Differential activation of T cells by antibody-modulated processing of the flanking sequences of class II-restricted peptides

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Abstract

Despite poor presentation of measles virus (MV) nucleoprotein (NP) by MHC class II of infected cells, NP-specific antibodies are one of the hallmarks of the early immune response against this virus. To study the influence of antibodies on processing and presentation of NP to three different T cell hybridomas, mAb recognizing distinctive linear NP epitopes were developed. Two T cell hybridomas TNP408B and TNP408 reacted with the same core epitope of NP (amino acids 383–391), but differed in their sensitivity to the flanking sequences of peptides containing this epitope. TNP408B reacted with minimal concentrations of NP when this was complexed with mAb BNP146. NP alone or saturating concentrations of other mAb did not activate this T cell. Both T cells, TNP408 and TNP408B, were similar in their sensitivity to NP in the presence of saturating concentrations of BNP146 or of appropriate peptide (NP379). TNP408B did not differ from another T cell hybridoma (TNP79) in its sensitivity to different mAb, suggesting a specificity-dependent and a specificity-independent effect of mAb. Antibody-mediated activation was attributed to FcR-mediated uptake independent of the fine specificity of the mAb. In the case of TNP408B, this effect was further enhanced by a specific effect of BNP146. While all NP-specific mAb were sufficient to enhance presentation to TNP408 and TNP79 of their respective peptides derived from processed NP, BNP146 was necessary to generate the peptides with the proper flanking sequences required by TNP408B. Since the binding site of BNP146 coincides with the T cell epitope of TNP408B (and TNP408) it is suggested that binding of this mAb modulates processing of the flanking sequences of the peptides corresponding to this epitope. This study shows that antibodies can influence the T cell response to an antigenic protein quantitatively and qualitatively by taking advantage of the sensitivity of T cells to flanking sequences of class II-restricted peptides.

Introduction

Despite the existence of efficient vaccines based on live attenuated measles virus (MV), the morbidity and mortality due to natural infections remain high in the developing countries (1,2). In the industrialized countries, even a high vaccine coverage does not seem to achieve the WHO goal of measles eradication (2). To improve strategies against measles, a better understanding of basic components and mechanisms of the immune response is required. Antibodies, such as passively acquired maternal IgG, play an important role in neutralizing the virus and in protecting against the disease (3,4). Neutralizing antibodies are directed mainly against the haemagglutinin protein (MV-H) (5,6) and to a lesser extent against the fusion protein (7). However, after MV infection the earliest and most abundant antibodies are directed against the nucleoprotein (NP) (8,9). These are also the major antibodies detected by complement fixation assays...
(9,10). However, NP antibodies are not known to play a direct role during virus neutralization (11). NP is not only an antibody target but it plays an important role also in the cell-mediated immune response. For instance, NP-specific MHC class II-restricted T cells seem to be sufficient to control MV infection of the central nervous system in rats (12). Class II-restricted cell-mediated immune response against NP was also found in humans (13). This appears to contrast with the relatively low efficiency of antigen presentation of this viral protein (14). It can therefore be hypothesized that the early advent of NP-specific antibodies may modulate the immune response against the MV as was observed in other systems (15,16).

We have investigated whether antibodies against the NP may interfere with class II presentation of peptides of this protein and whether such an effect may be related to the fine specificity of the anti-NP antibodies involved. For this purpose, we developed mAb against NP and selected those which cross-reacted with NP-derived peptides. All antibodies enhanced FcR-mediated uptake in a specificity-independent manner. In addition, one antibody which bound to the T cell epitope also modulated the flanking sequences of a nested set of class II-restricted peptides during processing. This resulted in a T cell which recognized NP only in the presence of antibody with the appropriate fine specificity.

**Methods**

**MV and recombinant nucleoprotein (rNP)**

The MV (Edmonston strain, ATCC VR-24) has been derived from chick embryo fibroblast cultures after ultrafiltration and purification by sucrose gradient centrifugation (17) or by affinity chromatography and inactivation with propiolactone (for immunization). The latter was a gift from Dr Berbers (Bilthoven, The Netherlands). rNP was obtained from Dr F. Wild (Lyon, France). It was produced in insect cells infected by the NP-recombinant baculovirus and purified as described (18).

**Peptide synthesis**

Peptides corresponding to the linear sequence of the NP protein (Edmonston strain, EMBL data bank accession no. P0485) were synthesized as amides from N-fluorenylmethoxycarbonyl protected amino acids as described earlier (19–21). In addition, 102 C-terminally biotinylated peptides of the MV-NP protein were used to characterize the mAb. These were prepared by multiple parallel solid-phase synthesis using a specially designed biotin resin (Fleckenstein et al., submitted). In the peptide–biotin conjugates a spacer composed of two ε-amino caproic acids and one lysine residue separates the peptide from the biotin residue. These peptides were 15 amino acids long and overlapped by 10 amino acids. All peptides are designated by the position of their first, i.e. N-terminal amino acid, within the NP sequence.

**ELISA**

MV-specific antibodies were detected using a certified commercial ELISA based on human diploid cells (Enzygnost, a kind gift of Dr Giesendorf, Behringwerke, Marburg, Germany) as described before (22). For the titration of the mAb, plates (Maxisorp, Nunc, Denmark) were coated overnight in bicarbonate buffer (10 mM, pH 9.6) with MV concentrate NP-specific antibodies have been detected by direct ELISA using half-area 96-well microtiter plates (Maxisorp) coated overnight with the rNP protein (40 μg/ml in 10 mM carbonate buffer, pH 9.6) and 2 h with blocking buffer (15 mM Tris, 8 g/l NaCl, 0.2 g/l KCl, 1% BSA pH 7.4). To detect antibodies reacting with biotinylated peptides, 96-well microtiter plates (Maxisorp) were coated with 20 μg/ml highly purified streptavidin (obtained from Dr L. Seik, Mediaplast, Tübingen, Germany). After a washing step with PBS, the biotinylated peptides (5 μg/ml in PBS) were added and incubated at least 2 h at room temperature. The plate was saturated with 10% BSA (Sigma, St Louis, MO), 10% saccharose (Sigma) and 2% v/v normal goat serum (ICN Biomedicals, Asse-Relegem, Belgium) in PBS. The plates were incubated overnight at 4°C with mouse sera or hybridoma supernatants at dilutions of 1/1000 and 1/20 respectively. In all of the above ELISAs, the binding of antibodies was revealed by alkaline phosphatase-conjugated goat Ig specific for the γ chain of murine IgG (Sigma) at a dilution of 1/500 in dilution buffer (10 mM Tris buffered saline, 1% BSA, 0.1% Tween, pH 7.4) and p-nitrophenylphosphate (Sigma) as a substrate. Absorbance was measured at 405 nm.

**Western blot**

BALB/c mice were immunized by multifocal s.c. injections of native or denatured MV emulsified in incomplete Freund's adjuvant (Sigma) and boosted i.p. with the same mixture on day 21 and 38. On day 42, the spleen cells were fused with murine myeloma cells Sp2/0 in the presence of 50% w/v polyethylene glycol 1500 (Boehringer Mannheim). Azasenne (0.006 mM; Sigma) was added to the culture to prevent cell fusion (24). For production of mAb the concentration of the FBS was gradually reduced to <1% v/v. mAb was purified with a Protein G-affinity column. The mAb 120 (designated here BNP120) was a kind gift from Dr F. Wild (Lyon, France). The rat anti-FcγRII mAb (2.4.G2) was a kind gift from Dr Gradehandt (Mainz, Germany).

**Western blot**

MV grown on chicken embryoblasts and purified by sucrose gradient centrifugation (22) was separated by PAGE (4% stacking, 10% resolving gel). The proteins were then electrophoresed (150 mA, 100 min, 0–4°C) onto a 0.45 μm nitrocellulose membrane (BioRad, Nazareth, Belgium). After blocking with TBS containing 10% w/v BSA and 2% v/v goat serum, the membranes were incubated with the antibody dilutions and antibody binding was detected with the same conjugate as for the ELISA (dilution 1/2000) using 5-bromo-4-chloro-3-indolyl phosphate (BCIP)/nitroblue tetrazolium (NBT; Sigma) as substrate dissolved in dimethyl formamide.
T cell assay

NP-specific, I-A<sup>d</sup>-restricted TNP408 (23), TNP408B and TNP79 T cell hybridomas and the B cell lymphoma line M12.4.1 were grown in DMEM supplemented with 5% FBS, 2 mM L-glutamine, 1 mM sodium pyruvate, 50 μM 2-mercaptoethanol, 100 μU/ml penicillin and 100 μg/ml streptomycin (all from Gibco). T cells (10<sup>6</sup>) and M12.4.1 cells (3X10<sup>5</sup>) as antigen-presenting cells (APC) (24) were co-cultured with antigen for 24 h in 96-well flat-bottom tissue culture microtiter plates (Nunc) in the presence or absence of NP mAb. T cell stimulation was measured using the IL-2-dependent cell line CTLL-2 (ATCC, Rockville, MD). Cells (10<sup>5</sup>) were added to cell-free supernatant (100 μl) in a half-area 96-well microtitre plate (Costar, Badhoevedorp, The Netherlands). After 24 h CTLL-2 cell survival was measured by adding 50 μg MTT/well (Sigma). After an additional 4 h the supernatant was removed and the cells were lysed with 100 μl/well DMSO containing 0.3% (v/v) 12 N HCl. The data are expressed as difference in absorbance measured at 540 and 690 nm (25).

Results

Polyclonal sera against NP

To generate antibodies against the NP of the MV, mice were immunized with purified native or denatured MV. MV-specific antibodies were detected by ELISA and by Western blot, where the dominant bands corresponded to H and NP indicating that the sera reacted also with linear epitopes of the NP. To map such linear epitopes the sera (dilution 1:1000) were tested by ELISA using 102 overlapping biotinylated 15-mer peptides covering the whole sequence of the NP protein (Fig. 1). The overall reactivity with peptides was weak in sera of mice immunized with native MV (Fig. 1A), whereas the antibodies induced with the denatured MV recognized a number of well defined linear epitopes (Fig. 1B).

Reactivity of mAb

In order to investigate which ones of the linear epitopes were also represented on the NP protein, mAb were derived. Some of these mAb recognized biotinylated peptides of the NP in the biotin–streptavidin ELISA (Fig. 1C–G). They reacted with one of the following five regions: peptides NP36/NP41 (BNP175), NP136/NP141 (BNP176), NP186/NP191 (BNP173) and NP126/131 (BNP120). BNP146 reacted with biotinylated peptides NP376 and NP381 (sharing amino acids 381–390), and binding to these peptides was inhibited by free peptides NP377/379 and less efficiently by NP373/375 (Fig. 2). Interestingly, free peptide NP381 did not inhibit mAb binding to biotinylated peptide.

The different NP-specific mAb used in this study reacted with MV in a commercial MV-specific ELISA and this reactivity

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**Fig. 1.** Definition of linear epitopes recognized by serum (A and B) (dilution 1:1000) or NP-specific mAb obtained from mice immunized with native (A and G) and denatured MV (B-F) measured in a streptavidin-based ELISA using 102 overlapping biotinylated 15mer peptides of the NP. The numbers correspond to the position of the N-terminal amino acid in the NP sequence.
could be blocked with fresh supernatant of MV cultures (data not shown). BNP146, BNP173 and BNP120 had similar binding affinities when titrated on supernatant from MV-infected cells (Fig. 3). The mAb reacted in a sandwich ELISA using BNP120 (lgG2a, gift from Dr F. Wild, Lyon, France) as a monoclonal capture antibody, culture supernatant from MV-infected cells and an IgG1 subclass-specific conjugate (data not shown). These results also showed that MV-infected cells release NP or MV to which NP-specific antibodies can bind. They also react with rNP in a direct ELISA. In Western blot the mAb revealed two bands of an estimated mol. wt of ~40 and/or 60 kDa corresponding to typical tryptic products of the NP protein (26). All mAb developed here were of the IgG1 subclass isotype.

**Reactivity of T cell hybridomas**

Three H-2d-restricted NP-specific T cell hybridomas were used in this study. With M12.4.1 cells as APC, TNP408 and TNP79 required 0.5 and 4.0 μg/ml recombinant NP respectively for half-maximal IL-2-secretion (S50%) (data not shown; but see also Fig. 6). A third hybridoma, TNP408B, did not respond to maximal concentrations (>15 μg/ml) of NP (in the absence of antibody).

The T cell epitope of TNP79 was defined by peptide NP329 (Giminez et al., in preparation). TNP408 and TNP408B reacted best with peptide NP379 and similar concentrations of this peptide were required for maximal stimulation. Fine mapping with overlapping peptides located the core of the epitope within amino acids 383-391 and 381-393 respectively (Fig. 4). However, both clones differed remarkably in their sensitivity to sequences flanking the epitope core. While TNP408 reacts with a nested set of four to five overlapping peptides, TNP408B reacts mainly with two peptides. The two observations that (i) TNP408 and TNP408B are equally sensitive to NP379, and (ii) that TNP408B does not react with normal concentrations of NP, suggest that during processing of the protein, peptide NP379 is not generated in sufficient amounts.

**Influence of the NP-specific mAb on presentation of rNP**

In the presence of a cocktail of NP-specific mAb, 35 or 150 times less rNP was sufficient for S50% of TNP408 and TNP79
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Fig. 4. Fine mapping of the T cell epitope of the clones TNP408 (A and B) and TNP408B (A and C). The data represent the formation of formazan measured with an microtiter plate reader of (the IL-2-sensitive) CTLL cells stimulated with supernatants of the T cell hybridomas cultured in the presence of peptide (see Methods). In [A], NP and peptide concentrations were 5 µg/ml respectively (data not shown). To study the influence of different mAb on antigen presentation, these were titrated in the presence of 250 ng/ml NP. At this concentration T cells reacted at best weakly to rNP alone. The dose–response curves showed considerable differences between antibodies to activate the T cell lines (Fig. 5). The antibody concentrations required for half-maximal stimulation of TNP79 and TNP408 were between 10 (BNP120 with TNP79) and 1000 ng/ml IgG (BNP176 with TNP408 or TNP79). This difference can partially be explained by the observation that a 10- to 30-fold higher concentration of BNP176 than of BNP146, BNP120 or BNP173 is required for 50% binding (cf. Fig. 2). Despite a 8-fold difference in sensitivity of the two T cell lines TNP408 and TNP79, the mAb concentration for maximal response at suboptimal NP concentration differs by two or less for all mAb. TNP408B, in contrast, fully responded to 250 ng/ml NP only in the presence of BNP146 and reacted weakly in the presence of BNP173. The other mAb did not significantly stimulate an NP-specific response of TNP408B over the concentration range tested.

This differential effect of mAb on TNP408B was further investigated by testing whether higher concentrations of NP would stimulate this cell line at 1500 ng/ml mAb. At this concentration, BNP146 maximally stimulated TNP408B and all other mAb (BNP146/173/120/176) fully activated the other two T cell lines at non-responsive doses of NP (cf. Fig. 5). Figure 6(A) shows that at 1500 ng/ml BNP146, 200 ng/ml NP was sufficient to stimulate TNP408B which required >100 times this concentration in the absence of antibody. Even at 2500 ng/ml NP (10 times more than in Fig. 5) only BNP146 induced a full response of TNP408B, while the same concentrations of other NP-specific mAb resulted only in a marginal activation of this clone.

At saturating concentrations of mAb (1500 ng/ml) up to 80 times less NP was required for half-maximal stimulation of TNP79 than without mAb: BNP173: 60 ng/ml NP; BNP120: 50 ng/ml; BNP146: 70 ng/ml; BNP176: 100 ng/ml; BHA 1500 ng/ml. no mAb >2500 ng/ml (Fig. 6C). Four times higher concentrations of these antibodies did not further decrease the S50% of NP. BNP173 and BNP146 reduced the S50% of
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Fig. 5. Differential effect of NP-specific mAb with different fine specificities on the stimulation of NP-specific T cell hybridomas in the presence of 250 ng/ml NP. BHA is a MV hemagglutinin-specific mAb (CTLL assay as in Fig. 4). CTLL responses in the presence or absence of optimal IL-2 concentrations were 800 ± 50 and 100 ± 20 mOD respectively.

Role of the FcR

Figure 7 shows that the antibody-mediated stimulation of the T cell hybridomas can be completely blocked with FcγRII-specific antibodies (2.4G2). Control experiments showed that under the conditions of the experiment (cf. legend to Fig. 7) (i) NP alone or in combination with an irrelevant antibody (BHA) did not stimulate T cells and (ii) the T cell response to appropriate peptide is not impaired. This demonstrates that the antibody-mediated enhancement of T cell stimulation was FcR dependent.

Discussion

Membrane-associated proteins are processed and presented by MHC class II in a much more efficient fashion than...
soluble cytosolic proteins which were taken up by fluid phase endocytosis (25,27). Targeting soluble antigens to membrane receptors of APC, e.g. by soluble Ig (28), slg of antigen-specific B cells (29) or antibody–antigen conjugates (30), greatly enhances receptor-mediated uptake and class II presentation (31–33).

Anti-NP mAb, recognizing distinctive linear epitopes, were developed to study the influence of the fine specificity of antibodies on processing and presentation of soluble NP to different T cell hybridomas. Two T cell hybridomas, TNP408B and TNP408, reacted with the same core epitope of NP (amino acids 383–391), but differed in their sensitivity to the flanking sequences of nested peptides containing this epitope (Figs 4 and 8). TNP408B reacted with rNP only when the protein was complexed with mAb BNP146. NP alone or with saturating concentrations of other mAb did not activate this T cell. Unresponsiveness in the presence of mAb has been explained in some cases by extreme antibody excess (34). However, BNP146, BNP120 and BNP173 were used at the same concentration, and had similar affinities for NP. This

![Graphs showing dose-response curves for TNP408B, TNP408, and TNP79](image)

**Fig. 6.** Dose–response curves of TNP408B (A), TNP408 (B) and TNP79 (C) to increasing concentrations of rNP in the presence of 1.5 µg/ml mAb (CTLL assay as in Fig 4). CTLL responses in the presence or absence of optimal IL-2 concentrations were 240 and 10 mOD respectively.
effect was also not merely due to a difference in sensitivity of the two T cell hybridomas. The sensitivities of both T cells were similar with respect (i) to NP in the presence of saturating concentrations of BNP146 (Fig. 6) and (ii) to appropriate peptide (NP379, Fig. 4). In contrast to TNP408B, TNP408 reacted with NP, also in the absence of antibody. In the presence of saturating concentrations of mAb with diverging specificities, the NP concentration required for maximal stimulation of the latter T cell hybridoma was similar to that of a T cell with a different specificity (TNP79). These observations suggest a specificity-independent effect operating in a similar manner on peptides recognized by TNP408 and TNP79. Unspecific antibody-mediated activation was attributed to FcR-mediated uptake. In the case of TNP408B, this effect was superimposed by a specific effect of BNP146.

The three mAb (BNP146, BNP120 and BNP173) enhanced presentation of peptides corresponding to the two epitopes of TNP79 and TNP408 (and TNP408B) with similar efficiency. Therefore, differential activation of TNP408 and TNP408B must be explained by the differences between these two T cells to recognize peptides of the same epitope (Fig. 8). (i) mAb BNP146 specifically enhanced the generation of peptides similar to NP379 by a mechanism not utilized by the other mAb and (ii) the absence of reactivity of TNP408B to NP protein would be explained by the lack of peptide NP379 in the nested set of peptides generated during NP processing in the absence of mAb BNP146.

While most NP mAb were sufficient to enhance presentation of antigenic NP peptides, BNP146 was required to generate the peptides with the proper flanking sequences seen by TNP408B (Fig. 8). We have previously reported the importance of the ragged tail of class II-restricted peptides for the activation of T cell lines (35). Since the binding site of BNP146 coincides with the T cell epitope of TNP408B (and TNP408) it is suggested that binding of this mAb modulates processing of the flanking sequence of the nested peptides corresponding to this epitope (Fig. 8). In light of these observations, TNP408B is an unusual T cell line in the sense that it recognizes its antigen only in the presence of antibodies binding to its epitope. After immunization with MV, low levels of such antibodies were detectable in mouse serum (Fig. 1B). Screening procedures with whole antigen may easily miss such T cells. TNP408B was detected by subcloning and testing against the adjacent peptides of its epitope.
Differential processing of the antigen by antibodies has been observed (36). Such a process requires the Ig–antigen complex as the initial substrate for processing, which has been shown at least for the antigen–sIg complex in specific B cells (16,37). It has also been demonstrated that the antibody binding site influences the nature of the fragments generated by limited proteolysis of immune complexes (38,39). Since BNP146 binds to the region NP376–396 which contains the T cell epitope of TNP408 and 408B, it is reasonable to assume that its binding to NP can enhance generation of peptide NP379 (e.g. by protection from intracellular degradation) in a way unrivalled by mAb binding to other regions of NP. Enhanced or suppressed T cell activation was observed earlier when antigen was presented by macrophages in the presence of different mAb or by specific B cells (15,36,40–43). Here, we show for the first time that antibodies can modulate the flanking sequences of nested peptides and that this can lead to differential activation of T cell clones. We have previously shown that T cells react with the ragged tail of class II-restricted peptides and that this interaction is important for T cell stimulation (35). We have speculated that the APC could regulate the recruitment of T cell clones by modulating the length of the flanking sequences. Antibody-modulated processing is an example of how the flanking sequence of a class II-restricted peptide can regulate T cell activation. This is a new mechanism by which antibodies can direct the immune response to a given T cell clone and determine preferential presentation of B cell epitopes to T cells leading to non-random pairing of T and B cell epitopes (44) as was observed by us in the immune response of late convalescent donors to the MV-H and MV-F (20,21) and by others in the mouse response to influenza hemagglutinin (45,46).

During fusion of the MV with the plasma membrane, the nucleocapsid is injected into the cytosol from where it does not have access to the endosomal pathway (14). Because NP processing was chloroquin-sensitive it was estimated that rare endosomal/lysosomal NP and not the abundant cytosolic NP was primarily presented by class II (14). We have shown here that also specific mAb greatly enhance class II presentation of NP. Our data suggest that during measles the early appearance of NP-specific antibodies (8) will independently of CD46 stimulate presentation of soluble NP leaking from MV-infected cells and thus could quickly compensate the less efficient NP presentation associated with the CD46-mediated virus/cell fusion process. Antibody targeting of NP may be particularly important, when in addition to inefficient CD46-mediated uptake and presentation, the MV receptor is downregulated in infected cells (47). Since early during acute measles complement-dependent cytolytic antibodies are induced (48) (which are largely NP specific) the release of free NP from infected cells and anti-NP antibodies combine to a self-enhancing process of antibody-mediated class II presentation which would explain the abundant production of NP-specific antibodies, observed early during measles infection (8) and to the efficient generation of class II-restricted NP-specific T cells, which in animals were found to be sufficient for viral clearance (12) and which were also detected in humans (49,50). Also, T<sub>C</sub> cells specific for the internal viral antigens such as NP can cooperate with specific B cells to induce antibodies against surface proteins as was observed in other viruses (HIV: 51; influenza: 52) in a process termed intrainfected help. Thus, the enhanced efficiency of antibody-mediated uptake of NP may be beneficial during the course of MV infection in several ways.

This study shows that antibodies can influence the T cell response to an antigenic protein quantitatively and qualitatively by taking advantage of the sensitivity of T cell to flanking sequences of class II-restricted peptides. Independent of CD46, class II presentation of NP can be greatly enhanced by early NP antibodies, and thus contribute to the expansion of number and size of MV-specific B cell clones. Later, the reciprocal presentation and activation of antigen-specific B cells as APC and T cells could limit, by antibody-mediated epitope-directed processing, the number of specific B cell clones to an economic but efficient size.

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Abbreviations

APC antigen-presenting cell
B/HA hemagglutinin-specific mAb
BNP NP-specific mAb
MV measles virus
NP379 15mer peptide starting with amino acid 379 of the NP
NIP recombinant nucleoprotein
TNP NP-specific T cell hybridoma

References

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