Chiral disulfonimidines were first examined as chiral counterion precursors in this reaction but had mediocre activity. Considering that the nature of counteranions strongly influences Lewis acidities of the cationic partners, Gatzenmeier et al. decided to investigate the Diels–Alder reaction with carbamions, which would be expected to form a combination of greater overall Lewis acidity. To evaluate these carbon-centered anions, they designed a range of enantiopure C–H acid precatalysts that would react in situ with the silyl-transfer reagent to generate an ion pair as a catalyst (see the figure, panels B and C). With respect to the substrate scope, Gatzenmeier et al. achieved impressive stereoinductions (up to 97:3 enantiomer ratio) and excellent yields in such a transformation. The protocol can be applied to a variety of substrates, including hetero-aromatic substrates, showing its wide applicability. Furthermore, this strategy cleverly combines the benefits of silylated compounds (nontoxic and air and water stable) with exceptionally low catalyst loadings (only 1 mole percent).

The work of Gatzenmeier et al. allows normally unreactive cinnamates to undergo Diels–Alder cyclization. This method of activation based on the tunability of Lewis acids could give rise to extensive applications in any challenging Lewis-acid-catalyzed reaction. More broadly, through its C–H acidic function, this new catalyst could turn into an effective alternative in reactions catalyzed by Brønsted acids. ■

**IMMUNOLOGY**

*Maternal T<sub>H17</sub> cells take a toll on baby’s brain*

Infection produces an immune molecule that interferes with brain development

By Myka L. Estes and A. Kimberley McAllister

The possibility that microcephaly is caused by Zika virus has made recent alarming headlines. Although few people had previously heard of an association between infection during pregnancy and changes in brain development, epidemiologists have known about this connection for many years. Moreover, mounting evidence suggests that maternal immune activation (MIA) alone is sufficient to alter brain development and may be causally linked to autism spectrum disorder (ASD) (1–3). How could the maternal immune system, which normally serves to protect mother and child from environmental insults, cause changes in brain development? On page 933 of this issue, Choi et al. (4) uncover an important component of this immune pathway: a critical signal from a special class of cells in the mother’s immune system, called T helper 17 (T<sub>H17</sub>) cells, that alters brain development in her fetal offspring (see the figure). These findings have exciting implications for the development of new treatments to prevent ASD caused by maternal infection.

How does the mother’s immune system, which has limited access to the fetal compartment, alter brain development? Cytokines, immune system signaling molecules that are generated in response to infection, can cross the placental boundary and are critical for MIA to change brain development and behavior in offspring. One of the first cytokines elevated in the serum of pregnant mice after immune activation is interleukin-6 (IL-6). This increase is necessary and sufficient for MIA to alter brain development and behavior in offspring (5). Choi et al. have now identified another cytokine, IL-17, that is necessary and sufficient to mediate the effects of MIA. But this isn’t just another cytokine to add to the steadily growing list of factors implicated in MIA. Choi et al. convincingly show, using several genetic mouse models and targeted blockade, that IL-17 acts downstream of IL-6 in offspring after MIA. Whereas previous studies identifying cytokines involved in MIA raised more questions than they answered, Choi et al. present an impressive series of experiments demonstrating the role of IL-17 in mediating the effects of MIA in offspring. Moreover, the authors have identified its cellular source: IL-17 is secreted by T<sub>H17</sub> cells present in the mother’s circulating blood, where it crosses the placenta and acts in the brain of developing offspring. IL-17 increases the cellular expression of IL-17 receptor, further increasing IL-17 signaling in the fetal brain.

This sequence of events is required for MIA to cause cortical malformations and the three core behavioral abnormalities associated with ASD (4). How IL-17 exerts its effects, and upon which cells and with what molecular consequences, is still a mystery, especially because the literature on IL-17 signaling in the brain remains limited and contradictory.

Although IL-17 and the cells that produce it, T<sub>H17</sub> cells, have been implicated in ASD through both genetic associations and observations of elevated IL-17 concentration in the blood of children (6–8), there was no evidence for a role for T<sub>H17</sub> cells in MIA until the Choi et al. study. T<sub>H17</sub> cells protect against bacterial and fungal pathogens, especially at mucosal surfaces such as the gut, and are an important part of an inflammatory response to infection (9). T<sub>H17</sub> cells may also be critical for the development of autoimmunity and have been implicated in numerous animal models of autoimmune disorders (10). For their study, Choi et al. used a specific mouse strain that is widely used to generate animal models for experimental autoimmune encephalomyelitis and obesity-induced diabetes (11). This choice may have produced a more relevant and robust phenotype relative to other mouse strains commonly used to study MIA.

The strain used in Choi et al. exhibits a propensity for T<sub>H17</sub> polarization due to a distinct microbiota signature, whereas mice lacking T<sub>H17</sub>-inducing microbiota, and therefore having barely detectable levels of T<sub>H17</sub>...
CRISPR goes retro

RNA contributes directly to the immunological memory recorded in CRISPR sequences

By Erik J. Sontheimer* and Luciano A. Marraffini*

Genetic invasions threaten nearly all cells and genomes. Bacteria and archaea “remember” encounters with invaders through an adaptive immunity strategy involving clustered, regularly interspaced, short palindromic repeats (CRISPRs). These repeats can store snippets of an invader’s genome as “spacers” (1), which then constitute a heritable memory that can instruct an immune response against future encounters with foreign DNAs carrying those same sequences. The ability to form new memories of invasion depends on the ability of a CRISPR to incorporate new spacers. The mechanistic basis for this acquisition from DNA is increasingly understood (2) and has often been assumed to be the sole mode of CRISPR adaptation. On page 932 of this issue, Silas et al. (3) describe an intriguing twist on bacterial adaptive immunity, identifying a subset of CRISPR systems with the remarkable ability to incorporate new spacers directly from RNA.

Detection of foreign DNA is achieved by CRISPR-associated (Cas) proteins (nucleases) that are guided to their targets by spacer-derived transcripts [CRISPR RNAs (crRNAs)]. Once crRNAs recognize the foreign DNA by base pairing, the Cas nuclease cleaves the target. CRISPR-Cas systems are exceptionally diverse (4). Most are classified as type I or type III, and both of these types depend on multisubunit complexes for target recognition and destruction (1, 4). A type III-A system was the first to be revealed as a DNA interference pathway (5), and DNA targeting is now known to be a shared feature of virtually all CRISPR-Cas systems (1). However, type IIB systems have long been known to have RNA-targeting capacity (6), and this capability was later uncovered in type III-A

1RNA Therapeutics Institute, Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, MA 01605, USA. 2Laboratory of Bacteriology, The Rockefeller University, New York, NY 10065, USA. E-mail: enrik.sontheimer@umassmed.edu; marraffini@rockefeller.edu

**CRISPR**

**References**

Maternal T H 17 cells take a toll on baby's brain
Myka L. Estes and A. Kimberley McAllister
Science 351, 919 (2016);
DOI: 10.1126/science.aaf2850

This copy is for your personal, non-commercial use only.

If you wish to distribute this article to others, you can order high-quality copies for your colleagues, clients, or customers by clicking here.

Permission to republish or repurpose articles or portions of articles can be obtained by following the guidelines here.

The following resources related to this article are available online at www.sciencemag.org (this information is current as of March 22, 2016):

Updated information and services, including high-resolution figures, can be found in the online version of this article at:
/content/351/6276/919.full.html

A list of selected additional articles on the Science Web sites related to this article can be found at:
/content/351/6276/919.full.html#related

This article cites 15 articles, 4 of which can be accessed free:
/content/351/6276/919.full.html#ref-list-1

This article appears in the following subject collections:
Immunology
/cgi/collection/immunology