

SUMMARY

Rheumatoid arthritis (RA) and multiple sclerosis (MS) are both inflammatory diseases of unknown origin. Peptidoglycan, a major cell wall component of gram-positive bacteria, is a candidate antigen. Peptidoglycan (PG) is composed of long sugar chains of alternating N-acetyl glucosamine (GlcNAc) and N-acetyl muramic acid (MurNAc) residues, which are interlinked by peptide bridges, resulting in a large complex macromolecular structure. Because of its capability to induce production of proinflammatory cytokines, to induce arthritis in rodents and the presence in antigen presenting cells (APC) in RA joints it is believed to play a role in the pathogenesis of RA.

In the present thesis we investigated whether PG is involved in the pathogenesis of RA and MS. We showed that PG present in human tissues is biologically active as it is able to induce the production of the pro-inflammatory cytokines TNF- α , IL-1 and IL-6 and to induce T cell proliferation. Furthermore, it is shown that a reduced systemic IgG response against PG derived from the gut flora is associated with rheumatoid arthritis, suggesting a protection against the spreading of PG in non-mucosal sites (chapter 3.1). T cell proliferation and cytokine production induced by PG did not differ between RA patients and healthy controls but PG is able to induce cytokines (IL-1 β , IL-6, IL-8, IL-10, IL-12, IFN- γ , TNF- α and the matrix metalloproteinase, gelatinase B (MMP-9) all associated with RA (chapter 3.2). To determine whether these *in vitro* activities of PG are also present *in vivo*, immunohistochemical studies were performed. To detect unstable immunological markers strong fixation agents have to be used which often results in suboptimal morphology. Fixation with pararosaniline resulted in better morphology of all tissues and inhibited endogenous alkaline phosphatase activity in brain tissue while maintaining antigenicity (chapter 4.1). *In situ*, PG can be detected in both macrophages and dendritic cells in RA joints. In chapter 4.2 it is shown that these cells coexpress HLA-DR, CD40, CD80 and CD86 suggesting that these cells are immunocompetent. Furthermore PG-containing cells coexpressed cytokines such as IL-6, IL-10 and TNF- α . Because it can be hypothesized that PG also plays a role in other chronic inflammatory diseases than RA we investigated the presence of PG in MS. It is shown that PG-containing cells are present in MS brain in APC coexpressing costimulatory molecules and cytokines. In addition, the presence of plasma cells specific for PG in MS brain and anti-PG antibodies in cerebrospinal fluid suggests that in MS PG is able to induce antibody production intrathecally.

Our studies identified PG as a bacterial modulator of inflammation (cytokines, matrix metalloproteinases), but also of specific adaptive immunity (T cell proliferation, anti-PG antibodies). Interfering with access of PG to non-mucosal sites may be a novel approach to anti-inflammatory therapy.