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Review

Mast cell activation and autism ☆

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ABSTRACT

Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by varying degrees of dysfunctional communication and social interactions, repetitive and stereotypic behaviors, as well as learning and sensory deficits. Despite the impressive rise in the prevalence of autism during the last two decades, there are few if any clues for its pathogenesis, early detection or treatment. Increasing evidence indicates high brain expression of pro-inflammatory cytokines and the presence of circulating antibodies against brain proteins. A number of papers, mostly based on parental reporting on their children's health problems, suggest that ASD children may present with "allergic-like" problems in the absence of elevated serum IgE and chronic urticaria. These findings suggest non-allergic mast cell activation, probably in response to environmental and stress triggers that could contribute to inflammation. *In utero* inflammation can lead to preterm labor and has itself been strongly associated with adverse neurodevelopmental outcomes. Premature babies have about four times higher risk of developing ASD and are also more vulnerable to infections, while delayed development of their gut–blood–brain barriers makes exposure to potential neurotoxins likely. Perinatal mast cell activation by infectious, stress-related, environmental or allergic triggers can lead to release of pro-inflammatory and neurotoxic molecules, thus contributing to brain inflammation and ASD pathogenesis, at least in a subgroup of ASD patients. This article is part of a Special Issue entitled: Mast cells in inflammation.

1. Prevalence and characteristics of autism spectrum disorders

Autism spectrum disorders (ASD) are pervasive developmental disorders that include autistic disorder, Asperger's disorder and pervasive developmental disorder-not otherwise specified (PDD-NOS) [1]. They are characterized by stereotypic behaviors, variable deficits in language and social skills and a wide range of other behavioral problems. ASD manifest during childhood and at least 30% present with sudden clinical regression of development around 3 years of age [2,3]. Over the last 20 years, there has been an impressive rise in ASD with current prevalence estimates being about 1/100 children [4,5].

In the majority of cases, the cause of ASD is unknown [6], although some possible autism susceptibility genes have been identified [7] and

Abbreviations: ASD, autism spectrum disorders; BDNF, brain-derived neurotrophic factor; BBB, blood–brain barrier; CGRP, calcitonin-gene related peptide; CRH, corticotropin-releasing hormone; CSF, cerebrospinal fluid; FcεRI, high affinity IgE receptor; GI, gastrointestinal; IFN, interferon; LPS, lipopolysaccharide; M-CHAT, Modified Checklist for Autism in Toddlers; MCP-1, chemoattractant protein-1; MIF, macrophage inhibitory factor; NGF, nerve growth factor; NK cells, natural killer cells; NT, neurotensin; PCB, polychlorinated biphenyl; PDD-NOS, pervasive developmental disorder-not otherwise specified; SP, substance P; TGF-β1, transforming growth factor-beta1; TLR, toll-like receptor; TNF, tumor necrosis factor; UP, urticaria pigmentosa; VEGF, vascular endothelial growth factor; VIP, vasoactive intestinal peptide

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gene interactions with environmental factors have been suspected [8]. Recent reviews have focused mostly on genomic screens that suggest there are multiple gene interactions in autism; however, no gene abnormality alone can explain the apparent increase in ASD prevalence. Increasing evidence suggests that there are different ASD endophenotypes, even within the ASD spectrum [9].

2. Immune dysregulation

The concept of some immune abnormality in ASD has been debated since the 1990s, when a study reported reduced numbers of CD4+ CD45RA+ lymphocytes (subpopulation responsible for induction of suppressor T cells or regulatory T cells) in autistic subjects ($n=36$) compared to healthy age-matched controls ($n=35$), indicating a functional deficit in the innate immune response [10]. Measurement of natural killer (NK) cell activity in blood samples of autistic children ($n=1027$) revealed that 45% of the subjects exhibited low NK cell activity compared to the controls ($n=113$). The correlation of this finding with low intracellular glutathione, IL-2 and IL-15 levels may indicate the underlying cause for NK cell dysfunction in a subset of autistic children [11]. Gene expression of perforin, granzyme B and interferon-γ (IFNγ) in peripheral blood NK cells of ASD patients ($n=52$) was decreased compared to the control group ($n=27$) under similar stimulation conditions, indicating depressed cytotoxicity [12].

In contrast to possibly depressed cell-mediated immunity, the role of pro-inflammatory molecules appears to be increased in autism. Peripheral blood mononuclear cells from ASD patients ($n=71$) secreted more tumor necrosis factor (TNF) in response to lipopolysaccharide (LPS) as compared to controls ($n=40$) [13]. Plasma levels of IL-12 and IFNγ were increased in autistic individuals [14] and IFNγ plasma levels were later found to be positively correlated with the generation of nitric oxide in autism [15]. IL-6 expression was elevated in the brains of deceased ASD patients [16]; it was detected at low levels in the cerebrospinal fluid (CSF) in subjects with autism ($n=35$) as compared to control subjects with other neurologic disorders, but only TNF receptor II was significantly elevated in the serum [17]. TNF levels were elevated in CSF of patients with ASD but were not elevated in the serum [18]. Elsewhere, there was significant increase in the serum concentration of IFNγ, and a trend towards increased production of IL-6 and TNF in *whole blood* of autistic children [19]. Macrophage inhibitory factor (MIF), a molecule shown to enhance immunity through different mechanisms, was higher in the plasma of probands with ASD than their unaffected siblings and correlated with severity of ASD symptoms [20].

We recently showed that levels of the peptide neurotensin (NT), which is present in both the brain and gut, were elevated in the serum of young autistic patients [21]. NT can stimulate lymphocyte proliferation [22], activate T cells [23], enhance IL-1 production from macrophages [24], and trigger mast cell activation [25]. Unlike NT, substance P (SP) was not elevated as also previously reported [26,27]; β-endorphin was also not elevated, even though it had been reported to be increased in the CSF of a small group of children ($n=9$) with infantile autism [28]. We also recently showed that NT can stimulate mast cells to release mitochondrial DNA extracellularly and that such DNA was significantly elevated in the serum of autistic children [29].

With respect to other neuropeptides, archived neonatal blood was analyzed with immunoaffinity chromatography, and serum levels of vasoactive intestinal peptide (VIP) and calcitonin-gene related peptide (CGRP) were reported to be higher in children with ASD ($n=69$) and those with mental retardation without ASD ($n=60$); in contrast, levels of substance P (SP) and nerve growth factor (NGF) were similar to those of controls [26]. Nevertheless, the same authors using Luminex immunoaffinity arrays later showed no difference in any of these peptides between autistic subjects and controls [27].

There may be a persistently inappropriate immune response of autistic subjects to antigenic stimuli, also observed in their unaffected siblings, suggesting a particular genetic background influenced by environmental triggers [30]. A number of papers have reviewed family or personal history of immune disorders in many children with ASD [31,32], prompting the suggestion that ASD may have a "neuroimmune" component [31–33].

3. "Allergic symptoms" in children with ASD

Many ASD children suffer from "allergic-like" symptoms [34], although their exact prevalence remains unknown compared to the general population. Many of the "allergic-like" symptoms reported by ASD children could be consistent with chronic idiopathic or chronic autoimmune urticaria [35]. A case-control study, nested within a cohort of infants born in California between 1995 and 1999, examined the association of "immune-related conditions" with ASD using health records and reported that prevalence of maternal psoriasis, asthma, hay fever and atopic dermatitis during the second trimester of pregnancy correlated with >2-fold elevated risk of ASD in their children [36]. Increased allergic problems (i.e., atopic dermatitis, asthma and rhinitis, as well as high serum IgE, number of eosinophils and positive skin tests) were present in 70% of Asperger patients ($n=15$) compared to 7% of age-matched healthy controls ($n=15$) [37]. In a National Survey of Children's Health, parents of autistic children ($n=483$) reported more symptoms of allergies (also anxiety/depression), with food allergies being the most prevalent complaint, than those of healthy control children ($n=84{,}789$) [38]. Nevertheless, there are limitations relevant to the subjective nature of parents' perception about allergies, since these were not confirmed by a clinician. A link between allergies and autism is also suggested by a recent preliminary study of children with ASD ($n=245$), which indicated that the strongest association of autism was with a history of allergies [39].

There is also evidence of non-IgE-mediated "allergic symptoms." In a hospital-based case-control study, based on questionnaires completed by the parents and scored blindly by an allergist, 30% of autistic children ($n=30$) had a family history of allergic features compared to 2.5% of age-matched "neurologic controls" ($n=39$) ($p<0.005$); however, there was no difference in serum IgE or skin prick tests to 12 common antigens between autistic subjects and controls [40], suggesting non-allergic mast cell activation. There was also no difference in IgG, IgA or IgM levels [40]. One study reported elevated IgG4 levels in children with autistic disorder ($n=114$) compared to normally developing children ($n=96$) [41]. However, the significance of this finding is not apparent because high levels of IgG4 antibodies to foods during infancy are associated with tolerance later in life [42], while many ASD children are in fact intolerant to foods. Moreover, testing for IgG4 against foods is not recommended for diagnosis of food hypersensitivity. Another study investigated the prevalence of atopic and non-IgE-mediated disorders in ASD children (a) with frequent infections and behavioral problems ($n=26$) and (b) without frequent infections ($n=107$), compared to non-ASD controls ($n=43$). Even though the prevalence of atopic disorders in ASD subjects was similar to that of the controls, non-IgE-mediated food allergy was observed at a significantly higher rate in both ASD subgroups compared to controls [43].

One representative case is that of a 12-year-old Caucasian male with a history of gastrointestinal (GI) complaints, diarrhea and frequent rashes at various parts of the body since birth (Fig. 1), often precipitated by certain foods. Exhaustive clinical testing including immune function, autoimmune indices, serum IgE, tryptase, number of eosinophils, tissue transglutaminase and gliadin antibodies, viral antibody titers were negative. This child was developing normally until 2.5 years of age, at which point he exhibited developmental delay and was diagnosed with regressive autism. At about 8 years old,

he developed hives after eating steak and was suspected of being sensitive to meat carbohydrate components (see Addendum In Press).

A preliminary report indicated that the prevalence of ASD is 10-fold higher (1/10 children) in mastocytosis patients than in the general population (1/100 children) [44]. Mastocytosis is a spectrum of disorders with a prevalence of about 1/4,000 children, which involves proliferation and activation of mast cells in the skin (urticaria pigmentosa, UP) and other organs [45], leading to skin reactions, food allergies often in the absence of positive skin testing, and food intolerance, but also behavioral problems [46,47]. One possible case is that of a 4-year-old Caucasian male who was diagnosed with UP at the age of 1 year. The pediatrician at that time suggested that the skin spots would go away with time; however, they increased after routine vaccination at age 3 years old (Fig. 2A). Soon thereafter, the child regressed and was diagnosed with PDD-NOS. The child also often experienced skin rashes (Fig. 2B), associated with worsening of his behavioral status, even though he tested negative to various antigens on skin prick and RAST tests. It should be noted, however, that this is an atypical case given that the diagnosis was made after 3 years of age, which does not comply with DSM-IV criteria. In addition, one would need to be sure that other potential contributing metabolic disorders, including a mitochondrial disorder, had been ruled out.

4. Non-immune mast cell triggers

Mast cells are critical for allergic reactions [48] but are also important in both innate and acquired immunity [49], as well as in inflammation [50]. Functional mast cell-neuron interactions occur in the GI tract [51] and the brain [52]. Mast cells are involved in GI pathology, inflammation and increased intestinal permeability [53], which may also explain frequent GI-related symptoms in ASD patients [54], especially abnormal intestinal permeability [55].

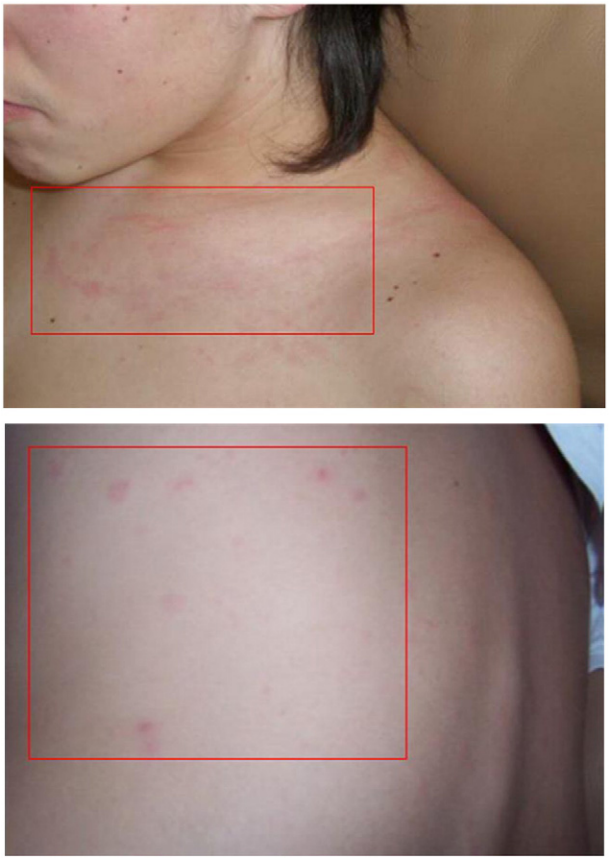

Fig. 1. Photographs of skin areas from a non-atopic, Caucasian male with ASD showing non-specific rashes (boxes) associated with eating steak.

Many substances originating in the environment, the intestine or the brain can trigger mast cell activation [48] (Fig. 3), leading to release of numerous bioactive mediators. These include histamine, prostaglandins, proteases, and vascular endothelial growth factor (VEGF), as well as cytokines, such as IL-6, IL-8, IL-9, IL-13, and TNF. Bacterial LPS activates toll-like receptor-4 (TLR-4) on mast cells and induces selective release of TNF [56]. High levels of TNF were reported in the CSF [18], and high IL-6 gene expression was noted in the brain [16] of autistic patients. CSF and microglia of ASD patients had high levels of macrophage chemoattractant protein-1 (MCP-1) [57], which is also a potent chemoattractant for mast cells [58]. In contrast, ASD plasma levels of transforming growth factor-beta1 (TGF-β1) were low [59], which is important in view of the fact that TGF-β1 inhibits mast cell function and high affinity IgE receptor (FcεRI) expression [60]. TGF-β is also an important mediator released by regulatory T cells [59] and the low plasma TGF-β levels in autistic patients indicate reduced regulatory T cell function in autism.

Mast cells also express viral TLR-3, activation of which by viral double-stranded RNA induces release of IL-6 and TNF without degranulation [61]. The ability of viruses to trigger mast cell activation is especially relevant, since a number of rotaviruses have been isolated from 75% of asymptomatic neonates [62] and could activate mast cells. Environmental toxins linked to developmental neurotoxicity [63], such as polychlorinated biphenyl (PCB) and mercury, have been associated with ASD [64,65], but they also activate mast cells [66,67]. Mast cells can be stimulated by non-allergic triggers to release some mediators selectively, without degranulation [68]. For instance, the peptide corticotropin-releasing hormone (CRH) stimulates selective release of VEGF [69]. CRH is typically secreted from the hypothalamus, but it can also be secreted from nerve endings outside the brain, where it exerts pro-inflammatory effects [70–72]. In fact, CRH acts synergistically with NT to increase vascular permeability [73]. It was recently reported that NT levels are increased in the serum of young children with autistic disorder as compared to normal, age-matched controls [21]. Most recently, we reported that NT induces extracellular release of mitochondrial DNA, which is a potent immunogen and was detected in the serum of young autistic patients [29].

5. The effect of perinatal stress

The effect of CRH may be relevant to ASD, because ASD patients have been reported to have high anxiety levels and cannot handle stress appropriately [74]. Prenatal or perinatal stress may also contribute to the development of ASD through excessive release of CRH. Specifically, CRH is increased in the serum of mothers who delivered preterm babies and correlates with their level of anxiety near the end of gestation [75]. Maternal serum CRH can cross the placenta, and high amounts of CRH could be produced by the placenta itself [76] in response to external or intrauterine stress. Recent reports suggest a potential association between preterm children and autism. In particular, one retrospective study investigated rates of autism in preterm children born in Atlanta, GA (1981–93), who survived to 3 years of age, through the Metropolitan Atlanta Developmental Disabilities Surveillance Program, and showed that preterm birth at <33 weeks gestation was associated with a two-fold higher risk of autism in all infants [77]. Another prospective follow-up assessment on 91 ex-preterm infants (<1500 g at birth) at a mean age of 22 months found 26% of these children to have a positive Modified Checklist for Autism in the Toddlers (M-CHAT) test [78]. A more recent study found that 21% of infants (212/988) born before 28 weeks of gestation screened positive using M-CHAT as compared to 5.7% of healthy children 16–30 months old [79]. Maternal separation stress and CRH are associated with a dysfunctional mucosal barrier in rodents [80]. A short period of restraint [81] or

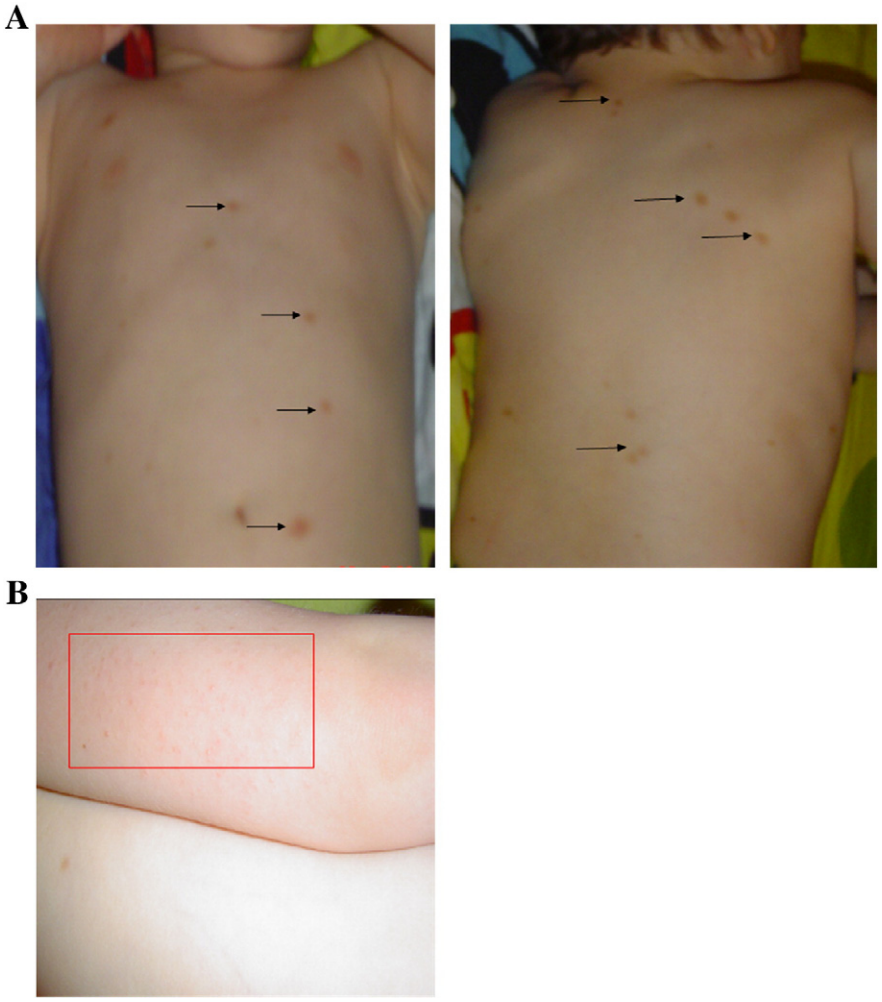

Fig. 2. (A) Photographs of skin areas from a non-atopic, Caucasian male with ASD and UP lesions (arrows), and (B) non-specific rash (box), associated with ASD symptoms.

maternal deprivation stress [82] also increased the severity of experimental autoimmune encephalomyelitis.

The blood–brain barrier (BBB) appears to be compromised in ASD patients as indicated by the presence of serum auto-antibodies against brain proteins (neuron-specific antigens, especially from the cerebellum, cross-reacting with encephalitogenic proteins from milk, Chlamydia pneumoniae and Streptococcus group A) in mothers and children with autism [32,83–86]. In fact, CRH can disrupt the BBB through mast cell activation [87] and also increases intestinal permeability of human colonic biopsies [88].

It is intriguing that mast cell-derived IL-9 induces intestinal permeability and predisposes to oral antigen hypersensitivity in children [89], while it also exacerbates newborn brain toxic lesions [90]. Perinatal mast cell activation, in response to allergic or non-immune triggers, could disrupt the gut–blood–brain barriers [70] through cytokines [87,91] and permit neurotoxic molecules to enter the brain and result in brain inflammation, thus contributing to ASD pathogenesis (Fig. 4). BBB disruption has also been documented in the brain of patients with other inflammatory diseases, such as multiple sclerosis, where it *precedes* any pathological or clinical symptoms [92–94]. This process may worsen by vulnerability due to genetic, metabolic, allergic, autoimmune, environmental and/or other factors.

6. Conclusion

The evidence discussed above does not imply a cause and effect relationship. The issue of "allergies" in ASD still remains poorly defined and controversial. The study designs used to elucidate evidence about atopic and "allergic-like" symptoms in patients with ASD are mostly case-control studies, inherently subject to possible reporting bias of parents. Subjects with ASD susceptibility genes and hypersensitive mast cells may represent a unique subgroup of patients who are more likely to respond to environmental and stress triggers, leading to worsening ASD. It is important to investigate mast cell-associated triggers and mediators in patients with ASD, especially at the time the diagnosis is made. Such efforts could help unveil novel aspects of the pathogenesis of ASD, identify potential biomarkers, as well as lead to new therapeutic approaches. Reduction of stress during gestation and infancy, as well as drugs that could inhibit mast cell activation and prevent BBB disruption or block brain inflammation, may prove useful in at least a subgroup of autistic children.

We have shown that the naturally occurring flavonoids quercetin and luteolin, which are safe [95], can inhibit human mast cell release of inflammatory molecules. Quercetin can reverse acute stress-induced autistic-like behavior and reduces brain glutathione levels in mice [96]. Quercetin also can protect against rat swimming-stress-induced increase in serum lipid hydroperoxide levels [97]. Luteolin inhibits maternal IL-6-induced autism-like behavioral deficits in social interaction in mice [98]. Luteolin also inhibits microglia production of IL-6 [99], can induce anti-inflammatory changes in glial cells [100] and can inhibit cytokine release from peripheral blood monocytes from multiple sclerosis patients [101]. Finally, luteolin (5, 7, 3', 4'-tetrahydroxyflavone) is closely related to 7, 8-dixydroxyflavone, recently shown to mimic brain-derived

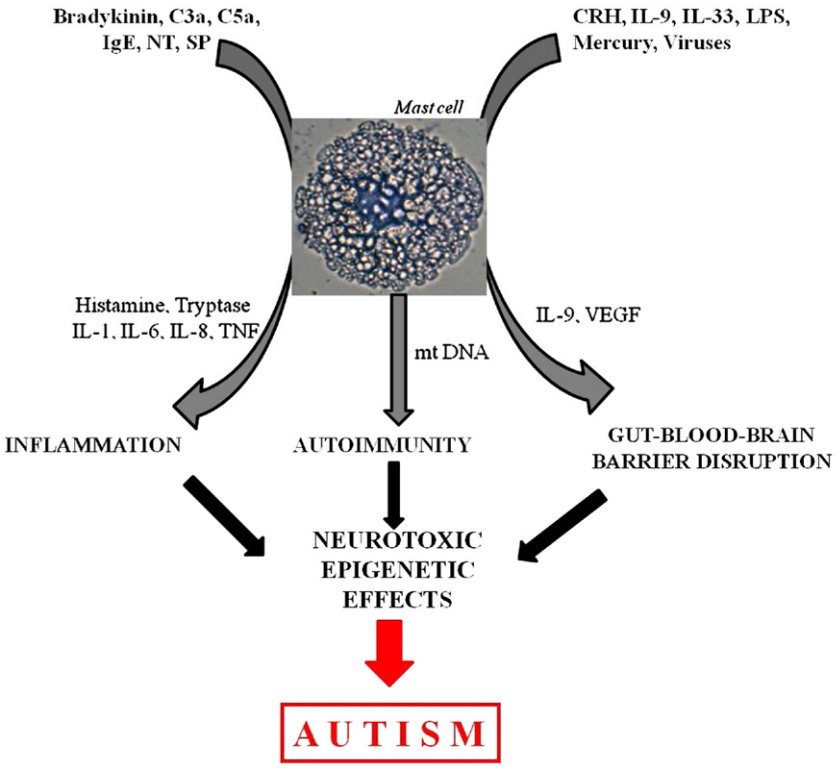

Fig. 3. Schematic representation of mast cell activation by allergic and non-immune triggers, and its possible involvement in the pathogenesis of autism.

neurotrophic factor (BDNF), which is neuroprotective [102]. Luteolin could, therefore, be useful in treating neuroinflammatory diseases, either alone or as an adjuvant to other therapeutic approaches [103]. Unfortunately, flavonoids, especially luteolin are lipophilic and poorly absorbed after oral administration, with significant liver metabolism [104,105]. The unique flavonoid-containing dietary supplement NeuroProtek has been formulated to increase oral bioavailability and holds promise for reducing gut–blood–brain barrier disruption and brain inflammation.

7. Disclosures

The authors declare that they have no competing interests. TCT is the inventor of patent application US 12/534,571 covering the diagnosis and treatment of ASD.

8. Addendum in Press

Additional papers reported increased prevalence of ASD especially after 1986 [106,107]. A recent paper reported increased plasma levels in children with ASD of the chemokines RANTES, MCP-1 and eotaxin [108], all of which are potent chemoattractants for mast cells [109,110,111]. It was also just reported that delayed angioedema and urticaria could develop after eating beef, lamb or pork due to IgE antibodies specific for the meat carbohydarate epitope galactose-a-1,3-galactose [112]. Finally, diagnostic criteria were just proposed for a new entity, "Mast Cell Activation Syndrome" [113], which could explain the findings in many ASD patients who "present with signs and symptoms involving the dermis, gastrointestinal track, and cardiovascular system frequently accompanied by neurologic complaints [113].

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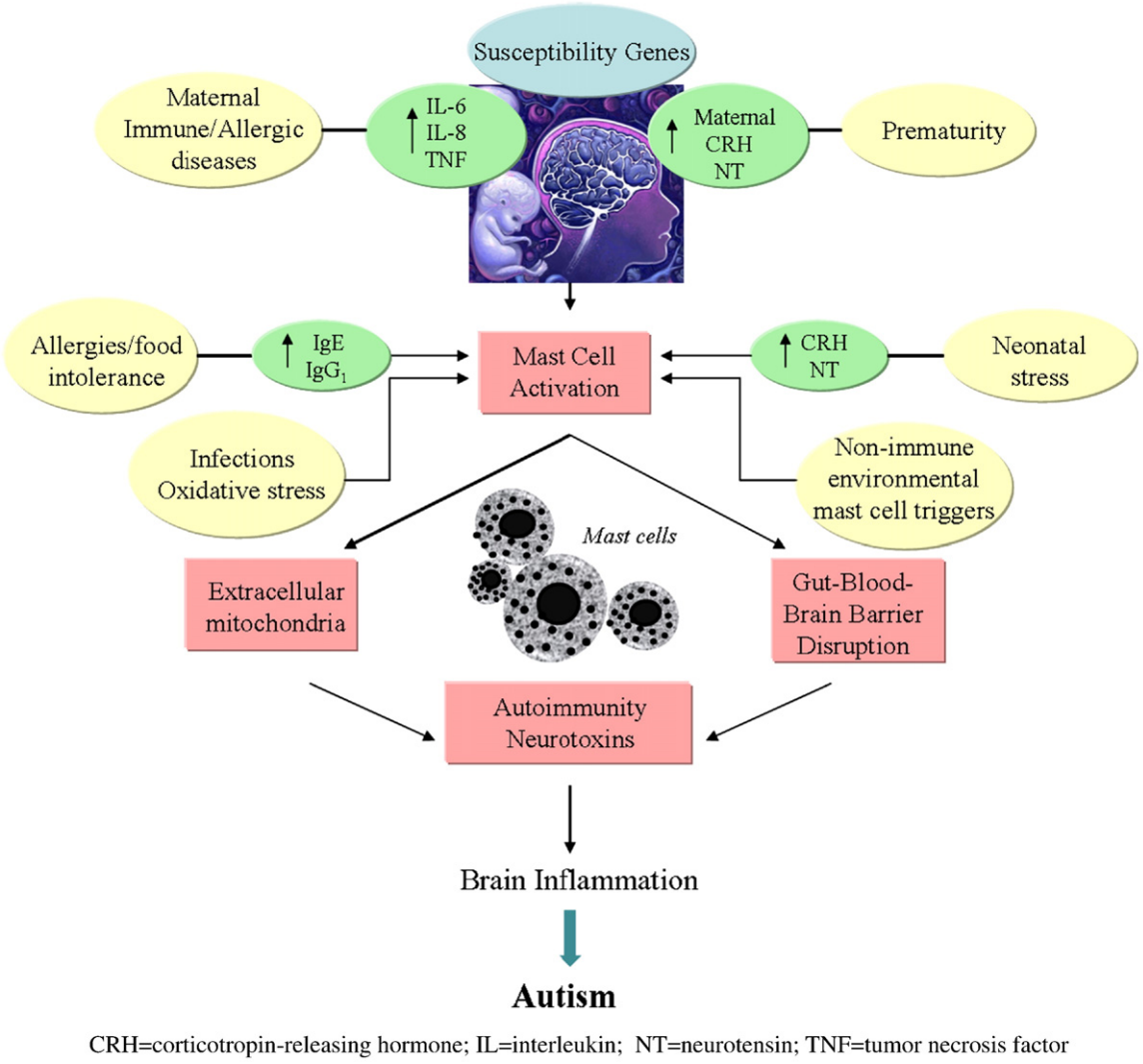

Fig. 4. Schematic representation of different processes involved in perinatal mast cell activation by allergic and non-immune triggers, leading to disruption of the blood–brain barrier, autoimmunity and inflammation that may contribute to the pathogenesis of autism.

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