OPEN ACCESS

COMMENTARY

The Innovation Nutrition

Deconstructing the breast milk "black box": Trans-vaccenic acid as a precision immune signal in neonatal development

Qian Li,[1,2] Xiating Li,[3] Liang V Tang,[1,2,4,*] and Yu Hu[1,2,4,*]

[1]Institute of Haematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

[2]Key Laboratory of Biological Targeted Therapy (Huazhong University of Science and Technology), Ministry of Education, Wuhan 430022, China

[3]Diagnostic Science Centre, Alberta Precision Laboratories, Calgary, AB T1Y 5S3, Canada

[4]These authors contributed equally

*Correspondence: dr_huyu@126.com (Y.H.); lancet.tang@qq.com (L.T.)

Received: June 26, 2026; Accepted: July 4, 2026; Published Online: July 16, 2026; https://doi.org/10.59717/j.xinn-nutri.2026.100021

Citation: Li Q., Li X., Tang L., et al. (2026). Deconstructing the breast milk "black box": Trans-vaccenic acid as a precision immune signal in neonatal development. *The Innovation Nutrition* **1**:100021.

Human breast milk has long been celebrated as a dynamic biological system exquisitely tailored to meet the nutritional and immunological needs of the developing infant. Its composition is complex, encompassing macronutrients and numerous bioactive factors, including immunoglobulins, cytokines, growth factors, antimicrobial peptides, and a commensal microbiome. This intricacy has led to a prevailing paradigm: the benefits of breastfeeding arise from the collective, synergistic actions of its many constituents. Indeed, while breastfeeding is consistently linked to improved infant health

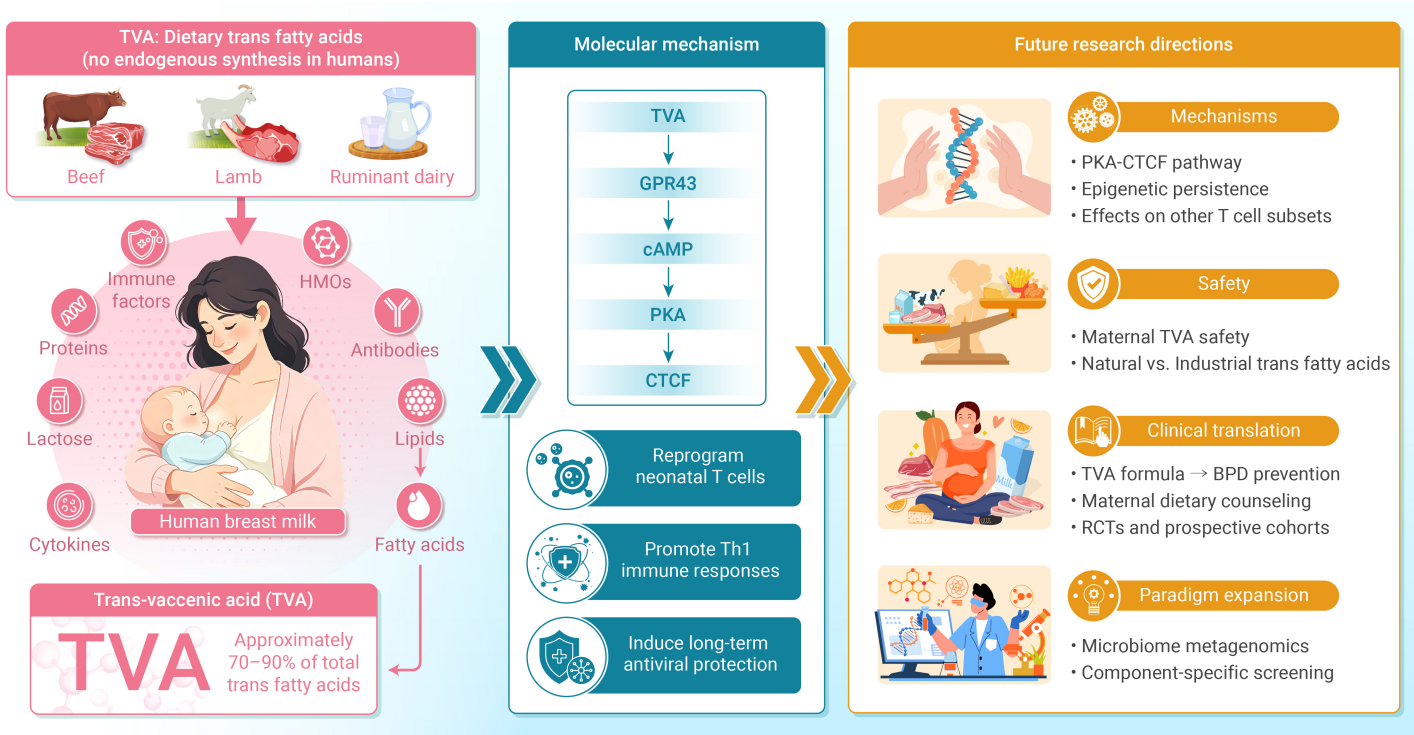

Figure 1. Maternal trans-vaccenic acid: From breast milk composition to neonatal T cell programming and clinical translation. Abbreviations: cAMP, cyclic adenosine monophosphate; CTCF, CCCTC-binding factor; GPR43, G protein-coupled receptor 43; HMOs, human milk oligosaccharides; PKA, protein kinase A; RCTs, randomized controlled trials; Th1, T helper type 1; TVA, trans-vaccenic acid.

outcomes,[1] disentangling the specific contribution of any single component has proven exceedingly difficult.

Consequently, the field has largely viewed breast milk as a "black box" of interacting molecules—a perspective that, while acknowledging its complexity, has obscured the possibility that individual dietary molecules might independently and directly instruct neonatal immune development. Fan and colleagues now deliver a paradigm-shifting discovery: trans-vaccenic acid (TVA), a naturally occurring trans fatty acid, functions as a dedicated signaling molecule that programs neonatal $CD4^+$ T cell development, shifts the T helper 1 (Th1)/T helper 2 (Th2) balance, and establishes durable immune imprinting that persists into adulthood.[2] This finding challenges the "synergy-only" view of breast milk and marks a transition from viewing breast milk as passive nutrition to recognizing it as an active conduit of bioactive instructions that sculpt the developing immune system.

TVA is the predominant naturally occurring trans fatty acid in human breast milk and is derived exclusively from maternal diet, as the human body lacks the enzymes for its endogenous synthesis. Its primary sources include beef, lamb, and dairy from ruminant animals. Unlike industrial trans fats such as elaidic acid, which are associated with cardiovascular harm, naturally occurring TVA exhibits distinct biological properties. Less than 20% of dietary TVA is metabolized, allowing a substantial fraction to circulate and accumulate in tissues, including breast milk.

Fan and colleagues capitalized on this by supplementing lactating mouse dams with TVA at physiological concentrations. They demonstrated that TVA transferred efficiently from maternal circulation into milk and pup serum, achieving sustained levels throughout lactation without affecting pup growth.[2] This well-controlled experimental system allowed the authors to isolate TVA's effects from broader nutritional context with reduced confounding.

The phenotypic consequences were striking. Pups nursed on TVA-enriched milk exhibited enlarged spleens and thymuses at two to three weeks, with marked expansion of total splenocytes, T cells, B cells, and myeloid subsets.[2] Most notably, the frequency and absolute number of naïve $CD4^+$ T cells—the foundation of adaptive immunity—were significantly increased.[2] This expansion was temporally restricted, peaking during the neonatal window and normalizing by five weeks.[2]

To dissect the underlying mechanisms, the authors employed single-nucleus multiomics on splenic cells from two-week-old pups, generating an atlas of 20 distinct cell clusters. Naïve CD4$^+$ T cells (cluster C3) emerged as the most expanded population in TVA-exposed pups.[2] Promoter accessibility analyses revealed increased chromatin openness at genes associated with T cell maturation (Il2rb), proliferation (Bcl2, Cd28), and trafficking (Ccl5, Cxcr6).[2] Importantly, the promoter of *Gpr43*—the gene encoding GPR43 (G protein-coupled receptor 43), previously identified as a TVA target in adult CD8$^+$ T cells [3]—showed increased accessibility, suggesting a conserved GPR43-mediated mechanism in neonatal CD4$^+$ T cells.

The mechanistic dissection was the study's most significant contribution. Building on prior work showing that TVA inactivates GPR43 in adult CD8$^+$ T cells,[3] the authors hypothesized that a parallel pathway operates in neonatal CD4$^+$ T cells. Through loss-of-function experiments, they established a linear cascade: TVA binding to GPR43 leads to receptor inactivation, relieving suppression of cyclic adenosine monophosphate (cAMP) production and activating protein kinase A (PKA).[2] Surprisingly, unlike in adult CD8$^+$ T cells, the downstream effector in neonatal CD4$^+$ T cells was not CREB but CCCTC-binding factor (CTCF)—a protein best known for organizing three-dimensional genome architecture.

This finding is intriguing because CTCF is traditionally viewed as a structural component rather than a signal-responsive transcription factor. Yet the authors show that TVA-induced PKA activation enhances CTCF DNA-binding activity without altering its expression. Activated CTCF then cooperates with TBX21 (T-bet), the master Th1 transcription factor, to promote chromatin accessibility at the promoters of Tbx21 and Ifng. Knockdown of Ctcf, but not Creb1, abolished TVA-enhanced Th1 polarization, establishing CTCF as the obligate downstream mediator. By modulating a genome-organizing protein, TVA may alter long-range chromatin interactions at key immunological loci—an "epigenetic priming" model that explains the durability of TVA's effects and their restriction to a developmental window when the T cell epigenome remains malleable. The complete pathway, from maternal dietary intake through breast milk transfer and GPR43-CTCF signaling to clinical translation, is schematized in Figure 1.

One of the most compelling dimensions is the temporal specificity. Through cross-fostering experiments, the authors demonstrated that postnatal, rather than prenatal, TVA exposure drives immune reprogramming. Pups exposed to TVA only during gestation did not exhibit enhanced resistance to subsequent influenza or Salmonella challenge, while those exposed only through lactation exhibited full protection against these infections.[2] More strikingly, when TVA exposure was initiated at five weeks of age—after weaning—it failed to confer any protection in adulthood, despite achieving comparable serum levels.[2] Whether gestational TVA influences other aspects of fetal immune development remains unexplored, but the clear dissociation between prenatal and postnatal effects establishes that the protective immune reprogramming is conferred through breastfeeding rather than in utero exposure. This suggests that naïve CD4$^+$ T cells are uniquely susceptible during a critical ontogenetic window, likely corresponding to thymic output and peripheral tolerance establishment. This "developmental immune imprinting" concept has evolutionary logic: early-life nutritional cues forecast future environmental conditions, allowing the immune system to calibrate accordingly. TVA, by virtue of its dietary origin, may serve as such a predictive signal.

The translational relevance is substantiated by correlative analyses in human preterm infants—a population vulnerable to immune dysregulation with inherently Th2-biased immunity. Bronchopulmonary dysplasia (BPD), a severe lung disease affecting preterm infants, is driven by inflammation and linked to insufficient Th1 immunity. Fan and colleagues found that higher TVA levels in dried blood spots correlated with increased IL-2 and elevated IFN-γ/IL-4 ratios, consistent with Th1 skewing.[2] More importantly, breast milk TVA levels were inversely associated with BPD incidence, ranking as the top discriminant fatty acid among dozens profiled.[2] While these associations do not establish causation, they align with the mechanistic data and provide a rationale for future interventional studies. These findings also resonate with epidemiological observations linking ruminant trans fat intake to favorable metabolic profiles.

Several limitations, rather than diminishing the findings, delineate the most urgent frontiers for future inquiry. First, the human data are correlational and derived from small cohorts; larger prospective studies are needed. Second, the mouse model uses pure TVA supplementation that may not fully reflect human dietary context. Third, and perhaps most critically, while GPR43 and CTCF are convincingly demonstrated as required nodes in the pathway, the precise molecular mechanism by which PKA modulates CTCF DNA-binding activity—and whether this involves direct phosphorylation, recruitment of cofactors, or altered chromatin interactions—remains incompletely characterized. Additionally, the safety of TVA supplementation during human pregnancy requires careful evaluation, given the historical concerns about industrial trans fats. The authors rightly emphasize this distinction; communicating it effectively to broader audiences will be essential to avoid conflation.

The correlative findings in preterm infants provide a translational anchor, but the path forward demands interventional studies Mechanistically, it will be critical to determine whether CTCF-mediated chromatin reorganization is sustained in memory T cells and whether TVA affects other T cell subsets. The neonatal microbiome—largely unaffected by maternal TVA by 16S rRNA analysis—should be further explored using metagenomic approaches, as subtle functional shifts may exist.[4] The identification of TVA as an immune-programming molecule raises concrete, testable questions: Could infant formula be supplemented with TVA to promote Th1 maturation in vulnerable preterm populations? Might targeted maternal dietary counseling during late gestation and lactation enhance neonatal immune fitness? Answering these questions will require randomized controlled trials and long-term cohort follow-up.[5]

More broadly, the study challenges the field to move beyond the "holistic" view of breast milk and adopt a component-specific approach that interrogates individual bioactive molecules. TVA's identification as an immune-programming agent exemplifies the potential of this strategy, pointing toward an era of precision immunonutrition in early life.

In conclusion, Fan and colleagues have identified maternal trans-vaccenic acid as a unique dietary signal that reprograms neonatal T cell development through a defined GPR43-cAMP-PKA-CTCF pathway, shifting immunity toward Th1 responses and establishing durable antiviral protection. This work fundamentally revises our understanding of breast milk: it is not merely a source of passive nutrition, but an active biological language through which maternal diet communicates with the developing immune system. While questions remain regarding human translation, particularly the generalizability to term infants and the long-term safety of supplementation, these findings lay the groundwork for a new era of precision immunonutrition in early life, one in which specific nutrients can be deliberately deployed to support immune health from the very first feed.

REFERENCES

1. Andres S., Scottoline B. and Good M. (2023) Shaping infant development from the inside out: Bioactive factors in human milk. *Semin. Perinatol.* **47**:151690. DOI: 10.1016/j.semperi.2022.151690
2. Fan H., Zheng Z., Oliphant K., et al. (2026). Maternal trans-vaccenic acid shapes neonatal T cell development and early-life immune imprinting. *Science* **392**:eaea4041. DOI: 10.1126/science.aea4041
3. Fan H., Xia S., Xiang J., et al. (2023). Trans-vaccenic acid reprograms CD8(+) T cells and anti-tumour immunity. *Nature* **623**:1034-1043. DOI: 10.1038/s41586-023-06749-3
4. Ju C., Lyu R., Li H., et al. (2026). Modifications of microbiome-derived cell-free RNA in plasma discriminates colorectal cancer samples. *Nat. Biotechnol.* **44**:752–8. DOI:10.1038/s41587-025-02731-8
5. Zhang J., Geng T., Wang Y., et al. (2026). Challenges, advances and future directions in nutritional epidemiology. *Innov. Nutri.* **1**:100009. DOI:10.59717/j.xinn-nutri.2026.100009

FUNDING AND ACKNOWLEDGMENTS

This study was supported by the National Natural Science Foundation of China (No. 82103827). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

Qian Li designed this study. Qian Li drafted the original manuscript. All authors review and revised the manuscript. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.