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Patients with autoimmune thyroid diseases have antibodies to plasmid encoded proteins of enteropathogenic Yersinia

B.E. Wenzel*, J. Heesemann**, K.W. Wenzel***, and P.C. Scriba*
*Department of Internal Medicine, Med. University Lübeck, FRG, **Institute of Med. Microbiology and Immunology, University of Hamburg, FRG, and ***Free University of Berlin, FRG

INTRODUCTION
There is a striking association between autoimmune thyroid disease (AITD) and humoral (1, 2) or cellular (1, 3) immunity to Yersinia enterocolitica, which also has binding sites for thyrotropin (4). The role Yersinia might play in the pathogenesis of AITD has not yet been understood. This is partly due to the fact that most studies were done with laboratory strains of Yersinia enterocolitica of different serotypes, which had lost their virulence. Recently, it became evident, that a prerequisite to virulence of the most common enteropathogenic Yersinia enterocolitica (Y.e.) and Yersinia pseudotuberculosis (Y.p.) strains is the presence of a 42 to 46 Megadalton plasmid which is rapidly lost after subcultivation (5). These virulence plasmids of the different serotypes and species of Yersinia are closely related. Virulence function such as serum resistance, phagocytosis resistance and cell adherence are mediated by these plasmids (6, 7). Furthermore, these plasmids encode for at least 6 proteins against which humans and animals produce antibodies after Yersinia infection (8, 9). In calcium-deficient nutrient broth virulent Yersinia releases these immunogenetic proteins (RPs) in high quantities (6, 8). On SDS-PAGE protein bands of RPs can be visualized at 25 kD, 34 (Y.p.)/36 (Y.e.) kD, 38 kD, 46 kD and 58 (Y.e.)/67 (Y.p.) kD. Using mouse monoclonal and polyclonal antibodies to RPs we could demonstrate a high degree of crossreactivity between RPs of different strains (8, 10). Thus, detection of serum antibodies to RPs should be indicative for an acute or recent infection with a virulent Yersinia species.

PATIENTS PROFILE AND METHODS
Sera from patients with AITD were investigated for antibodies to RPs and for the prevalence of specific immunoglobulin class IgA and IgG. For this the Western-blotting technique was used (9). The frequencies of RP-antibodies in 336 healthy blood donors and 25 patients with non toxic goiter were compared to 100 Graves patients (GD) and 38 patients with Hashimoto's thyroiditis. All GD-patients were hyperthyroid and had TSH-receptor antibodies. The onset of GD was estimated at admittance by the patients report of symptoms for hyperthyroidism. Hashimoto patients (HT) were on thyroxin for 1-7 years. Patients with non toxic goiters (NTG) were all void of thyroid antibodies. No abnormal frequencies of Yersinia infections were reported during the time of the study. For statistical analysis the x²-test was used.

RESULTS
The frequencies of antibodies to Y.e.-RPs were markedly increased in patients with AITD, when compared to control groups (Table 1). Antibodies of immunoglobulin class IgG and IgA as well as the rare antibodies to the 25 kD-RP were detected. Within 12 months after the onset of Graves’ disease both, the 25 kD and

<p>| Table 1 - Prevalence of antibodies to plasmid encoded proteins of enteropathogenic Yersinia in sera of patients with autoimmune thyroid diseases. |
|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>IgG</th>
<th>IgA</th>
<th>a-25 kD²</th>
</tr>
</thead>
<tbody>
<tr>
<td>BD</td>
<td>336</td>
<td>(116) 34.5%</td>
<td>(40) 11%</td>
<td>(10) 3%</td>
</tr>
<tr>
<td>NTG</td>
<td>25</td>
<td>(10) 40%</td>
<td>(3) 12%</td>
<td>0</td>
</tr>
<tr>
<td>GD total</td>
<td>100</td>
<td>(72) 72%***</td>
<td>(33) 33%***</td>
<td>(14) 14%***</td>
</tr>
<tr>
<td>6 m³</td>
<td>35</td>
<td>(21) 60%**</td>
<td>(11) 31%*</td>
<td>(3) 9%*</td>
</tr>
<tr>
<td>12 m³</td>
<td>38</td>
<td>(28) 74%**</td>
<td>(15) 39%*</td>
<td>(14) 36%*</td>
</tr>
<tr>
<td>GD Rec.</td>
<td>21</td>
<td>(17) 81%**</td>
<td>(6) 28%*</td>
<td>(3) 14%*</td>
</tr>
<tr>
<td>HT</td>
<td>38</td>
<td>(25) 66%***</td>
<td>(14) 37%***</td>
<td>(4) 10%***</td>
</tr>
</tbody>
</table>

BD-blood donors, NTG - non toxic goiter, GD - Graves’ disease, Rec. -recurrent, HT - Hashimoto’s thyroiditis; ³-month after occurrence of symptoms for hyperthyroidism; ²-antibodies to a 25 kD plasmid encoded protein.

For statistical analysis the x²-test was used.

1°p < 0.05; ²°p < 0.01; ³°p < 0.001 compared to BD
1°p < 0.05 compared to NTG.
Table 2 - Time course of antibody formation to Yersinia enterocolitica release proteins in sera from patients with Graves’ disease.

<table>
<thead>
<tr>
<th>Clin. symptoms*</th>
<th>58 kD</th>
<th>46 kD</th>
<th>36 kD</th>
<th>25 kD</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 weeks</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3 months</td>
<td>—</td>
<td>+ 2</td>
<td>+ 2</td>
<td>—</td>
</tr>
<tr>
<td>6 months</td>
<td>+</td>
<td>+ 2</td>
<td>+ 2</td>
<td>+ 3</td>
</tr>
<tr>
<td>12 months</td>
<td>—</td>
<td>+ 3</td>
<td>+ 3</td>
<td>—</td>
</tr>
<tr>
<td>24 months</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*The onset of GD was estimated by the patients’ report of first symptoms for hyperthyroidism

\( ^2 \) IgA and IgG antibodies

\( ^3 \) mostly IgG antibodies

the IgA class antibodies peaked, decreasing thereafter in recurrent GD. In contrast, IgG antibodies, especially those to the 36 kD-RP, were persisting and increased with ongoing GD to 81% in sera of recurrent GD. A prospective investigation of newly diagnosed GD-patients confirms this antibody profile (Table 2). At the time of diagnosis all GD-patients were void of antibodies to either RP, although they had TSH-receptor antibodies. Within 6 months all GD patients (n = 10) developed IgA, IgG and 25 kD RP-antibodies. Thereafter, first 58 kD and 25 kD antibodies disappeared, while the 36 kD antibodies were persisting in most cases. Presence or absence of antibodies to RP in sera were independent of the patients expressing severe endocrine ophthalmopathy.

CONCLUSIONS

We report here for the first time a strong association between thyroid autoimmune disease and antibodies against plasmid encoded proteins of enteropathogenic Yersinia. Crossreactivity of antibodies inAITD with Yersinia enterocolitica or Yersinia pseudotuberculosis is henceforth understood independently of epidemiological distribution of Yersinia serotypes. The manifestation of IgA antibodies and antibodies to 25 kD-RP would indicate recent or persistent Yersiniosis (8, 10). Antibodies to the 25 kD-RP are of special interest, since preliminary results suggest that the 25 kD-RP shares antigenic epitopes with the TSH-receptor (11). This taken together with the profile of antibodies to Y. enterocolitica RPs in patients with AITD might indicate antigenic mimicry between thyroid and Yersinia plasmid antigens. The 25 kD antibodies, however, emerge later than the TSH-receptor antibodies in GD-patients blood (Table 2). Therefore, a direct trigger of TSH-receptor antibodies by antigenic mimicry of the 25 kD-RP is not likely. On the other hand, the humoral immune response is only a late and incomplete mirror of the autoimmune reaction. There might very well be an early cellular crossreaction of Yersinia- and thyroid antigens in AITD.

REFERENCES