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## Aspects of the host-microflora interaction and its possible impact on auto-immune disease

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### *Aspects of the host-microflora interaction*

The gut ecosystem, constituted by the intestinal bacteria and their human host, is a rather unknown area. Since about 400 different species of bacteria are able to live in the gut, studying this total ecosystem harbors enormous difficulties. Yet such kind of a study is important, because there are experimental data directing towards a possible role of these intestinal bacteria in a systemic autoimmune disease such as Systemic Lupus Erythematosus (SLE). Therefore two tools were elaborated in this thesis that may provide insight in certain aspects of functioning of the gut ecosystem.

The first tool is measurement of Colonization Resistance (CR). CR is the resistance of the gastrointestinal tract against colonization by ingested bacteria and is mainly ascribed to the anaerobic bacteria in the gut. A good CR implies efficient control of the growth and therewith chance of translocation of potentially pathogenic bacteria across the gut wall. Upon a decrease in CR translocation of certain bacterial species may increase and the host may produce antibacterial antibodies. CR correlates inversely with the number of different biotypes of *Enterobacteriaceae* isolated from faecal samples. In chapter 2 the natural variation in the number of different biotypes of *Enterobacteriaceae* per faecal sample was assessed in healthy individuals. It followed that reliable determination of the mean number of different biotypes, the inverse of which is representative for the CR of an individual, required study of four faecal samples of this individual. In chapter 4 this way of measuring CR in humans was compared with the golden standard for measuring CR: 10 healthy individuals were contaminated orally with a neomycin resistant *E.coli* (NR-*E.coli*) strain and the faecal concentration of this strain was measured during 14 days after the contamination, this faecal concentration being the measure for the CR. Both methods for CR were correlated significantly ( $P < 0.01$ ).

The second tool is immunomorphometry. Immunomorphometry combines image analysis and indirect immunofluorescence. The antibacterial antibodies thus measured are a direct consequence of the interaction between the host and his microflora. First of all we showed in chapter 3 that it is possible to measure titres of antibodies directed against pure cultures of *Enterobacteriaceae* by combining classical indirect immunofluorescence (IIF) with reading of the IIF slides by an image processing system. Reading of IIF titres by the image processing system was more accurate than eye reading. With this method serum antibody titres against the NR-*E.coli* strain, used for oral contamination in chapter 4, were measured. Persons who eliminated the NR-*E.coli* strain fastest from their intestinal tract did not produce highest antibody titres against the NR-*E.coli* strain. On the contrary, the longer the NR-*E.coli* strain remained in the digestive tract the higher the antibody titres against the NR-*E.coli*. Therefore, elimination of an oral contaminant from the intestines is not IgG or IgM antibody mediated.

Faecal bacteria can be divided in morphologically different groups by image analysis. Combined with the IIF technique it results in immunomorphometry described in chapter 5,

## 8. Summary

which enables determination of plasma antibody titres of IgA, IgG and IgM isotype against morphologically defined groups (morphotypes) of faecal bacteria in healthy individuals. Each individual has his own pattern of antibacterial antibodies.

Immunomorphometry can be applied to study specificities of the serum antibodies against faecal bacteria. In chapter 6 it was shown that healthy individuals not only possess antibodies against their own autochthonous intestinal bacteria, but they also have antibodies of both the IgA, IgG and IgM isotype against allogenous faecal bacteria. These antibodies were left in their sera after removal of the antibodies against the autochthonous faecal bacteria by absorption. Relatively more IgA antibodies appeared to be directed against allogenous than against autochthonous faecal bacteria, indicating that the autochthonous microflora is less immunogenic than the allogenous microflora or that tolerance exists towards the autochthonous microflora. If a person has many antibodies of IgA and IgG isotype against his own microflora, this could mean that his indigenous microflora is not very stable. This could indicate that he could have had the chance of mounting a specific humoral immune response against many species of allogenous anaerobic intestinal bacteria, resulting in antibodies of IgA and IgG isotype against a wide range of allogenous intestinal bacteria. Indeed we found that persons who reacted with specific antibodies to many bacteria of their own microflora, also tended to react specifically to bacteria in the allogenous microflora of the other healthy volunteers.

Both tools described above were used in our study on the possible role of the indigenous intestinal microflora in SLE, in chapter 7. The CR of the indigenous intestinal microflora tended to be lower in SLE patients than in healthy individuals. Quantitative differences in the humoral response to indigenous intestinal bacteria were found between SLE patients and healthy individuals. IgM titres were found to be lower both in patients with active and inactive SLE as compared to healthy individuals. Specific (IgG) antibacterial antibody responses were increased in the group with inactive SLE. However, in the group with active SLE a much lower titre of IgG antibacterial antibody titres was found, although the concentration of total plasma IgG was almost doubled in comparison with the concentrations in the group with inactive SLE.

These results could indicate that in SLE patients more different bacteria may translocate across the gut wall due to a lower CR. Some of these bacteria may serve as antigen for the production of anti-bacterial antibodies crossreacting with DNA. IgM antibacterial antibody titres were decreased in patients with SLE indicating a failing network. As a result of this failing network and possibly of a lower CR, IgG antibacterial antibodies were increased in patients with inactive SLE. However, the production of IgG anti-bacterial antibodies was decreased in patients with active SLE. This could be in favour of increased, possibly antigen driven, production of those antibodies that play a role in exacerbations of SLE, or might be explained by usage of these IgG antibodies in immune complexes. The latter

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explanation could point at a role of the antibacterial antibodies in the etiology of part of the exacerbations of human SLE.