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Editorial Open Access

Probiotics: Microbial Experts in Immunomodulation of Mucosal Macrophage-Driven Responses

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Editorial

Probiotics are live microbes conferring health benefit to the host, by reinforcing mucosal barrier integrity and functionality. Recently, attention has focussed on their immunomodulatory role: a microbial on-off switch mediating homeostatic/tolerogenic mucosal responses, whilst maintaining responsiveness to pathogenic infection [1]. As with pathogenic bacteria and their conserved pathogen associated molecular patterns (PAMPs), probiotics exhibit microbial associated molecular patterns (MAMPs), thus pattern recognition is fundamental to understanding how probiotics modulate immune fate decisions: activation or tolerisation. Probiotic MAMPs, include LTA, PGN, LPS, flagellin and CpG DNA; initiating inflammatory responses through recognition by pattern recognition receptors, TLR2, NOD1/NOD2, TLR4, TLR5, TLR9, respectively. PRR recognition of both pathogen and probiotic MAMPs highlights our limited understanding of pattern recognition defining protective anti-pathogen responses or immunomodulatory responses to beneficial microbes.

PRRs drive mucosal cytokine responses

Probiotics modulate mucosal macrophages (Mϕs), which exhibit functional heterogeneity, from microbial killing and inflammation to antigen presentation and modulation of mucosal responses; consequent cytokine profiles driving innate and adaptive responses. PRR ligation drives both immune activation and suppression; determined by receptor expression, cell type, endogenous negative regulators and external environmental signals, hence MAMP responsiveness defines Mϕ immune phenotype. Intestinal Mϕs exhibit a homeostatic M2 subset phenotype, characterised by high phagocytic activity, scavenger receptors (CD36, CD68, CD206), secretion of regulatory, anti-inflammatory (TGFβ, IL-10) and low pro-inflammatory cytokine levels (TNFα, IL-1β, IL-6, IL-8), favouring humoral and tolerogenic responses [2-4]. In the context of inflammation, mucosal Mϕs display an inflammatory M1 phenotype, expressing iNOS, immune activators (HLA-DR, CD86) and pro-inflammatory cytokines (TNFα, IL-1β, IL-6, IL-12, IL-18, IL-23). Subset functional heterogeneity is determined by tissue environment, indeed, subset-specific MAMP-responsiveness results in discriminatory cytokine profiles with downstream effects on T cell subset differentiation and activation. How probiotics modulate cytokine production and innate-adaptive bridge responsiveness will facilitate controlling immune fate decisions.

Probiotic modulation of macrophage cytokines and immune fate

Probiotic cytokine modulation is Mϕ subset- and strain-dependent. Subset-dependence was demonstrated, where several lactobacilli augmented LPS-induced M1 TNFα and suppressed M2 homeostatic Mϕs [5], whereas other strains increased M1 IL-10:IL-12 ratio [6]. Thus, probiotics differentially modulate Mϕ cytokine production and plasticity between pro-inflammatory (M1) and anti-inflammatory/tolerogenic (M2) phenotypes. Investigating bioactive modulatory molecules, probiotic-derived LTA, suppressed and cross-regulated LPS-, LTA- and PGN-induced Mϕ TNFα [7-9] and differentially regulated TLR2-dependent IL-10:IL-12 ratios in a strain-dependent manner [10], hence modulating Mϕ-mediated tolerisation and CMI. Additional to this PRR crosstalk, gastrointestinal tract transit significantly induces bacterial death, hence releasing probiotic-derived MAMPs such as CpG DNA, recognised by TLR9. Indeed, probiotic DNA induced and up-regulated Mϕ IL-1β, IL-6, IL-12, TNFα, IL-10 [11,12], indicative of regulating both immune-activation and immunosuppression; whether it cross-regulates TLR2- and TLR4-mediated responses in both homeostatic and pathological environments awaits investigation.

There is not only TLR-mediated polarisation and plasticity, but also effects of TLR crosstalk on tolerisation. Cytokine suppression suggests endotoxin tolerisation (ET) mechanisms drive differential immune fate responsiveness to MAMPs and PAMPs. There are many ET mechanisms; including TLR down-regulation, expression of TLR negative regulators (Myd88s, IRAK-M, Tollip, A20, p50/p50 NFκB), and exogenously secreted feedback molecules (IL-10) [13]. Additionally, ET is dependent on Mϕ subset and further defined by MAMP encountered [14]. It is evident that commensals and probiotics coordinate tolerance [15]. *Lactobacillus paracasei* Cultech suppressed LPS-induced TNFα and IL-6 in a TLR2-dependant manner, associated with suppression of NFκB activation and up-regulation of negative regulators (A20, SOCS1, SOCS3, IRAK-M) [16]. Probiotics also modulate immune responses *via* miRNA induction, regulating mRNA expression and translation. Knockdown of proinflammatory miR-155 up-regulated SHIP1 and suppressed LPS-induced TNFα, IL-6, IL-12 [17,18] and M1 subset polarisation [19], whereas TLR2-induced miR-146a inhibited TNFα by suppressing IκBα phosphorylation and IRAK-1 expression [20]. Consequently, probiotic immunomodulation *via* ET and selective Mϕ polarisation may involve differentially regulating miR-155 and miR-146a expression.

Mucosal macrophages, pathology, probiotics and clinical translatability?

Dysregulated Mϕs drive chronic inflammatory pathology such as Crohn's disease (CD) and ulcerative colitis (UC), by M1-associated cell mediated-, and M2-associated humoral-immunity, respectively. Consequently, pathological involvement of distinct Mϕ subsets represents a realistic target for therapeutic intervention, modulating activation, suppression, or reprogramming plasticity. Ideally, future

probiotic-based therapeutics would restore Mϕ homeostasis: achieved by manipulating functional plasticity and selective subset suppression. Thus, in CD, selective M1 tolerisation or reprogramming towards anti-inflammatory M2-like cytokine profiles, whereas tolerising or manipulating M2 plasticity towards a pro-inflammatory M1 phenotype, to treat and manage UC. Mucosal breakdown characterises these diseases, resulting in dysregulated MAMP recognition. Consequently, probiotic treatment demonstrated mixed results, some augmenting pathology [1]. To harness probiotic immunoactivation and tolerogenicity, research must further characterise immunomodulatory capacity of these microbes, on not only homeostatic and pathological Mϕs, but on a variety of cells and their environments, mimicking healthy and diseased tissue. Ultimately, probiotic Mϕ-targetting therapies, may not be effective on their own; future rationale will consider 3-dimensional mucosal tissue, where pathological Mϕs are merely important bit-players in a complicated orchestral arrangement of pathological cells and their responses.

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