



## ISEV2020 Abstract Book

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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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