Immunology 1989 **67** 26–31

Regulation of IFN-γ-induced host cell MHC antigen expression by Kirsten MSV and MLV

II. EFFECTS ON CLASS II ANTIGEN EXPRESSION

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Accepted for publication 10 January 1989

SUMMARY

We have reported previously that the Kirsten murine sarcoma virus (Ki-MSV), which carries the v-Ki-*ras* oncogene, prevents the induction of the class II MHC antigen H-2A and reduces the induction of class I MHC antigens by interferon-gamma (IFN-γ) on C3H10T½ fibroblasts. It is here shown that the abolition by the virus of H-2A expression extends also to class II antigen H-2E and that this is maintained for at least 7 days after IFN treatment. In addition no concentration of IFN-γ tested, including supra-optimal concentrations for class I antigen expression, induced class II antigens on MSV-infected cells. Thus MSV inhibits the induction by IFN-γ of class II MHC antigens by a mechanism other than via a change in kinetics of response to, or in the sensitivity of the cells to, IFN. The possibility that transformation by MSV could result in the (selective) outgrowth of cells unresponsive to IFN was refuted by the observation that clones of C3H10T½, when infected with Ki-MSV, expressed no or dramatically reduced levels of H-2A or H-2E. One C3H10T½ clone chosen for high class II expression, when transformed with Ki-MSV, did express low levels of class II antigens at optimal concentrations of IFN-γ, suggesting that the degree of the reduction of class II expression varies with the cells that are infected. Comparison with mechanisms whereby other viruses inhibit MHC antigen display revealed an interesting possibility: IFN response sequences (IRS) identified in the virus genomes might act in *trans* to (down) regulate MHC antigen expression. This could be an important mechanism determining the tumourigenicity of, and immune evasion by, Ki-MSV and other viruses.

INTRODUCTION

The major histocompatibility complex (MHC) antigens are necessary for T-cell recognition of (foreign) antigen: class I antigens being required by cytotoxic T cells and class II being required by helper T cells. During the course of an infection these antigens are up-regulated by the interferons (IFN), especially IFN-γ produced by helper T cells (Maudsley, Morris & Tomkins, 1989). Several viruses have been reported either to inhibit this up-regulation or to otherwise down-regulate class I expression (e.g. adenovirus 12, Schrier *et al.*, 1983; adenovirus 2, Andersson *et al.*, 1985; Herpes simplex virus type 1 (HSV-1) and HSV-2, Jennings *et al.*, 1985; hepatitis B virus (HBV), Onji *et al.*, 1987; and Ki-MLV, Maudsley & Morris, 1989, see p. 21) or, in the case of Ki-MSV, to down-regulate class II expression (Maudsley & Morris, 1988). These effects are thought to have important immunological consequences, for example a decrease in MHC antigen expression by adenovirus 12 may contribute to its tumourigenicity (Barnards *et al.*, 1983). Likewise, down-regulation of class I expression by adenovirus 2 results in reduced susceptibility of infected cells to allo-specific cytotoxic T-cell lysis (Andersson, McMichael & Peterson, 1987).

The mechanisms whereby viruses reduce MHC expression are generally not clear, but Kirsten-MSV, like adenovirus 12, has the ability to transform cells and one of several aspects of transformation might be involved in inhibiting the induction of class II antigens on infected cells by IFN-γ. Firstly transformed cells grow more rapidly than untransformed cells, therefore the kinetics of the response to IFN-γ might be more rapid. This has partly been refuted (Maudsley & Morris, 1989) in that the kinetics of class I expression are not significantly changed by transformation. However, since the responses to IFN-γ of class I and class II (at least H-2A) expression are clearly uncoupled from each other by Ki-MSV (Maudsley & Morris, 1988) it was

Abbreviations: HBV, hepatitis B virus; HSV, herpes simplex virus; IFN-γ, interferon-gamma; IRS, interferon response sequence; Ki-, Kirsten; LTR, long terminal repeat; MHC, major histocompatibility complex; MLV, murine leukaemia virus; Mo-, Moloney; MSV, murine sarcoma virus.

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important to assess the expression of class II antigens (both H-2A and H-2E) on infected and uninfected cells over several days following IFN-γ exposure. Secondly transformation by Ki-MSV might be selecting out cells unresponsive to IFN-γ—either by the virus preferentially infecting or transforming unresponsive cells or by unresponsive cells growing more rapidly on transformation. This is perhaps unlikely since we have previously cloned C3H10T$\frac{1}{2}$ (Maudsley & Morris, 1988) and found that all the subclones tested were inducible for class II antigens. To rule out this possibility the effect of Ki-MSV infection on class II expression on clonal populations was investigated. Thirdly transformation could affect the sensitivity of the cells to stimuli, including IFN-γ. To address this question cells were treated with a range of IFN-γ concentrations and class II expression assessed.

Alternatively mechanisms of action are suggested for the several other viruses that affect MHC antigen expression and these might have parallels in the actions of Ki-MSV. These mechanisms include the apparent *trans* action of IFN response sequences (IRS) in HBV to inhibit responses to IFN (Thomas, Pigmatelli & Lever, 1986; Onji *et al.*, 1987).

In fact IRS of two types have been described: 'IRS-α' which responds to IFN-α and is located in front of class I (and, mysteriously, class II) genes (Friedman & Stark, 1985), and 'IRS-γ' which is important in the responses to IFN-γ and is found in the enhancer regions of class II genes (Basta, Sherman & Ting, 1987). The actual sequence varies between different genes but from these sequences consensus IRS have been proposed (Friedman & Stark, 1985; Basta *et al.*, 1987). The full IRS-α is approximately 30 base pairs long with a shorter core sequence, whereas IRS-γ is only 9 base pairs. If Ki-MLV or Ki-MSV possess IRS then comparison also with the Ki-MSV-related virus that also reduces MHC antigen expression, Mo-MSV (Flyer, Burakoff & Faller, 1985), might be profitable. Therefore, actions of Ki-MSV and Ki-MLV were compared with the HBV mechanism and with other viruses and their mechanisms for reducing MHC expression, in particular a search for IRS in Ki-MSV and Ki-MLV was carried out.

MATERIALS AND METHODS

Cells and viruses

Kirsten MLV-infected (KLVC3H), Ki-MSV-infected (C3H201), double-infected (KC3H), and uninfected C3H10T$\frac{1}{2}$ cells were maintained as described previously (Maudsley & Morris, 1988, 1989, see p. 21). Clones of C3H10T$\frac{1}{2}$, B9 and F11 were isolated by limiting dilution and picking single colony wells. Infection of B9 and F11 with helper-free Ki-MSV or Ki-MSV/MLV complex was as described for the parent cell line (Maudsley & Morris, 1988). Clones and their infected sublines were grown in medium with 10% heat-inactivated fetal calf serum (FCS) rather than 5% heat-inactivated newborn calf serum.

IFN and induction of MHC antigens

IFN and induction of MHC antigens were as described by Maudsley & Morris (1989).

Monoclonal antibodies and antisera

Monoclonal antibodies and antisera were as described by Maudsley & Morris (1989). In addition, the following monoclonal antibodies were used: anti-H-2A^k, TIB92; anti-H-2E^k, HB32.

Flow cytometry

Cell staining and analysis on a FACStar flow cytometer were as described in the accompanying report. Data are given as specific mean fluorescence, that is mean fluorescence of stained cells minus mean fluorescence of control-stained cells (FITC alone, or control monoclonal antibody anti-H-2A^d-stained cells).

Sequence analysis

The database and programs of the computer system Microgenie (Beckman, High Wycombe, Bucks) were used to search viral nucleotide sequences.

RESULTS

Time–course of induction by IFN-γ of H-2A on uninfected and MSV- or MLV-infected C3H10T$\frac{1}{2}$

C3H10T$\frac{1}{2}$ fibroblasts, MSV-infected (C3H201), MLV-infected (KLVC3H), MLV/MSV-infected (KC3H) or uninfected were treated with 100 U/ml IFN-γ and stained for H-2A expression every 24 hr up to 7 days after treatment. H-2A expression of these cells was measured using a FACStar flow cytometer. Cells not treated with IFN-γ showed no detectable expression of H-2A (Fig. 1). H-2A was detected on C3H10T$\frac{1}{2}$ and KLVC3H 2 days after IFN-γ treatment but not on C3H201 or KC3H (Fig. 1). Expression rose in both C3H10T$\frac{1}{2}$ and KLVC3H, peaking at Day 6 for C3H10T$\frac{1}{2}$. H-2A expression was virtually abolished across the whole time–course by infection with either MSV alone or MSV and MLV together (Fig. 1), although it is clear from the fluorescence profiles (Fig. 2) that at least a small number of C3H201 cells express low levels of H-2A. Similar results were seen in three further experiments (data not shown). Cells infected with MLV alone showed reduced expression of

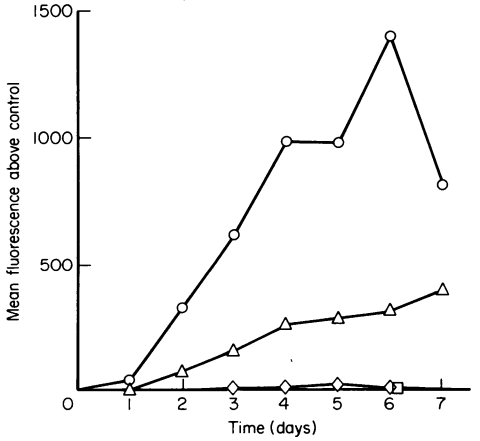

Figure 1. Induction of H-2A^k by INF-γ on uninfected (○), MSV-infected (◇), MLV-infected (△) or MSV/MLV-infected (□) C3H10T$\frac{1}{2}$ fibroblasts.

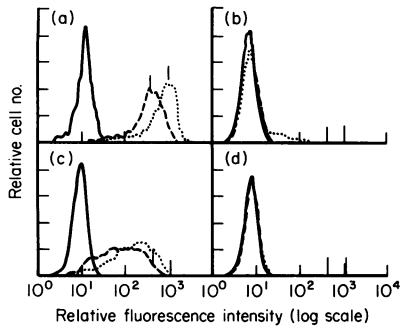

Figure 2. Expression of H-2A and H-2E on uninfected and infected C3H10T½ fibroblasts 4 days after treatment with 100 U/ml IFN-γ, as determined by FACS analysis. (a) Uninfected, (b) Ki-MSV-infected, (c) Ki-MLV-infected, and (b) Ki-MSV/MLV-infected cells. Dotted line, H-2A^k; dashed line, H-2E^k; solid line, H-2A^d control. Modes (i.e. peak channel values) for H-2A^k and H-2E^k expression on C3H10T½ cells are indicated on all histograms by vertical lines. Modes for H-2A^k and H-2E^k, respectively, on the four cell types were (a) 1065 and 416, (b) 8 and 8, (c) 280 and 44, and (d) 9 and 8. Modes for H-2A^d were 11, 8, 9 and 9, respectively.

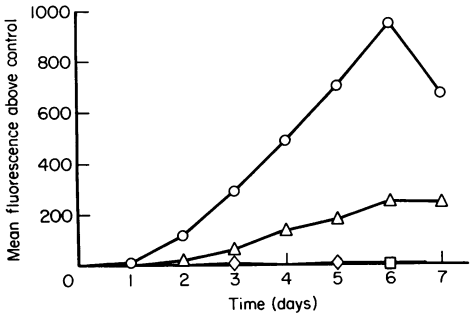

Figure 3. Induction of H-2E^k by IFN-γ on uninfected (○), Ki-MSV-infected (◇), Ki-MLV-infected (△) or Ki-MSV/MLV-infected (□) C3H10T½ fibroblasts.

class II antigen across the time–course, similar to the effects of MLV and MSV on class I expression; however, this reduction was not always as great as the effects seen on class I.

Time–course of H-2E expression on uninfected and infected C3H10T½

Expression of MHC antigens of one class is not always co-ordinate (e.g. Green & Phillips, 1986; Girdlestone & Milstein, 1988), therefore it was important to see whether MSV had similar effects on the other class II antigen H-2E. The induction of H-2E on uninfected, MSV-infected or MLV-infected C3H10T½ cells mimicked that for H-2A (Fig. 3): expression rose on C3H10T½ and KLVC3H until Day 6 (expression being clearly lower on the MLV-infected cells), whilst C3H201 and KC3H gave no significant expression of H-2E across the whole time–course. Fluoresecence profiles of H-2E expression on these cells, and peak channel values, are also shown (Fig. 2).

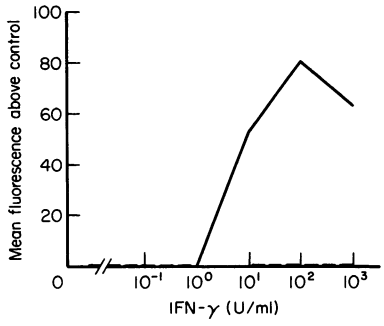

Figure 4. Effects of IFN-γ concentration on the induction of H-2A^k on C3H10T½ fibroblasts (solid lines) and on Ki-MSV-infected C3H10T½ fibroblasts (C3H201, dashed line).

Table 1. Effect of IFN-γ concentration on H-2 antigen induction on C3H10T½ subclone F11 and on Ki-MSV-(F11A) and Ki-MSV/MLV (F11B)-infected F11 cells

Antigen	Cell	IFN-γ conc. (U/ml)					
		0	0·1	1	10	100	1000
H-2K	F11	3*	0	156	787	900	636
	F11A (MSV infected)	0	2	39	371	480	488
	F11B (MSV/MLV infected)	0	4	23	411	499	480
H-2A	F11	0	0	0	63	156	139
	F11A (MSV infected)	6	0	0	0	17	6
	F11B (MSV/MLV infected)	0	1	4	3	23	23
H-2E	F11	4	0	0	53	110	90
	F11A (MSV infected)	0	0	0	0	1	0
	F11B (MSV/MLV infected)	0	0	0	1	3	7

* Increase in mean fluorescence of specifically stained cells above mean fluorescence of control-stained cells.

Effect of IFN-γ concentration on class II induction on MSV-infected or uninfected cells

C3H10T½ and C3H201 cells were incubated with varying concentrations of IFN-γ up to 1000 U/ml. The expression of H-2A 4 days after treatment (i.e. in the plateau of class I expression for both cell lines and in a region of high class II expression for C3H10T½) is shown (Fig. 4). Optimal concentration of IFN-γ for maximal expression of H-2A was found to be 100 U/ml for C3H10T½. Across the whole range of concentrations that induced H-2A on C3H10T½, including the supra-optimal concentration of 1000 U/ml, no H-2A was induced on C3H201 (Fig. 4). Similar results were obtained for H-2E induction (data not shown).

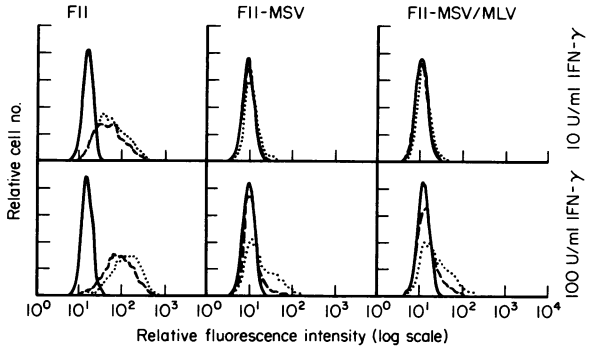

Figure 5. Expression of class II antigens on C3H10T½ clone F11 and Ki-MSV- or Ki-MSV/MLV-infected F11 4 days after treatment with 10 U/ml (top) or 100 U/ml (bottom) IFN-γ. Dotted line, H-2A^k; dashed line, H-2E^k; solid line, control. Left panels, F11; middle panels, Ki-MSV-infected F11; right panels, Ki-MSV/MLV-infected F11.

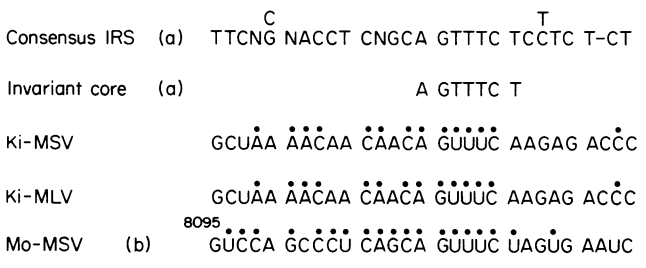

Figure 6. Comparison of IRS-α with sequences in Ki-MSV, Ki-MLV and Moloney-MSV. (a) Consensus IRS-α and 'invarient' core of IRS-α taken from Friedman & Stark (1985). (b) Numbering of bases from the beginning of the pro-virus: numbering unknown for Ki-MSV since only partial sequence data are available (Norton *et al.*, 1984). Dots indicate concordance with IRS-α. N indicates any nucleotide in that position of the IRS.

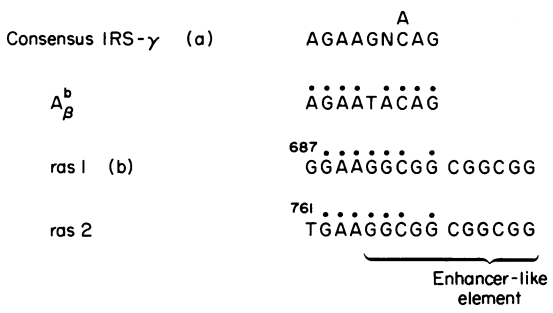

Figure 7. Comparison of IRS-γ with sequences in c-Ki-*ras* exon 0 presumed to be present in the v-Ki-*ras* gene of Ki-MSV. (a) Consensus IRS-γ and the IRS for the murine H-2Aβ gene taken from Basta *et al.* (1987). (b) Sequence data and numbering from Hoffman *et al.* (1987). N indicates any nucleotide in that position of the IRS. Dots indicate concordance with IRS-γ.

Induction of class II antigens on uninfected and MSV-infected clones of C3H10T½

Clone B9, typical of C3H10T½ clones, and clone F11, which tended to express higher levels of class II antigens, were infected either with MSV alone or with both MLV and MSV together. On treatment with IFN-γ little or no H-2A or H-2E was induced on MSV- or MSV/MLV-infected cells (data not shown). The expression of H-2A and H-2E on clone F11 infected with MSV or MLV/MSV was significantly above background at optimal concentrations (100 U/ml) of IFN-γ (Table 1) with many but not all cells expressing detectable levels of class II antigens (Fig. 5). This expression was clearly diminished at 10 U/ml IFN-γ (Table 1, Fig. 5). Reductions in class I expression by MSV were seen, confirming on a clone what was seen for the parent cell line (Maudsley & Morris, 1989).

IRS in MSV and MLV genomes

Searches for IRS in Ki-MSV, Ki-MLV and the distantly related Mo-MSV revealed IRS-α-like sequences in the LTR of all viruses (Fig. 6). IRS-γ-like sequences were found in the c-Ki-*ras* gene thought to be largely unchanged (apart from a point mutation at codon 12) in Ki-MSV (Fig. 7).

DISCUSSION

Several aspects of the reduction of class II expression by Ki-MSV were addressed by this study. The abolition by MSV of H-2A induction has been reported previously and might be important for the tumourigenicity of MSV-transformed cells. The data confirm this abolition of H-2A by MSV and show that it extends over a minimum of 7 days after IFN-γ exposure. Induction of H-2E is also shown to be abolished, again over a minimum of 7 days.

Several viruses which decrease MHC expression are also transforming, raising the possibility that the down-regulation could be a consequence of transformation. The data address three such possible links. The first possibility is a change (most likely an increase in speed) in the response kinetics to IFN-γ. This was shown not to be the case for class I antigens (Maudsley & Morris, 1989) and does not appear to contribute to the reduction in class II expression (this report). A second possibility is a change in sensitivity to stimuli. This too appeared not to be the case since for class I antigens the optimal concentration of IFN-γ remained the same (Maudsley & Morris, 1989) whereas neither this optimal concentration nor a range of concentrations including supraoptimal concentration of IFN-γ could induce significant class II expression on infected cells. The possibility that the two effects of IFN-γ could be mediated through different receptors is not ruled out. A third possibility, of clonal selection, although not excluded from occurring, was shown not to be necessary since clones mimicked the uncloned parent line in showing abolition or reduction of class II expression on transformation by MSV.

Interestingly one clone showed a slightly different effect: the abolition was not total, indicating that different cells show different effects of MSV. The strong correlation between reduced MHC class I expression and tumourigenicity described for adenovirus (Schrier *et al.*, 1983) suggests a similar role for reduced class II in the tumourigenicity of MSV-transformed cells; and in other systems class II expression has been shown to correlate with tumour regression, and lack of expression with tumour progression (Powell, Hala & Wick, 1987). The variations in class II antigen expression seen here might therefore have important consequences on the tumourigenicity of MSV (*ras*)-transformed cells. For example cells which on infection with MSV are still inducible for class II might be expected to be less tumourigenic than those that are not.

Confirmation of our previous observation that Ki-MLV does not abolish class II expression identifies regions not shared between the viruses as being responsible for the abolition by Ki-MSV of class II. As reported previously (Norton, Connor & Avery, 1984; Maudsley & Morris, 1988), this region includes one gene only, the v-Ki-*ras* oncogene encoding the protein $p21^{ras}$. The F/3′ orf gene in HIV, encoding a G-protein with some similarity of *ras*, has been shown to affect surface antigen CD4 (the T-cell molecule associated with class II recognition) expression in CEM cells (Guy *et al.*, 1987), supporting a possible role for this family of genes or their products in regulating cell surface antigen expression.

Other mechanisms whereby viruses might reduce host cell MHC antigen expression include the following. Firstly, adenovirus E1A gene products home in on the nucleus (Lyons, Ferguson & Rosenberg, 1987) where they affect transcription (Schrier *et al.*, 1983) or post-transcriptional processing (Vaessen, Houweling & van der Eb, 1987) of class I genes. Secondly, the adenovirus E3 gene product E3/19K binds MHC class I α chains, preventing them from going beyond the Golgi and hence from being expressed (Andersson *et al.*, 1985). Both of these mechanisms seem unlikely for Ki-MSV since the only protein for which it codes, $p21^{ras}$, is closely related to native host cell $p21^{ras}$ proteins and is located on the inner surface of the plasma membrane. Although unable to act directly on gene expression (or protein transport) the *ras* gene product has important effects on intracellular signalling (Michel & Kirk, 1986) and hence indirectly on gene expression (e.g. Imler *et al.*, 1988). It will be important to determine what role these effects might have on class II expression.

Thirdly, there is evidence that HBV suppresses responses to IFN via *trans* action of IRS-like sequences in its genome (Thomas *et al.*, 1986; Onji *et al.*, 1987). The finding of IRS-like sequences in Ki-MLV and Ki-MSV is interesting. Sequences like IRS-α, which is found in the enhancer region of class I MHC genes, were found in both viruses corresponding to the reduction of class I by both viruses. Interestingly, the related viruses Mo-MLV and Mo-MSV, which also regulate class I expression (Flyer *et al.*, 1985), have a similar IRS-α like sequence in their LTR. Indeed a role for the LTR in MHC antigen down-regulation is consistent with reports that 'non-coding' retroviral LTR contribute towards tumourigenicity (Savard *et al.*, 1987). Although the whole sequence of Ki-MSV is not available, sequences like IRS-γ, which is found in the enhancer region of class II genes, were found in the exon 0 of c-Ki-*ras* and presumed to be largely unaltered in Ki-MSV whilst absent from Ki-MLV. The role of these in the down-regulation of class II expression is not clear at this stage but a *trans* effect on class II induction analogous to the effects of IRS-α-like sequences of HBV on class I induction is suggested. The following of both IRS-γ-like sequences in Ki-MSV by identical enhancer-like sequences adds weight to this suggestion. It has been suggested that there may be a need for nuclear location of IRS-containing mRNA transcripts for this *trans* effect to occur: if so then both Ki-MSV and Ki-MLV are suitable since they integrate into the genome (as does HBV), and transcripts encompassing the whole provirus are produced. It is unknown whether these IRS act as conventional IRS to up (or down)-regulate gene transcription in *cis* in response to IFN(γ).

These various mechanisms are, of course, not mutually exclusive and it will be important to determine their respective roles in class I and class II MHC down-regulation by Ki-MSV. Down-regulation of MHC antigens by either mechanism could affect the immunogenicity and tumourigenicity of cells infected or transformed with Ki-MSV/v-Ki-*ras*, or with other viruses or oncogenes.

This report therefore shows that MSV abolishes class II induction in C3H10T½ cells by a mechanism other than via transformation-induced changes in the kinetics of the response to (response speed or duration), or in the optimal sensitivity *per se* of the cells to, IFN-γ. Downstream effects on gene transcription via effects of $p21^{ras}$ on intracellular second messengers are possible. A good correlation between IRS-α-like sequences and class I reduction on one hand, and IRS-γ-like sequences and class II abolition on the other suggests, by analogy to HBV, an important role for these sequences in the effects of Ki-MLV and Ki-MSV on both class I and class II expression.

Note added in proof

We have now shown that sublines of C3H201 selected for high and low class II MHC antigen inducibility here low and high tumourigenicity, respectively, thus confirming that the down-regulation of class II MHC antigens by r-ki-*ras* has functional significance for tumourigenicity.

ACKNOWLEDGMENTS

We thank the Cancer Research Campaign of Great Britain for supporting this work.

REFERENCES

ANDERSSON M., MCMICHAEL A. & PETERSON P.A. (1987) Reduced allorecognition of adenovirus-2 infected cells. *J. Immunol.* **138,** 3960.

ANDERSSON M., PÄÄBO S., NILSSON T. & PETERSON P.A. (1985) Impaired intracellular transport of class I MHC antigens as a possible means for adenoviruses to evade immune surveillance. *Cell,* **43,** 215.

BARNARDS R., SCHRIER P.I., HOUWELING A., BOS J.L., VAN DER EB, A. J., ZIJLSTRA M. & MELIEF C.J.M. (1983) Tumourigenicity of cells transformed by adenovirus type 12 by evasion of T-cell immunity. *Nature (Lond.),* **305,** 776.

BASTA P.V., SHERMAN P.A. & TING J.P.-Y. (1987) Identification of an interferon-γ response region 5′ of the human histocompatibility leucocyte antigen DRα chain gene which is active in human glioblastoma multiforme lines. *J. Immunol.* **138,** 1275.

FLYER D.C., BURAKOFF S.J. & FALLER D.V. (1985) Retrovirus-induced changes in major histocompatibility complex antigen expression influence susceptibility to lysis by cytotoxic T-lymphocytes. *J. Immunol.* **135,** 2287.

FRIEDMAN R. & STARK G.R. (1988) α-Interferon-induced transcription of HLA and metallothionein genes containing homologous upstream sequences. *Nature (Lond.),* **314,** 637.

GIRDLESTONE J. & MILSTEIN C. (1988) Differential expression and interferon response of HLA class I genes in thymocyte lines and response variants. *Eur. J. Immunol.* **18,** 139.

GREEN W.R. & PHILLIPS J.D. (1986) Differential induction of H-2K verses H-2D class I major histocompatibility complex antigen expression by murine recombinant interferon-γ. *J. Immunol.* **137,** 814.

GUY B., KIENY M.P., RIVIERE Y., LE PEUCH C., DOTT K., GIRARD M., MONTAGNIER L. & LECOQ J.-P. (1987) HIV F/3′ orf encodes a phosphorylated GTP-binding protein resembling an oncogene product. *Nature (Lond.),* **330,** 266.

HOFFMAN E.K., TRUSKO S.P., FREEMAN N. & GEORGE D.L. (1987) Structural and functional characterization of the promoter region of the mouse c-Ki-*ras* gene. *Mol. Cell. Biol.* **7,** 2592.

IMLER J.L., SCHATZ C., WASYLYK C., CHATTON B. & WASYLYK C. (1988) A Harvey-*ras* responsive transcription element is also responsive to a tumour-promoter and to serum. *Nature (Lond.)*, **332,** 275.

JENNINGS S.R., RICE P.L., KLOSZEWSKI E.D., ANDERSON R.W., THOMPSON D.L. & TEVETHIA S.S. (1985) Effect of herpes simplex types 1 and 2 on surface expression of class I major histocompatibility complex antigens on infected cells. *J. Virol.* **56,** 757.

LYONS R.H., FERGUSON B.Q. & ROSENBERG M. (1987) Pentapeptide nuclear localisation signal in adenovirus Ela. *Mol. Cell. Biol.* **7,** 2451.

MAUDSLEY D.J. & MORRIS A.G. (1988) Kirsten murine sarcoma virus abolishes interferon-γ-induced class II but not class I major histocompatibility antigen expression in a murine fibroblast line. *J. exp. Med.* **167,** 706.

MAUDSLEY D.J. & MORRIS A.G. (1989) Regulation of IFN-γ-induced host cell MHC antigen expression by Kirsten MSV and MLV. I. Effects on class I antigen expression. *Immunology*, **67,** 21.

MAUDSLEY D.J., MORRIS A.G. & TOMKINS P.T. (1989) Regulation by interferon of the immune response to viruses via the major histocompatibility complex antigens. In: *Immune Responses, Virus Infection and Disease* (eds N. J. Dimmock and P. D. Minor) (in press). IRL Press, Oxford.

MICHELL R. & KIRK C. (1986) G-protein control of inositol phosphate hydrolysis. *Nature (Lond.)*, **323,** 112.

NORTON J.D., CONNOR J. & AVERY R.J. (1984) Genesis of Kirsten murine sarcoma virus: sequence analysis reveals recombination points and potential leukaemogenic determinant on parental leukaemia virus genome. *Nucleic Acid Res.* **12,** 6839.

ONJI M., LEVER A.M.L., SAITO I. & THOMAS, H.C. (1987) Hepatitis B virus reduces the sensitivity of cells to interferons. *J. Interferon Res.* **7,** 690.

POWELL P.C., HALA K. & WICK G. (1987) Aberrant expression of Ia-like antigens on tumour cells of regressing but not progressing Rous sacromas. *Eur. J. Immunol.* **17,** 723.

SAVARD P., DESGROSEILLERS L., RASSART E., POIRIER Y. & JOLICOEUR P. (1987) Important role of the long terminal repeat of the helper Moloney murine leukaemia virus in Abelson virus-induced lymphoma. *J. Virol.* **61,** 3266.

SCHRIER P.I., BERNARDS R., VAESSEN R.T.M.J., HOUWELING A. & VAN DER EB A.J. (1983) Expression of class I major histocompatibility antigens switched off by highly oncogenic adenovirus 12 in transformed rat cells. *Nature (Lond.)*, **305,** 771.

THOMAS H.C., PIGNATELLI M. & LEVER A.M.L. (1986) Homology between hepatitis B virus DNA and a sequence regulating the interferon-induced antiviral system: possible mechanism of persistent infection. *J. Med. Virol.* **19,** 63.

VAESSEN R.T.M.J., HOUWELING A. & VAN DER EB A.J. (1987) Post-transcriptional control of class I MHC mRNA expression in adenovirus 12-transformed cells. *Science*, **235,** 1486.