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RESEARCH HIGHLIGHT

# Antibiotics deliver a gut punch to infant immunity

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**The development of the immune system is known to be shaped by the microbiota and their metabolites, yet the key players are poorly understood. Stevens and colleagues now show that microbiota-derived inosine is an important regulator of CD8$^+$ T cell immunity in early life, opening up new therapeutic opportunities to protect infants from severe viral infections.**

A key step in the development of the immune system occurs shortly after birth, when the fetus transitions from the protected environment of the uterus to the foreign, antigen-rich environment of the outside world. During this crucial step, the microbiota provides essential cues to educate and prepare the offspring's immune system for immune defense.[1,2] Early-life exposure to antibiotics, however, disrupts this natural training process, leading to increased susceptibility to infections and chronic inflammatory diseases.[3,4] To date, the links between microbial exposure, antibiotic use, and disease risk have come primarily from epidemiological studies, which are correlative in nature. As a result, the molecular mechanisms by which antibiotics alter immune functions in early life remain poorly understood.

In a recent study published in *Cell* by Stevens et al., the authors provide mechanistic insight into how antibiotic usage in early life alters the CD8$^+$ T cell response to respiratory viral infections in infants.[5] CD8$^+$ T cells are adaptive immune cells that protect the host by eliminating infected cells. To model early-life antibiotic exposure, the authors administered commonly used antibiotics (ampicillin, gentamycin, vancomycin) to pregnant mice around the time of birth, which led to an imbalance of the normal microbiota (referred to as dysbiosis) in the antibiotic-treated offspring. To determine whether antibiotic usage impacts immune defense in the offspring, the authors compared the ability of control and dysbiotic infant mice to respond to influenza virus. The dysbiotic mice exhibited more severe morbidity and mortality than control mice, which corresponded to an impaired ability to mount a robust virus-specific CD8$^+$ T cell response. Importantly, the poor primary CD8$^+$ T cell response in dysbiotic infant mice also resulted in the establishment of fewer tissue-resident memory (TRM) CD8$^+$ T cells in the lung, leaving them susceptible to secondary infections in adulthood. The decrease in influenza-specific CD8$^+$ T cells was also observed in dysbiotic human infants, suggesting that the regulation of infant CD8$^+$ T cells by microbiota is conserved in mice and humans.

The impaired CD8$^+$ T cell response in dysbiotic infants could be due to changes in the host environment or because the starting population of CD8$^+$ T cells are intrinsically different. To distinguish between these possibilities, the authors performed adoptive transfer experiments and found that donor CD8$^+$ T cells from dysbiotic infant mice exhibited an impaired ability to differentiate into effector and TRM cells after influenza infection. To understand how early-life antibiotic usage alters the programming of CD8$^+$ T cells, they also performed single-cell sequencing and discovered that a set of genes regulated by nuclear factor interleukin 3 (NFIL3) was reduced in CD8$^+$ T cells from dysbiotic infant mice. NFIL3 is best known for its role in the development of innate lymphocytes.[6] The authors found that T cell-specific deletion of NFIL3 in control mice resulted in a reduced ability to generate and maintain influenza-specific CD8$^+$ T cells, akin to the phenotype observed in dysbiotic infant mice. Mechanistically, they found that NFIL3 drives effector and memory CD8$^+$ T cell differentiation in control mice by reducing key regulators (Tcf7 and Lef1) that maintain the quiescent state of naïve, or not yet activated, T cells.[7]

A key question in the study is how the disruption of microbiota by antibiotics leads to the epigenetic remodeling of naïve CD8$^+$ T cells by NFIL3. To address this knowledge gap, the authors performed metagenomic sequencing and metabolic modeling on samples from control and dysbiotic infants. The findings present a compelling picture: the control infants are enriched in *Bifidobacterium*, which is known to produce a key metabolite (inosine) (Fig. 1). Inosine promotes expression of NFIL3 in CD8$^+$ T cells by increasing adenosine 2A receptor signaling. The induction of NFIL3 by inosine results in a decrease in Tcf7 expression in naïve CD8$^+$ T cells, facilitating increased numbers of influenza-specific TRM cells after infection. To establish the clinical significance of their findings, the authors also administered inosine to dysbiotic infant mice prior to influenza infection and showed that CD8$^+$ T cell immunity could be restored. Collectively, their findings demonstrate that microbiota-derived inosine regulates infant CD8$^+$ T cell immunity in an NFIL3-dependent manner.

The conclusions of the study are important for several reasons. First, previous work has largely focused on how the microbiome alters subsets of CD4$^+$ T cells (Th17 and Tregs).[8,9] The study by Stevens et al. provides new insight into how the microbial environment impacts a different branch of the adaptive immune system — the CD8$^+$ T cell compartment. Second, the discovery that microbiota-derived inosine promotes CD8$^+$ T cell immunity has important therapeutic implications. Indeed, inosine supplementation may offer a safer and more cost-effective option for boosting immunity in early life than fecal transplantations or

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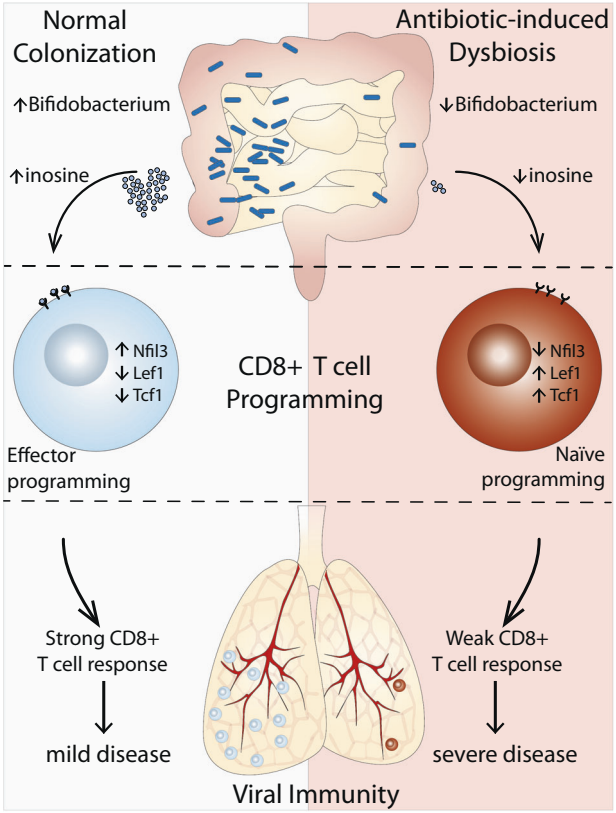


**Fig. 1 Proposed model for how early-life antibiotic usage impacts the CD8$^+$ T cell response to influenza.** In healthy infants, inosine produced from *Bifidobacterium* enhances effector programming in the starting pool of CD8$^+$ T cells by increasing NFIL3 expression, which facilitates a more robust CD8$^+$ T cell response to influenza in the lung. However, infants exposed to antibiotics in early life have lower amounts of *Bifidobacterium*, resulting in reduced levels of inosine, more naïve programming in the starting pool of CD8$^+$ T cells, and a weaker response to influenza.

probiotics.[10] Third, the new role for NFIL3 in CD8$^+$ T cells may also allow us to program naïve CD8$^+$ T cells to adopt specific fates after priming, which could be beneficial for certain adoptive T cell therapies (e.g., CAR-T cells).

The study also raises several interesting questions. For example, is there a window of opportunity in which inosine must be present to program the functions of CD8$^+$ T cells? Future studies are needed to determine whether disruption of microbiota-derived inosine is more consequential in utero or after birth. Another important question is whether microbiota-induced inosine also impacts susceptibility to autoimmune and chronic inflammatory diseases, which are more prevalent in individuals with perturbations to their microbiota in early life.[11] In light of the findings, it would be important to determine whether tolerance is impaired when inosine levels are decreased in dysbiotic infants.

Overall, the study by Stevens et al. may unlock new ways to prevent and treat immune-mediated diseases that are linked to the microbiome, which has important implications for the millions of children that are exposed to antibiotics in early life.

## REFERENCES

1. Ignacio, A., Czyz, S. & McCoy, K. D. *Semin Immunol.* **73**, 101885 (2024).
2. Torow, N. & Hornef, M. W. *J. Immunol.* **198**, 557–563 (2017).
3. Risnes, K. R. et al. *Am. J. Epidemiol.* **173**, 310–318 (2011).
4. Shaw, S. Y., Blanchard, J. F. & Bernstein, C. N. *Am. J. Gastroenterol.* **105**, 2687–2692 (2010).
5. Stevens, J. et al. *Cell* **188**, S0092–S8674 (2025).
6. Seillet, C. et al. *J. Exp. Med.* **211**, 1733–1740 (2014).
7. Xing, S. et al. *Nat. Immunol.* **17**, 695–703 (2016).
8. Atarashi, K. et al. *Cell* **163**, 367–380 (2015).
9. Atarashi, K. et al. *Nature* **500**, 232–236 (2013).
10. Hourigan, S. K. & Oliva-Hemker, M. *Pediatr. Res.* **80**, 2–6 (2016).
11. Kronman, M. P. et al. *Pediatrics* **130**, e794–e803 (2012).

## COMPETING INTERESTS

The author declares no competing interests.

## ADDITIONAL INFORMATION

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