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## **Immunogenetics of infection and inflammation of the urogenital and gastrointestinal tracts and probiotics**

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## Aims and Outline

### *Background*

The mucosal surfaces of the intestinal and female urogenital tracts are in intimate symbiosis with commensal microorganisms and occasionally exposed to pathogens. The mucosal immunity is responsible for creating a milieu that is beneficial for the host and the intestinal flora. The innate response is crucial in the control of the pathogens in the mucosal immune system.

The required balance between tolerance and immunity represents a regulatory challenge to the mucosal immune system. Therefore, signals from commensal bacteria have an essential role in the development of the peripheral and mucosal immune system.

The studies presented in this thesis were designed to understand the immunogenetic contribution to chronic inflammatory responses of the urogenital tract during Chlamydia infection and the intestinal tract in Crohn's disease and ulcerative colitis.

### *Aims of the thesis*

First, to assess the role of nucleotide polymorphisms in genes involved in the detection of pathogens and the regulation of the inflammatory response in order to determine their role in the susceptibility to and severity of urogenital diseases caused by *Chlamydia trachomatis* and in selected gastrointestinal chronic inflammatory diseases. The genes selected are important in the regulation of both the innate and acquired immune response.

Second, to use the knowledge obtained in these studies to better understand the underlying polygenic regulatory and sensory mechanisms involved in urogenital and gastrointestinal immune responses to different noxious agents, and pathogenic bacteria.

The epidemiology and susceptibility markers of *Chlamydia trachomatis* infection are the focus of the **first part** of the thesis.

Although Crohn's disease was previously classified as an autoimmune disease, it is now increasingly regarded as result of an impaired or dysregulated host response to intestinal microbiota. This may be due to a defect in the autophagic process that it is involved in the defence against intracellular microorganisms. This is approached in the **second part** of the thesis.

Recent findings indicate that an altered intestinal flora may be at the basis of the pathogenesis of these diseases and therefore probiotics and symbiotics are the focus of the **third part**.

The **Summary and Discussion** section reviews the results of the different parts of this thesis in the context of the current literature.

Aims and Outline

I hope this knowledge will deepen the insight into the immunogenetics underlying infection and inflammation of the human mucosal epithelia and provide a basis for further research into diseases of the gastrointestinal and urogenital tracts.



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## Aims and Outline Part I

*Chlamydia trachomatis* (Ct) is the most important bacterial of sexually transmitted infections and may cause considerable reproductive morbidity with the highest rates in adolescent women. Infections often remain asymptomatic and provide a huge reservoir for transmission of the disease. Repeated infections seem associated with severe upper genital tract pathology including pelvic inflammatory disease, ectopic pregnancy, and tubal infertility. Furthermore, infections may proceed to the abdominal cavity and cause ‘sterile’ peritonitis with ascites. Acute perihepatitis (Fitz-Hugh-Curtis syndrome) is commonly caused by Ct infections. The clinical course of Ct infections shows remarkable interindividual differences in transmission, symptomatic course, persistence or clearance of infection, and development of late complications.

This part of the thesis aims to assess the role of genes involved in the innate and acquired immune response in the susceptibility to and severity of Ct infections. Five chapters have been devoted to this end.

**Chapter 1** discusses the epidemiology, diagnostics and treatment of Ct infections in general.

**Chapter 2** gives an overview of Ct infections with regard to the identification of susceptibility markers for ocular and sexually transmitted infection by immunogenetics.

**Chapters 3 and 4** study the effects of toll-like receptor (*TLR*)2, *TLR*4 and *TLR*9 polymorphisms on susceptibility to and severity of Ct infections.

In **Chapter 5** both murine and human studies are used to understand the role *CXCR5* polymorphisms play in primary and secondary Ct infections and in the development of late complications.

## Aims and Outline Part II

Inflammatory bowel disease (IBD) is a chronic, relapsing intestinal inflammatory disorder of unknown origin. This disease is clinically classified into Crohn's disease, ulcerative colitis, and indeterminate colitis. Current advances suggest that an inappropriate response of a defective mucosal immune system to indigenous intestinal flora and other luminal antigens in a genetically susceptible host is at the core of this disease.

In this thesis some aspects of thromboembolism, a specific extraintestinal manifestation of IBD, which develops as the result of multiple interactions between acquired and genetic risk factors are studied. Arterial and venous thromboembolisms are important complications representing a significant cause of morbidity and mortality in IBD patients. **Chapter 6** addresses the question whether the *JAK2* V617F mutation, which is commonly found in myeloproliferative diseases associated with thromboembolism could also be detected in patients with IBD. **Chapter 7** investigates whether the polymorphisms Val34Leu and Pro564Leu in the gene encoding Factor XIII (*F13A1*) are associated with IBD.

In **chapter 8** we analyze the association of peroxisome proliferator-activated receptor- $\gamma$  Pro12Ala and C161T polymorphisms with IBD in Chinese and Dutch Caucasian patients.

**Chapter 9** provides an in depth view on the process of autophagy and its importance in the aetiopathogenesis of both Crohn's disease and Ct infections.

### Aims and Outline Part III

Recently, focus has been placed on prebiotic, probiotic, and synbiotic therapies, which aim to restore balance to the gastrointestinal microbiota and reduce intestinal inflammation. However, a greater understanding of the mechanisms behind their action on the gastrointestinal microbiota is required to determine which prebiotic, probiotic, or synbiotic is the most beneficial. Probiotics were defined by the WHO as live microorganisms which when consumed in adequate amounts as part of food confer a health benefit on the host, by improving its intestinal microbial balance. Thereby it improves the homeostatic balance between tolerance and immunity, which represents the unique regulatory challenge to the mucosal immune system. Finally, this probably complements the normal nutrition.

**Chapter 10** describes the preliminary results of the use of a mixture of probiotics (VSL#3) in arthralgia in patients with ulcerative colitis and Crohn's disease. **Chapter 11** discusses the mechanisms of action of Prebiotics, Probiotics, and Synbiotics and their beneficial effects based on immune modulation in several intestinal diseases and also in extraintestinal manifestations of IBD. **Chapter 12** provides an overview of the therapeutic use of probiotics in different enteric disorders.