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A Tale of Three Cytokines: How Gut Bacteria Regulate Immunity

By Alexander Rees

If you have been scrolling social media recently, you may have noticed an increase in articles or people talking about the gut microbiome. Many claims suggest that the gut microbiome may influence your energy levels, acne, mental health, and even hair loss. While some of these claims may come from social media influencers jumping on the latest trend without scientific backing, studies illustrate the significant impact the gut microbiome has on overall health. Examples include microbiome-mediated prevention of allergic inflammation in the lungs and its influence on BMI, body fat percentage, and insulin resistance.[1,2]

Growing evidence also suggests that the gut microbiota plays a large role in immune responses, including the maintenance of homeostasis and the shaping of mammalian immune responses.[3] Part of this immune response in mammals involves interferons, which are part of the frontline response in the immune system, helping to restrict viral propagation in locally infected areas of the body. Type 1 interferons (IFNs), including IFNα and IFNβ, create proinflammatory, antiviral, and antimicrobial responses through the activation of interferon-stimulated genes (ISGs).[4] Perhaps surprisingly, a healthy microbiota also triggers the production of IFNs in a manner required to maintain competently tuned immunity.[5] Ayala et al. explored whether and by what means commensal bacteria-produced IFNs may elicit a tolerogenic response.[6]

Using germ-free (GF) and specific pathogen-free (SPF) mice, ISG expression was examined in colon tissue under steady-state conditions. In the absence of commensal bacteria, IFNα—but not IFNβ—was found. However, the introduction of Bacteroides fragilis (Bf) restored IFNβ expression in the GF mice. This response was repeated in vitro, where Bf, B. thetaiotaomicron, or B. vulgatus all elicited IFNβ production, demonstrating a specific role for these microbiota in priming IFN responsiveness.

These results were further observed using colon explant tissue stimulated with the Toll-like receptor 3 (TLR-3) agonist, polyinosinic–polycytidylic acid (poly I:C). Because CD11c+ dendritic cells (DCs) are responsible for the constitutive expression of type 1 IFNs in the intestines,[7] the interaction between these cells' IFNβ production was investigated in the presence or absence of commensal bacteria in vitro, establishing a direct role for commensal priming of DC responsiveness. Of particular interest, Bf-monocolonized mouse tissue responded similarly to SPF-derived tissue, rather than GF-derived tissue. Further, the ISG response to stimulation was not reliant on differential IFN-receptor 1 (IFNAR1) expression, but only on the presence of commensals.

Bf has been shown in previous studies to help dendritic cells achieve immune tolerance.[8] What is less understood are the signaling pathways that are used to accomplish this. To identify how a deficiency of type 1 IFN would change the production of cytokines downstream, IFNAR1-deficient bone marrow-derived dendritic cells (BMDCs) and wild-type (wt) BMDCs were treated with Bf in vitro. The results showed a decrease in the expression of the anti-inflammatory cytokines IL-10 and IL-27 in mice lacking this receptor.

Without IFNAR1, BMDCs create a pro-inflammatory environment. To examine if regulatory T cells (Tregs) played a role in this, wt and IFNAR1-deficient BMDCs were co-cultured with wt CD4+ T cells and Bf. Where wt BMDCs showed production of IL-10 and the induction of Foxp3 (a transcription factor for Tregs) in Tregs, IFNAR1-deficient cells did not show these results, clarifying the involvement of type 1 IFNs for Treg-mediated tolerance.

Lastly, Zhang et al. have previously shown that IL-27 facilitates IL-10 expression in certain CD4+ T cell groups.[9] Knowing this, it was theorized that IL-27 could mediate commensal-initiated tolerance by Tregs. Using a CRE-Lox system, the tolerance-promoting IL-10 production by Tregs in response to co-culture with Bf was found to be IFNAR1-dependent in vitro and in vivo.

The diminished Treg environment has been associated with an expansion of other T cell subgroups, such as Th17 or Th1. Since the IFNAR1-deficient mice had a greatly reduced Treg population, it would make sense that there would be an increase in one of these groups. As expected, there was a significant increase in Th17-produced IL-17 in the IFNAR1-deficient animals compared to their wt counterparts, even in the presence of Bf.

The data generated by Ayala et al. shows just how important commensal bacteria are in IFN signaling and bringing about appropriate T cell responses. It remains to be seen by what mechanisms commensal-induced IFN signaling differs from pathogenic bacteria, which uniformly stimulate much higher levels of IFN compared to that elicited by commensal microbes.

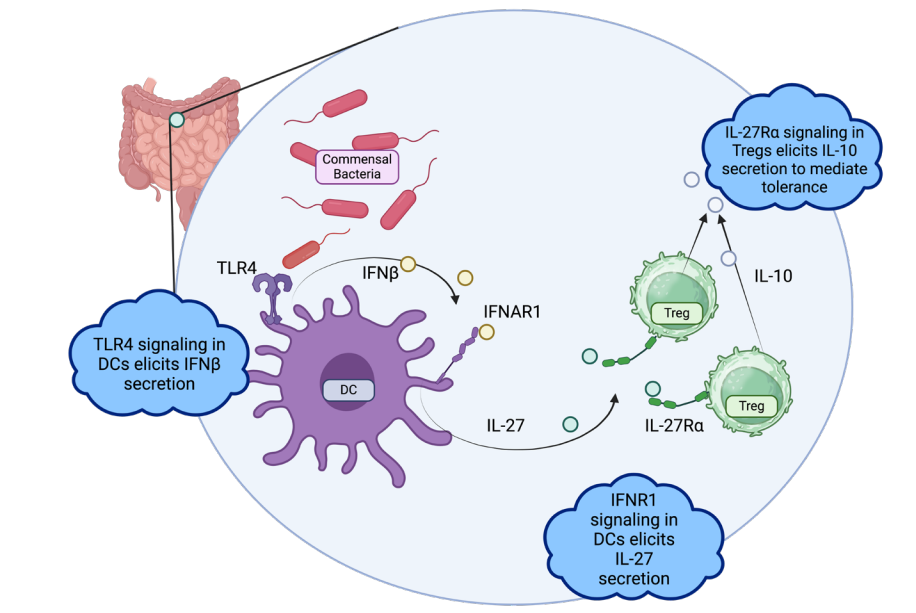

Figure 1 | Commensal Organisms initiate tolerance via Dendritic Cell signaling to Regulatory T Cells.

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