The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring

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Viral infection during pregnancy has been correlated with increased frequency of autism spectrum disorder (ASD) in offspring. This observation has been modeled in rodents subjected to maternal immune activation (MIA). The immune cell populations critical in the MIA model have not been identified. Using both genetic mutants and blocking antibodies in mice, we show that retinoic acid receptor gamma t (RORγt)–dependent effector T lymphocytes [for example, T helper 17 (T helpers 17) cells] and the effector cytokine interleukin-17a (IL-17a) are required in mothers for MIA-induced behavioral abnormalities in offspring. We find that MIA induces an abnormal cortical phenotype, which is also dependent on maternal IL-17a, in the fetal brain. Our data suggest that therapeutic targeting of T helpers 17 cells in susceptible pregnant mothers may reduce the likelihood of bearing children with inflammation-induced ASD-like phenotypes.

Several studies have suggested that viral infection of women during pregnancy correlates with an increased frequency of autism spectrum disorder (ASD) in the offspring (1–6). In the rodent maternal immune activation (MIA) model of this phenomenon (7), offspring from pregnant mice infected with virus or injected intraperitoneally with synthetic double-stranded RNA (dsRNA) [poly(I:C)], a mimic of viral infection, exhibit behavioral symptoms reminiscent of ASD: social deficits, abnormal communication, and repetitive behaviors (8). T helper 17 (T helpers 17) cells are responsible for immune responses against extracellular bacteria and fungi, and their dysregulation is thought to underlie numerous inflammatory and autoimmune diseases (9), such as asthma, rheumatoid arthritis, psoriasis, inflammatory bowel disease (IBD), and multiple sclerosis. The transcription factor retinoic acid receptor–related orphan nuclear receptor gamma t (RORγt) is expressed in several cell types in the immune system. It is a key transcriptional regulator for the development of T helpers 17 cells, as well as γδ T cells and innate lymphoid cells (such as ILC3) that express T helpers 17 cell–like cytokines, in both humans and mice (10–13).

T helpers 17 cells and their cytokine mediators have been suggested to have a role in ASD. For example, elevated levels of interleukin-17a (IL-17a) (14), the predominant T helpers 17 cytokine, have been detected in the serum of a subset of autistic children (14, 15). A genome-wide copy number variant (CNV) analysis identified IL17A as one of many genes enriched in autistic patients (16). Similarly, in the MIA mouse model, CD4+ T lymphocytes from affected offspring produced higher levels of IL-17a upon in vitro activation (17, 18). Although these data suggest that T helpers 17 cells may be involved in ASD patients, whether T helpers 17 cells are the specific immune cell population that is necessary for MIA phenotypes is unknown. Here, we show that maternal RORγt–expressing proinflammatory T cells, a major source of IL-17a, are required in the MIA model for induction of ASD-like phenotypes in offspring. Consistent with this notion, antibody blockade of IL-17a activity in pregnant mice protected against the development of MIA–induced behavioral abnormalities in the offspring. Also, we found atypical cortical development in affected offspring, and this abnormality was rescued by inhibition of maternal T helpers 17–IL-17a pathways.

Elevated fetal brain IL-17a mRNA follows increased maternal IL-17a in MIA

Pregnant mothers injected with poly(I:C) on embryonic day 12.5 (E12.5) had strong induction of serum cytokines IL-6, tumor necrosis factor-α (TNF-α), interferon-β (IFN-β), and IL-β at 3 hours, compared with phosphate-buffered saline (PBS)–injected control dams (fig. 1A and fig. S1, A to C). Additionally, poly(I:C) injection resulted in a strong increase of serum IL-17a at E14.5 (fig. 1B). On the other hand, poly(I:C) did not affect the levels of the anti-inflammatory cytokine IL-10 in the serum nor in placenta and decidua extracts (fig. S1D). It was previously shown that the pro-inflammatory effector cytokine IL-6, a key factor for T helpers 17 cell differentiation (19), is required in pregnant mothers for MIA to produce ASD-like phenotypes in the offspring (7). We found that poly(I:C) injection into pregnant dams lacking IL-6 (IL-6 knockout [KO]) failed to increase the serum levels of IL-17a at E14.5, consistent with IL-6 acting upstream of IL-17a. Conversely, recombinant IL-6 injections into wild-type (WT) mothers were sufficient to induce IL-17a levels comparable to those of poly(I:C)-injected WT mothers (fig. S1E). Placenta- and decidua-associated mononuclear cells, isolated from poly(I:C)-treated animals at E14.5 and cultured for 24 hours, expressed amounts of IL-6 mRNA similar to those of PBS controls (fig. 1C). In contrast, IL-17a mRNA expression in these cells was strongly up-regulated by poly(I:C) injection (fig. 1D). This increase in mRNA expression was correlated with enhanced secretion of IL-17a by placenta- and decidua-associated mononuclear cells from poly(I:C)-treated dams (fig. 1E), upon ex vivo stimulation with phorbol-myristate acetate (PMA) and ionomycin, which mimics T cell receptor (TCR) activation. IL-17a induction was specific to the placenta and decidua, as small intestine mononuclear cells from poly(I:C)-treated pregnant dams did not secrete more IL-17a than those from PBS-treated controls (fig. S1F).

We also observed that expression of the IL-17a receptor subunit A (IL-17Ra) mRNA, but not subunit C (IL-17Rc) mRNA, was strongly augmented in the fetal brain upon induction of MIA (Fig. 1, F and G). By in situ hybridization, IL-17Ra mRNA was detected in the mouse cortex, and its expression was strongly up-regulated in E14.5 fetal brains after poly(I:C) injection of pregnant dams (Fig. 1, H and I). The in situ probe detecting endogenous expression of IL-17Ra was specific, as it did not produce detectable signal in E14.5 fetal brain that lack IL-17Ra (fig. S2).

Maternal IL-17a promotes abnormal cortical development in offspring

We next investigated if pathological activation of the IL-17 pathway in pregnant mothers affects fetal brain development and subsequently contributes to the ASD-like behavioral phenotypes in offspring. To test this hypothesis, we pretreated pregnant mothers with isotype control or IL-17a–blocking antibodies before injecting them with PBS or poly(I:C) (fig. S3). We then examined cortical development in the fetus for the following reasons: (i) Poly(I:C) injection of mothers increases IL-17Ra expression in the cortex of the fetal brain (Fig. 1, H and I); (ii) cortical development starts at about E11 (20), which aligns well with the time points of potential fetal exposure to MIA (7); (iii) disorganized cortex and focal patches of abnormal laminar cytoarchitecture have been found in
the brains of ASD patients (21, 22); and (iv) MIA has been shown to affect cortical development (23, 24). We analyzed cortical lamination, an orderly layered structure of the cortex, in fetal brains at E14.5 and E18.5, as well as in the adult brain, using antibodies specific for proteins expressed in the cortex in a layer-specific manner (25): special AT-rich sequence-binding protein 2 (SATB2) (26), T-brain-1 (TBR1) (27), and chicken ovalbumin upstream promoter transcription factor–interacting protein 2 (CTIP2) (28). MIA led to delayed expression of SATB2 at E14.5 compared with fetuses of control animals (Fig. 2, A and C). At E18.5, MIA resulted in a patch of disorganized cortical cytoarchitecture (Fig. 2, B and D to G) but did not affect cortical thickness of the fetal brains (Fig. 2H). This singular patch of disorganized cortex occurred at a similar medial-lateral position in a majority of E18.5 fetal brains (Fig. 2, E and G) derived from mothers injected with poly(I:C) but not those injected with PBS. The abnormal expression patterns of SATB2, TBR1, and CTIP2 were maintained in adult MIA offspring (fig. S4). Note that normal expression of these cortical layer-specific markers, as well as laminar cortical organization, were largely preserved in the offspring of poly(I:C)-injected mothers pretreated with IL-17a-blocking antibody (Fig. 2, A to D, and fig. S4).

Pretreatment with IL-17a–blocking antibody also suppressed the MIA-mediated increase in IL-17Ra mRNA expression in fetal brain at E14.5 (Fig. 1F). This suppression was accompanied by a reduction in maternal serum IL-17a (Fig. 1B), which indicated that the up-regulation of IL-17Ra mRNA in fetal brains requires maternal IL-17a signaling. Of note, IL-17a antibody blockade of the IL-17a–IL-17Ra signaling pathway did not result in a concomitant increase of the serum IL-10 levels, and IL-17a mRNA expression was not detected in fetal brain at E14.5, regardless of poly(I:C) injection. Together, these data demonstrate that the maternal IL-17a–dependent pathway mediates disorganized cortical phenotypes in offspring after in utero MIA and suggest that this may be due to exposure of the fetus and its brain to increased levels of IL-17a.

**Maternal IL-17a promotes ASD-like behavioral abnormalities in offspring**

We next tested the functional relevance of the maternal IL-17a pathway for MIA-induced ASD-like behavioral abnormalities in offspring (fig. S3). We first assessed MIA offspring for abnormal communication by measuring pup ultrasonic vocalization (USV) responses (29). After separation from mothers, pups from poly(I:C)-injected mothers pretreated with immunoglobulin G (IgG) isotype control antibody emitted more USV calls than those from PBS-injected mothers (Fig. 3A), in agreement with previous studies (29, 30). Some studies have reported reduced USV calls upon MIA (8, 31), but these opposite effects may reflect differences in methodological approaches, including dose and number of exposures to poly(I:C), as well as timing of poly(I:C) administration. Altogether, these results indicate that MIA induces abnormal USV in offspring. Pretreating poly(I:C)-injected mothers with IL-17a–blocking antibody resulted in offspring that emitted a similar number of USV calls as the pups from PBS-injected control mothers (Fig. 3A), which demonstrated that IL-17a-mediated signaling events are necessary for the MIA-induced abnormal USV phenotype. As previously reported (7, 8), we found that prenatal exposure to MIA also caused social interaction deficits in adult offspring (Fig. 3B). This defect was fully rescued in offspring from poly(I:C)-injected

![Fig. 1. IL-17a increase in mothers subjected to MIA leads to elevated IL-17Ra mRNA expression in the offspring.](https://example.com/fig1)
mothers pretreated with IL-17a-blocking antibody (Fig. 3B). Repetitive and perseverative behaviors are another core feature in ASD that we tested next in our experimental mice using the marble-burying assay (32). Offspring from poly(I:C)-injected mothers displayed enhanced marble burying compared with offspring from PBS-injected mothers (Fig. 3C), consistent with previous studies (7, 29). Pretreatment with IL-17a-blocking antibody of poly(I:C)-injected mothers rescued marble-burying behavior in the offspring (Fig. 3C). Notably, distinct behavioral phenotypes

![Image](37x670 to 558x728)

**Fig. 2.** The IL-17a pathway promotes abnormal cortical development in the offspring of pregnant dams after MIA. (A) Immunofluorescence staining of SATB2 (a marker of postmitotic neurons in superficial cortical layers) in E14.5 male fetal brain, derived from PBS- or poly(I:C)-injected mothers, pretreated with isotype control (Cont) or anti-IL-17a. MZ, marginal zone; CP, cortical plate; SP, subplate; SVZ, subventricular zone; VZ, ventricular zone. (B) Staining of SATB2 and TBR1 (a marker restricted to deeper cortical layers) in E18.5 male fetal brains from animals treated as in (A). Cortical layers: II to IV, V, and VI. (C) Quantification of SATB2 intensity in the cortical plate of E14.5 fetal brains (n = 8 for all groups; three independent experiments). (D) Quantification of TBR1- and SATB2-positive cells in a 300 × 300 µm² region of interest (ROI) centered on the malformation in the cortical plate of E18.5 fetal brains (n = 20 [PBS, Cont]; n = 20 [PBS, anti-IL-17a]; n = 24 [poly(I:C), Cont]; n = 20 [poly(I:C), anti-IL-17a]; five independent experiments). (E) The spatial location of the cortical patch in E18.5 male fetal brains from poly(I:C)-injected mothers pretreated with control antibodies (n = 20 [poly(I:C), Cont]). (F) The disorganized patches of cortex observed in fetuses from poly(I:C)-injected mothers were categorized into groups based on morphology: Protrusions, intrusions, or other abnormal patterns and their representative images are shown. (G) Percentage of the cortical patches in each category (n = 24 [poly(I:C), Cont]). (H) Thickness of the cortical plate in E18.5 fetal brains, derived from PBS- or poly(I:C)-injected mothers, pretreated with isotype control or anti-IL-17a (n = 20 for all groups; five independent experiments). Scale bars in (A), (B), and (F), 100 µm. One-way ANOVA (C) and (H) and two-way ANOVA (D) with Tukey’s post hoc tests. **P < 0.01 and *P < 0.05. Means ± SEM.
were indistinguishable (Fig. 3D). Moreover, different treatment groups displayed comparable gender ratios, litter sizes, and weights (fig. S5). Taken together, these data indicate that the IL-17a pathway in pregnant mice is crucial in mediating the MIA-induced behavioral phenotypes in offspring.

Figure 3: The IL-17a pathway promotes ASD-like phenotypes in the MIA offspring. (A) USV assay. At P9, pups from the indicated experimental groups were separated from their mothers to elicit USV calls. The number of pup calls is plotted on the y axis (n = 25 [PBS, Cont]; n = 28 [PBS, anti-IL-17a]; n = 38 [Poly(I:C), Cont]; n = 34 [Poly(I:C), anti-IL-17a]; from six or seven independent experiments). (B) Social approach behavior. Graphed as a social preference index (% time spent investigating social or inanimate stimulus out of total object investigation time) (n = 15 [PBS, Cont]; n = 15 [PBS, anti-IL-17a]; n = 16 [Poly(I:C), Cont]; n = 20 [Poly(I:C), anti-IL-17a]; from six or seven independent experiments). (C) Marble-burying behavior. Percentage of the number of buried marbles is plotted on the y axis (n = 15 [PBS, Cont]; n = 15 [PBS, anti-IL-17a], n = 15 [Poly(I:C), Cont]; n = 20 [Poly(I:C), anti-IL-17a]; from six or seven independent experiments). (D) Total distance traveled during social approach behavior. (A), (C), and (D) One-way ANOVA with Tukey’s post hoc tests. (B) Two-way ANOVA with Tukey’s post hoc tests. ***P < 0.01 and *P < 0.05. Means ± SEM.

Figure 4: RORγt expression in maternal T cells is required for manifestation of ASD-like phenotypes in the MIA model. (A) SATB2 and TBR1 staining in the cortex of E18.5 male fetal brains after MIA induction with poly(I:C) in mothers with the indicated genotypes. Cortical layers: II to IV, V, and VI. Images are representative of three independent experiments. Scale bar, 100 μm. (B) Quantification of TBR1- and SATB2-positive cells in a 300 × 300 μm² ROI centered on the malformation in the cortical plate of E18.5 male fetal brains (n = 6 for all groups). (C) Number of USVs emitted by P9 pups. Total USVs emitted during test period (3 min) are plotted on the y axis (n = 16, 18, and 15 offspring from PBS-treated WT, RORγt HET, and RORγt TKO mothers, respectively; n = 15, 11, and 28 from poly(I:C)-treated WT, RORγt HET, and RORγt TKO mothers, respectively; data from four to seven independent dams). (D) Social approach behavior is shown as a social preference index as in Fig. 3. [n = 21, 15, and 15 adult offspring from PBS-treated WT, RORγt HET, and RORγt TKO mothers, respectively; n = 36, 15, and 21 from poly(I:C)-treated WT, RORγt HET, and RORγt TKO mothers, respectively; data from four to seven independent dams]. (E) Marble-burying behavior as in Fig. 3 [n = 14, 19, and 15 adult offspring from PBS-treated WT, RORγt HET, and RORγt TKO mothers, respectively; n = 32, 15, and 25 from poly(I:C)-treated WT, RORγt HET, and RORγt TKO mothers, respectively; data from four to seven independent dams]. (F) Total distance moved by offspring tested for social behavior. RORγt HET and RORγt TKO refer to RORγt floxed; CD4-Cre/+ and RORγt floxed; CD4-Cre/+, respectively. (C) One-way ANOVA with Holm-Sidak post hoc tests. (B) and (D) Two-way ANOVA with Tukey’s post hoc tests. (E) and (F) One-way ANOVA with Tukey’s post hoc tests. ***P < 0.001, **P < 0.01, and *P < 0.05. Means ± SEM.
RORγ expression in maternal T cells is required for ASD-like phenotypes in the MIA offspring.

As RORγt is a critical regulator of the IL-17a pathway (23), we next investigated the role of maternal RORγt in MIA-induced behavioral phenotypes in offspring. Note that T17 cells and IL-17A have been detected in the decidua, as well as in the serum, during pregnancy in humans (33-35). CD4+ mononuclear cells, including CD4+ T cells, isolated from placenta and decidua of immune-activated WT mothers, but not from immune-activated mothers lacking both RORγt and the closely related RORγt isof orm (RORγ KO), produced IL-17A upon ex vivo activation with PMA and ionomycin (fig. S6, A and B). Cells isolated from WT and RORγ KO mice secreted similar amounts of IFN-γ, consistent with the specific effect of RORγt on IL-17a expression (fig. S6C).

In line with this observation, poly(I:C) treatment increased placenta- and decidua-associated T17, but not regulatory T, cells in pregnant dams, compared with PBS treatment (fig. S6, D and E). RORγ KO mice lack RORγt and γt expression not only in CD4+ T cells but also in other lymphoid and non-immune system cells, and they have defective development of secondary and tertiary lymphoid organs (36, 37). To determine whether RORγt function specifically in T cells mediates MIA-induced phenotypes, we bred RORγt-FL animals (fig. S7) to CD4-Cre mice to selectively inactivate RORγt in the offspring (fig. 4, D and E). These regulatory deficits and excessive marble behaviors modeled in mouse offspring.

To determine whether IL-17a acts on receptors in the mother or the fetus to induce the MIA phenotype, we injected poly(I:C) into IL-17Ra WT, HET, or KO mothers that had been bred to IL-17A WT or HET males (39). Removing one or both copies of il17ra in the mother was sufficient to rescue the MIA-induced sociability deficit in offspring, regardless of their genotypes (fig. S6A). Moreover, we found that reduced expression of maternal IL-17A in il17ra HET mothers led to reduced serum IL-17a in poly(I:C)-treated mothers (fig. S6B). Thus, it is difficult, if not impossible, to test the functional significance of the IL-17Ra in offspring with a full germline il17ra KO without affecting maternal T17 cell activity. To circumvent this problem, we asked if increasing IL-17Ra activity in the offspring, by introducing IL-17a directly into the fetal brain in the absence of maternal inflammation, would be sufficient to induce MIA phenotypes. Injection of recombinant IL-17a protein into the ventricles of the fetal brain at E14.5 in the absence of MIA (fig. 5A) led to the appearance of disorganized cortical patches in a similar location to those induced by MIA (fig. 5, B to E). Unlike poly(I:C) injection, however, intraventricular injection of IL-17a resulted in thinned cortical plates at the medial but not lateral part of the brain (fig. S9). This effect may reflect...
Therapeutic treatment with IL-17a–blocking antibody in pregnant dams ameliorates MIA-associated behavioral abnormalities

Our results suggest that pathological activation of the T17 cell–IL-17a pathway during gestation in mothers with some inflammatory conditions may alter fetal brain development and contribute to the ASD-like behavioral phenotypes in offspring (Fig. S11). T17 cells require RORγt for their differentiation and exert their functions by secreting multiple cytokines, including IL-17a. Abrogation of RORγt expression in maternal T cells or blockade of the IL-17a pathway in pregnant dams resulted in the complete rescue of cortical developmental abnormalities and ASD-like behavioral phenotypes in offspring in the MIA rodent model. Thus, RORγt and T17 cells (as well as their cytokines) may serve as good therapeutic targets to prevent the development of ASD phenotypes in the children of susceptible mothers. To further test this idea, we administered IL-17a–blocking antibody to pregnant mice in a time window after MIA induction (Fig. 6A). We injected pregnant mothers with PBS or poly(I:C) at E12.5, followed by injection of IgG isotype control or IL-17a–blocking antibody at E14.5, when the delayed expression of SABT2 manifests in MIA-exposed fetal brains (Fig. 2, A and C). Compared with PBS injection followed by control antibody treatment, poly(I:C) injection followed by IL-17a–blocking antibody administration partially rescued USV and marble-burying phenotypes (Fig. 6, B and D). However, MIA-induced social interaction deficits were not corrected (Fig. 6C). These effects were not due to group differences in mobility (Fig. 6E). Thus, treating pregnant mothers with IL-17a–blocking antibody after MIA can correct some of the ASD-like features, but pretreatment with this antibody may have greater therapeutic potential.

Conclusions

Our results identify a specific maternal immune cell population that may have direct roles in inducing ASD-like phenotypes by acting on the developing fetal brain. These findings raise the possibility that modulation of the activity of a cytokine receptor, IL-17Ra, in the central nervous system can influence neuronal development, with implications as to specification of neuronal cell types and their connectivity. Furthermore, note that the loss of certain genes that induce ASD-like phenotypes were also found in mice with defects in cortical laminar (41, 42). These observations raise the possibility that some genetic and environmental factors that have roles in the etiology of ASD function by way of similar physiological pathways. A related question is whether IL-17Ra signaling has a normal physiological function in the fetal and adult brain, especially given the structural similarities observed between the IL-17 family cytokines and neurotrophin proteins (e.g., nerve growth factor (43, 44). Elucidating further downstream pathways of maternal IL-17–producing T cells, both in MIA mothers and their offspring, will likely yield a better understanding of the mechanisms by which inflammation in utero contributes to the development of neurodevelopmental disorders, such as ASD.

Fig. 6. Therapeutic effects of blocking IL-17a signaling in pregnant dams. (A) Schematic diagram of the experimental design. At E12.5, pregnant mothers were injected with PBS or poly(I:C) to induce MIA. Two days later (E14.5), the pregnant mothers were treated with isotype or anti–IL-17a. At P7 to ~P9, pups were separated from the dams to measure USV calls. At ~8 weeks, male offspring were subjected to the social approach test and marble-burying test. (B) USV assay. The number of pup calls is plotted on the y axis (n = 17 [PBS, Cont]; n = 17 [poly(I:C), Cont]; n = 27 [poly(I:C), anti–IL-17a]; from three or four independent dams per treatment). (C) Social approach behavior is shown as a social preference index (Fig. 3) (n = 12 [PBS, Cont], n = 10 [poly(I:C), Cont], n = 17 [poly(I:C), anti–IL-17a]; from three or four independent dams per treatment). (D) Marble-burying behavior as in Fig. 3 (n = 12 [PBS, Cont], n = 10 [poly(I:C), Cont], n = 17 [poly(I:C), anti–IL-17a]; from three or four independent dams per treatment). (E) Total distance traveled during social approach behavior. (B), (D), and (E) One-way ANOVA with Tukey’s post hoc tests. (C) Two-way ANOVA with Tukey’s post hoc test. *P < 0.01 and **P < 0.05. Means ± SEM.
A DNA topoisomerase VI-like complex initiates meiotic recombination
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The SPO11 protein catalyzes the formation of meiotic DNA double strand breaks (DSBs) and is homologous to the A subunit of an archaeal topoisomerase (topo VI). Topo VI are heterotetrameric enzymes comprising two A and two B subunits; however, no topo VI involved in meiotic recombination had been identified. We characterized a structural homolog of the archaeal topo VI subunit [meiotic topoisomerase VI–like (MTO/VIB)], which is essential for meiotic DSB formation. It forms a complex with the two Arabidopsis thaliana SPO11 orthologs required for meiotic DSB formation (SPO11-1 and SPO11-2) and is absolutely required for the formation of the catalytic core complex responsible for meiotic DSB formation in eukaryotes adopts a topo VI-like structure. 

meiotic recombination is the key step in sexual reproduction leading to the production of haploid gametes and is therefore essential for the fertility of most eukaryotes. It is initiated by the induction of DNA double strand breaks (DSBs), which are catalyzed by the evolutionarily conserved SPO11 protein (1). SPO11 shows sequence similarities to the A subunit of the archaeal type II topoisomerase (topo VI). Topo VI are heterotetrameric enzymes involved in meiotic recombination had previously been identified. We characterize a structural homolog of the archaeal topo VI subunit [meiotic topoisomerase VI–like (MTO/VIB)], which is essential for meiotic DSB formation. It forms a complex with the two Arabidopsis thaliana SPO11 orthologs required for meiotic DSB formation (SPO11-1 and SPO11-2) and is absolutely required for the formation of the catalytic core complex responsible for meiotic DSB formation in eukaryotes adopts a topo VI-like structure.

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SUPPLEMENTARY MATERIALS
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