UHMWPE but not PMMA Particles Induce Interferon-γ Expression in Natural Killer T cells

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Statement of Purpose: Two major issues in total joint arthroplasty are loosening of implants and osteolysis caused by wear particle-induced inflammation. Wear particles stimulate the release of pro-inflammatory cytokines, chemokines and other inflammatory mediators from macrophages and other cells. Although the biological response of macrophages to wear debris is well established, the role of other cell types such as natural killer T lymphocytes (NKT) and dendritic cells is limited. Upon activation, NKT cells are known to modulate the immune system by rapidly secreting either pro-inflammatory cytokines such as IFN-γ, or anti-inflammatory mediators such as IL-4. This ability to further activate or suppress the inflammatory response makes these cells unique. The purpose of current study is to evaluate cytokines released by NKT cells in response to phagocytosable polymer particles with/without dendritic cells.

Methods: NKT cells were isolated from the spleens of C57BL/6J male mice (6-8 weeks old) and exposed to two different particle types, ultra-high molecular weight polyethylene (UHMWPE) and polymethylmethacrylate (PMMA) with or without lipopolysaccharide (LPS). In addition, particle/LPS stimulated dendritic cells were co-cultured with NKT cells in specific groups. The expression profiles of IFN-γ and IL-4 were analyzed at both mRNA and protein levels using qPCR and ELISA respectively. The NKT cells activation ligand α-galactosylceramide (GalCer) was used as a positive control.

Results: UHMWPE particles stimulated the NKT cells to secrete IFN-γ; co-culture with dendritic cells further enhanced the production of both mRNA and protein levels. Treatment of LPS did not further stimulate cultures of both NKT cells and antigen presenting dendritic cells to produce increased levels of IFN-γ. Furthermore, UHMWPE particles did not stimulate the NKT cells to secrete IL-4, while α-GalCer treatment in the co-culture system significantly enhanced both INF-γ and IL-4 expression by NKT cells ($p<0.005$, Fig. 1). PMMA particles did not stimulate IFN-γ or IL-4 expression.

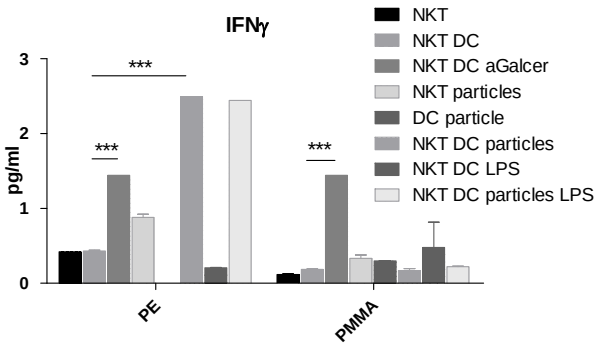

Figure 1 Secretion of Interferon-γ by NKT cells was determined by ELISA. The cells were exposed to UHMWPE (PE) only or different treatment combinations including dendritic cells (DC), α-GalCer, UHMWPE (PE), and lipopolysaccharide (LPS) for 24 hrs.

Discussion: Our results demonstrate that activation of NKT cells by UHMWPE particles modulates the pro-inflammatory response through secretion of IFN-γ in the presence of antigen presenting dendritic cells. It is well accepted that M1macrophages (which are induced by IFN-γ) can enhance the pro-inflammatory response, whereas M2 macrophages (which are induced by IL-4) mitigate this response. Thus, the resulting cytokine expression profile of NKT cells exposed to UHMWPE particles could potentially increase the amount of M1 macrophages. Our current findings suggest that NKT cells exposed to UHMWPE wear particles may enhance tissue damage and promote periprosthetic osteolysis.

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