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Monoclonal anti-tuberculosis antibodies react with DNA, and monoclonal anti-DNA autoantibodies react with *Mycobacterium tuberculosis*

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SUMMARY

Classical models of experimental autoimmune diseases, such as adjuvant arthritis entail the use of mycobacteria. Furthermore, BCG immunotherapy may be followed by arthritic symptoms. To test the infection–autoimmunity relationship of mycobacteria, we used monoclonal antibodies raised against *M. tuberculosis* and against DNA. Murine monoclonal anti-TB antibodies were found to react with ssDNA, dsDNA and other polynucleotides. Monoclonal anti-DNA autoantibodies derived from patients and mice with SLE bound to three glycolipids shared among all mycobacteria and derived from mycobacterial cell wall. Prior incubation of the antibodies with ssDNA and other polynucleotides or with glycolipid antigens inhibited binding. These results indicate that infecting mycobacteria share antigens with human tissue, thus accounting in part for the production of autoantibodies in mycobacterial infections.

Keywords anti-DNA antibodies tuberculosis autoimmune diseases autoantibodies

INTRODUCTION

Epidemiological, clinical and laboratory observations provide ample evidence indicating that micro-organisms such as viruses (Bodansky *et al.*, 1984; Datta & Schwartz, 1978; Haspel *et al.*, 1983; Denman, 1981; Simpson *et al.*, 1984), bacteria (Naparstek *et al.*, 1985; Weiss *et al.*, 1983; Lindquist, Coleman & Osterland, 1970; Murray, 1978) and parasites (Galvao-Castro *et al.*, 1984; Paterson, 1981) play a role as one of the aetiological factors in autoimmunity.

Mycobacteria may serve as a probe to study the infection–autoimmunity relationship because natural infection with atypical mycobacteria such as *M. kansassii* and *M. avium/intracellulare* is extremely common, occurring in up to 74% of the population from some areas of the United States (Edwards, Edwards & Palmer, 1959), and *M. tuberculosis* infection in developing countries is almost universal in adults. Evidence to support this notion comes from adjuvant arthritis (AA) which is one of the models of experimental autoimmune disease (Holoshitz, Matitiau & Cohen, 1984; Van Eden *et al.* 1985). AA presents with a pathological picture similar to that seen in

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rheumatoid arthritis and can be induced in susceptible strains of rats by a single injection of complete Freund's adjuvant containing killed *M. tuberculosis* in oil. An example of this phenomenon in man may be the development of arthritic symptoms in patients who were treated with *M. bovis* BCG immunotherapy for cancer (Torisu *et al.*, 1983). Furthermore, the appearance of anti-DNA antibodies as well as other autoantibodies following infection with *M. tuberculosis* is in agreement with the idea that these bacteria may be associated with autoimmunity (Lindquist *et al.*, 1971; Murray, 1978; Van-Eden *et al.*, 1985).

The present study entails the ligand binding characteristics of monoclonal antibodies derived from mice immunized with *M. tuberculosis* (Coates *et al.*, 1982; Hewitt *et al.*, 1982), and monoclonal lupus autoantibodies derived from mice and humans with SLE (Andrezejewski *et al.*, 1980; Shoenfeld *et al.*, 1983a).

MATERIALS AND METHODS

The production of the mouse monoclonal anti-TB antibodies. The production of the group of monoclonal antibodies directed at tubercle bacilli has been described previously by Coates *et al.* (1982). Seven cell lines were selected for this study (TB 71; TB 73; TB 77; TB 68; TB 23; TB 72). All the monoclonal antibodies reacted with *M. tuberculosis.* A further two hybridomas (TB41 TB44) were obtained from another fusion in which BALB/c mice were injected with cell walls extracted from *M. bovis* BCG. TB41 and TB44 bound to cell walls and to the B and C glycolipids prepared from *M. bovis* BCG and did not react with the glycolipid A. (A. Monomycolate of trehalose; B. Phosphatidyl inositol dimannoside; C. Phosphatidyl inositol pentamannoside (Pangborn & McKinney, 1966)). Ascitic fluids from the seven hybridomas were produced in BALB/c mice and were used in all ELISA assays. In the case of TB68 and TB23 we have used affinity purified material.

The production of human and murine monoclonal anti-DNA autoantibodies. The human monoclonal anti-DNA antibodies were produced by hybridomas derived from fusions of the human lymphoblastoid cell line GM 4672 with peripheral blood or splenic lymphocytes obtained from three lupus patients (Shoenfeld, Hsu Lin & Gabriels, 1982). All the antibodies were IgMk. Their ligand binding properties have been extensively described elsewhere (Shoenfeld *et al.*, 1983a; Andre-Schwartz *et al.*, 1984). Against two of these monoclonal autoantibodies (16/6 and 32/15), anti-idiotypic antibodies were prepared (Rabbit anti-16/6, Rabbit anti-32/15) (Shoenfeld *et al.*, 1983b).

The production, purification and antigen binding characteristics of monoclonal hybridoma anti-DNA antibodies derived from MRL/lpr mouse are reported elsewhere (Andrezejeweski *et al.*, 1980). The ten murine monoclonal anti-DNA antibodies were found in further studies also to bind to other polynucleotides (e.g. poly (dT), poly (I)) and the phospholipid cardiolipin. H-130 was an IgM immunoglobulin, while the rest were IgG molecules.

Binding of anti-TB antibodies to DNA, polynucleotides and cardiolipin. The hybridoma antibodies derived from mouse ascites as well as the purified antibodies were tested for their ability to bind to DNA, polynucleotides and cardiolipin by means of an ELISA as previously reported (Shoenfeld *et al.*, 1982; 1983a). The assay for binding of hybridoma anti-TB antibodies to cardiolipin was carried out as previously described (Shoenfeld *et al.*, 1983a).

Inhibition of binding of monoclonal anti-TB antibodies to DNA by polynucleotides and cardiolipin. Dilutions of monoclonal anti-TB antibody (TB-68) which gave 50% of maximal binding to ssDNA coated plates (concentration 5 μg/ml) were incubated with dilutions (40 μg/ml to 100 ng/ml) of poly (dT), poly (I), ssDNA, dsDNA, poly-L-lysine, and RNA for 1 h at 37°C, and then for 2 h at 4°C. The mixture was added to the polystyrene wells previously coated with ssDNA. The assay was continued as described above for the direct binding. Monoclonal anti-TB antibodies incubated with PBS were used as controls for 100% binding. RNA and poly-L-lysine were used as control competitors in this assay.

Binding of mouse and human anti-DNA antibodies to mycobacterial antigens. Polystyrene plates were coated with 5 μg/ml of the three mycobacterial glycolipids A, B and C (see above). The glycolipids were suspended in PBS and sodium desoxycholate (1 mg/ml). The fine suspension was

left for 15 min to allow evaporation of the chloroform methanol, the suspension was then diluted to borate buffer pH 8·6 (final concentration 5 μg/ml) and incubated for 18 h at 4°C. Dilutions of the mouse and human monoclonal anti-DNA antibodies in PBS-Tween were incubated for 2 h in the wells. The rest of the procedure was carried out as detailed above. Ten human and ten murine monoclonal anti-DNA antibodies were examined. Monoclonal IgM (Waldenstrom) and polyclonal IgM (pooled) were used as controls. TB_{23} and TB_{44} murine anti-TB monoclonal antibodies served as positive controls.

Inhibition of binding of the monoclonal anti-DNA antibodies to ssDNA by glycolipid antigens. Mouse and human monoclonal anti-DNA antibodies were diluted to concentrations which gave 50% of maximal binding to ssDNA and were incubated with dilutions of glycolipid antigens (10 μg/ml to 100 ng/ml). The mixture was then incubated in the polystyrene plates coated with the ssDNA. The binding of the monoclonal antibodies incubated with PBS served as controls for 100% binding. RNA and casein were used as control competitors.

Inhibition of binding of human anti-DNA antibodies to ssDNA by monoclonal anti-TB antibodies. Human monoclonal anti-DNA antibody 1/17 was incubated with various dilutions of mouse monoclonal anti-TB antibody TB_{68}. The rest of the binding of 1/17 to ssDNA coated plates was measured as detailed above. Similarly, the binding of TB_{68} to glycolipid coated plates was competed by the human antibody 1/17.

Detection of the dominant anti-DNA antibody idiotype 16/6 on anti-TB antibody. Polystyrene plates were coated with the monoclonal anti-TB antibodies (1 μg/ml). The detection of 16/6 idiotype on these antibodies and controls were performed as detailed previously (Shoenfeld *et al.*, 1983b).

RESULTS

All seven TB monoclonal antibodies reacted with ssDNA and with the different polynucleotides. Yet, TB_{71}, TB_{77} and TB_{73} were found to be stronger than the rest of the monoclonal anti-TB antibodies. Among the seven antibodies, only TB_{71} bound strongly to cardiolipin. The bindings of the anti-TB antibodies to the polynucleotides were similar to those observed with a monoclonal anti-DNA antibody derived from an MRL/lpr mouse (Table 1). None of the antibodies bound strongly to casein coated plates. Figure 1c demonstrates competition assays in which the binding of

Table 1. Direct binding of seven mouse monoclonal anti-TB antibodies to polynucleotides, cardiolipin and casein (2·5 μg/ml) coated polystyrene plates (results expressed as optical density reading ($\times 10^3$))

MoAb	ssDNA	dsDNA	Poly(dT)	Poly(I)	Cardiolipin	Casein
NC	194	203	153	271	197	171
PC	1800	710	933	1830	1985	298
TB_{23}	536	424	462	1023	515	144
TB_{78}	723	488	403	465	616	156
TB_{71}	1264	758	995	1353	1305	247
TB_{68}	512	301	456	916	437	109
TB_{72}	496	304	407	846	367	249
TB_{77}	1119	596	707	1329	689	288
TB_{73}	1553	617	806	1144	926	218

NC, Normal control.
PC, Positive control (mouse monoclonal anti-DNA antibody).
MoAb, Monoclonal antibody.
TB_{71}, Reacted also as anti-nuclear factor.

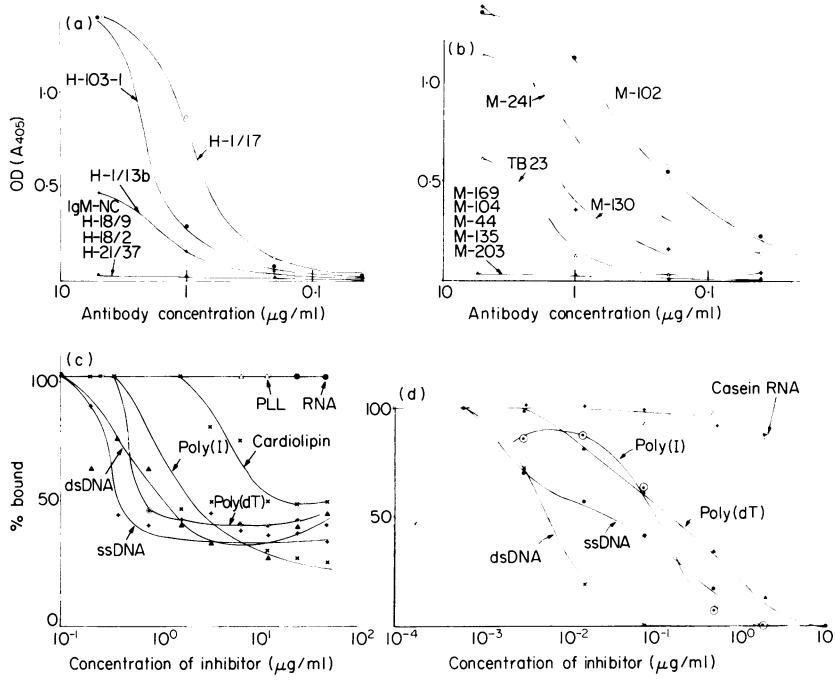

Fig. 1. (a, b) Direct binding of representative human (a) and murine (b) monoclonal anti-DNA autoantibodies to glycolipid antigens. In the case of human antibodies the reaction to glycolipid A is shown, while in the murine system glycolipid B is depicted. IgM NC denotes negative control from patient with macroglobulinaemia. TB_{23} was employed as a positive control. (c) Competition assay of the binding of mouse monoclonal anti-TB antibody (TB_{68}) to ssDNA coated plates with polynucleotides, cardiolipin, RNA and poly-L-lysine (PLL). (d) Competition assay in which the binding of human monoclonal anti-DNA antibody 1/13b to mycobacterial glycolipid-B coated plates was inhibited by polynucleotides. No inhibition was noted with casein or RNA.

anti-TB antibody TB_{68} to ssDNA coated plates is competed by polynucleotides. The best inhibitor was ssDNA itself. No competition was observed with RNA or PLL.

The binding of human and mouse monoclonal anti-DNA antibodies to the three mycobacterial antigens A, B, C (see methods) are shown in Table 2 (Fig. 1b). Six of the ten monoclonal anti-DNA antibodies derived from hybridomas established from spleen cells of a patient with SLE and severe thrombocytopenia were found to be a strong binder to the three fractions of the mycobacterial cell wall. In contrast, to the human monoclonal antibodies which bound better to antigen A, the mouse monoclonal antibodies derived from MRL/1pr mouse reacted more strongly with glycolipid antigens B and C. In some cases their binding was greater than the positive control (TB_{23}). Only minimal binding was recorded with the control IgMs (monoclonal and polyclonal) (Table 2).

Figure 1d demonstrates the competition assay where the binding of the human monoclonal anti-DNA antibody 1/13b to glycolipid B was inhibited by different polynucleotides.

Figure 2 depicts the competition assays in which the binding of the same human monoclonal anti-DNA antibody (1/13b) to ssDNA coated plates was inhibited by prior incubation with the glycolipid antigens (A, B and C). The human monoclonal anti-DNA antibody 18/8 was a weaker binder of the three glycolipid antigens.

TB_{68} antibody completely inhibited the binding of the human anti-DNA antibody 1/17 to ssDNA coated plates (100% inhibition at concentration of TB_{68} of 125 ng/ml, 2·5% inhibition at concentration of 18 ng/ml). Similar inhibitions were observed when the binding of TB_{68} to TB glycolipid B was completed by 1/17 antibody.

Table 2. Direct binding of 1 μg/ml of purified human and murine monoclonal anti-DNA autoantibodies to three glycolipid antigens (A, B, C, see Methods) derived from mycobacterial cell wall (TB_{23} and TB_{44} are monoclonal anti-TB antibodies, which served as positive controls (results expressed as optical density ($\times 10^3$))

Antibody	Glycolipid A	Glycolipid B	Glycolipid C
Human 103–1	290	327	ND
1/17	887	198	ND
12/33	365	192	ND
12/6	97	94	575
1/13b	165	50	ND
1/9b	73	0	ND
134	36	0	195
18/8	37	0	ND
18/2	10	48	ND
21/37	31	0	0
Monoclonal IgM	11	0	15
Polyclonal IgM	16	0	0
Murine 102	308	1132	1980
241	325	542	ND
225	16	46	ND
130	157	455	895
104	0	42	ND
44	0	32	ND
143	0	10	ND
135	0	17	ND
203	0	17	ND
169	0	31	ND
TB_{23}	50	117	930
TB_{44}	29	63	355
NC	20	0	15

NC, Normal control.
ND, Not done.

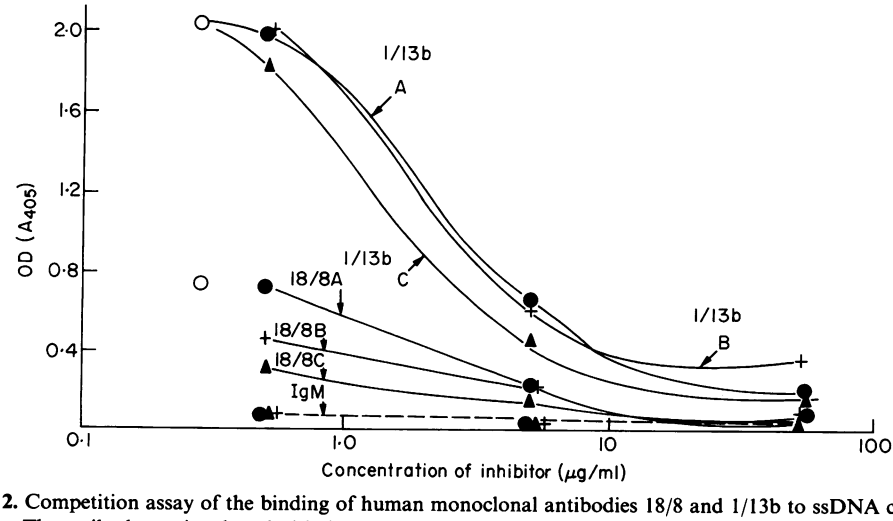

Fig. 2. Competition assay of the binding of human monoclonal antibodies 18/8 and 1/13b to ssDNA coated plates. The antibody was incubated with the mycobacteria glycolipid antigens A, B and C before being subjected to the plate. The binding is expressed in OD units. The open circles represent the binding of the antibody without prior incubation with the inhibitor.

TB_{68} was found to harbour the dominant idiotype 16/6 of anti-DNA antibodies. TB_{71} reacted as an anti-nuclear antibody with a diffuse speckled pattern (data not shown).

DISCUSSION

Chronic infections can be associated with the appearance of various autoantibodies. In most individuals the presence of the autoantibodies is asymptomatic and once the patient recovers from the infectious disease the autoantibodies can no longer be detected in the serum. In some cases autoimmune reactions of clinical significance can be recorded (Murray, 1978; Paterson, 1981). Mycobacterial infections could play a central role in this autoimmunity-infection relationship and are of particular interest because human infection is extremely common (Edwards *et al.*, 1959). Mycobacterial infections are quite often associated with the presence of autoantibodies. In one study of 60 patients with proven pulmonary tuberculosis anti-nuclear antibodies were detected in 46·6% (vs 7·1% of control population) and rheumatoid factor was recorded in 24 out of the 60 patients (40%) (Lindquist *et al.*, 1970). The association of mycobacterial infection with autoimmune disease is supported by classical models of experimental autoimmune diseases in animals which entails the use of mycobacterial antigens as adjuvants (Holoshitz *et al.*, 1984). Furthermore, the report of Torisu *et al.* (1983) on the development of arthritis symptoms in ten out of 159 patients during the course of BCG immunotherapy is in agreement with this notion. The incidence of the arthritis was closely correlated with the host's immunological responsiveness to BCG, and the symptoms usually occurred 1–5 months after the first injection. The symptoms were aggravated by additional BCG injections.

In this study monoclonal anti-TB antibodies which are known to react with different species of mycobacteria were found to bind to ssDNA as well as to other polynucleotides. The binding of the anti-TB antibodies to ssDNA could be inhibited by prior incubation of these antibodies with ssDNA and with the different polynucleotides. Human and mouse monoclonal anti-DNA antibodies derived from patients and mice with SLE were found to react with three mycobacterial cell wall glycolipids shared by all mycobacteria. This binding could also be inhibited by DNA and other polynucleotides. The anti-DNA antibodies and the anti-TB antibodies were found to compete with each other on their binding to ssDNA. Last but not least, the murine anti-TB antibody was shown to carry the dominant 16/6 idiotype of the human anti-DNA antibody 16/6, which was reported to have clinical relevance in human SLE (Isenberg *et al.*, 1984) and to react as an anti-nuclear factor. It should be pointed out recently, the 16/6 idiotype was also detected on mouse monoclonal anti-DNA antibodies derived from NZB/NZW (D. A. Isenberg, personal communication).

All these results indicate that the anti-TB antibodies and the anti-DNA antibodies may recognize a similar epitope on DNA and mycobacterial cell wall.

Previous works (Shoenfeld *et al.*, 1983a, 1985; Jacob *et al.*, 1984) have supported the notion that anti-DNA antibodies are polyspecific in nature. These studies entailed the analysis of monoclonal anti-DNA antibodies as well as antibodies isolated from the sera of patients with SLE. It has been proposed that a common epitope for these antibodies may be the phosphodiester compound (Schwartz & Stollar, 1985). Yet, not all of their binding properties can be explained by this common antigenic determinant. This doubt applies especially to antigens such as proteins (Shoenfeld *et al.*, 1985; Jacob *et al.*, 1984) and as in our case to glycolipids. Therefore, it seems conceivable that the polyfunctional nature of these antibodies may be due in part to the ability of their antibody combining site to accommodate more than one epitope, or to their ability to bind to similar conformational structures (Lane & Koprowski, 1982).

Our results imply that some of the antibodies raised against mycobacteria cross-react with DNA. Since mycobacterial infection is very common in the community, it is possible that in individuals with the appropriate immunogenetic background (Shoenfeld & Schwartz, 1984), infection could lead to anti-DNA antibody production with overt clinical manifestations of SLE.

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