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Gamma interferon expression and major histocompatibility complex induction during measles and vesicular stomatitis virus infections of the brain

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Summary

Lymphocytic interferon gamma (IFN-γ) production and major histocompatibility complex (MHC) antigen induction were studied in experimental measles and vesicular stomatitis virus infections in the brain. Fifteen-day-old Sprague-Dawley rats injected intracerebrally with the HNT strain of measles virus showed already within 1 day after infection an increased number of cells producing IFN-γ in the spleen, cervical lymph nodes and leptomeninges. These rats recovered after a transient neuronal infection in the brain. Rats infected intracerebrally with vesicular stomatitis virus, on the other hand, all succumbed after 2 days and showed no IFN-γ production in lymphoid cells. Immunohistochemically MHC class I antigen appeared in infected and uninfected cells in the brain during replication of both viruses. A role for the recently discovered nerve fibres with IFN-γ-like immunoreactivity, which are normally present in the brain, in the MHC antigen induction is discussed.

Introduction

Interferon gamma (IFN-γ) is a cytokine which in addition to its antiviral activity can serve as a regulatory factor for the cellular immune response to a virus infection since it can induce major histocompatibility complex (MHC) class I and II antigens, attract T cells and activate macrophages

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(see Demaeyer and Demaeyer-Grignard, 1988). In spite of its potential role in the pathogenesis of a virus infection in the brain there have been few experimental studies of IFN-γ during such infections except for the report by Frei et al. (1988) on increased levels of IFN-γ in the cerebrospinal fluid of lymphocytic choriomeningitis virus-infected rats. IFN-γ is produced by activated lymphocytes, but recently Ljungdahl et al. (1989) have observed IFN-γ-like immunoreactivity (IFN-γ-LI) in subpopulations of sensory neurons, in perivascular nerve fibres and in certain nerve fibres branching in the central nervous system (CNS) of

the rat; a finding corroborated by Kiefer and Kreutzberg (1990). Neuronal IFN-γ-LI can also be induced in regenerating motor neurons after axotomy (Olsson et al., 1989). The biological effect of this neuronal IFN-γ-like molecule is not known, although MHC antigens are induced also in and around axotomized motor neurons (Maehlen et al., 1988). In the present study we describe a marked induction of MHC antigens in the brain of rats infected both with a hamster-neuroadopted strain of measles virus and with vesicular stomatitis virus. Production of lymphocytic IFN-γ was found after infection with the former virus, but not with the latter, indicating a potential role for the neuronal IFN-γ-like molecule in regulating MHC levels in the brain.

Materials and methods

Viruses

The measles strain used was the HNT strain (Burnstein et al., 1964) obtained from Dr. Kottil W. Rammohan (Ohio State University, Columbus, OH, U.S.A.). The virus suspension was prepared by homogenizing brains from infected and moribund BALB/c mice in phosphate-buffered saline (PBS) (10% w/v, titre $10^{3.7}$ 50% intracerebral lethal dose/ml). The vesicular stomatitis virus (VSV)-Indiana wild-type strain was originally obtained from Dr. J. Závada, Bratislava, Czechoslovakia and was passed 2–3 times in green monkey kidney cells and once in Vero cells before use; the titre was 7×10^8 plaque-forming units (pfu) per ml.

Experimental procedure

15-day-old Sprague-Dawley rats (Alab, Stockholm, Sweden) were injected intracerebrally on the left side with 0.02 ml of either of the virus suspensions under ether anaesthesia. The animals were examined daily and measles-infected rats were sacrificed for examinations on 1, 3, 7 and 14 days post-inoculation (p.i.), while VSV-infected rats were taken on 1 and 2 days p.i. As controls, rats of the same age injected intracerebrally with PBS, pH 7.4, and uninjected rats were used.

Immunohistochemistry

For immunohistochemical examinations the brains were snap frozen, cryostat sections, 8 μm thick, were cut and fixed in Lana's fixative (14% picric acid and 4% paraformaldehyde in Sörensen's buffer, pH 6.9) for 30 s at room temperature, rinsed in PBS and post-fixed in cold acetone (−20°C) for 30 s. Sections were washed in PBS and incubated in 2% normal horse serum for 30 min and then with different primary antibodies in proper dilutions at 4°C overnight. The primary antibodies used were mouse monoclonal anti-rat IFN-γ (DB1; Van der Meide et al., 1986), anti-rat MHC class I (Ox18; Fukumoto et al., 1982), anti-rat MHC class II (Ox6; McMaster and Williams, 1979), anti-rat CD8 (Ox8; Brideau et al., 1980) and anti-rat CD4 (W3/25; Williams et al., 1977; Barclay, 1981). The hybridoma producing DB1 was provided by Dr. P. van der Meide (Primate Center, TNO, Rijswijk, The Netherlands) and the hybridomas producing Ox6, Ox8 and W3/25 were provided by Dr. A. Williams (University of Oxford, U.K.). Antibodies were purified from culture supernatants (Holmdahl et al., 1985). Ascitic fluid containing the Ox18 was purchased from SeraLab (Crawley-Down, U.K.). For detection of measles virus antigen, a mouse monoclonal antibody (16AC5) directed against the nucleoprotein (NP) was used (Norrby et al., 1982). After washing in PBS, the sections were incubated with rat serum absorbed biotinylated anti-mouse antibodies produced in horse (Vector Lab., Burlingame, CA, U.S.A.) diluted 1:30 in 2% rat serum for 60 min at room temperature, washed in PBS and incubated in ABC complex (Vectastain, Vector Lab.) for 60 min at room temperature. The peroxidase was visualized by incubating with 0.02% 3-amino-9-ethyl-carbazole as substrate for 15 min and the sections were then rinsed in distilled water and mounted in glycerin-gelatin.

For VSV antigen detection the peroxidase-anti-peroxidase (PAP) technique was used. The sections were fixed in acetone, −20°C, for 10 min. After washing in PBS they were incubated in 3% normal rabbit serum for 30 min, washed in PBS and incubated with sheep anti-VSV hyperimmune serum (obtained from Dr. J. Závada; the serum had 50% neutralization end-point for 100 pfu/ml of about 1:10⁶) diluted 1:2500 in PBS, pH 7.4

with 1% normal rabbit serum for 2 h at room temperature. A rabbit anti-sheep serum (Dakopatts, Copenhagen, Denmark) 1:20 was applied for 30 min at room temperature followed by a soluble PAP complex produced in sheep (Nordic Immunology, Tilburg, The Netherlands) 1:100, also for 30 min at room temperature. The enzyme activity was visualized according to Kaplow (1974). At each timepoint after infection four brains were examined from rats infected with either of the viruses.

Single-cell assay for IFN-γ production

Principally, the method described by Czerkinsky et al. (1988) was used. Nitrocellulose-bottomed 96-well microtitre plates (Millipore, Bedford, MA, U.S.A.) were coated overnight with 100 μl aliquots of DB1 15 μg/ml. After repeated washings with PBS, 2% bovine serum albumin was applied for 2–4 h. The plates were washed in PBS, and the mononuclear cell suspensions (see below) were applied followed by incubation overnight at 37°C, humidified atmosphere and 7% CO_2. Cells were then removed by flicking the plate followed by repeated washings. A polyclonal rabbit anti-rat IFN-γ (Van der Meide et al., 1986), diluted 1:5000, was applied for 4 h. After washing, biotinylated goat anti-rabbit IgG (Vector Lab.) was applied for 4 h, followed by avidin-biotin peroxidase complex (ABC Vectastain Elite Kit, Vector Lab.) and peroxidase staining (Kaplow, 1974). Spots corresponding to cells that had secreted IFN-γ were counted under a dissection microscope.

Preparation of mononuclear cell suspensions

Rats were killed and the deep cervical lymph nodes and spleen were dissected and crushed through a stainless steel meshwork in 10 ml of medium. Brains with their leptomeninges were washed in 10 ml of tissue culture medium for 40 min. The mononuclear cells from these preparations were then centrifuged once at 40 × g for 10 min. The medium consisted of Iscove's modification of Dulbecco's medium (Flow Lab.) with 5% fetal calf serum (Gibco), 1% minimal essential medium (Flow Lab.), 2 mM glutamine (Flow Lab.), 50 μg/ml penicillin, and 60 μg/ml streptomycin.

Red cells in the cell pellets from the spleen were haemolysed by adding 2 ml cold sterile water

for 30 s, followed by addition of 1 ml 2.7% NaCl. The cells were then washed in medium twice, rediluted to obtain a cell concentration of 10^7/ml and 100 μl aliquots were then applied into individual microtitre wells in triplicate.

Results

Clinical picture

VSV-infected rats showed signs of disease already 1 day after infection. They became lethargic and started to die 2 days after infection. Reduction of the inoculation titre of this rapidly replicating virus did not substantially prolong survival. Measles infected rats, on the other hand, all survived, but they showed a reduced weight gain as compared with controls 3 and 7 days p.i. By 14 days p.i. they had started to increase in weight again. They otherwise displayed no overt signs of disease.

Immunohistochemistry

In uninjected control brains, immunoreactivity for MHC class I antigen was limited to the leptomeninges, the choroid plexus and the endothelial cells of intracerebral blood vessels. MHC class II antibodies labelled only a few macrophage-like cells in the interstitium of the choroid plexus. Neuronal IFN-γ-LI was seen in a number of nerve fibres in the cerebral cortex. In the deeper layers they ran perpendicular to the surface, but in the superficial layers they appeared to ramify, were more in number and surrounded larger blood vessels (Fig. 1). Scattered neurons in the cortex also showed IFN-γ-LI and such neurons were numerous in the ventroposterior thalamic nuclei. In control brains injected with PBS there was a narrow zone of MHC class I LI around the needle track. MHC class II LI macrophage-like cells were found around the needle track, in the ventricles and in the leptomeninges. These brains showed otherwise similar immunoreactions as the uninjected ones.

One day after measles virus infection the brains showed no significant changes as compared to controls, but after 3 days measles virus antigen was seen in a few small groups of neurons in the hippocampus and in the cerebral cortex. The immunoreactivity was seen in the cell bodies and in
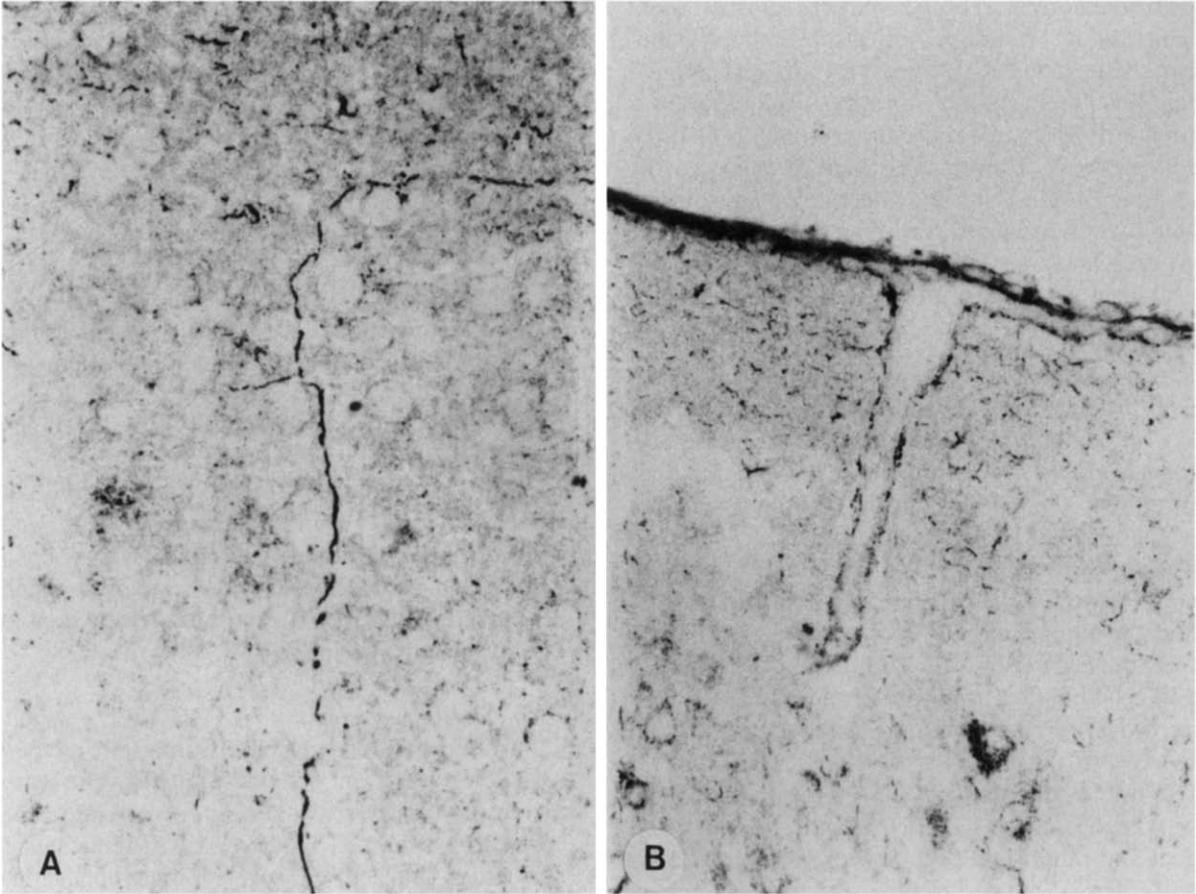
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Fig. 1. (a) Interferon-γ-like immunoreactivity in a long nerve fibre in the cerebral cortex of an uninfected 15-day-old rat. (b) Immunoreactive fibres also occur around larger blood vessels. ×350.

the dendritic trees of these neurons (Fig. 2a). In the areas around the infected neurons, MHC class I LI was seen diffusely in the neuropil, where it appeared to be present in all cell types. The immunoreactivity appeared to be strongest perivascularly (Fig. 2b). MHC class II antibodies labelled perivascular macrophage-like cells also in the areas of infection. Neuronal IFN-γ-LI occurred in the infected brains as in controls. In the leptomeninges and in the infected areas of the brain a few lymphocytes of both the CD4+ and CD8+ phenotype were seen.

Seven days p.i. there were larger areas of measles virus-infected neurons in the cerebral cortex and hippocampus. The MHC class I immunoreactivity was also more widely distributed in the brain. MHC class II immunoreactive macrophage-

like cells were seen more widespread in the brain parenchyma. Many CD8+ and some CD4+ cells had infiltrated the infected areas. Fourteen days after infection a number of measles-infected neurons were still present. The MHC class I LI was somewhat reduced as was that for MHC class II. Neuronal IFN-γ-LI was present in all infected brains with a similar distribution as in the controls.

In VSV-infected rats a large number of neurons in the cortex and in the hippocampus were labelled with the VSV antiserum already 1 day p.i. (Fig. 2c). In these areas there was a strong MHC class I LI, with a tendency for perivascular localization in the infected areas (Fig. 2d) and after 2 days there was a diffuse, strong LI in most of the brain. There was no MHC class II LI detectable and no
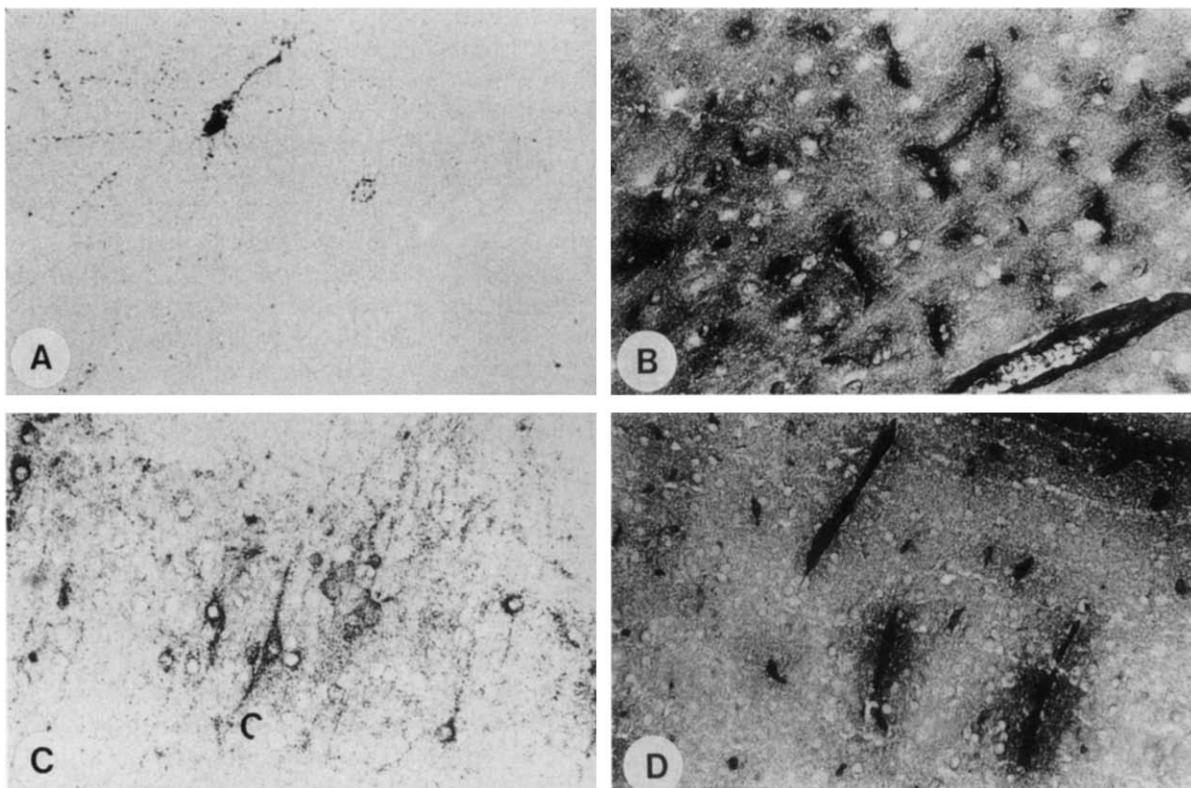
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Fig. 2. (*a*) Measles-infected neurons in the cerebral cortex 5 days p.i. (*b*) In a parallel section a diffuse MHC class I immunoreactivity is present in the neuropil with an accentuation around blood vessels. (*c*) Large numbers of VSV-infected neurons in the cerebral cortex 1 day p.i.; and (*d*) strong MHC class I immunoreactivity in a parallel section. ×145.

infiltration of lymphocytes. There was no apparent difference in the distribution of neuronal IFN-γ-LI between infected and uninfected rats.

Single-cell assay for IFN-γ production

Already 1 day after infection with measles virus there was an increased number of cells producing IFN-γ in the spleen, the cervical lymph nodes and the leptomeninges. The number of IFN-γ-producing cells continued to rise up to 7 days p.i. On day 14 their number had declined in the spleen and brain, but was still significantly higher than in the controls (Fig. 3). The number of IFN-γ-producing lymphocytes in the leptomeninges amounted maximally to 200 out of 10^5 lymphocytes, giving a maximum frequency of 1 per 500 mononuclear cells. Thus, although a marked increase in the number of IFN-γ-producing lymphocytes is evident with the immunospot technique, the low frequency among mononuclear cells did not allow

their immunohistochemical detection in tissue sections.

In VSV-infected rats, on the contrary, there was no increase in the number of IFN-γ-producing lymphocytes; in fact they appeared to be somewhat reduced in number as compared to the PBS-injected controls (Fig. 3).

Discussion

In the brain no or only low levels of MHC antigens are normally expressed (cf. Lampson, 1987), and it has been suggested that this may facilitate the persistence of viral infections in the brain (Oldstone, 1989), since fragments of viral proteins have to be presented on these molecules to the effector T cells (Doherty, 1985). Both MHC class I and II antigens can, however, be induced in the nervous system during various inflammatory
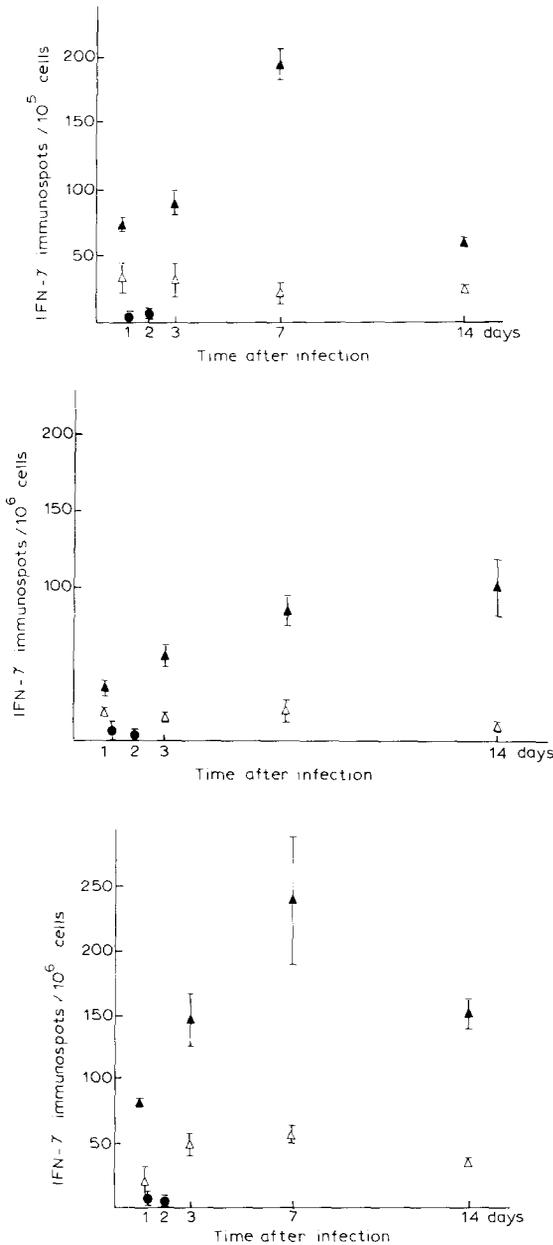
Fig. 3. Number of IFN-γ-producing mononuclear cells re-
covered from brain surfaces (top panel); lymph nodes (middle
panel); and spleen (bottom panel). Filled triangles = measles-
infected rats, unfilled triangles = control injected rats, circles =
VSV-infected rats. Each symbol represents readings from 4–8
animals. Bars show standard deviation.

conditions and virus infections in vivo (Sobel et
al., 1984; Craggs and Webster, 1985; Traugott et
al., 1985; Vass et al., 1986) and in vitro (Lampson

and Fisher, 1984; Wong et al., 1984; Fierz et al.,
1985; Massa et al., 1986; Suzumura et al., 1986).
Previously, we have found a brisk appearance of
MHC class I antigens during measles infection of
the rat brain (Olsson et al., 1987) and a promotion
of viral persistence in the brain by depletion of
$CD8^+$ T cells (Maehlen et al., 1989). In the pres-
ent study, we observed that in both VSV- and
measles-infected brains the MHC class I LI ap-
peared first in areas of the brain where infected
neurons were localized and in these areas the
immunoreaction was somewhat accentuated peri-
vascularly. Such immunoreactivity may either be
the result of MHC antigens circulating in the
blood (Singh et al., 1988) and leaking through an
altered blood–brain barrier caused by the virus-
induced inflammation, or due to an MHC-induc-
ing factor that either leaks into the brain or is
released in situ. IFN-γ has been shown to be a
most potent inducer of MHC antigens (Skoskie-
wicz et al., 1985). It is therefore tempting to sug-
gest that this cytokine is involved also in the
virus-induced appearance of MHC in the brain.
However, as MHC was expressed with a similar
intensity in the VSV-infected animals, which
showed no lymphocyte IFN-γ production, and in
the measles-infected rats, which showed a marked
lymphocyte IFN-γ production several days before
MHC appearance, it is unlikely that the MHC LI
is solely induced by IFN-γ released from activated
lymphocytes. Alternatively, an IFN-γ-like mole-
cule might be released from the nerve fibres in the
brain, which are labelled with the IFN-γ antibody.
By quantitative enzyme-linked immunoassay tech-
nique we have recently found an increase in the
levels of IFN-γ-LI in cultured rat sensory neurons
prior to MHC class I induction after a paramyxo-
virus infection (Eneroth et al., 1990). However,
other factors may also be involved in MHC induc-
tion, e.g. a combination of measles virus and tumor
necrosis factor can induce MHC class II antigen
on cultured astrocytes (Massa et al., 1987). Virus
particles may also directly induce MHC class II
antigens in astrocytes in vitro independent of
IFN-γ mechanisms (Massa et al., 1986; Massa
and ter Meulen, 1987).

The mechanisms by which measles virus trig-
gers lymphoid cells to IFN-γ production within 24
h after infection, while the more rapidly replicat-

ing vesicular stomatitis virus does not, remain to be clarified, as does a role of IFN-γ (whether neuronal or lymphocytic) in the pathogenesis of the infection. In addition to inducing MHC antigen expression, IFN-γ may act as a T cell homing factor, activate macrophages and have direct antiviral effects (cf. Demaeyer and Demaeyer-Grignard, 1988; Goldberg et al., 1989), which all may contribute to the recovery of the measles virus infection. Viruses can also disturb immune functions of a host animal, and measles virus is well known to induce an immunosuppression. The mechanisms for this are not clear although a direct effect of the virus on subpopulations of lymphocytes has been suggested (McChesney and Oldstone, 1987). In view of our finding of an early and marked induction of IFN-γ-producing lymphoid cells, a role for this cytokine in inducing immunosuppression during measles should also be considered. The effects of IFN-γ on the delayed hypersensitivity have received less attention than those of IFN-α/β, but it may under certain conditions inhibit local inflammatory reactions (Heremans et al., 1987) and reduce proliferative responses of antigen-specific T cells (Matis et al., 1983; Nurmi McKernan et al., 1988). In this context it is interesting to note that we found a similar brisk IFN-γ induction (within 12 h) in experimental infections with the extracellular parasite *Trypanosoma brucei brucei* in rats, which is an infection also associated with a marked immunosuppression (Askonas and Bancroft, 1984; Bakhiet et al., 1990).

Acknowledgements

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