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The role of the microbiota in the development of thymic-derived specific T-cells

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First published: 28 October 2021

<https://doi-org.bibliosan.clas.cineca.it/10.1111/all.15159>

Funding information:

RC is a participant in the USA National Institutes of Health (NIH) Graduate Partnership Program. He has been awarded the Fellowship “Progressi in Biologia e Medicina” from Fondazione Ghislieri, Collegio Ghislieri, Pavia, Italy, to support the investigation on microbiota–host interactions in inborn errors of immunity.

Abbreviations

DCs

dendritic cells

MAIT

mucosal-associated invariant T

TCR

T-cell receptor

Microbes, including bacteria, viruses, and fungi, have evolved and continue to live on and within humans. The massive presence of foreign microorganisms, known as microbiota, is allowed by the development of a delicate equilibrium between the colonizing microbes and the host immunity.¹ Through this symbiotic relationship, the microbiota provides, among others, nutritional benefits and protection from infections.

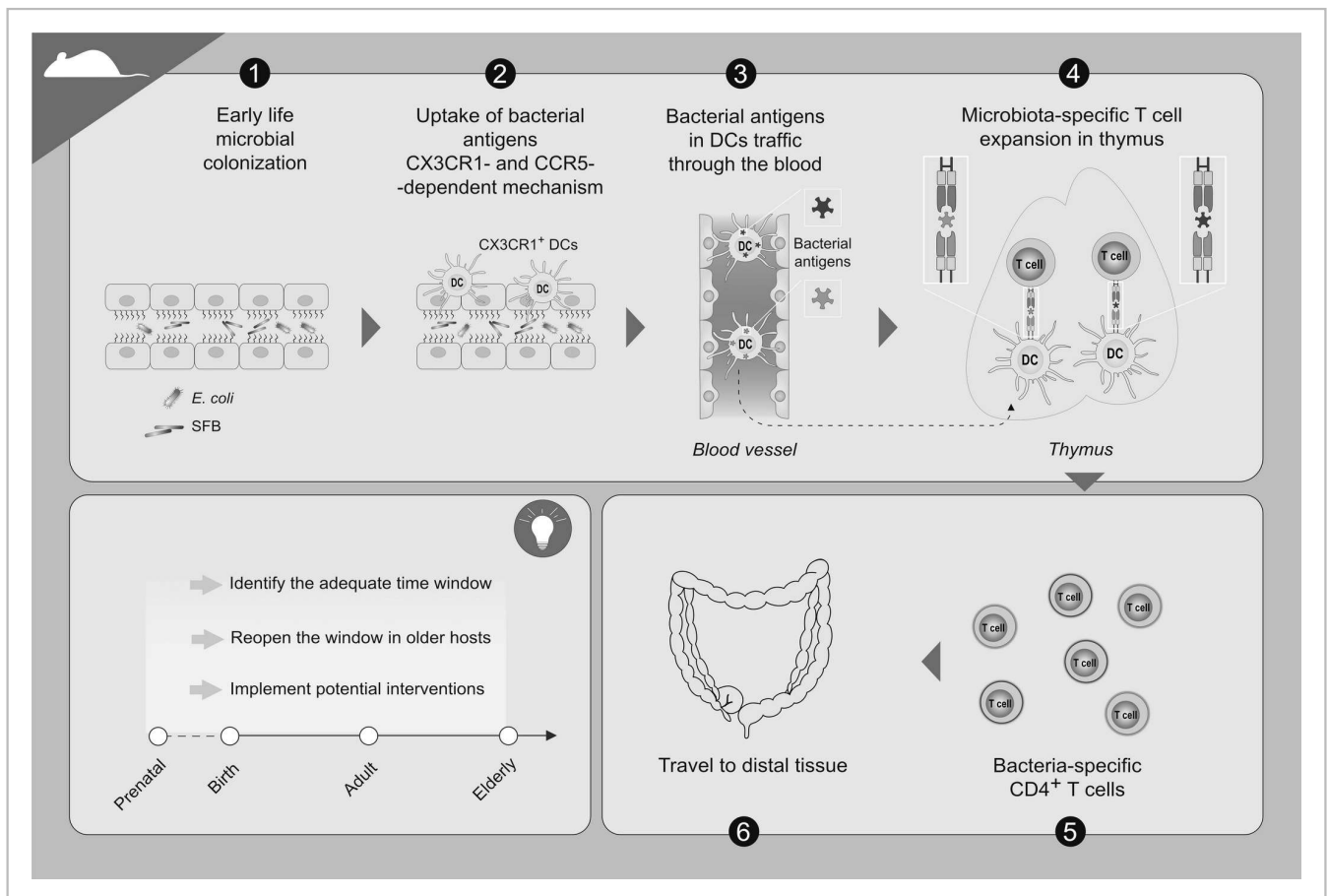
The application of multi-omics approaches, including shotgun metagenomics and metabolomics, has served to extensively characterize phenotypes of both the microbiota and the host.¹ Innate immunity quickly recognizes and reacts to pathogens. This first line of defense includes macrophages, dendritic cells (DCs), neutrophils and monocytes, as well as non-classical lymphoid cells such as innate lymphoid cells, mucosal-associated invariant T (MAIT) cells, $\gamma\delta$ T cells, natural killer (NK) and invariant natural killer T (iNKT) cells.

Immune cells can be trained by microbiota-derived metabolites. For example, it has been recently shown that the microbiota is essential for murine MAIT intrathymic development,

absent in germ-free mice.^{2, 3} MAIT cells identify small bacterial molecules presented by the major histocompatibility complex class Ib molecule MR1. Legoux et al.² demonstrated that murine MAIT intrathymic development is driven by the microbial metabolite 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil; this metabolite transfers to the thymus, where MR1 captures and presents it to forming MAIT cells. In addition, Constantinides et al.³ showed that MAIT cells adequately develop during a restricted, early-life time window and exposure to specific riboflavin-producing microbes is required. These works demonstrate that the microbiota drives the formation of the host immune system by secreting molecules that function like self-antigens.

Gut lamina propria harbors distinct T-cell subsets in a biunivocal relationship with the microbiota. The importance of the microbiota in T-cell education has been clearly demonstrated in murine models. Germ-free and antibiotic-treated mice present different intestinal T-cell receptor (TCR) repertoires when compared to mice with unaltered microbiota composition, showing that microbial antigens affect T-cell development.⁴

Although it is known that the local environment shapes effector-cell differentiation, the biological mechanism that leads to the thymic development of microbiota-specific T-cells was yet to be identified. Of note, human microbiota modifies during the first three years of life, concomitant with TCR expansion, to become that found in adults.⁵ Recently, Zegarar-Ruiz et al.⁶ showed that, in mice, early-life microbiota colonization allows for microbial antigen trafficking from the gut to the thymus through intestinal DCs, which then favor microbiota-dependent T-cell expansion (Figure 1). In this way, the colonizing microbiota shapes the thymic TCR repertoire, supporting the identification of intestinal commensals and pathogens. Interestingly, mice colonized with *Escherichia coli* early in life were more resistant to a lethal dose of *Salmonella* at an older age. The results support the notion that the immunity development to commensal microbiota also generates protection against pathogenic bacteria the body has yet to encounter. Altogether, these data show the key role of the thymus in the generation of microbiota-responsive T-cells with multiple effector potential after antigen re-exposure.⁶

**FIGURE 1**
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Scheme of early-life microbiota colonization leading to microbial antigen trafficking from the intestine to the thymus by intestinal dendritic cells (DCs). Specifically, in young mice, intestinal microorganisms are trafficked in a CX3CR1- and CCR5-dependent manner from the gut to the thymus through intestinal CX3CR1⁺ DC, which present microbial antigens to induce the generation of microbiota-specific CD4⁺ T-cells. Most of these T-cells are CD24⁻ TCRβ⁺ and express CD44 and CD69, implying that they are antigen-dependent positively selected T-cells. Moreover, RNA sequencing showed that these microbiota-specific CD4⁺ T-cells display higher expression of proliferation and TCR-signaling genes, proving that these are post-selection cells ready to emigrate from the thymus and reach distal tissues. These findings open up intriguing perspectives

Understanding microbe-specific T-cell development at a young age—including how to efficiently reopen the window for intra-thymic development of microbe-specific T-cells in older hosts, paves the way to several appealing perspectives (Figure 1). This line of inquiry could yield new strategies to treat specific immune disorders for which microbe-dependent signaling plays a fundamental role, such as inflammatory bowel disease, or to enhance immunity against pathogens. In this regard, the application of therapeutic approaches to correct intestinal dysbiosis may hold promise.

Gut microbiota manipulation, through fecal microbiota transplantation or pharmacologic modification/decontamination, may modify the microbial composition, eliminating harmful

microbes and/or reconstituting missing health bacteria that in turn could influence the immune system function. However, to benefit from gut microbiota interventions, it is fundamental to completely uncover the immunology behind gut microbiota–host interactions and clearly demonstrate the efficacy and safety of these procedures. Indeed, even if this potential strategy may appear auspicious, further extensive research data are needed to shed light on the complex host–microbiota relations.

ACKNOWLEDGEMENTS

The authors thank Dr. Anna Globinska for Figure 1 design and Dr. Jiménez-Saiz for critical review of the manuscript.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests to disclose in relation to this paper.

AUTHOR CONTRIBUTION

All authors approved the final version of the manuscript as submitted and agreed to be accountable for all aspects of the work.

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