that of tryptophan (≈5,000) at 280 nm. Furthermore, tryptophan comprises only 3 of the 336 amino acids in each *E. coli* envelope protein, but 25 of the amino acids are tyrosine and this moves the peak absorption to 275 nm (ref. 20). This accounts for *E. coli* and the other organisms enumerated above having peaks near 260 nm rather than 280 nm.

It is well known that the sterilization action spectrum of UV radiation from 300 to 220 nm parallels the absorption spectrum of bacteria[22,23] and that enzymes are inactivated by UV-induced damage to phenylalanine, tyrosine, tryptophan and cystine[24]. If tryptophan and these other amino acids were exposed to the interstellar UV, they would soon be destroyed. For example, the quantum yield for the production of ammonia, by 253.7-nm radiation, from tryptophan is 0.002 (ref. 24). If the amino acids were protected deep inside a grain covered by a polymeric coat, they could not be observed. However, a literature search failed to uncover any finding of tryptophan or any other indole derivative in either meteorites or IS clouds. One paper[10] concludes that the IR spectrum of the galactic centre source IRS7 contains strong evidence for bacterial grains on the basis of the IR spectrum of *E. coli*. However, from these results we have calculated that the same bacterial mass would cause an absorbance ≈100 times larger in the UV than in the IR and this has not been observed in the direction to any star. The same comparison excludes polysaccharides[25,26] associated with diatoms[9] and algae[8]. Finally, on the basis of experiments of Rosenbusch[20] and Setlow and Doyle[18], pure proteins in general[5,10] (including the major envelope protein of *E. coli*[20]) have a maximum UV absorbance at least 100 times larger than the highest IR absorbance. Because neither the required shape nor magnitude of the UV absorbances are observed, proteins are also excluded as explanation for these absorbances.

After this work was completed, Williams[27] and Hoyle and Wickramasinghe[28] published letters also describing the recent adverse comment[14] on the conclusions of Hoyle, Wickramasinghe and colleagues. Turner[29] expressed the need for much more stringent requirements than have recently been applied for molecular identification in the microwave region; although he is concerned only with highly resolved spectra, the same constraints apply even more forcibly to presently resolvable IR and UV molecular bands.

The M13 and *E. coli* JM 103 were gifts from Dr Roselyn Eisenberg; the DNA samples from Dr Phoebe S. Leboy; the other viruses and living organisms came from the Carolina Biological Supply Co., North Carolina.

Note added in proof: Greenberg's claim (see ref. 14) that the 280 nm feature[5] is spurious has now been published[30] together with summaries of papers given at the Royal Astronomical Society's Specialist Discussion, 'Are Interstellar Grains Bacteria?'[31]. Other adverse comments have appeared[32-35]. The response to these by Karim, Hoyle and Wickramasinghe[36,37] has in turn been answered by us[35].

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Rejection of transplantable AKR leukaemia cells following MHC DNA-mediated cell transformation

Kam Hui, Frank Grosveld* & Hilliard Festenstein

Department of Immunology, The London Hospital Medical College, Turner Street, London E1 2AD, UK
* Laboratory of Gene Structure and Expression, National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, UK

Major histocompatibility complex (MHC) class I molecules can function as specific target antigens in T-cell-mediated cytotoxity[1,2]. In addition, T cells can kill target cells through non-MHC antigens, for example, virally infected cells, if the target and effector cells express the same MHC class I antigens[2]. Consequently, quantitative and/or qualitative variations in the expression of the H–2/HLA antigens on the target cells could interfere with MHC-restricted immune reactions. We have reported that the AKR leukaemia cell line K36.16, a subline of K36 (ref. 3), on which the H–2K^k antigen cannot be detected, is resistant to T-cell lysis and grows very easily in AKR mice[4]. Other AKR tumour cell lines, like 369, which have a relatively large amount of H–2K^k on their surface, are easily killed by T cells *in vitro* and require a much larger inoculum to grow *in vivo*[4]. Monoclonal antibodies against H–2K^k, but not against H–2D^k, prevented the killing by T cells[4,5]. This suggests that some tumour cells grow *in vivo* because tumour-associated antigen(s) cannot be recognized efficiently by the host's immune system, due to the absence of MHC molecules which would function as restriction elements for T-cell cytotoxicity. We have tested this hypothesis by introducing the *H-2K^k* gene into the H–2K^k-deficient AKR tumour cell line K36.16 and have now demonstrated directly the biological relevance of H–2K^k antigen expression in the regulation of the *in vivo* growth of this tumour cell line.

Transformations were done by calcium phosphate co-precipitation[20] with a cosmid containing the *H-2K^k* gene (c27.2) and pTCF[6], the vector for the aminoglycosyl 3′-phosphotransferase gene (*agpt*), or pTCF alone. Between 8 and 20 transformants per 10^6 cells were selected in medium containing 800 μg ml^{-1} of the antibiotic G418. From over 300 transformants, we selected a series of clones that expressed different amounts of H-2K^k on the cell surface (see below). DNA and RNA were isolated from each of the selected transformants and analysed by Southern blot or S_1 nuclease protection analysis. Hybridization with a plasmid (vector) or an *H-2K^k* probe showed that each of the transformants contained one to three copies of the exogenous *H-2K^k* gene (data not shown). Figure 1 shows the level of *H-2K^k* mRNA determined by S_1 nuclease protection assay in the K36.16 tumour cells before and after transformation with *H-2K^k*. The negative control *H-2K^d* P_3-X63-Ag8 (Ag8) cells[7] (Fig. 1*b*) and the K36.16 cells show a low mRNA signal, probably due to incomplete S_1 digestion of RNA-DNA hybrids

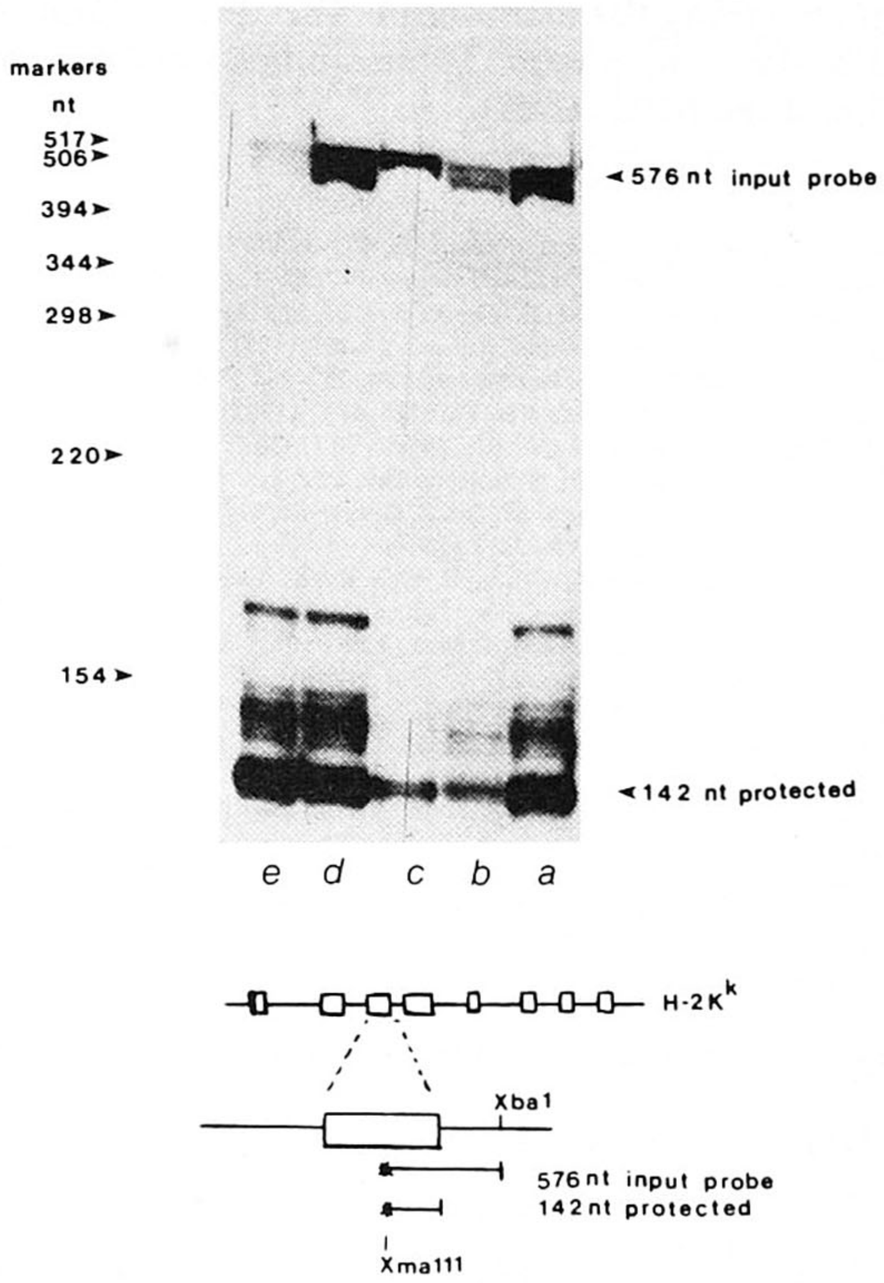

Fig. 1 S_1 nuclease protection analyses of mRNA isolated from the c27.2 transformants and control cell lines: *a*, 369 (H-2K^k, positive control); *b*, Ag8 (H-2K^d, and H-2K^k-negative control); *c*, K36.16; *d*, C27.2.2; and *e*, C27.2.3.
Methods: S_1 nuclease protection analysis was done using procedures described elsewhere[18,19]. The input probe is a 576-nucleotides (nt) *Xma*III-*Xba*I DNA fragment isolated from the third exon-intron boundary; 142 nt of this fragment are protected from S_1 nuclease digestion (S. Kvist, personal communication). 25 μg of total cytoplasmic RNA isolated from the different cell lines were hybridized overnight at 57 °C with the labelled DNA input probe. S_1 nuclease cleavage was at 37 °C for 2 h and electrophoretic separation was on 8 M urea–7% polyacrylamide gels, resulting in a 142-nucleotide protected fragment. Multiple protected bands shorter than 142 nt are due to overdigestion by S_1 nuclease.

formed between the DNA probe and mRNA molecules other than *H-2K^k*. The *H-2K^k*-transformed cells, however, show an increase of at least 20-fold of *H-2K^k* mRNA (Fig. 1*d*, *e*) to a level similar to that of the positive control, 369 (H-2K^k-positive) (Fig. 1*a*). This suggests that the absence of the H-2K^k antigen on the K36.16 cells is due to a failure to transcribe the *H-2K^k* gene efficiently, rather than any post-transcriptional event.

To demonstrate the presence of the H-2K^k antigen on the cell surface, we carried out radiobinding analysis with anti-H-2K^k monoclonal antibodies. Table 1 gives the results from only five *H-2K^k* DNA transformants and the control cell lines, because they cover a wide range of H-2K^k antigen expression on the cell surface and were subsequently used in experiments designed to evaluate the role of H-2K molecules in oncogenesis and host resistance to AKR leukaemias. All these cell lines express the same amount of H-2D^k, as expected (data not shown). In addition, a 45,000-molecular weight molecule was precipitated by anti-H-2K^k monoclonal antibody from ^{35}S-methionine-labelled lysates of one of the transformed clones. Competition by added unlabelled AKR (H-2K^k-positive) lysates specifically prevented the immunoprecipitation of this molecule (data not shown).

Because the H-2K^k antigen is important as a restriction element in T-cell-mediated killing of Gross virus tumours[4], we examined the ability of these transformed clones to induce tumours in syngeneic AKR and semi-syngeneic (AKR × BALB/c)F1 mice. Table 1 shows that inocula of 10^5 viable cells

Table 1 Radioimmunoassay and tumour inducibility of *H-2K^k*-transfected K36.16 cells

Transformant	Radiobinding (net c.p.m.)		No. of mice with tumours*	
K36.16	0	(0)	10/10	(10/10)
pTCF-K36.16	92	(21)	10/10	(10/10)
C27.2.1	364	(424)	0/10	(0/10)
C27.2.2	376	(529)	1/5	
C27.2.3	1,334	(1,073)	0/5	(0/5)
C27.2.4	257	(209)	4/5	
C27.2.5	230	(497)	0/5	
369	19,416	(6,350)		

For radiobinding, 5×10^5 cells were reacted with monoclonal antibodies as indicated. The anti-H-2K^k (refs. 15, 16) and anti-H-2D^k (ref. 15)-producing hybridoma cell lines were obtained from the American Type Culture Collection. The results are an average of two independent assays with anti-H-2K^k antibody 11.4.1 (ref. 15) (or 16-3-22S[16]) and are expressed as c.p.m. after subtraction of the background (200 c.p.m.) pTCF-K36.16 is a clone obtained by transformation of K36.16 with the vector pTCF alone. The positive control, 369, is an AKR leukaemia that expresses H-2 K^k antigen[4].
* 100,000 K36.16 tumour cells (in 0.1 ml phosphate-buffered saline, PBS) were injected subcutaneously (s.c.) into one thigh and the same number of c27.2 transfected clones into the other thigh of the recipient mouse. The diameters of the tumour masses were measured after 3 weeks. Mice were scored as positive for tumours when the diameters measured were 1.5–2.0 cm, whereas mice were scored as negative for tumours when the diameters observed were <0.6 cm. 3,000 K36.16 tumour cells were able to induce 100% tumour incidence in both AKR and (AKR × BALB/c)F1 mice in 14–20 days. The values for F_1 mice are given in parentheses.

Table 2 Induction of tumour by treatment of the transfected clones with monoclonal anti-H-2K^k antibody

Clone	Treatment of AKR recipients	No. of mice with tumours
C27.2.1	Anti-H-2K^k MoAb	3/5
C27 2 1	Anti-H-2K^b MoAb	0/5
C27.2.1	Culture medium	0/5
C27.2.3	Anti-H-2K^k MoAb	6/7
C27.2.3	Anti-H-2K^b MoAb	0/7

100,000 transfected clones treated with monoclonal antibody (MoAb) (anti-H-2K^k MoAb 16-3-22S[16] or anti-H-2K^b MoAb B8-24-3 (ref. 17) as indicated were injected s.c. into the thigh of one of the hind legs of the recipient, and K36.16 cells treated with the same antibody were injected into the other hind leg of the same mouse. This was followed by subsequent injections of the corresponding monoclonal antibody *in vivo* once every other day. The number of tumour incidences was recorded after 20 days. The K36.16 tumour cells were able to induce tumours in all cases.

Table 3 Mice immunized with the transfected clones reject a second challenge of the original K36.16 tumour cells

Mouse strain tested	Mice primed with clone	No. of mice with tumours
AKR	C27.2.3	0/5
AKR	C27.2.3 (mitomycin C)	4/5
(AKR × BALB/c)F1	C27.2.3	0/5
AKR	C27.2.2	0/5
AKR	C27.2.4	0/2
AKR	K36.16 (mitomycin C)	5/5

Mice were injected s.c. with 100,000 c27.2 transfected cells as indicated in Table 1. After 3–4 weeks, mice that did not show signs of tumours were given an additional dose (s.c.) of 100,000 K36.16 tumour cells. The number of mice with tumours was observed after 30 days. The K36.16 (mitomycin C) cells were treated with mitomycin C at 50 μg ml^{-1} 10^6 cells for 30 min at 37 °C, washed four times with PBS and subsequently injected s.c.

of the original K36.16 tumour cells and a clone of K36.16 tumour cells transformed with the vector pTCF alone, induced necrotic tumours within 20 days. However, inocula of 10^5 viable cells each of clones C27.2.1, C27.2.3 and C27.2.5 all failed to induce tumours in AKR and (AKR×BALB/c)F1 mice; these clones were able to induce tumours in all cases when the recipient AKR mice were irradiated (700 rad) before injection. Clones C27.2.2 and C27.2.4, which express relatively lower amounts of H-2K^k antigens (Table 1), were both able to induce tumours in some of the AKR mice. Interestingly, the diameters of the tumour masses which developed after inoculation of the latter clones were smaller (0.9–1.2 cm) and necrosis was absent even after 30 days. The oncogenicity of these transformed clones may thus be determined by: (1) the level of expression of the H-2K^k gene product in a particular transformant; (2) the ability of individual recipient mice to mount an efficient immune response against these inocula; and (3) the size of the inoculum needed to induce a tumour. When a higher dose of 5×10^6 viable cells was given, C27.1.1 and C27.2.3 were able to develop tumours in AKR mice (C27.2.5 was not tested). Conversely, clones C27.2.2 and C27.2.4 failed to induce tumours in AKR mice if a lower dose of 5×10^3 cells, instead of 10^5 cells, was given.

To prove that H-2K^k is the restriction element needed for the *in vivo* rejection of the transformed clones, C27.2.1 and C27.2.3 were first allowed to react separately with several different monoclonal antibodies (as shown by Table 2) before injection into the mice. The corresponding monoclonal antibodies were subsequently injected once every other day for 5 days. This procedure enabled the transformed clones to induce tumours in most AKR recipients (three out of five for C27.2.1, and six out of seven for C27.2.3; Table 2). Injection of the irrelevant anti-H-2K^b monoclonal antibody and culture medium were both ineffective.

To test whether the *H-2K^k* DNA-transformed clones can confer immunity, mice were injected with either the transformed clones, or mitomycin C-treated K36.16 tumour cells or C27.2.3 cells as indicated in Table 3. After 3 weeks, mice that did not show signs of tumours were again challenged with an additional 10^5 live K36.16 tumour cells. While only 3×10^3 K36.16 tumour cells always produced a tumour, the mice which had rejected the *H-2K^k*-transformed K36.16 clones were protected against a subsequent challenge of 10^5 live K36.16 tumour cells—this even included mice which had rejected the relatively low H-2K^k-expressing clone C27.2.4. Thus, once an efficient immune response was obtained, this protective immunity was as efficient as that elicited by the more immunogenic clones (for example, C27.2.3) against a subsequent challenge of the original K36.16 tumour cells. When the H-2K^k-positive C27.2.3 cells were prevented from dividing by treatment with mitomycin C before injection, their ability to induce protection against a second challenge of live K36.16 tumour cells was abrogated (Table 3).

These experiments raise several interesting questions. First, the importance of the expression of the H-2K^k product seems to be central to the host reponse to tumours. The examination of many AKR tumours showed that several of them had only a small amount of H-2K^k antigen on the surface[4]. These findings and those of others[8-11] suggest that the relative absence of the H-2K specificity provides such tumours with a selection advantage *in vivo*[12,13]. One might expect, as indeed is found, that the cell-mediated cytotoxicity of tumours which are H-2D-restricted would exhibit a relative absence of the *H-2D*-encoded products[14].

The results presented here strongly suggest that the selective loss of the H-2K^k restriction elements in K36.16 is caused by a 'switch-off' at the transcriptional level, rather than any changes in the amino acid sequences or any fault in the mechanism necessary for the insertion of the antigens in the cell membrane. Experiments to study the molecular basis of this suppression are in progress.

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Insertion of *N* regions into heavy-chain genes is correlated with expression of terminal deoxytransferase in B cells

Stephen V. Desiderio*, George D. Yancopoulos†, Michael Paskind*, Elise Thomas*‡, Michael A. Boss*‡, Nathaniel Landau*, Frederick W. Alt† & David Baltimore*

* Whitehead Institute for Biomedical Research, Cambridge, Massachusetts 02142, USA and Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA
† Columbia University, College of Physicians and Surgeons, Department of Biochemistry, New York, New York 10027, USA

The variable regions of immunoglobulin heavy chains are encoded in the germ line by three discrete DNA segments: V_H (variable) elements, *D* (diversity) elements and J_H (joining) elements. During the differentiation of B lymphocytes, individual segments from each group are brought together by recombination to form the complete V_HDJ_H variable region[1–8]. To understand these processes better, we have now isolated and sequenced molecular clones representing intermediates (DJ_H fusions) and final products (V_H-to-DJ_H joins) of heavy-chain gene rearrangement in two cell lines[9,10] that represent analogues of cells at early stages of B-lymphocyte differentiation[11–13]. Heavy-chain gene assembly in one cell line but not in the other is accompanied by the appearance of short nucleotide insertions at the recombinational junctions. The generation of such insertions is positively correlated with the expression of terminal deoxynucleotidyl transferase in these lines.

The two cell lines used in our study, 40E4 and 22D6, were produced by Abelson murine leukaemia virus (A-MuLV) transformation of BALB/c fetal liver at 13–14 and 17–19 days of gestation, respectively. These cell lines produce no detectable immunoglobulin[12]; they possess DJ_H rearrangements on both chromosomes and undergo further rearrangement during propagation[12–14]. Thus the 40E4 and 22D6 cell lines seem to represent the stage of differentiation during which lymphoid progenitor cells give rise to μ-positive pre-B cells.

Two clonal cell lines, 40E4-2 and 22D6-G, were isolated, carried in culture for about 25 generations and subcloned to generate sets of secondary clonal isolates. The clonal origin of these isolates was verified by analysis of the pattern of A-MuLV

‡ Present addresses: Tufts University, School of Veterinary Medicine, Boston, Massachusetts 02111, USA (E.T.); Celltech Ltd, Slough SL1 4DY, UK (M.A.B.).