Understanding Immunomodulatory Effects of Probiotics

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The intestinal microbiota is known to be the driving force in the development and maintenance of the immune system. While substantial shifts in the microbiota composition may influence the immune functionality in the longer term, short occasional changes might also be sensed. The latter opens considerable perspectives for the use of nutritional interventions intended to modulate immune functionality in a desired direction. Probiotics are one of the most promising ways currently used in a multitude of attempts to redirect immune parameters into a ‘safer’ direction. While it is already clear that probiotics will not rescue ‘heavily damaged’ immune systems, they may play a critical role in preventing disease or redirecting immune parameters that are subclinical but will increase the risk for disease in the longer term. Moreover, the understanding of their effects on immune tolerance parameters, their metabolic and physiological benefits, or their microbiological effects on pathogens, will yield fundamental knowledge leading to the development of new drugs and therapies. Although hopes are high that these approaches will be as effective as existing pharmaceutical homologs, even less effective compounds or strains will be welcomed as adjunct therapies because of the lack of side effects, too often seen with the current treatments.

Screening pipelines that use simple in vitro models allow to select strains that seem to perform well in e.g. animal models of inflammation. Further investigation using modern immunological techniques, metagenomic approaches, expression analysis, knockout animals, etc., has pointed out clear mechanisms of microbiological, metabolic or immunological activity, in some cases even allocated to active molecules at the bacterial surface or to metabolites produced under certain conditions. Knowledge of these mechanisms allows to understand and possibly circumvent differences in environmental conditions (skin, mouth, gut, vagina), lifestyle (drug, diets, stress, hygiene) or host status (genetic background, newborn, adult, elderly; healthy or diseased), which make clinical trials with probiotics extremely difficult.
We focused on only a few of these mechanisms, involving regulatory cells, cytokines, chemokines, defensins, which that manage immune responses, fight infections and toxins or cause immune-mediated anomalies. When these ‘natural’ control mechanisms fail, external intervention is necessary. Probiotics clearly have the potential to assist in this process. As an example, we described a pipeline that starts with a simple screening for ‘anti-inflammatory’ strains on peripheral blood mononuclear cells followed by a confirmation in a simple mice model for colitis, allowing the selection of two strains with opposite properties. Further testing using bone marrow-derived cells, pulsed or not with the respective bacteria, pointed out that dendritic cells were the host effector cells involved. Since Nod2^{−/−} knockout mice revealed that the protection against colitis was Nod2 dependent, the hypothesis was raised that peptidoglycan (PGN) at the bacterial surface might be involved. Purified PGN injected intraperitoneally yielded again comparable results as obtained with the intact strains and moreover was dose dependent. A final comparison by high-performance liquid chromatography of the chemical composition of PGN of both strains yielded a significantly different peak, identified as the monomer GlcN-MurNAc-l-Ala-γ-D-isoGln-l-Lys, released only by the anti-inflammatory strain. Using the chemically synthesized pure molecule, it was possible to mimic the probiotic effect of the live strain in mice. Further mechanistic research revealed that regulatory CD103+ DCs are involved, preferentially CD4^+Foxp3+ T regulatory cells, involved in intestinal homeostasis.

Using results of ongoing metagenomic work, it is very likely that other bacteria than the traditional lactobacilli and bifidobacteria will come up as possible therapeutic alternatives. The term pharmabiotics has been mentioned before and will probably be further elaborated to include heat-killed or irradiated strains as well as metabolically or genetically engineered bacteria. These will make optimal use of mechanistic studies providing insights in the molecular basis of the intended effects. The future of the *-biotics without any doubt is brilliant.