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Fasciola hepatica Fatty Acid Binding Protein induces a tolerogenic phenotype in human dendritic cells

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The liver fluke *Fasciola hepatica* is a trematode and infection in humans is regarded as an emerging food-borne zoonosis affecting at least 2.4 million people in more than 70 countries. This parasitic helminth is extremely successful to evade the host immune defense through secretion of various immune-modulatory molecules. Macrophages and dendritic cells (DCs), as antigen presenting cells, are interacting with helminth-derived molecules that could influence both their maturation and polarization state. Fatty Acid Binding Protein (FABP), a single molecule isolated from F. hepatica tissue extract, has been shown to display some anti-inflammatory properties, at least partly by inducing alternative activation of macrophages. However, little is currently known on its impact on DCs and their capacity to prime specific CD4+ T cell subsets. In the present study, we therefore investigate the immunomodulatory effects FABP on human dendritic cells.

Using an *in vitro* model of primary monocyte-derived human dendritic cells (moDC), we first characterized the effects of increasing concentratins of recombinant FABP on maturation markers and cytokines secretion in LPS-stimulated moDC. After 48h of stimulation with FABP, no differences in the expression of classical cell surface maturation markers, such as CD80, CD86, CD40 and HLA-DR, were observed. However, a significant and dose-dependent increase in CD103, which has been previously associated with tolerogenic DC, was found. Furthermore, a potent decrease in IL-6 and increase in IL-10 secretion were also evidenced in LPS-stimulated DC treated with FABP. After restimulation with a CD40L-expressing cell line mimicking the interaction with T cells the inhibition of IL-6 secretion was still present, together with a potent reduction in the other pro-inflammatory cytokines TNFα and IL-12p70. We next evaluate the impact of FABP priming in LPS-stimulated DCs on naive CD4+ T cell polarization using a model of DC-allogenic T cell co-culture. After 2 weeks, the cytokines production by T cells was determined by intracellular staining and a dose-dependent increase in the IL4/IFNγ ratio was observed, indicating that priming DC with FABP induces a Th2 immune response. In addition, a higher secretion of IL-10 by T cells was found after re-stimulation with anti-CD3 and anti-CD28, suggesting an increased capacity of FABP-primed DCs to promote regulatory T cells (Tregs).

Altogether, our data suggest that recombinant *F. hepatica* FABP induce a tolerogenic phenotype in human moDCs resulting in a higher capacity to skew naïve T cells towards a Th2 and Treg profile. Further studies are required to elucidate the exact underlying mechanism by which

FABP modulates DC functions and to explore the *in vivo* relevance of these findings in various models of inflammatory diseases.

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