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Genetic regulation of class I major histocompatibility complex (MHC) antigen induction on astrocytes

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Summary

Neural cells, including astrocytes, normally do not express detectable levels of class I major histocompatibility complex (MHC) molecules, unlike cells of most tissues. However, upon cultivation in vitro, astrocytes begin to express class I molecules, increasing with time after plating. This spontaneous expression was examined in the present study to characterize inducible expression on astrocytes among various strains of mice. Inducible expression, either as a consequence of cultivation or standard γ-interferon treatment, differed markedly among the strains examined. Analysis of congenic strains on a C57BL/10 (B10) background showed that expression was controlled by genes within the MHC locus. Examination of additional congenic animals with various recombinations within the MHC showed that high or low expression of MHC molecules correlates with the presence of particular MHC class I genes. In general, H-2^a and H-2^d class I products are expressed much higher on astrocytes than H-2^b and H-2^k products. This difference in expression is not seen on spleen cells indicating tissue specificity. Moreover, levels of expression at the cell surface are reflected by the steady-state level of RNA message within astrocytes of the different strains.

Introduction

The major histocompatibility complex (MHC) genes encode a series of molecules that control various aspects of immune responses. Class I MHC molecules are particularly important for T cell recognition of virus antigen expressed on the surface of infected cells (Zinkernagel and Doherty, 1979), which may account for the high levels of constitutive expression in most tissues. The central nervous system (CNS) is exceptional because constitutive expression of class I antigens is very low or absent (Williams et al., 1980; Schnitzer and Schachner, 1981). Persistent viral infections of the
CNS are common (Johnson, 1982) and in mice, a number of infections of the CNS lead to a variety of pathological states (Lipton and Dal Canto, 1979; Rammohan et al., 1980; Knobler et al., 1985). The relationship between the unique control of class I antigens found in brain and the ability of viruses to persist and induce neurological disease is presently unclear. In some instances, genetic susceptibility to virus infections in brain maps to particular murine class I MHC genes (Rodriguez et al., 1986; Clatch et al., 1987).

Because cells of the CNS normally lack class I MHC antigens, inducible expression (Wan et al., 1987) rather than constitutive expression (Miyasaki et al., 1986) is believed crucial for viral clearance from the brain. Among various cell types, astrocytes are thought to play an important role in antigen presentation in this tissue (Fontana et al., 1984, 1986; Skias et al., 1987). Here we describe spontaneous induction of class I expression on astrocytes of the CNS upon cultivation in vitro (Schnitzer and Schachner, 1981; Fontana et al., 1986; Massa et al., 1987a) that differs markedly among mouse strains of different H-2 haplotypes. Genetic mapping of this variable expression between strains identified differences in control among particular class I genes.

Materials and methods

Astrocyte cultures

Pregnant SJL/J, BALB/cJ, and B10.A(5R) mice were obtained from Jackson Laboratories. B10, B10.A, and B10 × B10.A F1, newborn mice were obtained from Harlan-Sprague-Dawley. B10.A(4R) pregnant mice were obtained from Simonsen Laboratories, Gilroy, CA, U.S.A. Cerebral hemispheres, dissected from the rest of the brain, were thoroughly freed of meninges, minced with fine scissors, then triturated in Dulbecco’s modified Eagle’s medium (DMEM) with a Pasteur pipet to dissociate the cells. The cells were centrifuged, resuspended in DMEM with 4.5 g/l glucose, 10 mM Hepes and 15% fetal bovine serum (FBS) (5 ml/hemisphere), and plated onto Costar 6-well multiplates (2 ml/well) coated with bovine type I collagen (Collaborative Research, Bedford, MA, U.S.A.). The cells were cultivated at 37°C with maximum humidity and 5% CO2, fed with fresh medium 3–4 days after plating and every other day thereafter. The cultured astrocytes proliferated with a doubling time of approximately 1 week and reached confluence between 8 and 10 days after plating. At 3 days and 7–10 days after plating, some cultures were processed for immunofluorescent staining of glial fibrillary acidic protein (GFAP). The cultures consisted of greater than 95% GFAP⁺ astrocytes.

Immunofluorescence staining of astrocytes and spleen cells

Cultivated astrocytes were trypsinized for 5 min, suspended in Hanks’ buffered salt solution (HBSS) with 1% FBS and centrifuged. The cell pellet was resuspended in various rat or mouse monoclonal antibodies directed at murine MHC antigens as indicated in Tables 1 and 2 (1:10 dilution of hybridoma supernatant in HBSS with 1% FBS), incubated for 0.5 h on ice, washed with HBSS/FBS by centrifugation, resuspended in 1:50 goat anti-rat or mouse IgG conjugated to fluorescein isothiocyanate (FITC) (Zymed, South San Francisco, CA, U.S.A.), washed again, then analyzed by both fluorescence microscopy and flow cytofluorimetry.

Spleens were dissected free of connective tissue and forced through a stainless steel screen. The dissociated cells were suspended in HBSS/FBS and centrifuged. After lysing erythrocytes, spleen cells were washed by centrifugation, and resuspended in HBSS containing the primary monoclonal antibodies. To avoid background associated with staining surface immunoglobulin on B cells (when utilizing mouse monoclonal IgGs as the primary reagent), spleen cells were subsequently incubated for 0.5 h on ice with an affinity-purified goat anti-mouse IgG (Fc fragment and γ-chain specific) conjugated to fluorescein isothiocyanate (FITC) (Zymed, South San Francisco, CA, U.S.A.), washed again, then analyzed by both fluorescence microscopy and flow cytofluorimetry.

Northern blot hybridization

Total RNA was extracted from astrocyte cultures using a guanidine isothiocyanate technique.
15 μg RNA from each specimen was electrophoresed in a 0.8% agarose gel then electroblotted onto a nylon filter. The filter was hybridized with a 32P-labelled cDNA probe, pH-2δ-3, encoding the conserved third external transmembrane and cytoplasmic region of H-2Ld (Lalanne et al., 1982). After washing the filter at high stringency, an autoradiogram was analyzed by densitometry.

Results

Spontaneous induction of class I molecules on astrocytes

Class I MHC molecules are not detectable on brain cells in situ (Williams et al., 1980) or on freshly isolated cells in vitro (Schnitzer and Schachner, 1981) by immunofluorescence. This is in contrast to nucleated cells of other tissues. However, cultivation of astrocytes in vitro leads to induction of class I MHC molecules (Schnitzer and Schachner, 1981; Massa et al., 1987a). After 3 days of in vitro culture, GFAP+ astrocytes comprise greater than 95% of the viable cells (Fontana et al., 1986; Massa et al., 1987b), and remain the predominant cell type in subsequent 7-day cultures. Inducible MHC class I expression was found to differ markedly among mouse strains of different H-2 haplotypes. Both BALB/c (H-2d) and SJL (H-2s) neonatal brain cells were totally devoid of class I molecules when examined immediately after isolation (Fig. 1a–d). However, upon plating, class I molecules were rapidly induced on the majority of the BALB/c cells in vitro (Fig. 1f) and increased further over 7 days of culture (Fig. 1h). In contrast, the induction of class I molecules on SJL astrocytes was much less over the same time period (Fig. 1e and g).

Strain-specific induction is controlled by the MHC locus

To determine whether this differential inducibility of class I molecules on astrocytes mapped to the MHC, congeneric mouse strains that differed at H-2 were examined. B10.A (H-2a) mouse astrocytes expressed much higher levels of class I molecules than B10 (H-2b) astrocytes when assessed with rat monoclonal antibodies (mAb) that detect monomorphic determinants (Ozato et al., 1985) (Table 1, experiment 1). Induction of additional molecules could be achieved by adding recombinant murine γ-interferon (IFN-γ) (Wong et al., 1984) to the cultures. Treatment of B10 astrocytes with up to 1000 units/ml IFN-γ led to a modest increase of class I antigen expression, but the level was less than that spontaneously induced on B10.A astrocytes. This indicated that the strain-related differences in the level of class I induction by IFN-γ parallels spontaneous induction in tissue cultures (experiment 1, within parentheses). No difference among strains in levels of class I expression was detected on spleen cells (Table 1), which indicated that variable inducibility on astrocytes was tissue specific.

Further mapping of class I regulation within the MHC

Because inducibility of class I molecules on astrocytes is controlled by genes present within the MHC, two additional B10 congeneric strains, B10.A(4R) and B10.A(5R) were examined in an attempt to map these genes (Table 1). The involvement of genes to the right of the I-A was first tested, because BALB/c and B10.A mice share the H-2d haplotype in this region. Astrocytes from B10.A(5R) mice, which have a haplotype identical to B10.A to the right of I-A, consistently expressed high levels of class I molecules (Table 1, experiment 2). This confirmed that inducibility is, in part, associated with genes to the right of I-A, including Ld and Dd genes. In addition, an influence of genes to the left of I-E, including Kk, was suggested because B10.A(4R) astrocytes expressed higher levels of class I molecules than B10 astrocytes (Table 1), but lower than both B10.A and B10.A(5R) astrocytes. Astrocytes from the B10 × B10.A F1 generation expressed levels intermediate between B10 and B10.A astrocytes, indicating that only the H-2a class I products were expressed at high levels (Table 1 and vide infra).

Particular class I products are highly expressed on astrocytes

To examine whether the products of K and D genes are regulated independently in the different strains, a panel of mAb with restricted or private
Fig. 1. FACS analysis of cell surface class I antigen expression on freshly isolated brain cells and cultivated astrocytes of BALB/c and SJL mice. Panels a–d represent freshly isolated brain cells of SJL (a + c) and BALB/c (b + d). Panels a and b are negative controls in which cells were incubated with secondary anti-rat IgG FITC conjugate without prior incubation with a primary antibody. Cells analyzed in c (SJL/J) and d (BALB/c) were stained with a rat monoclonal antibody to a monomorphic determinant on K, D and L class I antigens designated K204 (Ozato et al., 1985). Panels e and f show induced class I antigen on brain cells, cultivated for 3 days, consisting primarily of astrocytes. BALB/c astrocytes (f) are induced to higher levels of expression than SJL cells (e). Panels g (SJL) and h (BALB/c) brain cells cultivated for 7 days and consisting of greater than 95% astrocytes are further induced to express class I antigens compared to either freshly isolated cells or after 3 days of culture. BALB/c (h) astrocytes express much higher levels compared to SJL/J astrocytes (g) at 7 days. The mean fluorescence intensity of each sample of 10000 cells is given on the histograms.
TABLE 1
MEAN FLUORESCENCE INTENSITY (MFI) AFTER IMMUNOFLUORESCENCE STAINING OF MOUSE ASTROCYTES AND SPLEEN CELLS WITH THREE RAT MONOClonAL ANTIBODIES (DESIGNATED K44, K204, 42.3.9.8) WITH PUBLIC SPECIFICITIES TOWARD CLASS I MHC MOLECULES (OZATO ET AL., 1985)

Primary astrocytes were cultivated for 1–2 weeks with DMEM with 15% fetal bovine serum until staining, with the exception of some astrocytes that were treated for 24 h with either 200 or 1000 units/ml recombinant murine IFN-γ (a generous gift of Genentech, South San Francisco, CA, U.S.A.) as indicated within parentheses in the table. Astrocytes from strains listed under experiments 1, 2 or 3 are matched with respect to date of culture preparation, immunofluorescence staining and FACS analysis. The H-2 haplotype of each strain is also given for comparison. The MFI represents fluorescence of 100% of the 10000 cells in each sample.

| Experiment No. | Mouse strain | Haplotype | Astrocytes | Spleen cells |
|----------------|--------------|-----------|------------|--------------|
|                | Mouse Haplotype | KAESDL |            |              |
|                |               | K204 | K44 | 42.3.9.8 | K44 | 42.3.9.8 |
| 1              | B10           | bbbbb - | 20 | 9 (32) | 6 (31) | 42 | 26 |
|                | B10.A         | kkkddd | 83 | 78 (259) | 43 (65) | 49 | 26 |
|                | B10.A(4R)     | kkbh - | 30 | 45 | 33 (49) |  |
| 2              | B10           | bbbbb - | 33 | 10 | 7 |  |
|                | B10.A(5R)     | bbkddd | 262 | 41 | 26 |  |
| 3              | B10           | H-2 b | 28 | 10 | 35 |  |
|                | B10.A         | H-2 a | - | 49 | 62 |  |
|                | B10 × B10.A F1 | H-2 a/b | 96 | 35 | 50 |  |

* Treated with 1000 units/ml IFN-γ.
* Treated with 200 units/ml IFN-γ.

TABLE 2
IMMUNOFLUORESCENCE ANALYSIS OF H-2K OR H-2D GENE PRODUCTS IN DIFFERENT MHC HAPLOTYPES

Astrocytes cultured for 1–2 weeks or fresh spleen cells were stained with mouse monoclonal antibodies with either private or restricted specificities to K or D gene products. The number designation and specificity of the monoclonal antibodies is given at the top of the table. Both spleen cells (S) and astrocytes (A) of each strain were stained and were analyzed by epifluorescence microscopy. The ‘+’ indicates positive immunofluorescence staining while ‘−’ indicates that fluorescence is undetectable. Data in each box are from the same experiment and include the mean fluorescence intensity (in parentheses) showing quantitative differences in K product expression between different strains. K^K is compared between B10.A and B10.A(4R) astrocytes, K^K and D^K are compared between SJL and BALB/c astrocytes and K^K is compared between B10 and B10.A(5R) astrocytes. Monoclonal antibodies 34.2.12 (Ozato et al., 1982; Hansen et al., 1983) and 36.7.5, 16.1.2, 28.13.3, 28.8.6, and 20.8.4 (Ozato et al., 1980) are previously described.

| Mouse strain | Mouse monoclonal antibody |
|--------------|---------------------------|
|              | K^K | 36.7.5 | 16.12 | K^K \ D^K | K^K \ b,a,d | K^K | 34.2.12 |
| SJL/J        | S   | – | – | – | + | – | – |
|              | A   | – | – | – | + (44) | – | – |
| BALB/c       | S   | – | – | – | – | – | + |
|              | A   | – | – | – | + (79) | – | – |
| B10.A        | S   | + | – | – | – | + | – |
|              | A   | + (26) | + (40) | – | – | – | + |
| B10.A(4R)    | S   | + | – | – | – | + | – |
|              | A   | + (29) | + (41) | – | – | – | – |
| B10.A(5R)    | S   | – | – | – | + (70) | – | + (236) |
|              | A   | – | – | – | + | – | – |
| B10          | S   | – | – | – | – | – | – |
|              | A   | – | – | – | – | + | – |

* Treated with 1000 units/ml IFN-γ.
* Treated with 200 units/ml IFN-γ.
specificities to particular products of the K and D class I genes were used. The specificity of these antibodies was confirmed using freshly isolated spleen cells prepared from the various strains. As anticipated, mouse mAb with either restricted or private specificity for the D^d (34.2.12) (Ozato et al., 1982; Hansen et al., 1983), K^k (36.7.5, 16.1.2) (Ozato et al., 1980) or K^b (28.13.3) (Ozato et al., 1980) gene product gave intense staining of astrocytes of B10.A, B10.A(5R), B10.A(4R), and BALB/c mice (Table 2). Induced expression of H-2L^d was also high on B10.A, B10.A(5R) and BALB/c astrocytes (data not shown). SJL astrocytes expressed very low levels of K^s and B10 and B10.A(4R) astrocytes did not express detectable K^b and D^b class I molecules (Table 2). In the F_1 (H-2^{a/b}) hybrid astrocytes, only H-2^a products (K^k and D^a) were expressed at high levels indicating independent control of the H-2^a and H-2^b genes (data not shown). Different antibody affinities are unlikely to account for these findings because two anti-D^d antibodies, two anti-K^k antibodies, and three antibodies recognizing K^b and/or D^b (Ozato et al., 1980) gave similar results.

**Steady-state RNA levels reflect class I expression**

The relative amounts of messenger RNA for class I antigens in total RNA extracts of astrocytes derived from the different mouse strains were examined by Northern blot analysis. Levels of message correlated with levels of class I antigen induction at the astrocyte cell surface (Fig. 2). B10 and SJL mouse astrocytes had only trace levels of RNA message while those of BALB/c, B10.A(5R), and B10 × B10.A F_1 mice had up to 20 times higher levels. These results indicate that the differences found in cell surface expression of class I antigen is controlled at the level of steady-state class I RNA message.

**Discussion**

The absence of MHC antigens in brain, as well as the findings in this study indicate that the expression of class I molecules on astrocytes is regulated differently from those on spleen cells, as well as cells of other tissues. This regulation is governed by genes that map within the MHC, most likely to the individual class I genes. In particular, D^d, K^d, and K^k genes are more highly expressed than D^b and K^s genes in the astrocyte. K^b expression was low in B10 astrocytes but was consistently high in B10.A(5R) astrocytes, demonstrating strain-specific regulation of this particular product.

A highly conserved cis-acting sequence present in the upstream region of most classical class I genes controls transcription of the genes in various cultured cells (Wan et al., 1987). This class I regulatory element (CRE) mediates control by interactions with trans-acting nuclear protein (Miya-saki et al., 1986; Shirayoshi et al., 1987; Korber et al., 1988). The CRE may exert negative regulation in brain cells in vivo which is relieved in the astrocytes of particular mouse strains, upon culture in vitro. This could occur through induction of a positive trans-acting factor and/or attenuation of a negative trans-acting factor. Because the
CRE is highly conserved, other regions in the 5' upstream DNA sequences may be responsible for regulatory differences seen in the various class I MHC genes in astrocytes.

The CNS is particularly susceptible to a variety of autoimmune and infectious diseases and the rules governing various aspects of cellular immunity in brain are probably unique to most other tissues (Oldstone et al., 1986; Doherty et al., 1988). Elucidation of brain-specific regulatory mechanisms of MHC antigen expression is therefore likely to be important in understanding genetic differences in lymphocyte–neural cell interactions.

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