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 Culttech 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 immunooactivation 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.

References