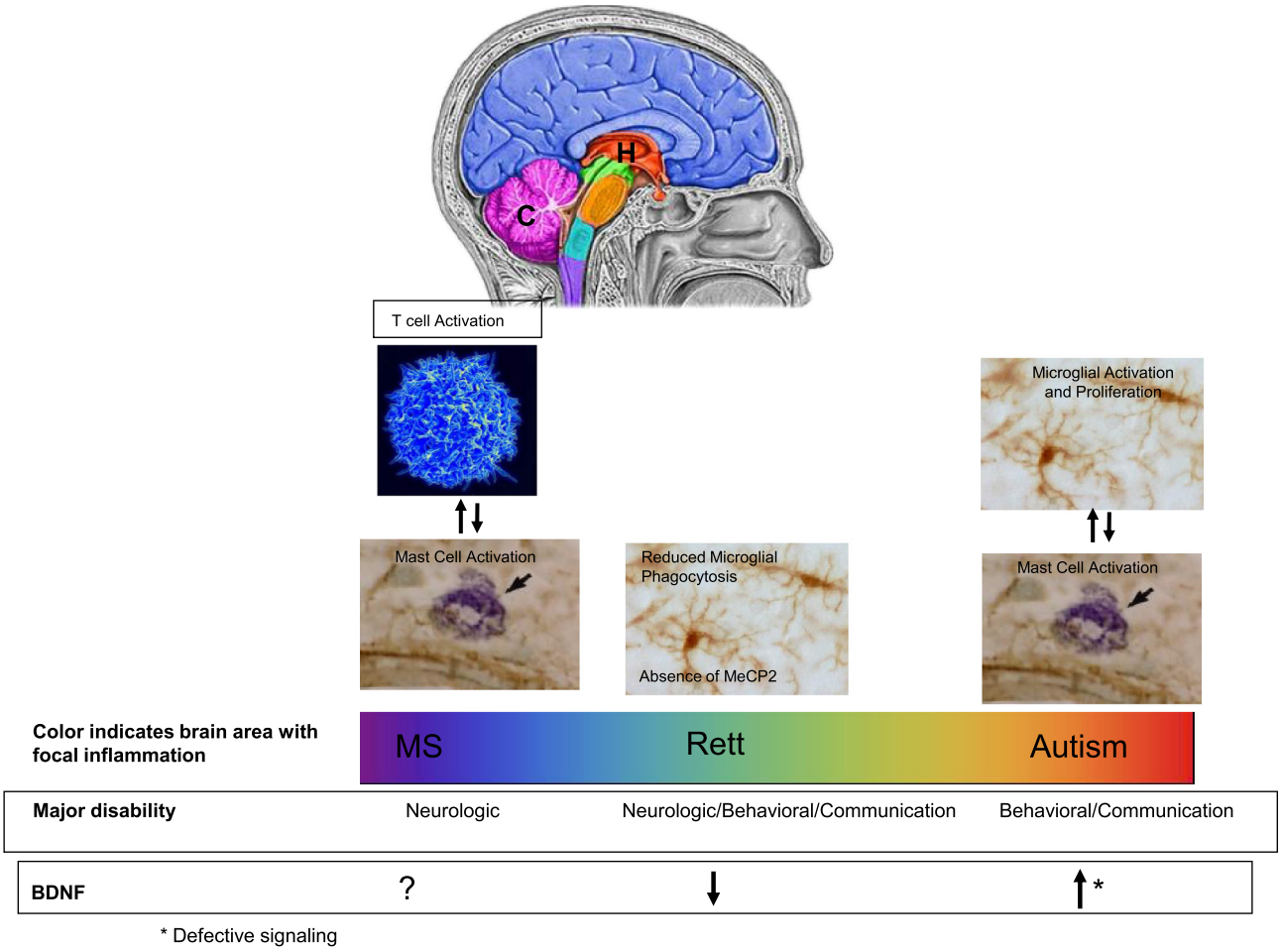

Fig. 1. Mast cells are located perivascularly at the BBB especially in the cerebellum (C) and hypothalamus (H) close to microglia and nerve endings. Absence of MeCP2 and reduced BDNF levels could lead to Rett syndrome. Instead, MC–microglia activation and focal brain inflammation could contribute to ASDs. MC–cell activation and T cell recruitment could contribute to the pathogenesis of MS. BBB = blood–brain barrier; TNF = tumor necrosis factor.

7. Possible novel treatment options

The US Center for Disease Control (CDC) found that 20% of children in the US suffer from a mental disorder with an approximate aggregate cost of $250 billion per year (Yaghmaie et al., 2013). To make matters worse, there are no effective therapies for the core symptoms of either Rett syndrome (Banerjee et al., 2012; Castro et al., 2013) or ASDs (Theoharides et al., 2008, 2009). The flavonoid 7,8-dihydroxyflavone was reported to mimic the activity of BDNF (Jang et al., 2010) and was beneficial in a mouse model of Rett syndrome (Tsai, 2012; Johnson et al., 2012). The related flavonoids 4′-methoxyflavone and 3′,4′-dimethoxyflavone were shown to be neuroprotective (Fatokun et al., 2013). These flavonoids are closely related structurally to luteolin (5,7,3′5′-tetrahydroxyflavone), which inhibited autism-like behavior in a maternal immune mouse model (Parker-Athill et al., 2009). Moreover, a luteolin containing formulation was recently reported to significantly improve sociability in children with ASDs (Theoharides et al., 2012b; Taliou et al., 2013).

Luteolin has potent antioxidant, anti-inflammatory (Middleton et al., 2000) and MC inhibitory activity (Kimata et al., 2000; Weng et al., 2014, in press). In addition, luteolin inhibits microglial IL-6 release (Jang et al., 2008), MC-dependent stimulation of activated T cells (Kempuraj et al., 2008; Theoharides et al., 2012b; Taliou et al., 2013) and mercury-induced MC activation (Asadi and Theoharides, 2012). Given the methylation defect present in Rett syndrome, the possible use of tetramethoxyluteolin should be particularly appealing, especially since we recently reported that it is a more potent MC inhibitor than luteolin (Weng et al., 2014, in press) and methylated flavonoids are also less metabolized (Walle, 2007). Even though these flavonoids are not specific, they are generally considered safe (Harwood et al., 2007). In fact, flavonoids, have been considered as therapeutic options for brain disorders (Jager and Saaby, 2011; Jones et al., 2012).

Recent papers reported the potential benefit of the anti-parasitic drug Suramin in the MIA mouse model of autism (Naviaux et al., 2013, 2014), and of the natural molecule sulforaphane in adult patients with ASDs, who had been selected because their symptoms improved with high temperature (Singh et al., 2014). It would be interesting to see if these approaches benefit the core symptoms of children with either Rett syndrome or ASDs.

8. Conclusion

The evidence reviewed above indicates that a methylation defect, microglia dysfunction, and focal brain inflammation, along with a lack of neurotrophic factors, may contribute to the pathogenesis of at least subcategories of Rett syndrome. Luteolin and methylated analogues, which also mimic BDNF, may serve as a novel treatment agents.

Disclosures

TCT is the inventor of US patents No. 7906153; No. 8268365 and PCT application No. 13/722,397 for the treatment of neuroinflammatory conditions, as well as US patent applications No. 12/534,571 and No. 13/009,282 for the diagnosis and treatment of ASDs. TCT is also the

inventor of the dietary supplement NeuroProtek®, with US trademark No. 3225924, which was used in two clinical trials discussed above.

Conflicts of interest

There is no conflict of interest.

Authors' contributions

TCT formulated the hypothesis, wrote most of the manuscript and approved it. MA and SP researched the database and prepared the manuscript. SP drew the figure. RD discussed and corrected the manuscript.

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References

Abraham, S.N., St John, A.L., 2010. Mast cell-orchestrated immunity to pathogens. Nat. Rev. Immunol. 10, 440–452.
Abuhatzira, L., et al., 2007. MeCP2 deficiency in the brain decreases BDNF levels by REST/CoREST-mediated repression and increases TRKB production. Epigenetics 2, 214–222.
Akin, C., et al., 2010. Mast cell activation syndrome: proposed diagnostic criteria. J. Allergy Clin. Immunol. 126, 1099–1104.
Aldinger, K.A., et al., 2011. SnapShot: genetics of autism. Neuron 72, 418.
Angelidou, A., et al., 2010. Neurotensin is increased in serum of young children with autistic disorder. J. Neuroinflammation 7, 48.
Angelidou, A., et al., 2011. Brief report: "allergic symptoms" in children with autism spectrum disorders. More than meets the eye? J. Autism Dev. Disord. 41, 1579–1585.
Angelidou, A., et al., 2012. Perinatal stress, brain inflammation and risk of autism—review and proposal. BMC Pediatr. 12, 89.
Antonelli, T., et al., 2004. Neurotensin enhances endogenous extracellular glutamate levels in primary cultures of rat cortical neurons: involvement of neurotensin receptor in NMDA induced excitotoxicity. Cereb. Cortex 14, 466–473.
Armstrong, D.D., 2005. Neuropathology of Rett syndrome. J. Child Neurol. 20, 747–753.
Asadi, S., Theoharides, T.C., 2012. Corticotropin-releasing hormone and extracellular mitochondria augment IgE-stimulated human mast-cell vascular endothelial growth factor release, which is inhibited by luteolin. J. Neuroinflammation 9, 85.
Ashwood, P., Van de Water, J., 2004. Is autism an autoimmune disease? Autoimmun. Rev. 3, 557–562.
Autry, A.E., Monteggia, L.M., 2012. Brain-derived neurotrophic factor and neuropsychiatric disorders. Pharmacol. Rev. 64, 238–258.
Banerjee, A., et al., 2012. Rett syndrome: genes, synapses, circuits, and therapeutics. Front. Psychiatry 3, 34.
Bauman, M.L., 2010. Medical comorbidities in autism: challenges to diagnosis and treatment. Neurotherapeutics 7, 320–327.
Beversdorf, D.Q., et al., 2005. Timing of prenatal stressors and autism. J. Autism Dev. Disord. 35, 471–478.
Blackman, M.P., et al., 2012. A critical and cell-autonomous role for MeCP2 in synaptic scaling up. J. Neurosci. 32, 13529–13536.
Braunschweig, D., Van de Water, J., 2012. Maternal autoantibodies in autism. Arch. Neurol. 69, 693–699.
Brimberg, L., et al., 2013 Nov. Brain-reactive IgG correlates with autoimmunity in mothers of a child with an autism spectrum disorder 18 (11), 1171–1177.
Cao, J., et al., 2005. Human mast cells express corticotropin-releasing hormone (CRH) receptors and CRH leads to selective secretion of vascular endothelial growth factor. J. Immunol. 174, 7665–7675.
Careaga, M., et al., 2013. Increased anti-phospholipid antibodies in autism spectrum disorders. Mediat. Inflamm. 2013, 935608.
Castro, J., et al., 2013. Mechanisms and therapeutic challenges in autism spectrum disorders: insights from Rett syndrome. Curr. Opin. Neurol. 26, 154–159.
Chahrour, M., et al., 2008. MeCP2, a key contributor to neurological disease, activates and represses transcription. Science 320, 1224–1229.
Correia, C.T., et al., 2010. Increased BDNF levels and NTRK2 gene association suggest a disruption of BDNF/TrkB signaling in autism. Genes Brain Behav. 9, 841–848.
Corriden, R., Insel, P.A., 2010. Basal release of ATP: an autocrine–paracrine mechanism for cell regulation. Sci. Signal. 3, re1.
Dahlgren, J., et al., 2006. Interleukin-6 in the maternal circulation reaches the rat fetus in mid-gestation. Pediatr. Res. 60, 147–151.
Degano, A.L., et al., 2009. MeCP2 deficiency disrupts axonal guidance, fasciculation, and targeting by altering Semaphorin 3 F function. Mol. Cell. Neurosci. 42, 243–254.
Delgado, I.J., et al., 2006. Expression profiling of clonal lymphocyte cell cultures from Rett syndrome patients. BMC Med. Genet. 7, 61.
Derecki, N.C., et al., 2010. Rett syndrome and other autism spectrum disorders—brain diseases of immune malfunction? Mol. Psychiatry 15, 355–363.
Derecki, N.C., et al., 2012. Wild-type microglia arrest pathology in a mouse model of Rett syndrome. Nature 484, 105–109.
Derecki, N.C., et al., 2013. The role of microglia in brain maintenance: implications for Rett syndrome. Trends Immunol. 34, 144–150.
Donelan, J., et al., 2006. Corticotropin-releasing hormone induces skin vascular permeability through a neurotensin-dependent process. Proc. Natl. Acad. Sci. U. S. A. 103, 7759–7764.
Esposito, P., et al., 2002. Corticotropin-releasing hormone (CRH) and brain mast cells regulate blood–brain-barrier permeability induced by acute stress. J. Pharmacol. Exp. Ther. 303, 1061–1066.
Fatokun, A.A., et al., 2013. Identification through high-throughput screening of 4′-methoxyflavone and 3′,4′-dimethoxyflavone as novel neuroprotective inhibitors of parthanatos. Br. J. Pharmacol. 169, 1263–1278.
Feng, J., Fan, G., 2009. The role of DNA methylation in the central nervous system and neuropsychiatric disorders. Int. Rev. Neurobiol. 89, 67–84.
Fombonne, E., 2009. Epidemiology of pervasive developmental disorders. Pediatr. Res. 65, 591–598.
Galli, S.J., et al., 2008. The development of allergic inflammation. Nature 454, 445–454.
Gesundheit, B., et al., 2013. Immunological and autoimmune considerations of autism spectrum disorders. J. Autoimmun. 44, 1–7.
Ghanizadeh, A., 2010. Targeting neurotensin as a potential novel approach for the treatment of autism. J. Neuroinflammation 7, 58.
Gillott, A., Standen, P.J., 2007. Levels of anxiety and sources of stress in adults with autism. J. Intellect. Disabil. 11, 359–370.
Guy, J., et al., 2007. Reversal of neurological defects in a mouse model of Rett syndrome. Science 315, 1143–1147.
Hallmayer, J., et al., 2011. Genetic heritability and shared environmental factors among twin pairs with autism. Arch. Gen. Psychiatry 68, 1095–1102.
Harwood, M., et al., 2007. A critical review of the data related to the safety of quercetin and lack of evidence of in vivo toxicity, including lack of genotoxic/carcinogenic properties. Food Chem. Toxicol. 45, 2179–2205.
Herbert, M.R., 2010. Contributions of the environment and environmentally vulnerable physiology to autism spectrum disorders. Curr. Opin. Neurol. 23, 103–110.
Hsiao, E.Y., et al., 2012. Modeling an autism risk factor in mice leads to permanent immune dysregulation. Proc. Natl. Acad. Sci. U. S. A. 109, 12776–12781.
Jager, A.K., Saaby, L., 2011. Flavonoids and the CNS. Molecules 16, 1471–1485.
Jang, S., et al., 2008. Luteolin reduces IL-6 production in microglia by inhibiting JNK phosphorylation and activation of AP-1. Proc. Natl. Acad. Sci. U. S. A. 105, 7534–7539.
Jang, S.W., et al., 2010. A selective TrkB agonist with potent neurotrophic activities by 7,8-dihydroxyflavone. Proc. Natl. Acad. Sci. U. S. A. 107, 2687–2692.
Johnson, R.A., et al., 2012. 7,8-Dihydroxyflavone exhibits therapeutic efficacy in a mouse model of Rett syndrome. J. Appl. Physiol. 112, 704–710.
Jones, Q.R., et al., 2012. Target-based selection of flavonoids for neurodegenerative disorders. Trends Pharmacol. Sci. 33, 602–610.
Jyonouchi, H., 2010. Autism spectrum disorders and allergy: observation from a pediatric allergy/immunology clinic. Expert. Rev. Clin. Immunol. 6, 397–411.
Kandere-Grzybowska, K., et al., 2003. IL-1 induces vesicular secretion of IL-6 without degranulation from human mast cells. J. Immunol. 171, 4830–4836.
Karagkouni, A., et al., 2013. Effect of stress on brain inflammation and multiple sclerosis. Autoimmun. Rev. 12, 947–953.
Katz, D.M., 2014. Brain-derived neurotrophic factor and Rett syndrome. Handb. Exp. Pharmacol. 220, 481–495.
Kempuraj, D., et al., 2008. Luteolin inhibits myelin basic protein-induced human mast cell activation and mast cell dependent stimulation of Jurkat T cells. Br. J. Pharmacol. 155, 1076–1084.
Kimata, M., et al., 2000. Effects of luteolin, quercetin and baicalein on immunoglobulin E-mediated mediator release from human cultured mast cells. Clin. Exp. Allergy 30, 501–508.
Klushnik, T.P., et al., 2001. Brain-directed autoantibodies levels in the serum of Rett syndrome patients. Brain Dev. 23 (Suppl. 1), S113–S117.
Kogan, M.D., et al., 2009. Prevalence of parent-reported diagnosis of autism spectrum disorder among children in the US, 2007. Pediatrics 5, 1395–1403.
Ku, C.S., et al., 2013. A new paradigm emerges from the study of de novo mutations in the context of neurodevelopmental disease. Mol. Psychiatry 18, 141–153.
Lauritzen, K.H., et al., 2010. Mitochondrial DNA toxicity in forebrain neurons causes apoptosis, neurodegeneration, and impaired behavior. Mol. Cell. Biol. 30, 1357–1367.
Li, W., Pozzo-Miller, L., 2014. BDNF deregulation in Rett syndrome. Neuropharmacology 76 Pt C, 737–746.
Li, X., et al., 2009. Elevated immune response in the brain of autistic patients. J. Neuroimmunol. 207, 111–116.
Lilja, T., et al., 2013. Novel alterations in the epigenetic signature of MeCP2-targeted promoters in lymphocytes of Rett syndrome patients. Epigenetics 8, 246–251.
Maezawa, I., et al., 2009. Rett syndrome astrocytes are abnormal and spread MeCP2 deficiency through gap junctions. J. Neurosci. 29, 5051–5061.
Maezawa, I., et al., 2011. Does microglial dysfunction play a role in autism and Rett syndrome? Neuron Glia Biol. 7, 85–97.
Matijevic, T., et al., 2009. Rett syndrome: from the gene to the disease. Eur. Neurol. 61, 3–10.
Matsuishi, T., et al., 2011. Rett syndrome: the state of clinical and basic research, and future perspectives. Brain Dev. 33, 627–631.
Mazur-Kolecka, B., et al., 2014. Autoantibodies against neuronal progenitors in sera from children with autism. Brain Dev. 36, 322–329.
Middleton, E.J., et al., 2000. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease and cancer. Pharmacol. Rev. 52, 673–751.

Morgan, J.T., et al., 2012. Abnormal microglial–neuronal spatial organization in the dorsolateral prefrontal cortex in autism. Brain Res. 1456, 72–81.
Mostafa, G.A., Al-Ayadhi, L.Y., 2013. The possible relationship between allergic manifestations and elevated serum levels of brain specific auto-antibodies in autistic children. J. Neuroimmunol. 261, 77–81.
Moura, D.S., et al., 2014. Neuropsychological features of adult mastocytosis. Immunol. Allergy Clin. N. Am. 34, 407–422.
Mustain, W.C., et al., 2011. The role of neurotensin in physiologic and pathologic processes. Curr. Opin. Endocrinol. Diabetes Obes. 18, 75–82.
Na, E.S., et al., 2013. The impact of MeCP2 loss- or gain-of-function on synaptic plasticity. Neuropsychopharmacology 38, 212–219.
Nakae, S., et al., 2007. Mast cell-derived TNF can promote Th17 cell-dependent neutrophil recruitment in ovalbumin-challenged OTII mice. Blood 109, 3640–3648.
Naviaux, R.K., et al., 2013. Antipurinergic therapy corrects the autism-like features in the poly(IC) mouse model. PLoS One 8, e57380.
Naviaux, J.C., et al., 2014. Reversal of autism-like behaviors and metabolism in adult mice with single-dose antipurinergic therapy. Transl. Psychiatry 4, e400.
Neul, J.L., et al., 2010. Rett syndrome: revised diagnostic criteria and nomenclature. Ann. Neurol. 68, 944–950.
Nguyen, M.V., et al., 2012. MeCP2 is critical for maintaining mature neuronal networks and global brain anatomy during late stages of postnatal brain development and in the mature adult brain. J. Neurosci. 32, 10021–10034.
Nishimura, K., et al., 2007. Genetic analyses of the brain-derived neurotrophic factor (BDNF) gene in autism. Biochem. Biophys. Res. Commun. 356, 200–206.
Parker-Athill, E., et al., 2009. Flavonoids, a prenatal prophylaxis via targeting JAK2/STAT3 signaling to oppose IL-6/MIA associated autism. J. Neuroimmunol. 217, 20–27.
Petra, A.I., et al., 2014. Spectrum of mast cell activation disorders. Expert. Rev. Clin. Immunol. 10, 729–739.
Piras, I.S., et al., 2014. Anti-brain antibodies are associated with more severe cognitive and behavioral profiles in Italian children with autism spectrum disorder. Brain Behav. Immun. 38, 91–99.
Qiu, Z., et al., 2012. The Rett syndrome protein MeCP2 regulates synaptic scaling. J. Neurosci. 32, 989–994.
Rangasamy, S., et al., 2013. Epigenetics, autism spectrum, and neurodevelopmental disorders. Neurotherapeutics 10, 742–756.
Ricci, S., et al., 2013. Altered cytokine and BDNF levels in autism spectrum disorder. Neurotox. Res. 24, 491–501.
Rodriguez, J.I., Kern, J.K., 2011. Evidence of microglial activation in autism and its possible role in brain underconnectivity. Neuron Glia Biol. 7, 205–213.
Ronald, A., et al., 2010. Prenatal maternal stress associated with ADHD and autistic traits in early childhood. Front. Psychol. 1, 223.
Rossi, C.C., et al., 2011. Detection of plasma autoantibodies to brain tissue in young children with and without autism spectrum disorders. Brain Behav. Immun. 25, 1123–1135.
Rossignol, D.A., Frye, R.E., 2012. Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis. Mol. Psychiatry 17, 290–314.
Rossignol, D.A., Frye, R.E., 2014. Evidence linking oxidative stress, mitochondrial dysfunction, and inflammation in the brain of individuals with autism. Front. Physiol. 5.
Rottem, M., Mekori, Y.A., 2005. Mast cells and autoimmunity. Autoimmun. Rev. 4, 21–27.
Sadakata, T., et al., 2012. Reduced axonal localization of a Caps2 splice variant impairs axonal release of BDNF and causes autistic-like behavior in mice. Proc. Natl. Acad. Sci. U. S. A. 109, 21104–21109.
Samaco, R.C., et al., 2009. Loss of MeCP2 in aminergic neurons causes cell-autonomous defects in neurotransmitter synthesis and specific behavioral abnormalities. Proc. Natl. Acad. Sci. U. S. A. 106, 21966–21971.
Schaevitz, L.R., et al., 2010. Cognitive and social functions and growth factors in a mouse model of Rett syndrome. Physiol. Behav. 100, 255–263.
Singh, K., et al., 2014 Oct 28. Sulforaphane treatment of autism spectrum disorder (ASD). Proc. Natl. Acad. Sci. U. S. A. 111 (43), 15550–15555.
Skaper, S.D., et al., 2012. Microglia and mast cells: two tracks on the road to neuroinflammation. FASEB J. 26, 3103–3117.
Smith, S.E., et al., 2007. Maternal immune activation alters fetal brain development through interleukin-6. J. Neurosci. 27, 10695–10702.
Smith, J.H., et al., 2011. Neurologic symptoms and diagnosis in adults with mast cell disease. Clin. Neurol. Neurosurg. 113, 570–574.
Suurmond, J., et al., 2011. Mast cells are the main interleukin 17-positive cells in anticitrullinated protein antibody-positive and -negative rheumatoid arthritis and osteoarthritis synovium. Arthritis Res. Ther. 13, R150.
Taliou, A., et al., 2013. An open-label pilot study of a formulation containing the anti-inflammatory flavonoid luteolin and its effects on behavior in children with autism spectrum disorders. Clin. Ther. 35, 592–602.
Theoharides, T.C., 1990. Mast cells: the immune gate to the brain. Life Sci. 46, 607–617.
Theoharides, T.C., 2009. Autism spectrum disorders and mastocytosis. Int. J. Immunopathol. Pharmacol. 22, 859–865.
Theoharides, T.C., 2013a. Extracellular mitochondrial components secreted from activated live mast cells act as innate pathogens and contribute to autism pathogenesis. Int. Trends Immun. 1, 5–10.
Theoharides, T.C., 2013b. Is a subtype of autism "allergy of the brain"? Clin. Ther. 35, 584–591.
Theoharides, T.C., Doyle, R., 2008. Autism, gut–blood–brain barrier and mast cells. J. Clin. Psychopharmacol. 28, 479–483.
Theoharides, T.C., Konstantinidou, A., 2007. Corticotropin-releasing hormone and the blood–brain-barrier. Front. Biosci. 12, 1615–1628.
Theoharides, T.C., et al., 2002. Serum interleukin-6 reflects disease severity and osteoporosis in mastocytosis patients. Int. Arch. Allergy Immunol. 128, 344–350.
Theoharides, T.C., et al., 2007. Differential release of mast cell mediators and the pathogenesis of inflammation. Immunol. Rev. 217, 65–78.
Theoharides, T.C., et al., 2008. Novel therapeutic targets for autism. Trends Pharmacol. Sci. 29, 375–382.
Theoharides, T.C., et al., 2009. Autism: an emerging 'neuroimmune disorder' in search of therapy. Expert. Opin. Pharmacother. 10, 2127–2143.
Theoharides, T.C., et al., 2010a. Mast cells and inflammation. Biochim. Biophys. Acta 1822, 21–33.
Theoharides, T.C., et al., 2010b. IL-33 augments substance P-induced VEGF secretion from human mast cells and is increased in psoriatic skin. Proc. Natl. Acad. Sci. U. S. A. 107, 4448–4453.
Theoharides, T.C., et al., 2011. Decreased mitochondrial function and increased brain inflammation in bipolar disorder and other neuropsychiatric diseases. J. Clin. Psychopharmacol. 31, 685–687.
Theoharides, T.C., et al., 2012a. Mast cell activation and autism. Biochim. Biophys. Acta 1822, 34–41.
Theoharides, T.C., et al., 2012b. A case series of a luteolin formulation (NeuroProtek(R)) in children with autism spectrum disorders. Int. J. Immunopathol. Pharmacol. 25, 317–323.
Theoharides, T.C., et al., 2013. The "missing link" in autoimmunity and autism: extracellular mitochondrial components secreted from activated live mast cells. Autoimmun. Rev. 12, 1136–1142.
Theoharides, T.C., et al., 2014. High serum corticotropin-releasing hormone (CRH) and bone marrow mast cell CRH receptor expression in a mastocytosis patient. J. Allergy Clin. Immunol. (in press).
Tsai, S.J., 2012. Peripheral administration of brain-derived neurotrophic factor to Rett syndrome animal model: a possible approach for the treatment of Rett syndrome. Med. Sci. Monit. 18, HY33–HY36.
Tsilioni, I., et al., 2014. Elevated serum neurotensin and CRH levels in children with autistic spectrum disorders and tail-chasing bull terriers with a phenotype similar to autism. Transl. Psychiatry 4, e466.
Urdinguio, R.G., et al., 2008. Mecp2-null mice provide new neuronal targets for Rett syndrome. PLoS One 3, e3669.
varez-Saavedra, M., et al., 2007. Cell-specific expression of wild-type MeCP2 in mouse models of Rett syndrome yields insight about pathogenesis. Hum. Mol. Genet. 16, 2315–2325.
Vargas, D.L., et al., 2005. Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann. Neurol. 57, 67–81.
Voehringer, D., 2013. Protective and pathological roles of mast cells and basophils. Nat. Rev. Immunol. 13, 362–375.
Volkmar, F.R., et al., 2009. Autism and autism spectrum disorders: diagnostic issues for the coming decade. J. Child Psychol. Psychiatry 50, 108–115.
Walker, M.E., et al., 2012. New insights into the role of mast cells in autoimmunity: evidence for a common mechanism of action? Biochim. Biophys. Acta 1822, 57–65.
Walle, T., 2007. Methylation of dietary flavones greatly improves their hepatic metabolic stability and intestinal absorption. Mol. Pharm. 4, 826–832.
Walsh, J.T., et al., 2014a. T cells in the central nervous system: messengers of destruction or purveyors of protection? Immunology 141, 340–344.
Walsh, J.T., et al., 2014b. Regulatory T cells in central nervous system injury: a double-edged sword. J. Immunol. 193, 5013–5022.
Webb, R., et al., 2009. Variants within MECP2, a key transcription regulator, are associated with increased susceptibility to lupus and differential gene expression in patients with systemic lupus erythematosus. Arthritis Rheum. 60, 1076–1084.
Weiss, L.A., et al., 2009. A genome-wide linkage and association scan reveals novel loci for autism. Nature 461, 802–808.
Weng, Z., et al., 2014. Luteolin inhibits human keratinocyte activation and decreases NF-kappaB induction that is increased in psoriatic skin. PLoS One 9, e90739.
Weng, Z., et al., 2014. The novel flavone tetramethoxyluteolin is a potent inhibitor of human mast cells. J. Allergy Clin. Immunol. (in press).
Williams, S.C., 2012. Genetics: searching for answers. Nature 491, S4–S6.
Wills, S., et al., 2009. Detection of autoantibodies to neural cells of the cerebellum in the plasma of subjects with autism spectrum disorders. Brain Behav. Immun. 23, 64–74.
Yaghmaie, P., et al., 2013. Mental health comorbidity in patients with atopic dermatitis. J. Allergy Clin. Immunol. 131, 428–433.
Zachariah, R.M., et al., 2012. Novel MeCP2 isoform-specific antibody reveals the endogenous MeCP2E1 expression in murine brain, primary neurons and astrocytes. PLoS One 7, e49763.
Zhang, B., et al., 2010. Mitochondrial DNA and anti-mitochondrial antibodies in serum of autistic children. J. Neuroinflammation 7, 80.
Zhang, B., et al., 2011. Human mast cell degranulation and preformed TNF secretion require mitochondrial translocation to exocytosis sites: relevance to atopic dermatitis. J. Allergy Clin. Immunol. 127, 1522–1531.
Zhang, B., et al., 2012a. Stimulated human mast cells secrete mitochondrial components that have autocrine and paracrine inflammatory actions. PLoS One 7, e49767.
Zhang, B., et al., 2012b. Mitochondria distinguish granule-stored from de novo synthesized tumor necrosis factor secretion in human mast cells. Int. Arch. Allergy Immunol. 159, 23–32.
Zhang, S., et al., 2012c. Mast cell tryptase induces microglia activation via protease-activated receptor 2 signaling. Cell. Physiol. Biochem. 29, 931–940.
Zimmerman, A.W., et al., 2005. Cerebrospinal fluid and serum markers of inflammation in autism. Pediatr. Neurol. 33, 195–201.