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PF03.04

Enhancement of intestinal IgA production via Peyer's patch dendritic cells by membrane vesicles derived from lactic acid bacteria (Lactobacillus sakei)

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Introduction: Intestinal bacteria and probiotics such as lactic acid bacteria are involved in the development and regulation of gut immunity. We previously found that Lactobacillus sakei subsp. sakei NBRC 15893, a lactic acid bacterium, enhances immunoglobulin A (IgA) production in mouse intestinal Peyer's patch (PP) cells. IgA plays a key role in preventing pathogenic infections and maintaining the gut environment. Here, we report on the IgA-enhancing effects of membrane vesicles (MVs) derived from the same bacterial strain as well as the on mechanisms underlying that effect.

Methods: Lactobacillus sakei NBRC 15893 was cultured in MRS medium. The broth was centrifuged (8,500 × g, 5 min) and then filtered (0.22 μm). MVs were collected by ultracentrifugation (100,000 × g, 1 h) and purified by density gradient ultracentrifugation. PP cells and bone marrow-derived dendritic cells (DCs) were prepared from BALB/c mice. IgA concentration was determined by ELISA.

Results: MVs enhanced IgA production from PP cells, and the MV-mediated enhancement was abolished by the depletion of DCs or the neutralization of Toll-like receptor (TLR) 2, indicating that MVs stimulate DCs in PP cells via TLR2. MVs upregulated mRNA expression of inflammatory cytokines (e.g., interleukin [IL]-6), inducible nitric oxide synthase (iNOS), and retinal dehydrogenase 2 (RALDH) in bone marrow-derived DCs. Inhibition of iNOS and RALDH or neutralization of IL-6 inhibited the MV-mediated effect in IgA production in PP cells, indicating that in PP cells, IgA production secondary to MVs stimulation is dependent on NO, retinoic acid, and IL-6 production. Furthermore, MVs were found into the subepithelial dome region of PPs, where DCs reside, indicating that MVs might also regulate the intestinal immune system in vivo.

Summary/Conclusion: We hypothesize that L. sakei NBRC 15893–derived MVs enhance IgA production in PP cells via three processes: 1) TLR2-mediated DCs activation, 2) NO – and retinoic acid–mediated IgA class switch recombination in B cells, and 3) IL-6–mediated B cells' differentiation into plasma cells. Our results show that when assessing the effects of probiotics, it is necessary to consider not only the effects of bacteria per se but also of bacteria-derived MVs.

PF08.17

Tumour cell-derived small extracellular vesicles modulate macrophage immunosuppressive phenotype associated with PD-L1 expression

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Introduction: Tumour-associated macrophages (TAMs) play a key role in promoting tumour progression, by exerting an immunosuppressive phenotype associated with M2 polarization and with the expression of CD204 and programmed cell death ligand 1 (PD-L1). It is well known that tumour-derived extracellular vesicles (TEVs) play a pivotal role in the tumour microenvironment, influencing TAM behaviour. The study was aimed to examine the effect of TEVs derived from colon cancer and multiple myeloma cells on macrophage functions.

Methods: Non-polarized macrophages (M0) differentiated from THP-1 cells were co-cultured, for 3 up to 48 hours, with TEVs derived from a colon cancer cell line, SW480, and multiple myeloma cell line, MM1.S. The expression of M2 and TAM markers (respectively

CD163 and CD204) as well as of PD-L1 and Interleukin 6 (IL6) were evaluated at mRNA and protein level. The apoptotic rate of CD3 + T cells co-cultured with TEV-treated M0 macrophages was analysed by FACS.

Results: Our results indicate that TEVs can significantly upregulate the expression of surface markers of M2-like phenotype (CD163) and TAM (CD204) as well as of PD-L1, inducing macrophages to acquire an immunosuppressive phenotype. In parallel, we found that TEVs were also able to induce a significant increase of IL6 expression at both mRNA and protein levels and to activate the STAT3 signalling pathway. Since PD-1/PD-L1 axis is involved in the inhibition of T cells, we assessed the ability of macrophages treated with TEVs to affect T cell viability. We found that CD3 + T cells co-cultured with TEVs-treated M0 showed an increase of their apoptotic rate in comparison to CD3 + T cells grown in the presence of untreated macrophages.

Summary/Conclusion: Cumulatively, these preliminary data suggest that TEVs contribute to the immunosuppressive status of TAMs, promoting tumour growth and progression.

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