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COMMENTARY

Motherhood Imprints Tissue-Resident CD8$^+$ Immunity for Long-Term Tissue Surveillance

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A full reproductive cycle (pregnancy followed by lactation and involution) imprints long-lived CD8$^+$ tissue-resident-memory-like T cells in the breast. These cells restrain tumor growth in mice and are linked to a more inflamed tumor microenvironment and better outcomes in human triple-negative breast cancer.

Breast cancer remains the most frequently diagnosed malignancy among women worldwide and a leading cause of cancer-related mortality [1,2]. Despite major advances in screening and systemic therapies, disease progression and recurrence remain substantial clinical challenges, particularly in aggressive subtypes such as triple-negative breast cancer (TNBC). Increasing evidence indicates that tumor evolution is profoundly shaped by interactions with the tumor microenvironment, where malignant cells deploy diverse immune-evasion strategies to undermine effective antitumor surveillance [3,4]. Epidemiological studies indicate that parity reduces lifetime breast cancer risk (particularly for hormone-receptor-positive malignancies), whereas prolonged breastfeeding offers more specific protection against TNBC [5]. Classical models attributed this parity-induced protection to the terminal differentiation of mammary epithelial cells during pregnancy, which limits proliferative potential and susceptibility to oncogenic transformation [5]. Yet, this epithelial-centric view falls short of explaining why protection can persist for decades and why it is particularly evident in TNBC. Rather, the reproductive cycle represents an immunologically and stromally active phase in which the mammary epithelium, its surrounding stroma, and the associated vasculature undergo extensive remodeling (driven by coordinated epithelial–stromal–immune interactions) [4]. These transitions constitute one of the most dynamic inflammatory and regenerative events in adult tissues, suggesting that reproductive history may durably reprogram the mammary immune microenvironment. In this context, the recent study by Virassamy et al. [6] provides critical mechanistic insight into how the reproductive cycle imprints long-term immune surveillance in mammary tissue.

Against this backdrop, several unanswered questions persisted: (a) the lack of a long-lived, causal cellular mechanism linking reproductive history to tumor restraint; (b) uncertainty about which immune subsets persist after lactation and how they are induced and maintained; and (c) limited evidence that any such program is functionally protective rather than correlative. Prior studies have implicated immune processes, including dendritic-cell-mediated T-cell priming and chemokine-guided immune recruitment, and have underscored the prognostic importance of CD8$^+$ tumor-infiltrating lymphocytes in TNBC [7]. However, they did not establish that a full reproductive cycle installs a resident, self-maintaining CD8$^+$ antitumor compartment within the intraepithelial and periductal zones of the breast.

To resolve these uncertainties, Virassamy and colleagues [6] evaluated a tissue-resident memory T cell (T_{RM})-centric mechanism. The rationale is that T_{RM} biology suits prevention at an epithelial barrier: locality (nonrecirculating sentinels near ducts), longevity (niche self-renewal), and speed (rapid recall). They pair human single-cell and bulk profiling with spatial and flow-cytometric readouts and then use mouse models to test cause and effect. This work reframes parity-linked protection as an immunological imprint, a physiological program that educates and sustains resident CD8$^+$ surveillance in the mammary gland (Fig. 1).

A core strength of this work is how elegantly the methodological choices serve the central question. Across 4 human datasets, parous tissue contains higher proportions of CD3$^+$, CD8$^+$, and T_{RM} CD8$^+$ cells. They then confirm these findings with independent methods that add clear cell counts and spatial context. In cancer-free prophylactic mastectomy samples from women, flow cytometry shows increased CD69$^+$CD103$^+$ T_{RM} CD8$^+$ cells, and spatial imaging places them within intraepithelial and periductal regions. Because these tissues are cancer-unaffected, the T_{RM}-like enrichment is observed in nonmalignant human breast tissue, consistent with a preexisting immune state. To define this state molecularly, bulk RNA sequencing of human breast T_{RM} CD8$^+$ cells versus matched circulating CD8$^+$ cells identifies a residency-linked program with increased ITGAE, ITGA1, and CXCR6, which the authors term the parous breast T_{RM} (PB-T_{RM}) signature. Together, these human tissue analyses support a long-lived, tissue-anchored CD8$^+$ T_{RM} state in normal breast that is associated with parity. This human tissue foundation is important because it frames parity as a

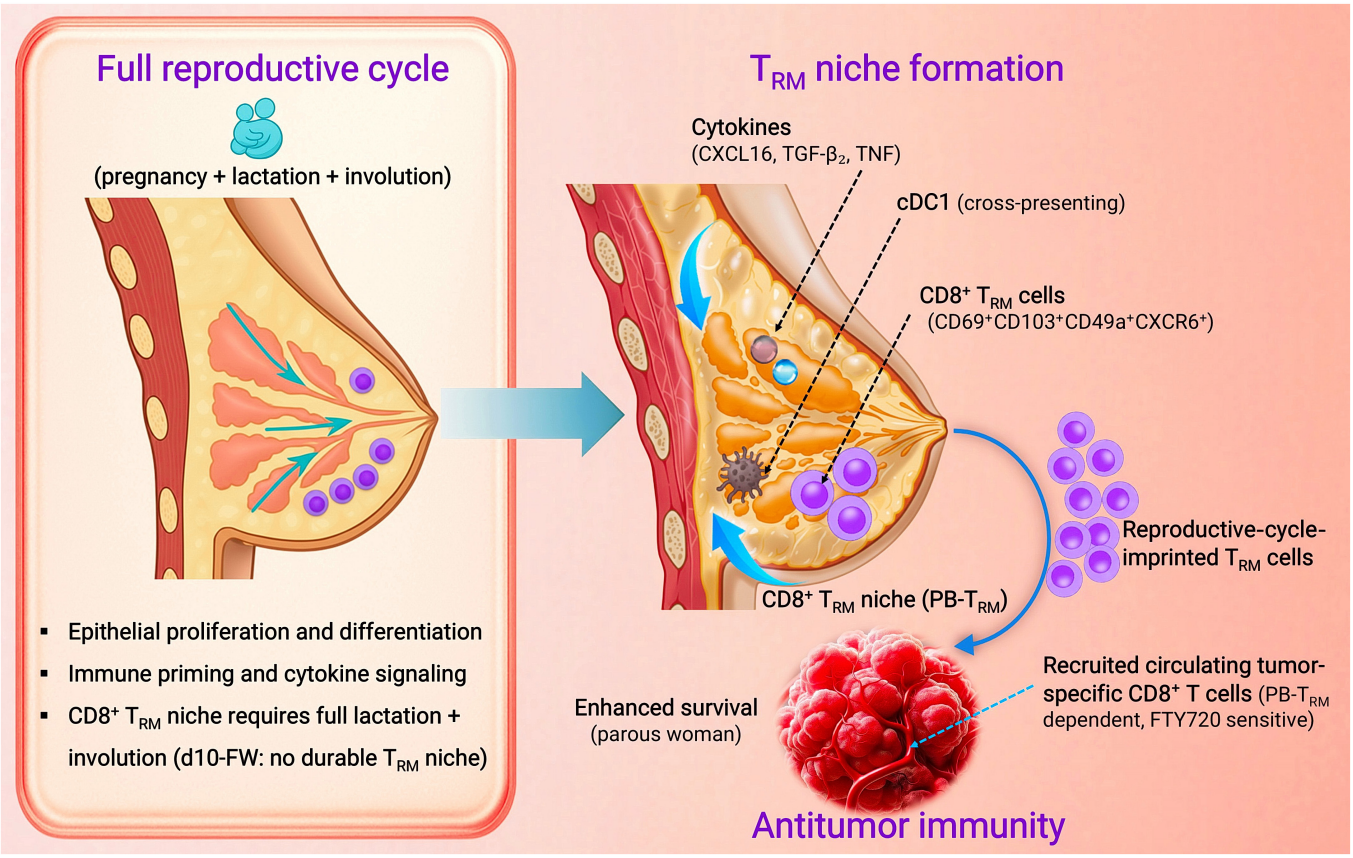


Fig. 1 Full reproductive-cycle-associated $CD8^+$ tissue-resident-memory-like T cell (T_{RM}-like) niche and cooperative antitumor immunity. Conceptual schematic summarizing the key findings reported by Virassamy et al. [6]. The mammary gland is illustrated using a simplified human breast schematic for conceptual visualization. Pregnancy, sustained lactation, and physiological involution are associated with the enrichment of a parous breast tissue-resident memory $CD8^+$ T cell population (PB-T_{RM}) in the mammary gland, alongside T_{RM}-associated cues (CXCL16, TGF-β2, and TNF) and cross-presenting conventional type 1 dendritic cells (cDC1). Mechanistic evidence from mouse models demonstrates that completion of lactation followed by involution establishes this durable $CD8^+$ T_{RM} niche. Upon tumor challenge in mouse models, resident T_{RM}-like cells cooperate with recruited circulating tumor-reactive $CD8^+$ T cells (FTY720 sensitive) to enhance control of triple-negative breast cancer. d10-FW denotes day 10 post early force-weaning in the mouse model, a condition used to evaluate the requirement of sustained lactation for T_{RM} niche establishment. Some components of this figure were created with BioRender.com.

lasting shift in local immune architecture, rather than a transient hormonal exposure.

Building on this baseline, the authors connect PB-T_{RM} biology to human tumors and then test causality in mouse models. The PB-T_{RM} signature holds across independent patient cohorts and aligns with more immune-inflamed tumors in women with parity and even more so with breastfeeding. Clinically, breastfeeding has been reported to be associated with improved overall survival in a high-risk hormone-receptor-negative patient cohort [6]. However, as this signal comes from observational analyses, it must be interpreted as an association rather than causation and may be influenced by residual confounding. Mechanistic experiments in mice then clarify when the niche is established and identify key requirements for protection. In these models, completed lactation followed by full postlactational involution expands the mammary $CD8^+/T_{RM}$ compartment and limits later tumor growth, whereas early weaning does not. The protection in mice depends on $CD8^+$ T cells, since depleting CD8α or CD8β removes the benefit [6]. Blocking lymphocyte egress in the mouse model with FTY720 also abolishes tumor control and suggests that resident T_{RM} work with recruited T cells during tumor challenge [8]. Together, the results support a clear mechanistic arc: lactation followed by full involution installs and maintains a $CD8^+$ T_{RM}-enriched niche that is ready to respond when malignancy emerges [6].

This work helps bridge an important gap by linking parity and sustained lactation to a durable, $CD8^+$ T_{RM}-enriched immune niche in the breast. First, the antigen specificity of the resident $CD8^+$ pool remains undefined: whether these cells are maintained by self-antigens, microbe-related cues, or recurrent tumor-associated targets is not yet known. Clarifying this will determine whether these cells can be safely boosted or redirected by vaccines, microbiome cues, or tumor-directed immunotherapies. Second, the reported durability of human T_{RM}-like enrichment is inferred from cross-sectional tissue spanning decades. Prospective, longitudinal follow-up could clarify the longevity and function of this memory state. Such data are essential to know whether this imprint is stable, remodeled by aging and therapy, or amenable to late-life intervention. Third (critical for broad applicability), the observed clinical signal is strongest in basal-like/TNBC. Its relevance in hormone-receptor-positive disease remains to be defined.

To translate these insights, future studies should prospectively test the clinical utility of the PB-T_{RM} niche. This means enrolling cohorts with carefully recorded reproductive histories and evaluating whether the PB-T_{RM} transcriptomic signature or the spatial density of $CD69^+CD103^+CD8^+$ T cells near ducts is associated with prognosis or therapeutic outcomes. Because

longitudinal sampling of normal human breast tissue is limited to occasional biopsies or surgical specimens, direct assessment of T_{RM} persistence remains challenging. Imaging or blood-based sampling could be explored as surrogate readouts, as is already being investigated for other immunological biomarkers [9]. Preclinical studies should also define the optimal postweaning interval during which the T_{RM}-supportive niche is established and stabilized.

Looking ahead, 2 high-priority translational strategies follow naturally. One is biomarker-driven risk adaptation. It then applies the PB-T_{RM} transcriptomic signature and the spatial density of $CD69^+CD103^+CD8^+$ T cells near ducts to refine patient stratification, particularly where TNBC risk and a T-cell-inflamed microenvironment are suspected. Other cancers already use immune signatures to guide prognosis and treatment, providing a model that breast cancer management could similarly follow [10].

The other is local niche engineering. Rational engineering of tissue immune niches is increasingly recognized as a way to boost local antitumor immunity while minimizing systemic toxicity [11]. To make this practical, the next step is to define the minimal T_{RM}-supporting cues and deliver them locally, and then test feasibility by sustained periductal $CD8^+$ T_{RM}-like enrichment with minimal systemic immune perturbation. In rigorously controlled preclinical models, targeted delivery of the relevant cues (e.g., transforming growth factor beta 2 and tumor necrosis factor) together with conventional type 1 dendritic cells support could test whether the postinvolution, T_{RM}-supportive niche can be safely recreated. Advanced drug-delivery platforms (particularly those designed to target the tumor microenvironment [12]) may enable such immunomodulatory cues to be spatially confined within defined tissue niches, including the mammary microenvironment, thereby enabling the localized reconstruction of T_{RM}-supportive signaling circuits while minimizing systemic immune perturbation. Importantly, such approaches would likely be most relevant in defined clinical contexts, such as individuals at elevated risk of TNBC or patients undergoing treatment for breast cancer, rather than as universal preventive interventions. These findings do not suggest pregnancy or lactation as prevention; rather, they could inform targeted, localized interventions. Any future application should aim to emulate the resolved postinvolution state rather than the transient postpartum inflammatory phase, with appropriate safety monitoring.

In conclusion, the study by Virassamy et al. [6] outlines a physiological blueprint for durable, localized immunoprevention. The next steps are to define antigen specificity, confirm long-term persistence, and test niche-stabilizing interventions, aiming to translate this natural immune imprint into a clinically actionable tool.

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