By Peter Terness, Michael Kirschfink, Dan Navolan, Christoph Dufter, Ingrid Kohl, Gerhard Opelz, and Dieter Roelcke

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

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 ($P = .0028; \rho = −0.175$). 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 ($P = .0057; \rho = −0.180$). Interestingly, the association was present only in patients whose disease was caused by noninfectious agents ($P < .0001; \rho = −0.423$). 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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RESULTS

The average IgG anti-F(ab’)$_2$ antibody concentration of CA patients (211 ± 8.3 OD) was not different from that of healthy individuals (195 ± 6.7 OD). However, the patients presented a weak but significant inverse correlation between anti-F(ab’)$_2$ and CA. Increasing CA titers were paralleled by decreasing anti-F(ab’)$_2$ titers ($P = .0028; \rho = −0.175$) (Fig 1).

We further analyzed whether this association is related to a certain CA antibody specificity. Patients’ sera were accordingly divided into three groups containing anti-I, anti-i, and anti-Pr antibodies, respectively (Fig 2). Interestingly, the inverse correlation appeared only in patients with anti-I antibodies ($P = .0057; \rho = −0.180$) (Fig 2a).

To better understand this phenomenon, the patients with anti-I and anti-i antibodies were subdivided into two groups, one with a recent infection (IgM antibodies against mycoplasma pneumoniae or EBV) and one without a demonstrable infection (Fig 3). However, because only one anti-Pr patient had antirubella antibodies, subdivision of this group was not possible. A striking association was found in noninfection anti-I patients ($P < .0001; \rho = −0.423$) (Fig 3a). Noninfection anti-i patients also showed the same association ($\rho = −0.160$) but it was not statistically significant ($P < .5$) (Fig 3c). Patients with postinfection CA showed no correlation between anti-F(ab’)$_2$ and cold agglutinins (Fig 3b and d).

DISCUSSION

It is known that CA-producing B cells are part of the physiologic immune repertoire. Under normal conditions these clones are controlled by suppressive mechanisms. Consequently, only low CA titers are found in the sera of healthy individuals. Factors that disturb this equilibrium induce an increased production of CA and lead to CA. The best known
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(\(\text{ab}'\))\(_2\) antibodies strongly suppress the anterythrocyte autoantibody-producing B cells of healthy persons in cell cultures. Anti-F(\(\text{ab}'\))\(_2\) antibodies bind with their antigen binding site to mIg 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(\(\text{ab}'\))\(_2\) antibody selectively suppresses antigen receptor-occupied B cells. Since autoreactive B cells are continuously exposed to autoantigens, they are ideal targets for anti-F(\(\text{ab}'\))\(_2\)-induced suppression.

If the anti-F(\(\text{ab}'\))\(_2\) 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(\(\text{ab}'\))\(_2\) titers are paralleled by decreasing anti-F(\(\text{ab}'\))\(_2\) titers.

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 etiopathogenetic entity in which the anti-F(\(\text{ab}'\))\(_2\) antibody has no regulatory function.
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 anterythrocyte autoantibody production and vice versa.

Interestingly, similar correlations have been described in systemic lupus erythematosus (SLE) and, more recently, in human immunodeficiency virus (HIV) infection. 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.

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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