Commentary

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An Emerging Layer of Gut Microbiota–Host Communication: Type III Secretion System Effectors

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Research over the last two decades has substantially expanded evidence showing that gut microbiota actively participate in a host's biological processes, establishing continuous interactions with both immune and non-immune cells [1,2,3,4,5,6]. Through the production of metabolites, signaling molecules, and structural microbial components, gut bacteria contribute to the development and function of both innate and adaptive immunity from early life through adulthood [7,8]. Evidence from germ-free animal models strongly supports this concept, as the absence of microorganisms results in impaired immune maturation, including underdeveloped Peyer's patches, reduced Th17 differentiation, and lower secretory immunoglobulin A (IgA) levels, many of which are partially restored following microbial colonization [9,10,11].

Current models of communication between the microbiota and the immune system primarily involve extracellular and receptor-mediated mechanisms. Among the best-characterized are short-chain fatty acids (SCFAs), which regulate macrophage activity, promote regulatory T-cell differentiation, and contribute to immune tolerance [12,13,14], and microbial-associated molecular patterns (MAMPs), which are recognized by pattern-recognition receptors (including Toll-like receptors), activating signaling pathways involved in cytokine production and immune regulation [15,16]. The gut microbiota also contributes to preserving the integrity of the epithelial barrier, thereby limiting the systemic spread of pathogens and pro-inflammatory molecules [17]. Microbial metabolites and signaling molecules can also influence immune responses outside the gut, highlighting the systemic effects of the gut microbiota [18,19].

Together, these observations have established the current paradigm of microbiota-mediated immune regulation. However, an interesting recent study conducted by Young et al. [20] provides evidence of an additional mechanism by demonstrating that commensal bacteria encode effector proteins capable of directly interacting with host immune signaling pathways.

A New Perspective on Microbiome–Host Interactions

The study by Young et al. [20] introduced an additional perspective, proposing that some commensal bacteria may interact with host cells through direct protein delivery mechanisms traditionally associated with pathogenic microorganisms. Historically, type III secretion systems (T3SSs) have been identified as hallmarks of Gram-negative pathogens and represent specialized protein delivery systems employed by bacteria [21]. These complex "molecular syringes" consist of a basal body spanning the bacterial membranes, a needle-like filament, and a translocon capable of perforating the host's plasma membrane, thereby allowing bacteria to inject effector proteins directly into the host cytoplasm [21]. Once inside, these effectors interfere with a wide range of biological processes—from cytoskeletal dynamics and vesicular trafficking to inflammatory cascades, apoptosis, autophagy, and innate immunity—thereby creating ideal conditions for bacterial colonization and persistence [21]. The identification of these T3SS-associated effectors, encoded by members of the healthy human gut microbiota, suggests that such secretion systems may represent an additional route of host–microbiota communication [20]. However, a crucial caveat remains: The identification of intact T3SS and candidate effector-encoding genes in the genomes of commensal microorganisms does not constitute definitive proof that these systems are actually activated within the human gut *in vivo*. In summary, although the genomic data from Young et al. [20] outline a fascinating model for T3SS-mediated protein release, the physiological signals governing their expression and activation *in vivo* remain to be clarified.

By combining computational screening with large-scale experimental validation, Young et al. [20] identified numerous T3SS-associated effector proteins in strains of Pseudomonadota (formerly known as Proteobacteria), a group widely represented in the healthy human gut microbiota. To elucidate the biological relevance of these molecules, the authors mapped a comprehensive effector–host interactome. This approach, which integrated structural modeling with high-throughput protein–protein interaction assays, revealed hundreds of potential interactions

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between bacterial effectors and human proteins. Their data showed not only that specific bacterial effectors bind to human targets but also that a subset of these candidates can effectively penetrate human cells under experimental conditions [20]. Using both a heterologous T3SS delivery system and native commensal strains, the authors obtained empirical evidence of T3SS-mediated translocation. Although these data confirm that certain T3SS proteins from commensal bacteria possess the molecular machinery required to infiltrate human cells *in vitro*, they do not yet demonstrate that such translocation actually occurs within the complex physiological context of an intact human gut. The biological significance of these observations becomes apparent when considering the specific host targets selected by these bacterial effectors. Many play key roles in inflammation, cytokine networks, and immune regulation—particularly those associated with the NF-κB signaling axis. These findings have been confirmed using functional assays demonstrating that individual effectors from commensal bacteria are indeed capable of modulating NF-κB-dependent transcription and cytokine production *in vitro*.

This broadens our perspective on microbiota-mediated immunity, pointing to the intracellular transfer of proteins as a hidden level of communication between host and microorganism. If it were to emerge that gut bacteria commonly utilize such molecular networks, the clear boundary separating pathogens from commensals would inevitably become blurred. From this perspective, possessing a T3SS does not automatically render a microorganism harmful. A plausible evolutionary scenario is that such secretion systems originally evolved within ancient symbiotic relationships and were subsequently co-opted by pathogenic lineages to support infections; this remains, however, a fascinating hypothesis.

This interpretation shifts the focus to the biological context in which these molecular systems operate (Fig. 1, Ref. [20]).

At the same time, caution is warranted: The detection of T3SS-associated effectors in commensal strains does not automatically imply a beneficial outcome for the host. Indeed, Young et al. [20] found that multiple T3SS effectors were significantly more prevalent in metagenomes from individuals with Crohn's disease, whereas an opposite trend was observed in ulcerative colitis. Although this link is correlative rather than causative, it serves as a warning sign: Should regulatory control mechanisms fail, these same T3SS-mediated pathways could easily become pathogenic. Identical molecular interactions can lead to vastly different outcomes depending on the biological context—including microbial community dynamics, host genetics, epithelial barrier permeability, and baseline inflammation levels. This highlights the crucial distinction between a microorganism's theoretical molecular repertoire and its actual physiological behavior within the gut. While the study by Young et al. [20] confirms that commensal genomes harbor intact T3SSs, that these systems can be activated *in vitro*, and that individual effectors can alter immune signaling, we do not yet know whether these injection systems are active in the gut *in vivo*, which host cells are actually targeted, or whether their activity promotes homeostasis or pathology. Clarifying these dynamics will be of great interest for uncovering the situation *in vivo*.

As highlighted by the authors, it also remains unknown whether epithelial or immune cells actively induce the microbiota to deploy these "molecular syringes", or whether these systems activate in response to stress caused by environmental changes that drive commensal microorganisms toward a pathobiont-like phenotype [20]. It is equally crucial to determine whether the genomically identified T3SSs are transcriptionally active in the gut *in vivo* and whether their effectors reach host targets at biologically relevant concentrations. Answering these questions is the only way to demonstrate whether the interactions observed *in vitro* hold true *in vivo*. Furthermore, future research must establish whether this effector-mediated dialogue is a universal feature across human populations or whether it varies according to specific individual microbiome signatures. In parallel, the evolutionary history of these commensal secretion systems requires clarification. Young et al. [20] argue that these networks are not merely attenuated versions of the pathogen arsenal; rather, comparative analyses of sequence, structure, and host–target interactions reveal a largely distinct repertoire of effectors. This strongly supports the hypothesis that commensal T3SSs have evolved functional roles specific to symbiosis, rather than representing attenuated virulence systems. If future studies confirm this hypothesis, our understanding of T3SS biology would be radically transformed, demonstrating that these secretion systems can serve as bridges for cooperative communication rather than simply as weapons of infection.

Concluding Remarks

Recent research into the gut microbiome has rewritten our perspective on the mechanisms of immune regulation. What was once considered a mere collection of microbes in the gastrointestinal tract is now recognized as an indispensable component of host physiology. A vast number of studies—drawing on experimental models, human cohorts, and translational research findings—converge on a single truth: microbial communities actively shape immune system development, reinforce tissue homeostasis, and participate in host defense mechanisms throughout life.

The study by Young et al. [20] further expands this conceptual paradigm by demonstrating that commensal bacteria possess the mechanisms necessary to interact directly with host immune networks via T3SS effector proteins. Far from subverting the established paradigm, this newly discovered mechanism adds a fascinating layer of complexity to host–microbiota dynamics, offering new in-

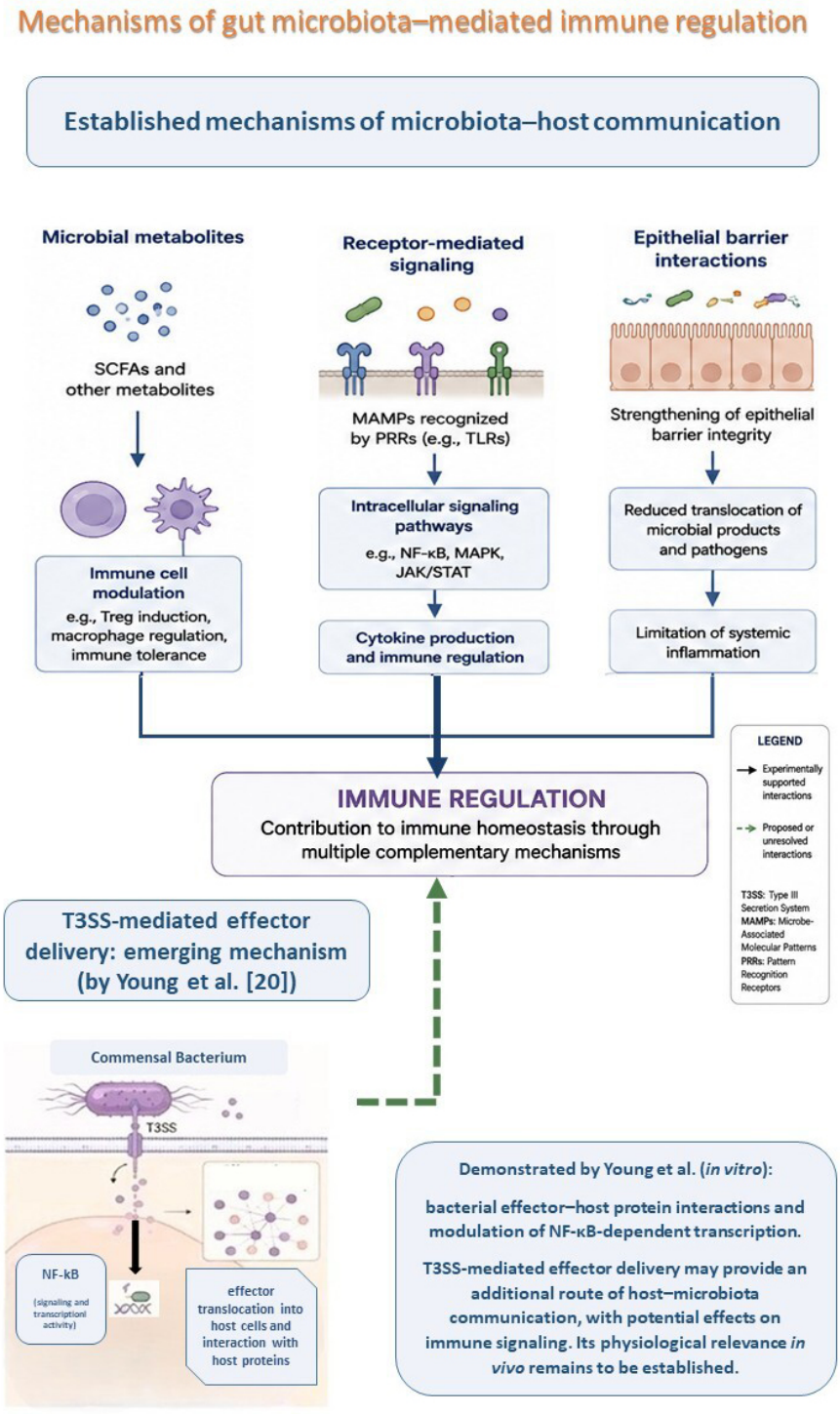


Fig. 1. Mechanisms of gut microbiota-mediated immune regulation. Gut microbiota contribute to host immune regulation through multiple complementary mechanisms, including microbial metabolites, interactions with the epithelial barrier, and receptor-mediated signaling. Commensal bacteria carrying a type III secretion system (T3SS) have been shown to encode effector proteins capable of interacting with host cellular pathways, including pathways related to NF-κB-dependent signaling. The potential contribution of these interactions may promote either homeostasis through balanced immune regulation or dysregulation associated with inflammation and disease [20]. The figure was created by the authors using Microsoft Paint (Microsoft Corporation, Paint version included with Windows 11, Redmond, WA, USA) and Microsoft Photos (Version 2026; Microsoft Corporation, Redmond, WA, USA) and finalized using Microsoft PowerPoint for Microsoft 365 (Version 16; Microsoft Corporation, Redmond, WA, USA). SCFAs, short-chain fatty acids; PRRs, pattern recognition receptors; TLRs, Toll-like receptors.

sights into how microbial functions determine the balance between health and disease. The emerging picture is that of a highly dynamic system. Extracellular, intracellular, and receptor-mediated effector pathways do not operate in isolation; they likely act synergistically, exerting a reciprocal influence that varies according to changes in microbial community structure, host physiology, and environmental stimuli. This complex network helps explain why the same microbial mechanisms can support baseline immune tolerance or, if altered, promote the onset of chronic inflammatory diseases. However, bridging the gap between these sophisticated experimental discoveries and actual clinical applications remains a formidable challenge.

Future research must elucidate the precise biological conditions governing these T3SS-mediated interactions. This requires deciphering the specific signals—originating from either the host or the microbiota—that trigger effector secretion, in addition to identifying the critical moments when such crosstalk shifts from promoting homeostasis to inducing pathology. Such insights will be crucial for determining the contribution of these processes to immune regulation and for establishing whether they represent a host–microbiota communication mechanism of broad significance.

Availability of Data and Materials

Not applicable.

Author Contributions

SM contributed to the conceptualization and project administration of the study. IS and MC contributed to the conceptualization and drafting of the manuscript. SM contributed to the critical revision of the manuscript for important intellectual content. All authors have read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

Sonia Moretti was a member of the Editorial Board of this journal at the time of acceptance. Sonia Moretti had no involvement in the review of this article and has no access to information regarding its review. The other authors declare no conflicts of interest.

Declaration of Generative AI and AI-Assisted Technologies in Manuscript Preparation

During the preparation of this manuscript, the authors used ChatGPT (OpenAI, GPT-5.5 model) exclusively for language editing and stylistic improvement. After its use, the authors thoroughly reviewed, verified, and revised all content to ensure accuracy and originality.

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