Birte Kristensen – PhD Project Description

Title – B-cell and fibrocyte-elicited autoimmune responses in patients with autoimmune thyroiditis and healthy controls

Background – In addition to producing antibodies, B cells are very efficient at antigen presentation and cytokine production. Human B cells were recently discovered to produce interleukin-10 (IL-10) after strong mitogenic stimuli leading to the discovery of a potential subset of B cells with a regulatory function. However, B cells may also produce pro-inflammatory cytokines such as IL-6, tumor necrosis factor alpha (TNF-α) and interferon-gamma (IFN-γ). Little is known about the factors that drive harmful or protective B cell activities. The potential IL-10 producing regulatory B cells are believed to dampen autoimmune diseases in humans.

It is not been demonstrated whether these IL-10 producing B cells can be induced by self-antigens. It was recently demonstrated by our group that Bregs can be induced using the human self-antigen thyroglobulin as a stimulant. More research is needed regarding the frequency of Bregs between autoimmune patients and healthy individuals. As well as what factors are necessary for their activation, or whether protective and harmful B cells can be distinguished on the basis of their surface markers.

A proportion of Graves' disease patients might suffer from thyroid related eye symptoms known as Graves' Ophthalmopathy, which is where a large amount of fibroblasts enter the orbital tissue causing inflammation. The immuno-pathology is currently unknown but T cells may play an essential role. The IGF1-receptor may be capable of acting as a self-antigen and may have a role in the pathology.

Aims –

- To understand the ability of human B cells to present antigen with special focus on autoimmune thyroid disease (AITD) associated self-antigens. Cytokines will be measured after B cells stimulation with AITD associated self-antigens including thyroglobulin, thyroid peroxidase, thyroid stimulating hormone receptor and insulin growth factor 1 receptor.
- To determine whether B cells in AITD can be subdivided into separate functional sub-populations depending on their phenotype and cytokine production.
- To better understand fibroblasts/fibrocytes carrying the IGF1-R auto-antigen and their role within Graves' diesase pathogenesis.

Methods – Briefly, the methods include flow cytometry for phenotype characterisation and cytokine expression. There will be isolation of peripheral blood mononuclear cells along with various cell subsets such as monocytes, B and T lymphocytes. Cytokine measurements will occur via intracellular staining and cytometric bead array (CBA). Intracellular staining is to identify single cell cytokine production. CBA will be used to determine the overall cytokine production. RT-PCR will be used to investigate the genetic component of some cytokines after stimulation.