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Modulation of MHC antigen expression by viruses and oncogenes

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It is becoming increasingly clear that regulation of MHC antigen expression by viruses and oncogenes, leading to either immune evasion or autoimmunity, is widespread and important in disease. At a recent meeting, which brought together workers interested in tumour immunology, viral infection and the MHC, a number of mechanisms for the regulation of MHC antigen expression were revealed and the importance of balanced expression of MHC gene products to effective immunity was underlined.*

The classical picture of major histocompatibility complex (MHC) antigen expression following infection is one of a dramatic rise, due primarily to an increase in production of interferons and other cytokines¹. This leads to enhanced recognition of infected cells by responding T cells, which recognize peptides of pathogen antigens in association with MHC antigens, and eradication of the infection. That this is not always the case is exemplified by hepatitis B virus (HBV) (G. Foster, London) which chronically infects some 200 million people worldwide. The ability of this virus to inhibit both alpha-interferon (IFN- α) production and the capacity of infected cells to respond to IFN are probably important in the maintenance of chronic infection. Treatment of chronic hepatitis with IFN- α can lead to acute hepatitis followed by recovery, presumably as a result of enhancement of MHC class I expression by IFN- α leading to activation of HBV-specific T cells. The ability of the virus to inhibit responses to IFN may explain why some patients do not respond to IFN therapy. Spontaneous recovery from HBV infection is normally preceded by an acute hepatitis and archival analysis of liver tissue of individuals who died of acute hepatitis demonstrates the production of IFN- α and elevated MHC class I antigen expression (A. Foulis, Glasgow). The ability of HBV to block the response of infected cells to IFN is due to the carboxy-terminal protein of the polymerase (G. Foster). Carboxy-terminal protein appears to act by inhibiting the activation of E factor for binding to interferon-stimulable response elements (ISRE)².

Another DNA virus that affects MHC class I antigen expression is

adenovirus 12. In this case the virus is known to decrease constitutive as well as IFN-induced MHC antigen expression (E. Blair, Leeds) and the effect of the Ad12 gene is, again, at the level of gene transcription. Both the 12 S and 13 S transcripts of the *E1a* gene cause a reduction in MHC class I expression (13 S is more efficient), suggesting that there is more than one mechanism for reduction of expression (R. Merrick, Birmingham). The immune evasion that results from downregulation of MHC class I antigen expression is important in producing the tumourigenic phenotype of Ad12-transformed cells³.

A virus from a different major virus group was used to illustrate further themes of viral downregulation of MHC antigen expression. Human cytomegalovirus (CMV, a member of the herpes virus group) encodes a protein, the H301 gene product, that binds to β_2 -microglobulin (β_2 -m) (J. Grundy, London). H301 facilitates binding to, and infection of, target cells, but

also blocks transport of β_2 -m, and hence of MHC class I antigens, to the cell surface. The result is a decrease in MHC antigen expression by a mechanism similar to that used by adenovirus 2: the E3-gene-encoded 19 kDa protein of Ad2 binds to MHC class I heavy chains and prevents transport to the cell surface, which in turn results in reduced recognition and reduced lysis of infected cells by cytotoxic T cells⁴.

Interestingly, the reduced MHC class I expression induced by CMV is also a signal for increased natural killer (NK) cell recognition and lysis (J. Grundy). This is reminiscent of the downregulation of class I by *myc* resulting in increased susceptibility to NK cell lysis (P. Schrier, Leiden; see below). Hence, the loss of MHC expression has both negative (for T cells) and positive (for NK cells) effects on the ability of the host to clear infected cells and the balance of these factors may determine the time and extent of recovery from infection. The increased susceptibility of CMV-infected cells to NK cell lysis is probably enhanced by an increase in expression of cell adhesion molecules, in particular lymphocyte function-associated molecule 3 (LFA-3) (CD58) and intercellular adhesion molecule 1 (ICAM-1) (CD54).

Adhesion molecules

The role of cell adhesion molecules was a theme taken up for Epstein-Barr virus (EBV) (M. Rowe, Birmingham). A number of cell surface antigens are upregulated on EBV-transformed lymphoblastoid cell lines, including cell adhesion molecules LFA-1 (CD11a/CD18), ICAM-1 (CD54) and LFA-3 (CD58). However, on EBV-positive Burkitt's lymphoma cells, LFA-3

*The meeting on Cytokines, MHC Expression and Disease was organized by the East and West Midlands Regional Groups of the British Society for Immunology and was held at the University of Warwick, UK on 19–20 June 1991.

Table 1. Effects of viruses on MHC expression

| Virus group | Virus | Gene responsible | Effects on MHC | | Refs |
|-----------------|------------------|------------------|----------------|----------|-------|
| | | | class I | class II | |
| Adenoviruses | Ad12 | E1A | ↓ | | 5 |
| | Ad2 | E3(19 K) | ↓ | | 4 |
| Hepadnaviruses | HBV | pol | ↓ | | 2 |
| Papilloma virus | HPV16 | E6/E7 | | ↕ | a |
| Herpes viruses | CMV | H301;? | ↓ | ↓ | 6,7 |
| | HSV 1 and 2 | | ↓ | | 8 |
| Pox viruses | Vaccinia virus | | ↓ | | 9 |
| | Ectromelia virus | | ↓ | | 10 |
| Rhabdovirus | VSV | | ↓ | | 11 |
| Flavivirus | West Nile virus | | ↑ | ↑ | 12 |
| Coronaviruses | JHM virus | | | ↑ | 13 |
| Paramyxoviruses | Measles | | ↑ | ↑ | 14 |
| Retroviruses | HIV | | ↓ | ↑ | 15,16 |
| | SIV | | | ↑ | 16 |
| | RaLV | | ↑ | | 17 |
| | RSV | <i>src?</i> | ↓ | ↓? | 18,19 |
| | Mo-MLV | | ↑ | | 20 |
| | Mo-MSV | <i>mos?</i> | ↑ | | 20 |
| | Mo-MLV/MSV | <i>mos?</i> | — | ↓ | b |
| | Ki-MLV | | ↓ | ↓ | 21,22 |
| | Ki-MSV | <i>v-Ki-ras</i> | ↓ | ↓ | 21,22 |
| | (Ha-MSV) | <i>v-Ha-ras</i> | — | ↓ | 23 |

^aI. Illingworth, Manchester; ^bJ. Maudsley, Warwick. ↑ increase in expression; ↓ decrease in expression; — no effect on MHC antigen expression. Ad12: adenovirus 12; Ad2: adenovirus 2; HBV: hepatitis B virus; HPV16: human papilloma virus 16; CMV: cytomegalovirus; HSV: herpes simplex virus; VSV: vesicular stomatitis virus; HIV: human immunodeficiency virus; SIV: simian immunodeficiency virus; RaLV: radiation leukaemia virus; RSV: Rous sarcoma virus; Mo-MLV: Moloney-murine leukaemia virus; Mo-MSV: Moloney-murine sarcoma virus; Ki-MLV: Kirsten-MLV; Ha-MSV: Harvey-MSV.

and ICAM-1 were downregulated and this probably underlies escape by tumour cells from virus-specific immune surveillance. The EBV gene product, BCRF1, unlike its host homologue interleukin 10 (IL-10), does not enhance MHC class II antigen expression on B cells, but, like IL-10, it does inhibit the production of IFN- γ by helper T 1 (T_H1) cells and, hence, indirectly inhibits MHC antigen induction.

A number of other viruses, summarized in Table 1, modulate MHC antigen expression. It can be concluded that viral regulation of host cell MHC antigen expression is a widespread phenomenon, found in a number of different viral groups including DNA and RNA viruses. Although the mechanisms involved are often unknown, some similarities are apparent. First, there are effects on transcription factors for MHC genes (Ad12 and HBV). Second, there are viral proteins that block transport of MHC antigens to the cell surface (Ad2 and CMV). Third, signalling via viral oncogenes

may lead to effects on transcription of MHC genes²³ (several retroviruses) similar to the effects of cellular oncogenes (J. Maudsley). It is interesting to note that those viruses that upregulate MHC antigen expression independently of IFN may gain some advantage by triggering an inappropriate autoimmune response.

Tumour cells

Transformation by viral oncogenes that downregulate either MHC class I or class II antigen expression (Ad12 E1a³; Ki-MuSV *v-Ki-ras*²⁴) results in the production of tumour cells that evade the immune system. What is the relative importance of class I versus class II and of the different genes within these regions? Transfection of the gross leukaemia-virus-infected AKR leukaemia cell line, K36.16, with either class I (H-2K^k) or class II (I-E^k) partially answers the question. Both antigens reduce tumourigenicity and both provide protection against future challenge with untransfected

cells (R. James, Leicester). However, H-2K^k-transfected cells are still tumourigenic at high cell numbers and, unlike I-E^k transfectants, do not provide any protection if given simultaneously with untransfected cells, suggesting that, while both are important, expression of class II antigens may be more effective at generating an immune response²⁵.

Locus-specific effects are suggested by the effect of *myc* oncogenes; in a melanoma model, *c-myc* downregulates HLA-B in a locus-specific manner (P. Schrier). This appears to occur via the activation of a repressor that binds to the enh b regions and results in increased susceptibility to NK cell lysis. Resistance to NK cell lysis can be restored by treatment with IFN or transfection with HLA-B, both of which restore expression of HLA-B to the cell surface.

The clinical picture of MHC antigen expression on tumour cells is one of great diversity (P. Schrier; A. Nouri, London; R. Angus, Bristol). Loss of all MHC class I expression or allele-specific loss can occur; focal loss, that is where cells in some areas of a tumour do not express class I whereas other regions do, has also been described. Lack of expression of MHC class I antigen correlates with an absence of tumour-infiltrating lymphocytes. This type of information may have prognostic value in that, for example, in melanoma a high expression of MHC class I indicates a good prognosis while a high expression of MHC class II (though nonfunctional) appears to indicate a poor prognosis. There are a variety of phenotypes with respect to the ability of the cells to respond normally to IFN- γ with increased MHC class I and class II antigen expression.

The size and complexity of the MHC was highlighted by J. Trowsdale (London). Although the role of interferons has been emphasized in this report, MHC antigen expression can be modulated by a wide range of cytokines, including tumour necrosis factor (TNF), IL-4, macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), transforming growth factor β (TGF- β), TGF- α and epidermal growth factor (EGF) (I. Todd,

Nottingham; F. Brennan, London; R. Darley, Warwick).

Conclusion

There is a growing recognition of the importance of the regulation of MHC antigen expression by viruses and tumour cells (especially by oncogenes), and its relevance to eradication of virus or tumour cells and development of autoimmune disease. Loss of MHC antigen expression from infected or transformed cells may be a strategy for survival and escape from the host immune system common to both viruses and tumour cells. However, the ideal levels of expression for the host are unclear since opposing factors, for example maximizing cytotoxic function and NK cell function, have to be balanced with the need to minimize tissue damage and induction of autoimmune reactions.

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