Regardless of the stimulus, defective TGF-β signaling appears to unleash pro-inflammatory cytokine production. Further experiments showed that IL-1 can induce its own gene expression in mouse smooth muscle cells, consistent with prior results in human smooth muscle cells (Warner et al., 1987). Some strains of mice deficient in the endogenous antagonist of IL-1 also develop arterial aneurysms (Nicklin et al., 2000). In contrast, some reports find that IL-1 signaling can favor outward remodeling of atherosclerotic arteries in mice (Alexander et al., 2012). Resolving this apparent paradox will require further research. Yet, this ensemble of findings strongly implicates IL-1β as a key link between inflammation and altered extracellular matrix metabolism in the formation of arterial aneurysms and, quite likely, other forms of arterial disease.

Da Ros et al. (2017) closed the circle of causality in further studies of mice doubly deficient in smooth muscle cell *Smad4* and *Ccr2*, the receptor for MCP-1 (also known as CCL2), which showed muted recruitment of the pro-inflammatory subset of monocytes to arteries. They further administered an antibody that neutralizes mouse IL-1β and demonstrated reduced aneurysm formation in the smooth muscle cell Smad4-deficient mice. These findings may have considerable clinical consequences, as therapeutic antibodies that neutralize both isoforms of IL-1 and MCP-1 (CCL2) in humans have become available as well. Indeed, a recent large-scale randomized controlled clinical trial demonstrated that patients with stable coronary artery disease with residual inflammation despite standard-of-care treatment had reduced recurrent cardiovascular events when treated with the anti-IL-1β antibody canakinumab (Ridker et al., 2017). Thus, the results of Da Ros and colleagues not only provide additional mechanistic information derived from mouse experiments but also affirm pro-inflammatory cytokines such as IL-1β as therapeutic targets for combatting adverse arterial remodeling, a feature common to many common cardiovascular conditions.

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Brain, Immunity, Gut: "BIG" Links between Pregnancy and Autism

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Although dysregulation of brain, immune, and gut physiology during pregnancy have each been implicated in neuropsychiatric disorders, whether and how these presumably distinct systems are linked to cause disease is unclear. Kim et al. (2017) and Shin Yim et al. (2017) identify a pathway to explain how these aspects of our physiology are deeply and inextricably connected.

When considering the connection between pregnancy and atypical social behavior, maternal viral infection, autoimmunity, the gut microbiome, and fetal brain development are typically studied as unrelated biological processes. Two recent papers in *Nature* from the Choi and Huh laboratories now provide evidence for convergence of these disparate areas of research into a simpler and holistic model for neuropsychiatric disease (Kim et al., 2017; Shin Yim et al., 2017).

Maternal infection has long been implicated in a range of neuropsychiatric disorders, each with its own developmental trajectory and constellation of symptoms. The "how" of this promiscuous risk factor has puzzled researchers since the 1970s, when case studies showed an association between rubella and autism (Estes and McAllister, 2016). From there, viruses of

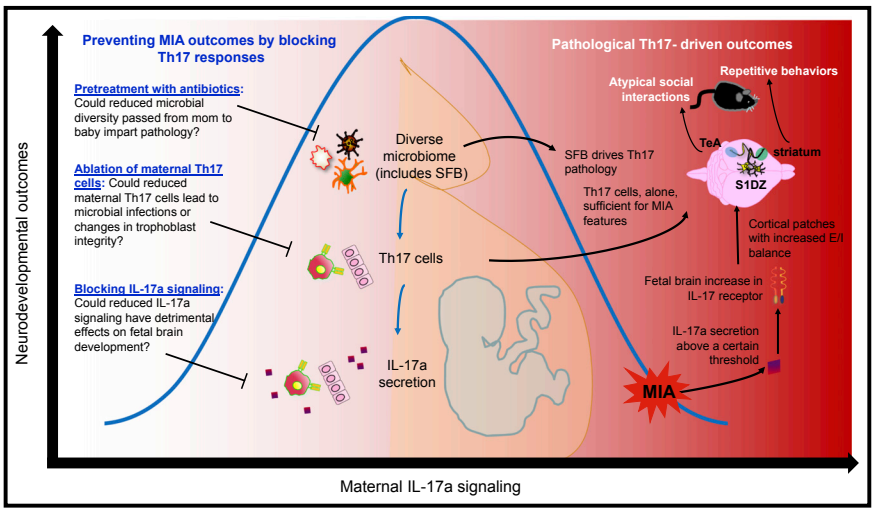

Figure 1. Healthy Pregnancy Outcomes Are Influenced by Maternal Microbiomes and Optimal Th17 Function

The maternal microbiome supports mother and fetus by imparting immunological tolerance, mucosal barrier defense, nutrients, and heightened metabolic capacities. Under physiological conditions, segmented filamentous bacteria (SFB) induce differentiation of all $CD4^+$ T helper cell fates (including regulatory T cells) and production of IgA. SFB is also required for Th17 differentiation. Th17 cells are recruited to the decidua in healthy pregnancies to promote trophoblast insertion and growth in the first trimester (in humans). Local IL-17a signaling may protect against bacterial infections during pregnancy. However, it is unclear if maternal IL-17a plays a physiological role in fetal brain development during the time when IL-17 receptors are expressed but fetal IL-17a is not.

Right: in mouse models, MIA increases maternal IL-17a, which passes into the fetal compartment. Maternal IL-17a signaling increases IL-17 receptor expression in the fetal cortex, leading to cortical malformations. Optogenetic activation of cortical S1DZ—frequently associated with MIA-induced cortical patches—drives atypical behaviors. Activation of S1DZ then increases neuronal activity in two connecting regions underlying atypical social behaviors (TeA) and repetitive behaviors (striatum). Thus, excessive Th17 activation and IL-17 signaling caused by MIA can cause cortical malformations and ASD-like behaviors in offspring.

Left: treatment with antibiotics protects against the development of MIA outcomes in murine offspring. However, decreasing microbial diversity could have adverse effects on fetal development through alterations in nutrition, decreases in brain-supportive metabolites, and immune system hyper-reactivity. Elimination of Th17 cells can also prevent MIA features, yet Th17 cells may be required to fend off microbial infections and maintain mucosal integrity and trophoblast growth during pregnancy. Finally, IL-17a signaling blockade can protect against MIA but may have a physiological neuromodulatory role during development.

all classes, bacteria, and protozoa were also implicated (Estes and McAllister, 2016), but no single pathogen specified a unique disease trajectory. Thus, it is the common phenomenon of maternal immune activation (MIA) that does the damage.

A mouse model of MIA was developed more than a decade ago based on observations that injection of the Toll-like receptor 3 (TLR3) agonist, polyinosinic: polycytidylic acid (poly[I:C]), in mid-gestation caused similar behavioral and neuropathological abnormalities in adult offspring as those reported for offspring born to flu-infected dams and as found in autism spectrum disorder (ASD) and schizophrenia (SZ) (Estes and McAllister, 2016). Approximately 150 subsequent reports using this model have provided overwhelming evidence that the poly(I:C) MIA model has construct, face, and predictive validity for both ASD and SZ.

Until recently, little was understood about how MIA causes disease-related outcomes in adult offspring. One of the first steps following MIA is elevation of maternal cytokines. Serum interleukin-6 (IL-6) increases in dams within an hour following poly(I:C) injection, which is necessary and sufficient to trigger life-long changes in the neurodevelopment of offspring (Estes and McAllister, 2016). A previous report by Choi, Huh, and colleagues extended these findings by discovering that IL-6 acts to stimulate the secretion of IL-17a from maternal T helper 17 (Th17) cells within the murine placenta and decidua (Choi et al., 2016). This maternal IL-17a is necessary and sufficient to cause aberrant behaviors in offspring and leads to upregulation of IL-17a receptor expression in the fetal cortex, in addition to a spectrum of cortical malformations within 48 hr of MIA induction (Choi et al., 2016) (Figure 1). Although this study identified a culprit cytokine, a cellular source, an anatomical consequence, and a behavioral output, it left unanswered the key mechanistic questions of whether and how cortical patches mediate a diverse set of atypical behaviors.

Shin Yim et al. (2017) began by characterizing the "where" of cortical patch spatial distributions. MIA offspring display substantial diversity in patch number and location, but patches are most often localized to the secondary motor (M2), somatosensory (S1), and temporal association (TeA) cortices (Shin Yim et al., 2017). A little more than half of MIA offspring presented patches in the dysgranular zone of S1 (S1DZ), and the size of the patches in this specific location correlated with the severity of behaviors in offspring. Notably, there was evidence for decreased inhibition and increased neuronal activity within these patches (Shin Yim et al., 2017). Alterations in excitatory/inhibitory (E/I) balance have long been hypothesized as a basis for neuropsychiatric disorders. Here, MIA offspring embody a combination of two phenomena observed in humans with ASD—cortical disorganization and increased E/I balance. Although cortical patches have been found in a small number of individuals with autism, they are present in different brain regions (Stoner et al., 2014). Thus, post-mortem analyses are required to confirm the specific involvement of S1DZ in humans with ASD. Studies should also be undertaken to determine if cortical patches are a common feature of environmental and genetic models of ASD and other disorders.

The identification of S1DZ as a specific brain region associated with MIA offspring behaviors is a big deal—and a first. To fully test causation, the authors employed optogenetics to control network activity within specific cortical regions (Shin Yim et al., 2017). Activating S1DZ recapitulated MIA-like behaviors in the absence of MIA, while

increasing network activity in regions anterior or posterior to S1DZ had no effect. The authors then identified two regions receiving projections from S1DZ that, when independently activated, dissociated social interactions (TeA) from repetitive behaviors (striatum). Perhaps most importantly, reducing activity in the S1DZ, TeA, and the striatum of MIA offspring rescued their aberrant social and repetitive behaviors (Shin Yim et al., 2017). The potential significance of these specific S1DZ circuits in mediating ASD-related behaviors cannot be overstated, especially if future work finds these to be responsible for aberrant behaviors in other genetic ASD models.

With these results in hand, the Choi and Huh labs turned their attention to another key issue in the field: identifying at-risk populations. In scientific and public spheres, as well as between them, the "why" of recent increases in the incidence of neuropsychiatric disorders, most notably autism, foments all manner of disputes. Diagnostic drift? Increased awareness? Parental age? Environment? There are many heavily invested stakeholders in these debates. Less disputed, however, is the parallel rise in autoimmune disorders. What if the presence of one condition influenced the likelihood of developing the other?

Previous work from these groups hinted at this connection because they employed a mouse model whose commensal microbiota conferred an autoimmune propensity (Choi et al., 2016; Yang et al., 2014). This particular Taconic Farms mouse line harbors segmented filamentous bacteria (SFB), which drive Th17 cell differentiation. It is well known that pathological Th17 cell responses are implicated in several autoimmune disorders, including multiple sclerosis, rheumatoid arthritis, and lupus. Mice without SFB lack Th17 cells, and MIA induction in the mothers fails to elicit the abnormal features of MIA offspring (Kim et al., 2017). Furthermore, *IL-17a*-deficient dams reconstituted with SFB antigen-specific Th17 cells (in the absence of MIA induction) produced offspring with the full spectrum of MIA abnormalities; this is remarkable—and worrisome. It suggests that, if these findings can be translated to humans, certain autoimmune conditions alone might potentially pose a risk for the development of neuropsychiatric disorders in offspring. As a therapeutic test, the authors treated SFB-harboring female mice with antibiotics prior to and during pregnancy, which completely prevented the pathological effects of MIA (Kim et al., 2017).

So, a course of antibiotics prior to and throughout pregnancy can prevent neuropathologies in offspring in a mouse model of autoimmunity. Can it be this simple? A recent headline from the *Lancashire Evening Post* titled "Could Autism Be Prevented in Pregnancy?" led readers to hope so. Before we further expand the use of antibiotics as a putative prophylactic for ASD, especially for the duration of pregnancy, it is worth pausing to consider why autoimmune disorders are so prevalent in westernized countries—an estimated 1 in 13 Americans (Okada et al., 2010). A theory with increasing evidentiary support implicates our modern, antiseptic environment with its reduced pathogen exposure and microbial diversity. Our immune systems co-evolved with a parasitic ecosystem and recurrent infections. In the absence of these encounters early in life, our immune systems can skew toward hyper-reactivity, wherein responses to "self" eventually lead to chronic illness (Okada et al., 2010). Increased antibiotic use may thus have the unintended and devastating consequence of increasing the risk for autoimmunity.

Even if it were possible to target just the offending microbes, it isn't clear why they are potentiating this pathological response. Unless you are a rainbow trout, SFB is a benign and even beneficial parasite that enhances the fitness of the host through immunological education and mucosal barrier defense (Ericsson et al., 2014) (Figure 1). SFB promotes differentiation of the T cell repertoire and IgA production, which, in turn, promotes diversity of normal gut microbiota. In disease models, SFB confers protection from irritable bowel syndrome and type 1 diabetes (Ericsson et al., 2014).

Th17 cells are similarly protective in a range of disorders involving mucosal barriers. Targeting Th17 cells during pregnancy could be problematic given that Th17 cells are recruited to the decidua in healthy pregnancies where they combat extracellular microbial pathogens, restrain mucosal inflammation, and promote trophoblast growth (Lombardelli et al., 2016). In addition, blocking IL-17a also runs the risk of detrimental unintended consequences, including altered neuromodulation during brain development and increased risk of suicide (Silverstein and Huh, 2017). Thus, the presence of IL-17a signaling, or of SFB and Th17 cells at the feto-maternal interface, does not denote pathology and may instead be salutary (Figure 1).

Finally, despite the elegant and compelling data in these papers, there are discrepancies with previous work in the MIA model. For instance, mice lacking SFB (from Jax laboratories) have been used successfully by several labs to generate MIA phenotypes. Additionally, while Shin Yim et al. (2017) found that MIA features were exclusive to MIA induction at mid-gestation, this conflicts with several reports in which late-gestation poly(I:C) injection produced offspring with atypical social interactions and repetitive behaviors (Estes and McAllister, 2016). The results from the Choi and Huh labs also suggest additional mechanisms: all three studies from this group show atypical behaviors in nearly all MIA offspring, with effect sizes that are completely separable from control offspring (Kim et al., 2017; Shin Yim et al., 2017; Choi et al., 2016). Yet, Shin Yim et al. (2017) report that nearly half of the MIA offspring lack cortical patches in S1DZ. Clearly, more research is needed to identify the range of contexts in which viral infection alters fetal development and to determine the relative prevalence of the possible parallel mechanisms that mediate the effects of MIA on offspring. Understanding the nature of that variability will be important to increase the likelihood that future clinical trials will translate to our complex and variable human population.

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