Striking Inverse Correlation Between IgG Anti-F(ab’)_2 and Autoantibody Production in Patients With Cold Agglutination

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Previous experiments showed that the physiologic IgG anti-F(ab’)_2 antibody suppresses the response of human autoreactive B cells. In the present study, we analyzed the IgG anti-F(ab’)_2 antibody in 293 patients with cold agglutination (CA). Their average IgG anti-F(ab’)_2 titer was not much different (211 ± 8.3) from that of 279 healthy persons (195 ± 6.7). However, CA patients with high anti-F(ab’)_2 titers had low CA autoantibody titers and vice versa. The stratification of patients according to the autoantibody’s specificity (anti-I, anti-i, anti-Pr) showed an inverse correlation between anti-F(ab’)_2 and CA in the anti-I group (P = .0057; p = −0.180). Interestingly, the association was present only in patients whose disease was caused by noninfectious agents (P < .0001; p = −0.423). The inverse correlation argues for an important role of the IgG anti-F(ab’)_2 in the regulation of autoantibody production in CA patients.

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factors responsible for CA disease are infectious agents and chronic lymphoproliferations. Although the etiologic link between CA and certain agents is well established, the exact mechanism leading to autoantibody production is poorly understood. We showed in previous experiments that anti-F(ab')<sub>2</sub> antibodies strongly suppress the anterythrocyte autoantibody-producing B cells of healthy persons in cell cultures. Anti-F(ab')<sub>2</sub> antibodies bind with their antigen binding site to mlg and with their Fc region to the B cell’s Fc receptor. The crosslinking of these two receptors induces an inactivating signal. The anti-F(ab')<sub>2</sub> antibody selectively suppresses antigen receptor-occupied B cells. Since autoreactive B cells are continuously exposed to autoantigens, they are ideal targets for anti-F(ab')<sub>2</sub>-induced suppression.

If the anti-F(ab')<sub>2</sub> plays a role in the regulation of autoantibody production in CA patients, it would be expected that high titers of the suppressive antibody are associated with low titers of CA and vice versa. A large number of sera from CA patients offered us the possibility to study this correlation. Our findings clearly show that increasing anti-F(ab')<sub>2</sub> titers are paralleled by decreasing CA titers. As shown by our analyses, this correlation only exists in patients with anti-I antibodies not induced by infection. Noninfection anti-I patients presented the same association. Because of the small number of cases however, it was not statistically significant. The noninfection CAs were thus responsible for the statistical association in the entire group of CA patients. Evidently, the noninfection patients are an etiologically heterogeneous group. Most of them have an idiopathic or symptomatic form of chronic CA. The symptomatic form is caused by malignant gammopathies including chronic lymphatic leukemia and Waldenström’s macroglobulinemia. In rare cases, chronic CA is induced by nonhematological malignancies. Unidentified infections may also contribute to this group. Cytomegalovirus and varicella virus are possible candidates. Because of their heterogeneity, it was not possible to further stratify the noninfection patients in statistically relevant subgroups. The affiliation to infectious etiologie relied strictly on the presence of IgM antibodies to mycoplasma pneumonia and EBV.

We do not have an explanation for the presence of this association in noninfection and its absence in postinfection CA patients. The CA induced by infection may be a different etiopathogenic entity in which the anti-F(ab')<sub>2</sub> antibody has no regulatory function.
Fig 3. Correlation between IgG anti-F(ab')2 antibody and cold agglutinins in CA patients with and without infections. Patients with high antibody titers against mycoplasma pneumonia or EBV were included in the postinfection group, patients with low antibody titers in the noninfection group. An inverse association between anti-F(ab')2 and CA was found in noninfection anti-l patients. In noninfection anti-i patients, the inverse association was present but not statistically significant (P = .5; \( p = -0.160 \)). Postinfection anti-l and anti-i patients showed no significant association (P = .34; \( p = 0.095 \) and P = .39; \( p = 0.172 \)).

The statistical correlation shown in this study does not, of course, automatically establish a causal relation between the anti-F(ab')2 and CA. However, in the light of our previous findings, it is tempting to speculate that high anti-F(ab')2 titers lower the antierythrocyte autoantibody production and vice versa.

Interestingly, similar correlations have been described in systemic lupus erythematosus (SLE) and, more recently, in human immunodeficiency virus (HIV) infections.\(^5\) Patients with severe SLE showed high levels of anti-DNA and low levels of anti-F(ab')2, whereas those with quiescent disease presented low levels of anti-DNA and high levels of anti-F(ab')2 autoantibodies.\(^5\)

If further studies confirm the regulatory role of the anti-F(ab')2 antibody in the production of CA, this suppressive antibody could conceivably be used as a therapeutic agent.

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