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COMMENTARY

Postprandial lipid as a fourth signal priming T cell activation via translational fitness

Chenlei Xu[1] **and Dan Lu**[1,*]

[1]Institute of Systems Biomedicine, School of Basic Medical Sciences, Peking University, Beijing 100191, China

*Correspondence: taotao@bjmu.edu.cn

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T cell activation is commonly described using a three-signal model.[1] Antigen recognition through the T cell receptor provides specificity, co-stimulation through receptors such as CD28 supports activation and prevents anergy, and cytokines guide differentiation into effector and memory states. This framework has been useful for understanding how T cells integrate antigenic and inflammatory inputs.

What it does not capture well is the metabolic context in which these processes occur. Immune cells are not insulated from systemic physiology, and nutrient availability changes with feeding and fasting.[2] Whether such fluctuations carry instructive value for T cell function has been largely unclear. *Kumar* et al. now provide evidence that postprandial lipid metabolism directly shapes T cell behavior,[3] pointing to an additional layer of regulation

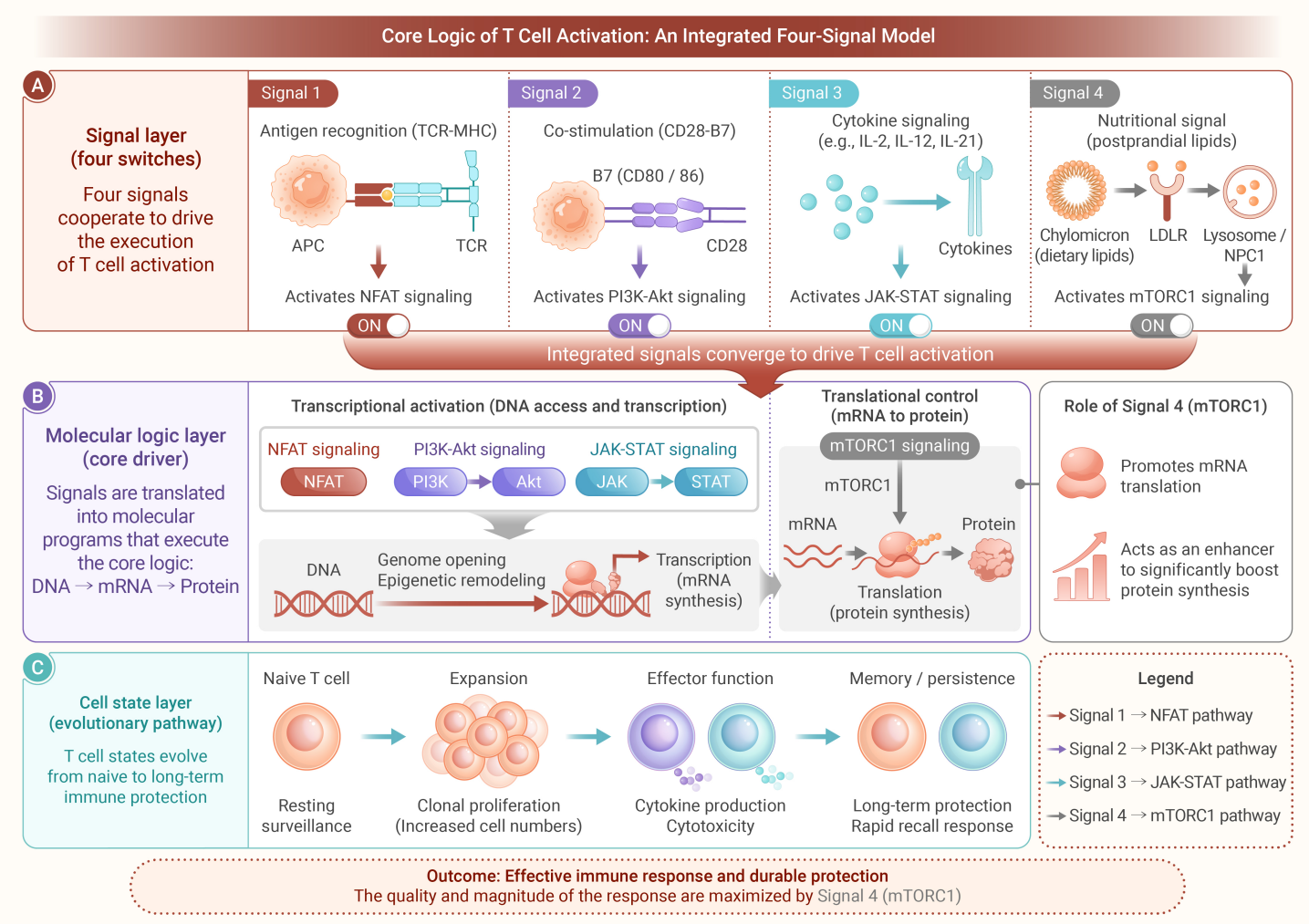

Figure 1. An integrated four-signal model of T cell activation.

that can be considered a fourth signal (Figure 1).

A key insight from this work is that nutrients, particularly lipids, do not merely fuel T cell responses but actively shape their functional potential. Following a meal, triglyceride-rich chylomicrons enter the circulation and are taken up by T cells, mainly through low-density lipoprotein receptor (LDLR) dependent pathways. These lipoprotein particles deliver lipid substrates and cholesterol into intracellular compartments, connecting systemic metabolic flux to cell-intrinsic signaling pathways.

The most striking aspect of the study is where the regulation occurs. Postprandial T cells show no significant changes in gene expression or chromatin accessibility compared to fasting cells. Instead, the difference lies in protein synthesis. Translation is globally increased, accompanied by broad proteomic remodeling. This shift appears to be driven by activation of mechanistic target of rapamycin complex 1 (mTORC1), likely through lysosomal cholesterol sensing involving Niemann-Pick C1 (NPC1) dependent trafficking. The result is enhanced ribosomal activity without the need for large transcriptional changes.

This state of increased translational capacity is accompanied by higher mitochondrial content, greater spare respiratory capacity, and enhanced glycolytic potential. These features are established before antigen encounter

and persist after activation, suggesting that even transient exposure to postprandial metabolites leaves a lasting imprint on T cell function. Functionally, this is reflected in stronger cytokine production, greater expansion, and a tendency toward effector memory differentiation.

A defining feature of this proposed fourth signal is that it operates through a fundamentally different regulatory layer. Whereas antigen recognition, co-stimulation, and cytokines primarily shape T cell fate through transcriptional and epigenetic programs that unfold over hours to days, postprandial lipid metabolism acts rapidly by enhancing translational fitness. By increasing protein synthesis capacity before antigen encounter, Signal 4 establishes a metabolically poised state without extensive genome-dependent reprogramming. This distinction suggests that translational fitness may represent an additional dimension of immune regulation that complements, rather than replaces, the classical three-signal framework.

Unlike the first three signals, which are primarily delivered by antigen-presenting cells and local inflammatory cues, Signal 4 reflects the metabolic state of the entire organism. In this framework, feeding behavior, nutrient flux, and systemic lipid metabolism become physiologically relevant determinants of T cell responsiveness. The four-signal model therefore extends immune regulation beyond the local microenvironment and provides a conceptual bridge linking cell-intrinsic immune programs to whole-body physiology.

Mechanistically, the work also clarifies how lipid metabolism intersects with immune signaling. Postprandial lipids act as more than substrates for β-oxidation; they feed into lysosomal sensing pathways that regulate mTORC1. The lysosome, in this view, integrates extracellular nutrient information with intracellular programs that control translation and metabolism. This differs from the more familiar glucose- or amino acid-centered models and points to a distinct role for lipid-derived signals.

The implications are not only conceptual. From a translational perspective, these findings raise the possibility that donor nutritional status may represent a controllable variable during chimeric antigen receptor T-cell (CAR-T) manufacturing. Optimizing metabolic conditions before leukapheresis could potentially improve T cell fitness and product quality without genetic manipulation. This idea also aligns with the emerging view that metabolism is not merely a local feature of individual cells, but a central node linking cellular function, the immune microenvironment, therapeutic response, and systemic physiology.[4] More broadly, the findings raise the question of whether studying immune cells under metabolically neutral conditions obscures important aspects of their biology.[5]

Several questions follow. It will be important to understand how different dietary inputs influence this pathway, and whether lipid composition or feeding patterns matter. An additional question is whether all dietary lipids exert equivalent immunological effects. Distinct lipid species differ substantially in their metabolism, cholesterol handling, and signaling properties. Future studies should determine whether specific dietary lipid compositions preferentially engage the LDLR-mTORC1 axis and thereby differentially shape T cell fitness. The interaction between this metabolic priming and established transcriptional programs, including those controlling exhaustion and memory formation, also remains to be defined. Given the links between mTOR and nuclear factor of activated T cells (NFAT) signaling, there may be consequences for T cell fate in chronic infection or cancer. Finally, whether sustained activation of this pathway contributes to pathology in autoimmune or metabolic disease is still unclear.

Taken together, these findings place postprandial lipid metabolism alongside antigen, co-stimulation, and cytokines as a determinant of T cell activation. By acting at the level of translation rather than transcription, this mechanism adds a different dimension to how immune responses are regulated and suggests new ways to think about the relationship between metabolism and immunity.

T cell activation can be conceptualized as a three-layered process. At the signal layer, antigen recognition through TCR-MHC, co-stimulation through CD28-B7, cytokine signaling, and nutritional cues collectively function as four regulatory switches. At the molecular logic layer, Signals 1-3 primarily activate NFAT-, PI3K-Akt-, and JAK-STAT-dependent programs that promote genome accessibility and transcription, thereby driving the transition from DNA to mRNA. In contrast, Signal 4, represented by postprandial lipid metabolism, engages the LDLR-NPC1-mTORC1 pathway to enhance translational capacity, acting as a metabolic accelerator that promotes the conversion of mRNA into protein. This division of labor links genome-dependent transcriptional programming with nutrient-sensitive translational control. Together, these coordinated inputs support the progression of T cells from a naïve state to clonal expansion, effector function, and memory or persistent immune states.

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AUTHOR CONTRIBUTIONS

C.X.: visualization, and writing–reviewing and editing. D.L.: conceptualization, methodology, supervision and writing–original draft preparation. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.