



# A systematic review of gut-immune-brain mechanisms in Autism Spectrum Disorder

Atiqah Azhari<sup>1</sup> | Farouq Azizan<sup>1</sup> | Gianluca Esposito<sup>1,2</sup>

<sup>1</sup>Psychology Program, School of Social Sciences, Nanyang Technological University, Singapore, Singapore

<sup>2</sup>Department of Psychology and Cognitive Science, University of Trento, Rovereto, TN, Italy

## Correspondence

Gianluca Esposito, Psychology Program, School of Social Sciences, Nanyang Technological University, Singapore, Singapore.  
Email: gianluca.esposito@ntu.edu.sg

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## Abstract

Despite decades of research, the etiological origins of Autism Spectrum Disorder (ASD) remain elusive. Recently, the mechanisms of ASD have encompassed emerging theories involving the gastrointestinal, immune, and nervous systems. While each of these perspectives presents its own set of supporting evidence, the field requires an integration of these modular concepts and an overarching view of how these subsystems intersect. In this systematic review, we have synthesized relevant evidences from the existing literature, evaluating them in an interdependent manner and in doing so, outlining their possible connections. Specifically, we first discussed gastrointestinal and immuno-inflammation pathways in-depth, exploring the relationships between microbial composition, bacterial metabolites, gut mucosa, and immune system constituents. Accounting for temporal differences in the mechanisms involved in neurodevelopment, prenatal and postnatal phases were further elucidated, where the former focused on maternal immune activation (MIA) and fetal development, while the latter addressed the role of immune dysregulation in contributing to atypical neurodevelopment. As autism remains, foremost, a neurodevelopmental disorder, this review presents an integration of disparate modules into a “Gut-Immune-Brain” paradigm. Existing gaps in the literature have been highlighted, and possible avenues for future research with an integrated physiological perspective underlying ASD have also been suggested.

## KEYWORDS

Autism Spectrum Disorder, gut-brain axis, immune system, physiological mechanisms

## 1 | INTRODUCTION

### 1.1 | Autism Spectrum Disorder

Deficits in social communication and restricted, repetitive patterns of behaviors and interests have been identified as the two overarching branches of symptoms in Autism Spectrum Disorder (ASD; American Psychiatric Association, 2013). However, the unique constellation of symptoms that differs strikingly across individuals hints at more complex underlying mechanisms. The past decades have since witnessed a paradigm shift in ASD research, veering from its once predominantly genetic focus to encompass more systemic approaches (Arndt, Stodgell, & Rodier, 2005; Frye & Rossignol,

2011; Herbert, 2010; Jyonouchi, Sun, & Itokazu, 2002; Rossignol & Frye, 2012a, 2012b). Emerging evidence shows that ASD is associated with extensive dysregulation across numerous biological modules, the most prominent of which implicate the gastrointestinal environment (Adams, Johansen, Powell, Quig, & Rubin, 2011; Arentsen, Raith, Qian, Forssberg, & Heijtz, 2015; Clarke et al., 2012; Desbonnet, Clarke, Shanahan, Dinan, & Cryan, 2014; Diaz Heijtz et al., 2011; McElhanon, McCracken, Karpen, & Sharp, 2014; Neufeld, Kang, Bienenstock, & Foster, 2011; Sudo et al., 2004), immuno-inflammation pathways (El-Ansary & Al-Ayadhi, 2014; Pardo, Vargas, & Zimmerman, 2005; Rossignol & Frye, 2012a; Vargas, Nascimbene, Krishnan, Zimmerman, & Pardo, 2004), and nervous system (Catani

et al., 2016; Ha, Sohn, Kim, Sim, & Cheon, 2015; Herrington, Miller, Pandey, & Schultz, 2016; Yang, Beam, Pelphrey, Abdullahi, & Jou, 2016).

## 1.2 | The gut-brain axis

Notable features of gastrointestinal abnormalities associated with autism include alterations of microbial composition (Adams, Johansen, et al., 2011; Finegold et al., 2010, 2002; Kang et al., 2013; Kinross, Darzi, & Nicholson, 2011; Parracho, Bingham, Gibson, & McCartney, 2005; Song et al., 2004; Song, Liu, & Finegold, 2004; de Theije, Koelink, et al., 2014; de Theije, Wopereis, et al., 2014; Williams et al., 2011), overproduction of bacterial metabolites (Calabrese & Rizza, 1999; Macfabe, 2013; Wajner, Latini, Wyse, & Dutra-Filho, 2004; Wang et al., 2012) and increase in gastrointestinal mucosa permeability (Adams, Audhya, et al., 2011; Cade et al., 2000; de Magistris et al., 2010; D'Eufemia et al., 1996; D'Eufemia et al., 1996; Hsiao et al., 2013). Dysbiosis of the gut is hypothesized to influence mammalian brain development via communication between gastrointestinal microbiota and the central nervous system (CNS; Bercik et al., 2011; McVey Neufeld, Mao, Bienenstock, Foster, & Kunze, 2013; Sarkar et al., 2016), which is usually modulated by immune responses (Alkanani et al., 2015; Breban et al., 2017; Carabotti, Scirocco, Maselli, & Severi, 2015; Diaz Heijtz et al., 2011; Erny et al., 2015; Köhling, Plummer, Marchesi, Davidge, & Ludgate, 2017; Ma, Shi, Li, Chen, & Niu, 2015; Midtvedt, 2012; Miyake et al., 2015; Nicholson et al., 2012).

## 1.3 | The immuno-inflammation pathways

Accumulating evidence drives at the indubitable link between ASD and generalized immune dysfunction. A subset of children with ASD has been shown to exhibit upregulated quantities of natural killer (NK) cells, interferon gamma (INF- $\gamma$ ; Enstrom, Lit, et al., 2009; Gregg et al., 2008; Vargas et al., 2004), tumor necrosis factor alpha (TNF- $\alpha$ ; Chez, Dowling, Patel, Khanna, & Kominsky, 2007), TNF-receptor II (Zimmerman et al., 2005), interleukin-6 (IL-6; Li et al., 2009; Wei et al., 2011), IL-8 (Li et al., 2009), IL-1 $\beta$  (Ashwood, Schauer, Pessah, & Van de Water, 2009), and autoantibodies (Frye, Sequeira, Quadros, James, & Rossignol, 2013; Gesundheit et al., 2013; Rossignol & Frye, 2012a; Rossignol & Frye, 2012a), with concomitant reduction in concentration of plasma transforming growth factor-beta (TGF- $\beta$ 1; Ashwood et al., 2008). Contradicting results have surrounded findings on immunoglobulin atypicalities in ASD (Croonenberghs, Wauters, et al., 2002; Gupta, 2000; Stern et al., 2005). Neuroinflammation in microglial activation has also been reported in various brain regions (Morgan et al., 2010; Suzuki et al., 2013; Tetreault et al., 2012; Vargas et al., 2004). Finally, the presence of immuno-inflammatory biomarkers has been shown to correlate with acuteness of ASD symptoms (Al-ayadhi & Mostafa, 2011, 2012a, 2013; Khakzad et al., 2012; Mostafa & Kitchener, 2009).

The current review will begin by unraveling the mechanistic connections between the gut and immune system, followed by the immune system and brain development. This discussion will coalesce on the multiple routes that these networks can possibly take to influence brain maturity, linking etiological mechanisms of autism across the "gut-immune-brain" axis.

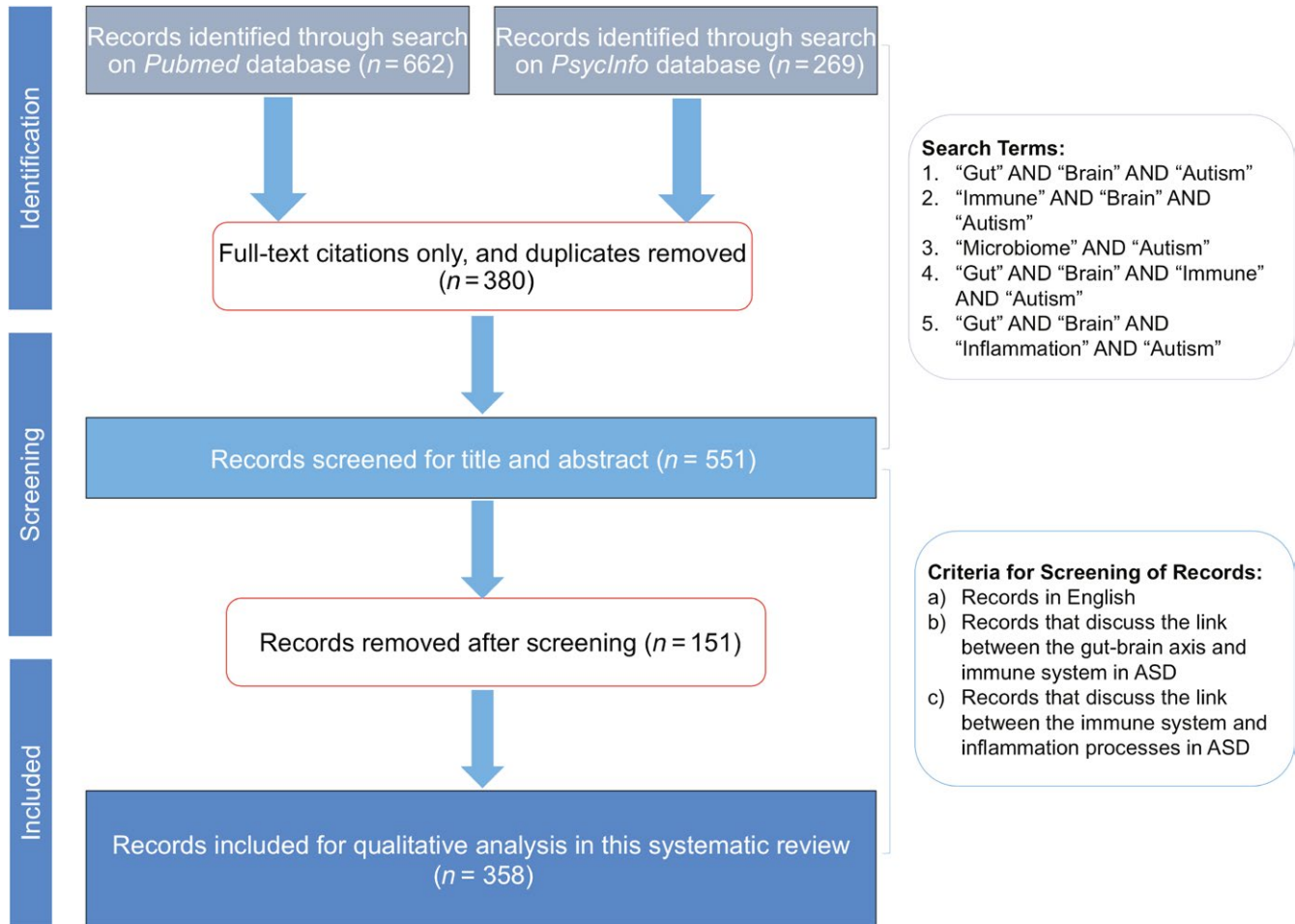
## 2 | METHODS

PubMed and PsycINFO databases were utilized to browse for articles, from the year 2000 to 2018, relating to the gut-brain axis and immune/inflammation system in Autism Spectrum Disorder (ASD). Firstly, five database searches were made using the Boolean operator "AND": (1) Gut, Brain, and Autism; (2) Immune, Brain, and Autism; (3) Microbiome and Autism; (4) Gut, Brain, Immune, and Autism; (5) Gut, Brain, Inflammation, and Autism. These searches generated a long list of records ( $n = 931$ ), which were subsequently organized into a database and screened according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as illustrated in Figure 1. A total of 358 records were eventually included for qualitative analysis.

## 3 | THE GUT AND IMMUNO-INFLAMMATION

### 3.1 | Microbiota, T cells, and Cytokines

The human gastrointestinal (GI) tract is home to 100 trillion microorganisms, collectively known as the microbiota (Weinstock, 2012). The medley of gut microbiota has astounding implications on the profile of circulating cytokines (e.g., IL-12p40, IFN- $\gamma$ , TGF $\beta$ , IL- $\beta$ , IL-6, TNF- $\alpha$ , and MCP-1; El-Ansary & Al-Ayadhi, 2014; Jyonouchi, Sun, & Le, 2001; Suzuki et al., 2011; Xu, Li, & Zhong, 2015; Jyonouchi, Geng, Ruby, & Zimmerman-Bier, 2005), and lymphocyte development, with some species stimulating the differentiation of specific T cell subtypes (Estes & McAllister, 2015; Hsiao, 2013; Morgan et al., 2010; Vargas et al., 2004). In ASD, a dysbiosis in microbiota, featuring an overrepresentation of *Clostridial*, *Bacteroidetes*, *Firmicutes*, and *Lactobacilli* (Finegold, Downes, & Summanen, 2012; Tomova et al., 2015; Wang, Conlon, Christophersen, Sorich, & Angley, 2014) has been observed. Synthesis of T regulatory (T-reg) cells producing anti-inflammatory IL-10 is only enhanced by a strain-specific cluster of *Clostridial* species and *Bacteroides fragilis* (Ochoa-Reparaz et al., 2010; Round et al., 2011), whereas accretion of Th17 cells producing pro-inflammatory IL-17 is stimulated by segmented filamentous bacteria (SFB; Lee, Menezes, Umesaki, & Mazmanian, 2011; Wu et al., 2010). The balance between Th1/Th2 cytokine responses has also been shown to be modulated by specific bacterial species (Mulle, Sharp, & Cubells, 2013), although conflicting findings of Th1 and Th2 dominance in ASD have been reported (Anthony et al., 1998; Furlano et al., 2001). Recently, Rose et al. (2018)



**FIGURE 1** PRISMA Flow for Inclusion of Records in Systematic Review. Records were identified on *PubMed* and *PsycINFO* databases from the following five searches: "Gut" AND "Brain" AND "Autism"; "Immune" AND "Brain" AND "Autism"; "Microbiome" AND "Autism"; "Gut" AND "Brain" AND "Immune" AND "Autism"; "Gut" AND "Brain" AND "Inflammation" AND "Autism". Records written in English were screened for content relevant to connections across the gut-brain axis, immune system, inflammation processes, and autism. A total of 358 records were included for qualitative analysis

stratified subgroups of children with (ASD) and without ASD (TD), who either displayed irregular (GI) or normal GI symptoms (NoGI). Upon endotoxin stimulation, the ASD-GI group was found to display higher levels of IL-5, IL-15, and IL-17 than ASD-noGI. This group also exhibited lower concentrations of anti-inflammatory TGF- $\beta$ 1 than ASD-noGI and TD-noGI, and their bacterial composition was distinctly different from other groups. In a similar study, Luna et al. (2017) observed an increased abundance in *Clostridiales* genera and reduced levels of *Sutterella*, *Dorea*, and *Blautia*, with parallel elevations in IL-6 and tryptophan concentrations amongst ASD-GI, as compared to other groups. Gene sequencing analyses by Foley, MacFabe, Kavaliers, and Ossenkopp (2015) revealed that infants with ASD have a higher abundance of bacterial genera *Faecalibacterium*, and lower levels of *Blautia*, in fecal and blood samples. Recently, a study by Coretti et al. (2017) on mice models have elucidated markedly unique microbial and immune profiles in male and female autistic mice, suggesting the possible role of the microbiota in influencing sex-specific susceptibility to autism.

### 3.2 | Microbiota and antibodies

An altered gut microbiome may be sufficient to stimulate the production of an army of antibodies (Gutzeit, Magri, & Cerutti, 2014). Indeed, Immunoglobulin A (IgA), the main antibody secreted in the gut, has been shown to be significantly higher in ASD populations as compared to controls (Zhou et al., 2017). IgA is responsible for maintaining mucosal immunity (Lutgendorff, Akkermans, & Soderholm, 2008), the overstimulation of which suggests a consistent assault to the gut. Several species of microbiota have been postulated to be associated with ASD. In particular, the presence of *Micobacterium paratuberculosis* may evoke antibodies that interact with the myelin basic protein in the CNS (Dow, 2011), while *Clostridium bolteae* and *Sutterella* species have been proposed to elicit antibody production that aggravates gastrointestinal co-morbidities (Pequegnat et al., 2013; Williams, Hornig, Parekh, & Lipkin, 2012). Re-establishing microbial balance through Fecal Microbiota Transplant (FMT) has been shown to alleviate gastrointestinal and core autistic symptoms (Kang et al., 2017; Moon et al., 2015; Palm et al., 2014).

### 3.3 | Microbiota and interferon (IFN) signaling

In autism, mechanisms of interferon (IFN), a signaling protein released in response to pathogens (De Andrea, Ravera, Gioia, Gariglio, & Landolfo, 2002), are altered. Genes associated with type-I IFN signaling have been shown to be substantially reduced in germ-free (GF) mice devoid of gut microbiota (Erny et al., 2015). Inoue et al. (2016) recently discovered that, as compared to healthy controls, autistic infants exhibited significantly different expression patterns of genes implicated in IFN- $\gamma$  and type-I IFN signaling. Elevated quantities of IFN- $\alpha$  or IFN- $\gamma$ , with (Jyonouchi et al., 2002) and without endotoxin induction, have also been reported in the cerebrospinal fluid (CSF) and peripheral mononuclear blood cells (PBMC) of autistic children (Singh, 1996; Stubbs, 1995; Vargas et al., 2004). Interestingly, correlation analysis generated significant association between IFN-related genes and quantity of *Faecalibacterium* (Ashwood et al., 2011; Suzuki et al., 2011).

### 3.4 | Microbiota and maternal immune activation (MIA)

While earlier reports have associated specific infectious agents (e.g., rubella, influenza), during the prenatal phase, to an increased incidence of ASD, it was later discovered that it was the inflammatory response towards an infection, known as maternal immune activation (MIA; Wong & Hoeffler, 2018), rather than a specific causative agent, that presents a risk (Atladóttir et al., 2010; Atladóttir, Henriksen, Schendel, & Parner, 2012; Libbey, Sweeten, McMahon, & Fujinami, 2005; Lintas, Altieri, Lombardi, Sacco, & Persico, 2010; Meltzer & Van de Water, 2016; Wilkerson, Volpe, Dean, & Titus, 2002; Zhang, Lv, et al., 2010). In addition to MIA, evidence points to the involvement of functional Toll-like receptor 3 (TLR3) and commensal microflora in inducing autistic phenotypes (Atarashi et al., 2015). In a study by Kim et al. (2017) on mice, administration of the antibiotic vancomycin prior to inducing MIA by poly (I:C) treatment did not lead to observation of abnormal behavioral phenotypes. Moreover, vancomycin treatment substantially diminished Th17 levels in the offspring's small intestine. The study also revealed that certain maternal intestinal bacteria modulate Th17 abundance and the emergence of autistic behaviors. Specifically, offspring which came from mothers with human commensal bacteria or mouse commensal SFB showed significantly more Th17 cell differentiation (Kim et al., 2017), which is potentially linked to aberrant behaviors mediated by an increase in expression of IL-17a receptor in the offspring's frontal cortex (Choi et al., 2016a).

### 3.5 | Gastrointestinal mucosa permeability

The "leaky gut theory" postulates that an exceptionally increased permeability of the intestinal mucosa barrier represents a fundamental mechanism underlying autistic pathology (de Magistris et al., 2010; D'Eufemia et al., 1996; Horvath & Perman, 2002; Panksepp, 1979; Wakefield et al., 1998). Studies on subgroups of ASD subjects

have revealed that this deficiency is partly contributed by (a) alterations in microbial composition, with an overrepresentation of bacterium *Akkermansia muciniphila*, known to degrade the mucus lining (Wang et al., 2011), (b) prevalence of *Clostridia* and reduced abundance of *Bifidobacteria*, increasing pro-inflammatory cytokines production, which aggravates mucosa permeability (Heberling, Dhurjati, & Sasser, 2013), (c) elevated plasma levels of zonulin, a protein that regulates permeability (Esnafoglu et al., 2017), (d) decreased amounts of tight junction proteins at the intestinal barrier (Fiorentino et al., 2016), potentially due to increased toxins from *Clostridia* (Hecht, Pothoulakis, LaMont, & Madara, 1988), (e) infection by *Escherichia coli*, which leads to transformation of actin and tight junction structures (Long, Nisa, Donnenberg, & Hassel, 2014), (f) abundance of *Candida* fungi, which expresses root-like formations that invade the intestinal wall (de Magistris et al., 2010), and (g) increased levels of claudin, a molecule that contributes to pores formation (Fiorentino et al., 2016). Individuals with both autistic and gastrointestinal disorders exhibit a distinct cytokine (Ashwood & Wakefield, 2006; Torrente et al., 2002) and regulatory (Ashwood, Anthony, Torrente, & Wakefield, 2004) profile. However, while Ashwood et al. (2003) reported a link between ASD with GI symptoms and intestinal permeability, de Magistris et al. (2010) found no association. Animal model studies suggest that the composition of microbiota modulates the integrity of both the intestinal barrier (Jakobsson et al., 2014) and the blood-brain barrier (BBB; Braniste et al., 2014). Permeability of the brain and the GI appears to be developmentally sensitive. Stolp, Dziegielewska, Ek Potter, and Saunders (2005) revealed that BBB permeability in rats is propagated by inflammation in early life, while Braniste et al. (2014) and Cani et al. (2009) showed that the gut microbiota determines permeability of the gut mucosa lining in later adulthood.

An impaired intestinal barrier leads to resoundingly detrimental outcomes. Firstly, intestinal permeability upsets normative levels of major histocompatibility complex (MHC)-presenting epithelial cells, which affects activation of T-regs (Rabinowitz & Mayer, 2012) and exacerbates inflammation (Pastorelli, De Salvo, Mercado, Vecchi, & Pizarro, 2013). Secondly, neuroactive opioids from digested products, such as amyloid beta peptides, have been shown to leak into the bloodstream and permeate the BBB, influencing only neural but not glial cells (Clifford et al., 2007), to elicit ASD symptoms (Panksepp, 1979; Shattock & Whiteley, 2002). However, no significant difference in opioid levels has been found between those with and without ASD (Cass et al., 2008). Lastly, toxins from the gut that pass through the intestinal barrier have been shown to induce antibody production (de Magistris et al., 2014) that exacerbates chronic inflammation (Visser, Rozing, Sapone, Lammers, & Fasano, 2009). Indeed, deposition of IgG and complement C1q at the epithelium supports the presence of an autoimmune reaction (Torrente et al., 2002). Additionally, bacterial lipopolysaccharides (LPS) from the gut stimulate liver cells to secrete TNF- $\alpha$ , which modulates BBB permeability (Kim, Wass, Cross, & Opal, 1992). Studies on ASD patients revealed that TNF- $\alpha$  cascades to produce pro-inflammatory cytokines, which leads to peripheral

**TABLE 1** Mechanisms of interaction between gastrointestinal and immuno-inflammation pathways in Autism Spectrum Disorder (ASD)

	Physiological mechanisms	Authors
Microbiota	<p>Microbiota and interleukin (IL) profiles</p> <p>Human Studies</p> <ul style="list-style-type: none"> <li>• IL-10 levels were enhanced by strain-specific cluster of <i>Clostridial</i> species and <i>Bacteroides fragilis</i></li> <li>• IL-17 levels were elevated by accretion of Th17 cells, stimulated by segmented filamentous bacteria (SFB)</li> <li>• Human commensal bacteria or mouse commensal segmented filamentous bacteria (SFB) in the maternal microflora regulates Th17 and IL-17 production and the emergence of autistic traits in the offspring</li> <li>• IL-5, IL-15, and IL-17 were found to be higher, and anti-inflammatory TGF-<math>\beta</math>1 was lower, in ASD group with GI symptoms than in ASD group without GI; distinct differences in microbial compositions between the groups</li> <li>• IL-6 levels and <i>Clostridia</i> bacteria were elevated, and prevalence of <i>Sutterella</i>, <i>Dorea</i> and <i>Blautia</i> was reduced, in ASD group with GI symptoms</li> </ul> <p>Animal Studies</p> <ul style="list-style-type: none"> <li>• IL-10 levels in male autistic mice models were reduced, with simultaneous abundance of <i>Helicobacteriaceae</i> and underrepresentation of <i>Ruminococcus</i>, <i>Desulfovibrio</i>, and <i>Dehalobacterium</i></li> <li>• TNF-<math>\alpha</math> levels in female autistic mice models were elevated, with simultaneous reduction in expression of <i>Dehalobacterium</i> and <i>Oscillospira</i> genera and an overrepresentation of <i>Parabacteroides</i> and <i>Sutterella</i></li> <li>• IL-22 production was associated with a lack of Trp-metabolizing bacteria in mice with microbial dysbiosis</li> </ul> <p>Microbiota and Antibodies</p> <ul style="list-style-type: none"> <li>• <i>Mycobacterium paratuberculosis</i> elicit antibodies that interact with myelin basic proteins in the central nervous system</li> <li>• <i>Clostridium bolteae</i> and <i>Sutterella</i> species elicit antibodies that aggravate gastrointestinal symptoms</li> </ul> <p>Microbiota and Interferon (IFN)</p> <ul style="list-style-type: none"> <li>• IFN-associated genes were associated with an abundance of <i>Faecalibacterium</i> in persons with autism</li> <li>• Type-I IFN signaling genes were present in fewer quantities in germ-free (GF) mice, without microbiota.</li> </ul>	<p>Ochoa-Reparaz et al. (2010), Round et al. (2011) Lee et al. (2011), Wu et al. (2010), Furlano et al. (2001) Choi et al. (2016a) Rose et al. (2018) Luna et al. (2017) Coretti et al. (2017) Coretti et al. (2017) Hashimoto et al. (2012), Lamas et al. (2016)</p> <p>Dow (2011) Pequegnat et al. (2013), Williams et al. (2012)</p> <p>Ashwood et al. (2011); Suzuki et al. (2011) Erny et al. (2015)</p>
Mucosa permeability	<p>Mucosa permeability and microbial dysbiosis</p> <ul style="list-style-type: none"> <li>• Prevalence of bacterium <i>Akkermansia muciniphila</i>, which has been shown to degrade the mucus lining</li> <li>• Increased abundance of <i>Clostridia</i> and reduced proliferation of <i>Bifidobacteria</i>, which has been associated with the increase in pro-inflammatory cytokines that exacerbates mucosa permeability</li> <li>• Increased abundance of <i>Clostridia</i> which release toxins that decrease the quantity of tight junction proteins at the intestinal barrier</li> <li>• Infection of bacterium <i>Escherichia coli</i>, which compromises actin and tight junction structures</li> <li>• Overgrowth of <i>Candida</i> fungi, which protrudes root-like formations that colonize the intestinal barrier.</li> </ul> <p>Mucosa permeability and immune dysregulation</p> <p>Imbalance of T cells</p> <ul style="list-style-type: none"> <li>• Concomitant with an inflammatory immune profile, which induces an imbalance of Th1/Th2 cells</li> <li>• Leads to dysregulated levels of MHC-presenting epithelial cells which impairs activation of T-regs</li> </ul> <p>Imbalance of Cytokines</p> <ul style="list-style-type: none"> <li>• Leads to increased TNF-<math>\alpha</math>, which inhibits INF<math>\beta</math>, a molecule that protects the mucosa lining</li> </ul> <p>Dysregulated Infiltration</p> <ul style="list-style-type: none"> <li>• Neuroactive opioids infiltrate into the bloodstreams and through the BBB to modulate neural cells and induce autistic symptoms</li> <li>• Toxins infiltrate bloodstream to trigger antibody production, including of IgG and complement C1q</li> <li>• Increased infiltration of immune cells, including pro-inflammatory lymphocytes, into the GI in ASD populations with GI disorders, as compared to healthy populations with GI symptoms.</li> </ul>	<p>Wang et al. (2011) Heberling et al., (2013) Fiorentino et al. (2016) Long et al. (2014) de Magistris et al. (2010)</p> <p>Ashwood and Wakefield, (2006), Torrente et al. (2002); Rabinowitz and Mayer (2012) Long et al. (2014) Clifford et al. (2007); Panksepp (1979); Shattock and Whiteley, (2002); de Magistris et al. (2014), Torrente et al. (2002) Ashwood et al. (2003, 2004 ), Ashwood and Wakefield (2006), Furlano et al. (2001), Torrente et al. (2002), Torrente et al. (2004)</p>

(Continues)



TABLE 1 (Continued)

	Physiological mechanisms	Authors
Bacterial Metabolites	Short-chain Fatty Acids (SCFA) SCFA and Microbiota <ul style="list-style-type: none"> <li>• MIA model of male mice resulted in overrepresentation of <i>Firmicutes</i> bacteria, reduced populations of <i>Bacteroidetes</i>, with a concomitant increase in butyric acid</li> <li>• MIA model of mice found an increase in the prevalence of <i>Clostridium</i> and <i>Bacteroides</i>, with no increase in butyric acid</li> </ul> SCFA and Interleukin (IL) Production <ul style="list-style-type: none"> <li>• Administration of sodium butyrate alleviated autistic symptoms, potentially through down-regulation of IL-17 and IL-23 and upregulation of T-regs, IL-10, and IL-12</li> <li>• Microbiota can produce SCFAs through amino acids metabolism, generating tryptophan catabolites (e.g., propionic acid) that influence T cells differentiation, IL-22 production, and T-reg/Th17 balance</li> </ul>	de Theije, Koelink, et al., 2014; de Theije, Wopereis, et al. (2014) Hsiao et al. (2013) Kratsman et al. (2016), Takuma et al., (2014) Maes and Rief (2012); Fallarino et al. (2012), Mezrich et al. (2010), Opitz et al. (2011), Qiu et al. (2013), Zhang et al. (2014)

inflammation (Breese et al., 1994), followed by activation of microglia in the brain (Qin et al., 2007), indicating neuroinflammation (Derecki et al., 2012; Laurence & Fatemi, 2005; Morgan et al., 2010; Tetreault et al., 2012). Moreover, TNF- $\alpha$  indirectly inhibits interferon beta (INF $\beta$ ), a molecule which defends the mucosa lining (Long et al., 2014). Most interestingly, studies comparing ASD and typical populations with GI symptoms found that increased permeability of the intestinal barrier allows for an almost imperceptible infiltration of immune cells into the GI (Ashwood & Wakefield, 2006; Ashwood et al., 2003, 2004; Furlano et al., 2001; Torrente et al., 2004, 2002), including lymphocytes bearing pro-inflammatory characteristics (i.e., CD3+ staining revealed increased TNF- $\alpha$ +, IFN- $\gamma$ +, and reduced IL-10+), although Fernell Fagerberg and Hellström (2007) did not find any association between gastrointestinal inflammation and autism.

### 3.6 | Bacterial metabolites

The gut microbiome produces three classes of short-chain fatty acids (SCFA): propionic acid (PPA), acetic acid, and butyric acid (Stilling, Dinan, & Cryan, 2014), which were all shown to be overexpressed in ASD populations (Wang et al., 2012), though contradictory findings remain prevalent (Cryan & Dinan, 2012; Louis, 2012; Mangiola et al., 2016; Vuong & Hsiao, 2017). Animal model studies that replicate autistic-like behaviors have elucidated an overgrowth in *Firmicutes* bacteria, a reduction in *Bacteroidetes*, along with increased levels of SCFA, especially butyric acid, in male mice (de Theije, Koelink, et al., 2014; de Theije, Wopereis, et al., 2014). Although Hsiao et al. (2013) did not generate similar findings using MIA mice models, they demonstrated an increase in diversity of *Clostridium* and *Bacteroides*, in line with predominant findings in ASD human subjects (Parracho et al., 2005; Tomova et al., 2015). Several studies have illustrated that SCFAs are capable of permeating the BBB (Karuri, Dobrowsky, & Tannock, 1993) to modulate neural characteristics of brain cells (El-Ansary, Ben Bacha, & Kotb, 2012; Erny et al., 2015; Kratsman, Getselter, & Elliott, 2016; Macfabe, 2012). Indeed, administration of PPA in rats, prenatally through a pregnant mother (Foley, Ossenkopp, Kavaliers, & Macfabe, 2014) and in early life (Foley

et al., 2015; MacFabe, 2015; Thomas et al., 2012; Wikoff et al., 2009), as well as increasing PPA diet in children (Mellon, Deshpande, Mathers, & Bartlett, 2000), facilitated the emergence of autistic-like behaviors across animal and human studies. Intriguingly, administration of sodium butyrate alleviated autistic symptoms (Kratsman et al., 2016; Takuma et al., 2014), either by reducing concentrations of IL-17 and IL-23 while simultaneously increasing T-regs, IL-10, and IL-12 production (Zhang, Liao, Sparks, & Luo, 2014) or through different metabolic processes (Jung, Park, Jeon, & Han, 2015; Peng, Li, Green, Holzman, & Lin, 2009; Ríos-Covián et al., 2016).

SCFAs from bacterial species act upon specific GI and immune pathways. A consortium of *Clostridia* species is capable of inducing the production of tryptophan catabolites (Maes & Rief, 2012), such as propionic acid, that interact with aryl hydrocarbon receptor on the surface of differentiating T cells to stimulate production of IL-22 (Fallarino, Grohmann, & Puccetti, 2012; Mezrich et al., 2010; Opitz et al., 2011; Qiu et al., 2013), which promotes T cells differentiation (Cavaglieri et al., 2003; Qiu et al., 2012; Veldhoen et al., 2008). This process regulates T-reg/Th17 balance (Zhang et al., 2014) and intestinal barrier integrity (Mjösberg, Bernink, Peters, & Spits, 2012; Qiu et al., 2012). Previous animal studies have revealed that mice with microbial dysbiosis, lacking Trp-metabolising bacteria, or gene (e.g., ACE2, Card9 knockout mice), subsequently synthesized low amounts of IL-22, creating pro-inflammatory conditions (Hashimoto et al., 2012; Lamas et al., 2016) and disrupting the intestinal barrier (Mjösberg et al., 2012; Qiu et al., 2012). Table 1 summarizes central gastrointestinal immune mechanisms in ASD.

## 4 | PRENATAL PHASE: MATERNAL IMMUNE SYSTEM AND FETAL DEVELOPMENT

### 4.1 | Maternal immune activation (MIA) and neurodevelopment

Fetal development of organs tethers on a delicate course that, when interrupted, leads to deleterious consequences. Extensive

retrospective studies have suggested a link between prenatal maternal infection and altered neurodevelopment that ultimately elevates the risk of ASD in infants (Lee et al., 2015; Meltzer & Van de Water, 2016). Moreover, maternal immune activation (MIA) during the prenatal phase has long been established to play a crucial role in inducing inflammatory states (Atladdottir et al., 2012; Lintas et al., 2010) and behavioral dysregulation (Bauman et al., 2014a; Machado, Whitaker, Smith, Patterson, & Bauman, 2015; Malkova, Yu, Hsiao, Moore, & Patterson, 2012). The immune system comprises of a myriad of cells which are capable of producing pro-inflammatory cytokines responsible for the inflammatory state observed in MIA (Meltzer & Van de Water, 2016). Animal studies do not only support this observation, but also further suggest that the mere activation of immune response in the mother, devoid of any infection, is sufficient enough to propagate changes in the offspring (Shi, Fatemi, Sidwell, & Patterson, 2003).

Regardless of whether immune activation was triggered by direct infection (i.e., Influenza), dsRNA mimic poly (I:C), or bacterial LPS, MIA models have replicated significant autistic traits in their offspring, further buffeting the role of a generalized inflammatory state in ASD (Fernández de Cossío, Guzmán, Van de Veldt, & Luheshi, 2017; Gilmore, Jarskog, & Vadlamudi, 2005; Meltzer & Water, 2016; Meyer, Feldon, Schedlowski, & Yee, 2005; Urakubo, Jarskog, Lieberman, & Gilmore, 2001; Zuckerman & Weiner, 2005). In one study, the authors utilized a direct infection of human influenza and poly (I:C) to trigger immune activation in two separate groups of pregnant mice and found that both experiments yielded similar autism-relevant traits in offspring (Shi et al., 2003). These findings suggest that MIA was responsible for the offspring's aberrant phenotypes (Shi et al., 2003). Interestingly, altered cerebellar development, also observed in autistic individuals, was demonstrated in a follow-up study (Shi et al., 2009). Poly (I:C) injection in pregnant rhesus macaques at either the late-first or late-second trimester presented atypical social interactions and vocal communications along with repetitive behaviors, all of which align with ASD traits (Bauman et al., 2014a). Another study injected bacterial LPS in pregnant mice, producing offspring where only the males exhibited autistic-relevant behavioral changes, with an associated reduction in CX3CR1 expression—a receptor involved in neuronal pruning (Fernández de Cossío et al., 2017). MIA models have thus proven to be successful in establishing and replicating autism-relevant socio-behaviors. However, much of the mechanistic approach remains unresolved (Gilmore et al., 2005; Meyer et al., 2005; Urakubo et al., 2001; Zuckerman & Weiner, 2005).

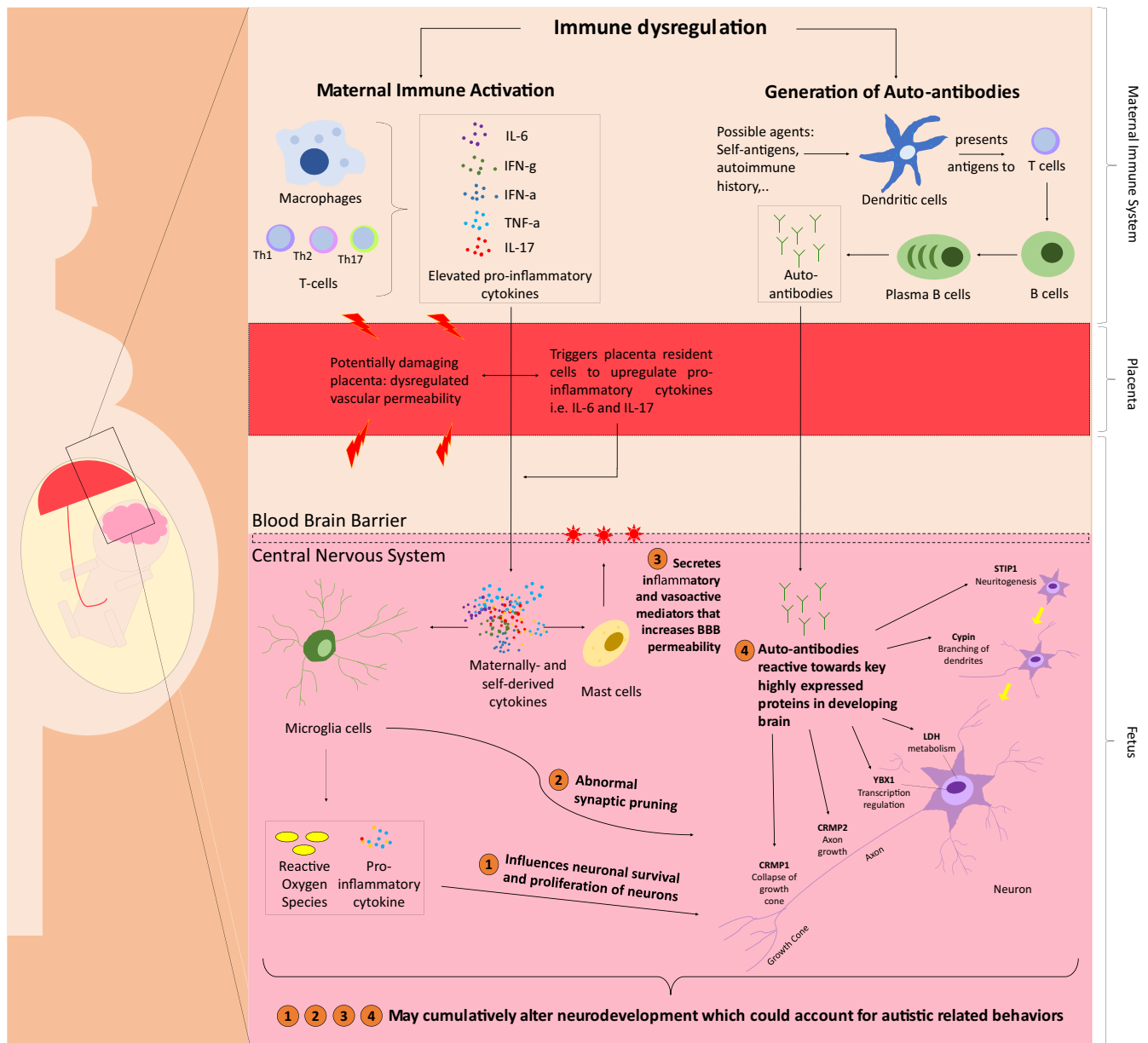
## 4.2 | Maternal pro-inflammatory cytokine profile

Atypical cytokine profiles in pregnant mothers and their offspring have become a ubiquitous observation associated with autism. A study done in 2007 revealed that upon injection of pregnant mice with IL-6, one of the main pro-inflammatory cytokines, offspring with autism-relevant behaviors were observed (Smith, Li, Garbett, Mirnics, & Patterson, 2007). Interestingly, these behaviors were

not seen in offspring of pregnant mice that were injected with other relevant pro-inflammatory cytokines such as IL-1 $\alpha$ , TNF- $\alpha$ , or IFN- $\gamma$  (Smith et al., 2007). The authors went on to prove IL-6's key role in ASD when autistic-related behaviors were rescued upon the co-injection of anti-IL-6 antibody onto pregnant dams (Smith et al., 2007). Rescued phenotype was not apparent upon co-injection with anti-IFN- $\gamma$  or anti-IL-1 $\beta$ . An extended study demonstrated no significant difference in social behavior between poly (I:C) treated IL-6 knockout (KO) mice and untreated IL-6 KO mice, thus further supporting the integral role of IL-6 in the etiology of ASD (Smith et al., 2007). Besides IL-6, Choi et al. (2016a) recently discovered that atypical socio-behaviors were observed in the offspring of IL-17 injected dams. Likewise, pre-treatment of dams with anti-IL-17 produced offspring with "rescued" phenotypes (Choi et al., 2016a). Indeed, Th17 cells may be another critical player in MIA-induced ASD, that is, acting downstream of elevated IL-6 levels (Choi et al., 2016a). The authors showed that other pro-inflammatory cytokines such as TNF- $\alpha$ , IFN- $\beta$ , and IL-1 $\beta$  were increased in MIA-induced models (Choi et al., 2016a). This was also reflected in a recent human study that saw elevated pro-inflammatory cytokines, at mid-gestational stage, in mothers of children with ASD (Jones et al., 2017). More importantly, some of these cytokines are capable of crossing the placenta and fetal BBB via active transport mechanisms. These cytokines potentially activate fetal microglia and mast cells, exacerbating the neuro-environment which could contribute to autism (Abdallah, Larsen, Grove, Nørgaard-Pedersen, et al., 2013b; Ferretti & Hollander, 2015a; Zaretsky, Alexander, Byrd, & Bawdon, 2004).

## 4.3 | Autoantibodies against fetal brain protein

Aside from MIA, emerging findings of maternal autoantibodies against fetal proteins strongly support the correlation between maternal immune dysregulation and ASD (Braunschweig et al., 2013a; Croen et al., 2008; Dalton et al., 2003; Enstrom, Van de Water, & Ashwood, 2009; Singer et al., 2008; Zimmerman et al., 2007). During pregnancy, protective maternal IgG antibodies cross the placenta to transfer immunity to the developing fetus. Consequently, maternal autoantibodies against fetal brain can cross the placenta and through the BBB, which, although is actively forming, remains permissive and as such results in the disruption of neurodevelopment (Bake, Friedman, & Sohrabji, 2009). Injection of IgG from mothers of children with autism into pregnant macaque monkeys produced offspring of enlarged brain volume, as well as aberrant social behavior (Bauman et al., 2013; Dalton et al., 2003). Interestingly, a specific set of maternal antibodies, found in 12% of mothers with autistic children, were shown to be reactive towards fetal brain proteins of sizes 37 kDa, 73 kDa (Braunschweig & Van de Water, 2012; Braunschweig et al., 2008; Fox, Amaral, & Van de Water, 2012), and around 39 kDa (Piras et al., 2014). Subsequently, seven developmentally regulated proteins were identified from the bands: Lactate Dehydrogenase A and B (LDH-A and LDH-B), stress-induced phosphoprotein 1 (STIP1), collapsin response mediator proteins



**FIGURE 2** Schematic diagram consolidating the main mechanisms underlying Autism Spectrum Disorder (ASD) in the prenatal phase. (1) Maternal immune activation (MIA) generates maternally derived cytokines that cross the fetal blood-brain barrier (BBB), leading to excessive production of reactive oxygen species (ROS) and pro-inflammatory cytokines from microglial cells, influencing neuronal survival and proliferation; (2) Dysfunction in microglial cells contribute to abnormal synaptic pruning; (3) Maternally derived cytokines induces mast cells to secrete inflammatory and vasoactive substances, which further corrodes BBB integrity; (4) Maternal autoantibodies crosses the BBB and targets highly expressed proteins in the fetal brain

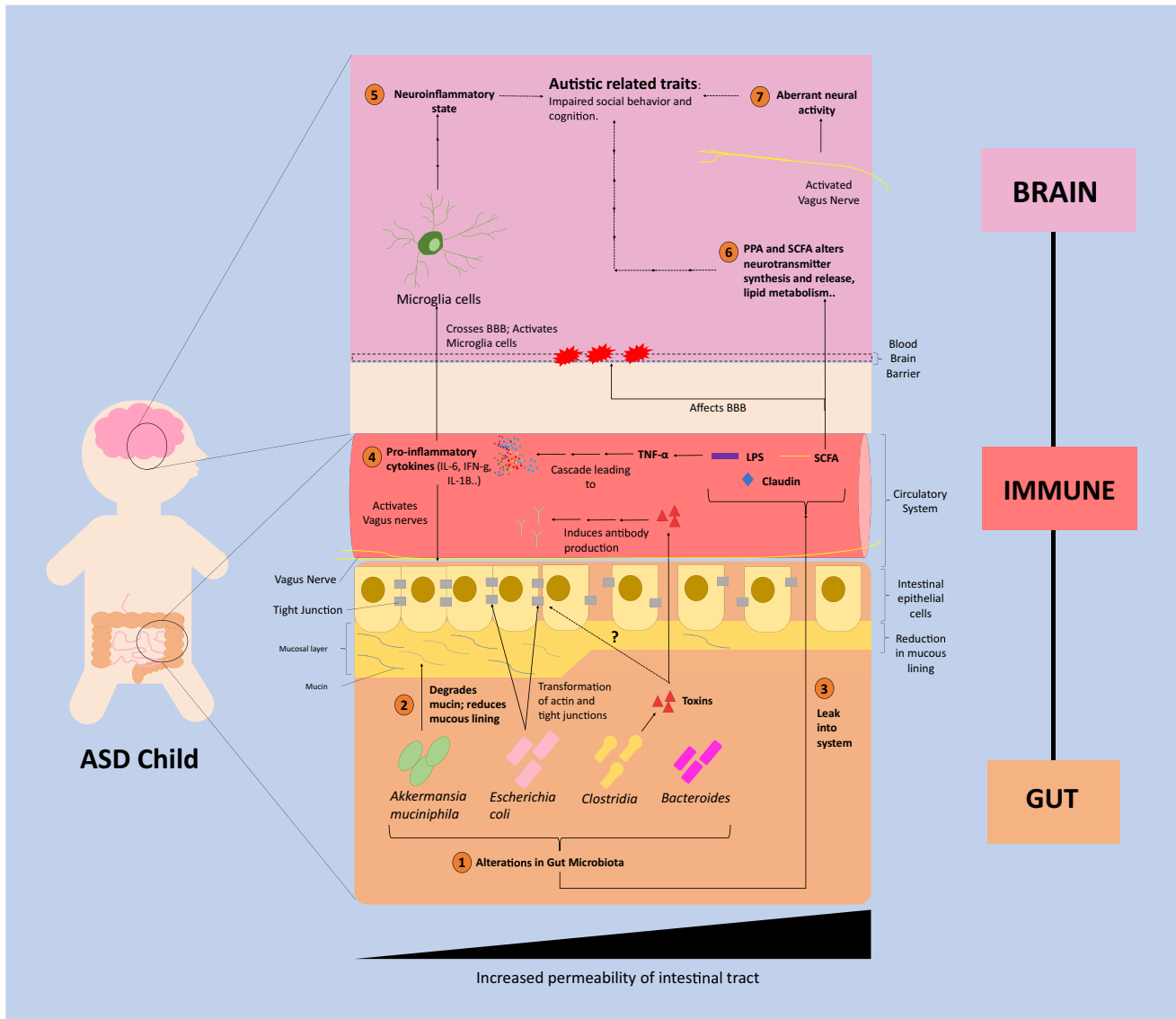
1 and 2 (CRMP1 and CRMP2), cylin, and Y-box binding protein 1 (YBX1; Braunschweig et al., 2013a). These findings not only provide insights into the mechanisms of autoantibodies, but also highlight the potential predictive markers for autism risk (Meltzer & Van de Water, 2016). Animal model studies that injected maternal anti-brain antibodies from mothers of children with autism into pregnant mice and monkeys, at varying gestational stages, yielded offspring with autism-relevant traits, supporting the promising clinical utility of antibodies (Braunschweig et al., 2012; Dalton et al., 2003; Martin et al., 2008; Singer et al., 2009).

## 5 | POSTNATAL PHASE: IMMUNE SYSTEM AND NEUROINFLAMMATION

### 5.1 | Immune dysregulation

Once thought to be immune-privileged, the CNS has been shown to be in constant communication relay with the immune system (Skaper, Facci, Zusso, & Giusti, 2018). Immune cell-derived mediators influence the CNS environment through interaction with key players such as microglia and mast cells (Garden & Möller, 2006; Hanisch & Kettenmann, 2007a). Post-mortem of brain specimens in ASD





**FIGURE 3** Schematic diagram consolidating Gut-Immune-Brain mechanisms underlying Autism Spectrum Disorder (ASD) in the postnatal phase. (1) Alteration in composition of gut microbiota; (2) Microbiota degrades mucin, further compromising the intestinal gut mucosa; (3) Compromised BBB allows bacterial metabolites (e.g., short-chain fatty acids; SCFA), toxin, and bacterial components (e.g., lipopolysaccharides; LPS) to leak into the bloodstream; (4) Elevated levels of pro-inflammatory cytokines cross the BBB, which causes microglial dysregulation; (5) Dysfunction of microglial cells contribute to neuro-inflammatory state in the child's brain; (6) Propionic acid (PPA) and SCFA compromises the BBB and influence neurotransmitter and metabolic functions; (7) Pro-inflammatory cytokines activate the vagus nerve, which leads to aberrant neural activity. (Dashed arrows indicate probable mechanisms that are involved which ought to be further investigated)

individual's ages four to forty-five suggests chronic neuroinflammation as well as increased microglial abundance and activation, with greatest activity found in the cerebella and anterior cingulate gyrus (Li et al., 2009; Morgan et al., 2010; Vargas et al., 2004). Interestingly, growing evidences have suggested that neuroinflammation is a double-edged sword that provides both neuroprotection and deleterious consequences (Griffiths, Neal, & Gasque, 2007; Skaper, 2007; Tilleux & Hermans, 2007). Persistent activation of microglia, mast cells and astroglia contribute heavily to elevation in pro-inflammatory cytokine levels that shift the exquisite balance between pro- and anti-inflammatory states to favor a perilous pro-inflammatory

condition, hindering neurodevelopmental processes (Abdallah et al., 2012; Abdallah, Larsen, Grove, Bonefeld-Jørgensen, et al., 2013; Zerbo et al., 2014). While extensive postnatal studies saw elevated levels of pro-inflammatory cytokines, including IL-6, IL-8, IL-12, IFN- $\gamma$ , TNF- $\alpha$ , and TH1, in both the brain and CSF, there were also contradictory findings which reported that, as compared to controls, ASD individuals exhibited lesser IL-6, one of the prominent pro-inflammatory cytokines (Abdallah, Larsen, Grove, Nørgaard-Pedersen, et al., 2013b; Al-Ayadi & Mostafa, 2012b; Chez & Guido-Estrada, 2010; Chez et al., 2007; Croonenberghs, Bosmans, Deboutte, Kenis, & Maes, 2002; Croonenberghs, Wauters, et al., 2002; Falcone &

**TABLE 2** Mechanisms of interaction between immuno-inflammation pathways and neurodevelopment in Autism Spectrum Disorder (ASD)

	Physiological Mechanisms	Authors
Microglial Cells	<p>Microglial Cells and Neurodevelopment</p> <p>Dysregulation in Microglial Activation</p> <ul style="list-style-type: none"> <li>• Brains of individuals with autism exhibited greater states of activation (M1)</li> <li>• Post-mortem brains of autistic persons showed significant abnormalities in activation of microglia in the cerebral cortex, cerebellum, dorsolateral prefrontal cortex, fronto-insular cortex, and white matter</li> <li>• Post-mortem of brains of autistic individuals showed increased microglial abundance and activation in the cerebellar and anterior cingulate gyrus</li> </ul> <p>Synaptic Dysregulation</p> <ul style="list-style-type: none"> <li>• Synaptic pruning depends upon microglial activation, and aberrant microglial activation influences abnormal synaptic development</li> </ul> <p>Cytokine Dysregulation</p> <ul style="list-style-type: none"> <li>• Activated microglia generate increased levels of pro-inflammatory cytokines (IL-6, IL-1<math>\beta</math>, Tumor Necrosis Factor Alpha (TNF-<math>\alpha</math>), and reactive oxygen species, which modify the central nervous system.</li> </ul>	<p>Morgan et al. (2010), Tetreault et al. (2012), Vargas et al. (2004)</p> <p>Li et al. (2009), Morgan et al. (2010), Vargas et al. (2004)</p> <p>Schafer et al. (2012)</p> <p>Garden and Möller (2006), Hanisch and Kettenmann, (2007a)</p>
Mast Cells	<p>Mast Cells and Neuroinflammation</p> <p>Mast Cell Secretion and Neurotensin</p> <ul style="list-style-type: none"> <li>• Neurotensin, which has been reported at heightened levels in autism, induces mast cell secretion of pro-inflammatory cytokines (e.g., IL-6, IL-8, IL-13, and TNF) and vasoactive substances</li> <li>• Neurotensin in autistic patients has been found to trigger the secretion of mitochondrial DNA from mast cells, which may have inflammatory actions</li> </ul> <p>Mast Cell Secretion and BBB</p> <ul style="list-style-type: none"> <li>• Molecules secreted from mast cells aggravate BBB permeability and propagates neuroinflammation</li> </ul>	<p>Theoharides and Kalogeromitros (2006); Angelidou et al. (2010)</p> <p>Ramez et al. (2001), Zhang, Angelidou, et al. (2010), Zhang et al. (2012)</p> <p>Theoharides, Tsilioni, et al. (2016)</p>
Maternal Autoantibodies	<p>Maternal Autoantibodies and Fetal Neurodevelopment</p> <p>Maternal Immunoglobulin (Ig)</p> <ul style="list-style-type: none"> <li>• Maternal IgG infiltrate the blood-brain barrier (BBB)</li> <li>• Injection of IgG from mothers of children with autism into pregnant macaque monkeys produced offspring with increased brain volume and autism-relevant behaviors</li> </ul> <p>Fetal Brain Protein</p> <ul style="list-style-type: none"> <li>• Specific maternal antibodies were found to recognize and react to fetal brain proteins of sizes 37 kDA, 73 kDA, and near 39 kDA, corresponding to Lactate Dehydrogenase A and B (LDH-A and LDH-B), stress-induced phosphoprotein 1 (STIP1), collapsin response mediator proteins 1 and 2 (CRMP1 and CRMP2), cypin, and Y-box binding protein 1 (YBX1)</li> </ul> <p>Developmental Specificity</p> <ul style="list-style-type: none"> <li>• Maternal anti-brain antibodies injected at various gestational phases resulted in autism-relevant traits, ranging from reduced exploration to alterations in sociability and anxiety</li> </ul>	<p>Bake et al., (2009)</p> <p>Dalton et al. (2003); Bauman et al. (2013)</p> <p>Braunschweig and Van de Water (2012), Fox et al. (2012), Daniel Braunschweig et al. (2008), Piras et al. (2014), Braunschweig et al. (2013a)</p> <p>Dalton et al. (2003), Singer et al. (2009), Braunschweig et al. (2012), Martin et al. (2008)</p>

(Continues)

TABLE 2 (Continued)

	Physiological Mechanisms	Authors
Maternal Immune Activation (MIA)	MIA and Autistic Phenotype	
	Human Studies	Wong and Hoeffler (2018)
	<ul style="list-style-type: none"> <li>Ubiquitous observations have linked autism to various types of infectious agents, which suggest that an inflammatory response towards an infection, rather than a specific agent, underlies ASD</li> </ul>	Gilmore et al. (2005); Meyer et al. (2005), Urakubo et al. (2001), Zuckerman and Weiner, (2005), Meltzer and Van de Water (2016)
	Animal Studies	Shi et al. (2003)
	<ul style="list-style-type: none"> <li>MIA led to the development of autistic traits in rat and macaque offspring, regardless of whether immune activation was triggered directly (i.e., poly (I:C)) or through infectious agents (i.e., virus)</li> <li>Both direct and indirect methods of maternal immune activation resulted in rodent offspring with abnormal social behaviors</li> <li>Injection of poly (I:C) injection of pregnant rhesus macaques during a specific time window, late-first or late-second trimester, elicited offspring with autistic-like behaviors</li> </ul>	Bauman et al. (2014a)
	MIA and Interleukin (IL) Profiles	
	IL-6 and IL-17 Upregulation	Bauman et al. (2014a)
	<ul style="list-style-type: none"> <li>Upregulation of IL-6 and IL-17 levels were evident in pregnant rodent mothers upon MIA induction; IL-6 propagates the secretion of pro-inflammatory IL-17</li> <li>IL-6 crosses the placenta and potentially influences fetal microglia and mast cells to modulate the trajectory of fetal neurodevelopment</li> </ul>	Abdallah, Larsen, Grove, Nørgaard-Pedersen, et al. (2013b), Zaretsky et al. (2004)
	IL-6, IL-17 and Poly (I:C) Administration	Smith et al. (2007)
	<ul style="list-style-type: none"> <li>Pregnant mice injected with pro-inflammatory IL-6 yielded offspring with aberrant autistic-like behaviors</li> <li>Poly (I:C)-treated and -untreated IL-6 knockout mice did not show significant difference in social behavior</li> <li>Pregnant mice injected with pro-inflammatory IL-17 produced offspring with autistic-like behaviors</li> <li>Injection of pregnant mice with other pro-inflammatory cytokines did not result in offspring with autistic-like traits</li> </ul>	Choi et al. (2016a) Kim et al. (2017) Smith et al. (2007)
Antibiotics and Antibody Administration	Choi et al. (2016a)	
<ul style="list-style-type: none"> <li>Administration of the antibiotic vancomycin did not result in abnormal behaviour upon MIA; Th17 levels in the small intestine of autistic rat models were reduced, as compared to controls</li> <li>Preclusion of IL-6-induced autistic phenotype was possible with anti-IL-6 antibody injection, but not anti-IFN-<math>\gamma</math> or anti-IL-1<math>\beta</math>, in pregnant dams</li> <li>Preclusion of IL-17-induced autistic phenotype was possible with anti-IL-17 antibody injection in dams.</li> </ul>		

Franco, 2015; Garbett et al., 2008; Goines & Ashwood, 2013; Li et al., 2009; Masi et al., 2014; Pardo et al., 2005; Ricci et al., 2013).

## 5.2 | Microglial cell activation

Microglia, a resident mononuclear phagocytic cell, contributes greatly towards neurodevelopment by modulating synaptic pruning, maturation of brain circuitry, and immunosurveillance (Bessis, Béchade, Bernard, & Roumier, 2007; Blinzinger & Kreutzberg, 1968; Di Marco, Bonaccorso, Aloisi, D'Antoni, & Catania, 2016; Hanisch & Kettenmann, 2007a; Kettenmann, Kirchhoff, & Verkhratsky, 2013; Paolicelli et al., 2011; Schafer et al., 2012; Tremblay et al., 2011). Both animal studies and post-mortem on brains of ASD individuals showed salient pathology differences as compared to controls, with an abundance of activated microglial cells in various brain regions (Careaga, Schwartz, & Ashwood, 2015; Morgan et al., 2010;

Tetreault et al., 2012; Vargas et al., 2004). Activated microglial cells undergo two major changes that begin with a drastic cell morphology transformation from a highly branched order to an amoeboid form (M1) before a final transformation into active phagocytes (M2; Hanisch & Kettenmann, 2007a). The former is responsible for neuronal homeostasis while the latter results in neuroinflammation (Kalkman & Feuerbach, 2016). Morphological assessments of ASD brains have shown greater proportions of microglia in M1 activated state, which further supports its role in neuroinflammation (Morgan et al., 2010; Tetreault et al., 2012). Influenced greatly by external immune signals, activated microglia secrete numerous pro-inflammatory cytokines such as IL-6, IL-1 $\beta$ , and TNF- $\alpha$  and generate reactive oxygen species that alter the CNS environment (Garden & Möller, 2006; Hanisch & Kettenmann, 2007a). Phagocytic events during neuronal debris clearance may occur without the induction of pro-inflammatory cytokines (Kettenmann et al., 2013; Ransohoff

& Perry, 2009). As such, an upregulation of cytokines associated with the activation of microglia presents evidence of chronic neuroinflammation (Ferretti & Hollander, 2015b). Consequently, these findings espouse the critical role of abnormal microglial activation in neurodevelopment (Fernández de Cossío et al., 2017), and in creating a neuro-inflammatory state which may underlie the pathogenesis of ASD (Di Marco et al., 2016).

### 5.3 | Mast cell activation

Alongside microglia, mast cells, which belong to the innate arm of the immune system, were also reported to be activated in autism (Theoharides et al., 2012; Theoharides, Doyle, Francis, Conti, & Kalogeromitros, 2008; Theoharides, Stewart, Panagiotidou, & Melamed, 2016). Indeed, the incidence of ASD increases by 10-folds in children with mastocytosis, a condition defined as the accumulation of functionally defective mast cells that contribute greatly to pro-inflammatory secretions (Kempuraj et al., 2010). Aside from immune cells-derived mediators, other substances, such as neurotensin, microbial products, and immunoglobulin-free light chains from the gut can also trigger mast cell activation (Theoharides & Kalogeromitros, 2006). In turn, mast cells secrete numerous pro-inflammatory cytokines, as well as vasoactive molecules such as histamines (Abbott, 2000; de Boer & Breimer, 1998; Kim et al., 1992). Recent findings have shown that neurotensin is present at elevated levels in both the brain and gut of ASD patients (Angelidou et al., 2010). Aside from stimulating lymphocyte proliferation and activating T cells and mast cells, neurotensin is also capable of stimulating mast cells to secrete mitochondrial DNA extracellularly, a phenomenon that has inflammatory consequences (Zhang, Asadi, Weng, Sismanopoulos, & Theoharides, 2012), and which is also observed in ASD patients (Carraway et al., 1982; Evers et al., 1994; Lemaire, 1988; Ramez et al., 2001; Zhang, Angelidou, et al., 2010). More importantly, these mast cells-derived inflammatory and vasoactive mediators increase BBB permeability, which further exacerbates the neuro-inflammatory state (Theoharides, Tsiloni, Patel, & Doyle, 2016). Table 2 summarizes fundamental immune-brain mechanisms in ASD.

## 6 | PERSPECTIVE

This section integrates the main etiological pathways of ASD in Figures 2 and 3. Future research in this field may opt to adopt three key suggestions. Firstly, the interconnected nature of these processes emphasizes the need for extensive systemic approaches with an eye for detailed mechanistic investigation. Researchers should direct their focus on reinforcing or extending existing theories, allowing for sequential processes to be elucidated. Secondly, the literature is rife with glaring missing connections. For instance, the dearth of longitudinal studies that continuously investigate pre- and postnatal processes is concerning, given that autism is a temporally sensitive neurodevelopmental disorder with processes in both stages

of development being implicated. Another unaddressed matter is how little in the way of testing has been conducted to investigate how neuroinflammation leads to autistic behavioral phenotypes, although numerous studies have cited this phenomenon to be a central etiological factor. The disjoint between systemic pathways and the manifestation of abnormal behaviors should be bridged with rigorous testing for causality. Indeed, the final suggestion reiterates the need for the field to unearth causal mechanisms. With studies on the association of systems dysfunction and ASD sketching the scaffold of autistic etiology, it is time for causal mechanisms to be brought to the fore, allowing for more definitive etiological pathways to be uncovered.

## 7 | CONCLUSION

Autism remains one of the most perplexing unsolved mysteries of the human condition. Taking the reader through the gastrointestinal, immune and nervous systems, this review has holistically elucidated the mechanisms of the “gut-immune-brain” pathway in ASD. Drawing from studies that have investigated these modular connections, potential gaps in the literature were deciphered. Future studies in this field should adopt a more systemic and causal approach, explicating missing links and conflicting evidences in a systematic manner.

### ORCID

Atiqah Azhari  <https://orcid.org/0000-0002-8809-5635>

Gianluca Esposito  <http://orcid.org/0000-0002-9442-0254>

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