Induction of interferon by virus glycoprotein(s) in lymphoid cells through interaction with the cellular receptors via lectin-like action: An alternative interferon induction mechanism

Brief Review

Y. Ito
Department of Microbiology, Mie University School of Medicine, Mie, Japan
Accepted May 25, 1994

Summary. When animals and cells are infected with a virus, interferon is produced. Viral-nucleic acid is considered to be one of actual components for interferon induction. In addition, viral glycoproteins trigger interferon induction in lymphoid cells by membrane-membrane interaction via a lectin-like activity. A biological significance of lectin-like activity of viral glycoproteins is discussed.

Introduction

There are different levels of host defence mechanisms against viral infection. Viruses are unable to replicate on their own but must enter a host cells and used the host-cell macromolecular machinery and energy supplies to replicate. Therefore, reactions of hosts to virus-infected cells are more characteristic of anti-viral mechanisms than those to virus particles. Furthermore, since lymphoid cells have the principal role in anti-viral mechanisms of a host, analysis of interactions between lymphoid cells and infected cells expressing virus genes is one of the main subjects of research on anti-viral mechanisms. Interferon is also known as anti-viral factor and has been proven to play an important role in the anti-viral defence mechanism. We found that mouse spleen cells produced interferon through interaction with virus-infected cells in vitro and in vivo [29, 30]. Consequently, mechanisms by which interferon is induced should be clarified for better understanding of cellular and humoral events of the host defence mechanism against virus infection.

When animals and cells are infected with a virus, interferon is produced. A large number of interferon genes have been cloned and regulation mechanisms on interferon gene expression have been extensively investigated [55]. However, what component(s) of the virus triggers interferon induction remains unclarified.
By using temperature-sensitive mutants [4, 7, 48, 65], defective interfering particles [50], UV-inactivated viruses [10, 18, 53] or cell lines nonpermissive for virus replication, a close relationship between interferon induction and double-stranded RNA was revealed: for instance, the fact that prolonged ultraviolet irradiation disrupts the interferon-inducing ability of a virus suggests that the interferon induction is related to the function of virus nucleic acid. In addition, some of the cellular proteins induced by interferon such as 2–5 A synthetase and a protein kinase are specifically activated by double-stranded RNA, indicating that the interferon system is intimately related to double-stranded RNA. Furthermore, since the interferon inducing activity of a man-made double-stranded RNA, poly I: C, is found to be high potent, virus nucleic acid, especially double stranded RNA, is thought to be the actual component for interferon induction by viruses. This conception is drawn from the experimental results in virus-fibroblast cell systems, however. Whether the mechanism of virus-interferon production in lymphoid cells is identical with that in fibroblasts has not been elucidated. This nucleic acid mediated triggering pathway of interferon induction found in fibroblast is defined as a classical and major pathway. In this review, I propose that there is another, alternative, triggering pathway of interferon induction in lymphoid cells, in which virus glycoprotein(s) is involved in interferon induction.

**Lymphoid cells produce interferon through contact with virus-infected cells**

Interferon-α/β is found in the culture fluid of mouse spleen cells cocultivated with BHK-SV cells, a baby hamster kidney (BHK) cell line persistently infected with Sendai virus, but not in the medium with normal BHK cells [29, 57]. No interferon is detected when either L929 cells, a mouse fibroblast cell line, or mouse liver cells are cocultivated with BHK-SV cells [29]. These findings suggest that mouse lymphoid cells have a capacity to produce interferon-α/β when cocultivated with virus-infected cells, whereas nonlymphoid somatic cells lack this capacity [29]. Interposition of a Millipore filter between BHK-SV monolayer and mouse spleen cells, or pretreatment of BHK-SV cells with anti-SV antiserum, results in a blockage of interferon production [29]. These findings suggest that the following sequence is necessary for the mouse spleen cells cocultivated with BHK-SV cells to produce interferon: first, attachment of the spleen cells to BHK-SV cells and, second, recognition by the former of virus antigen(s) present on the surface of the latter. Therefore, interferon production in this system is considered to be initiated by membrane-membrane interaction between lymphoid cells and virus-infected cells [34–36]. The BHK-SV cell membrane is found to be an active inducer of interferon in mouse spleen cells, but not in L929 cells [29]. However, sonication of BHK-SV cells causes a loss of capacity for interferon induction, suggesting that some structural integrity of membranes is necessary for the interferon triggering [29]. When mice are inoculated intraperitoneally with BHK-SV cells, interferon is detected
in the peripheral blood [30]. However, sonication of BHK-SV cells also suppresses their in vivo interferon-inducing ability [30]. Naturally, uninfected BHK cells have no ability to induce interferon in mice [30]. These findings indicate that the interferon inducing mechanism by membrane-membrane interaction functions in vivo.

**Virus glycoproteins(s) induce(s) interferon in lymphoid cells**

Prolonged (15–30 min) UV-irradiation results in complete loss of the interferon-inducing ability of Sendai virus in mouse L929 cells [32]. In contrast to this result, Sendai virus irradiated for 2 h can induce interferon in mouse spleen cells as efficiently as untreated Sendai virus [32], showing that the actual inducer of interferon in mouse spleen cells is not viral nucleic acid, but some other viral component(s). When Sendai virus is treated with potassium periodate (0.125 M) at 37 °C for 1 h, infectivity for eggs and the hemolytic and neuraminidase activities of the virus are not detectable, but a considerable portion of its hemagglutinating activities is retained [32]. Although this inactivated Sendai virus shows no interferon-inducing ability in either L929 cells or mouse spleen cells, the binding of this inactivated virus to erythrocytes restores an interferon-inducing ability in mouse spleen cells but not in L929 cells [32]. These results indicate that hemolytic and neuraminidase activities are not essential for interferon and that hemagglutinating activity may be closely related to interferon induction in mouse spleen cells, although the presence of hemagglutinating activity alone is not sufficient for interferon induction in the cells.

La sota and Ulster strains of NDV possess uncleaved F0 glycoprotein and are characterized by an apparent lack of hemolytic and cell fusion activity and infectivity for tissue culture cells. These viruses cannot induce interferon in L929 cells, whereas a high titer of interferon is induced in mouse spleen cells [38]. Treatment of La sota and Ulster strains with trypsin results in cleavage of F protein and restores the hemolytic activity and infectivity [38]. An appearance of interferon-inducing activity in L929 cells correlates to the cleavage of Fo protein. In addition, HeLa cell-grown Sendai virus, which has a similar property to the La Sota strain of NDV, that is, it is characterized by its inability to penetrate into tissue culture cells, is found to stimulate interferon production in mouse spleen cells but not in L929 cells [32]. These findings also indicate that penetration of the virus into mouse spleen cells is not needed for interferon induction and simple contact of the viral glycoprotein with the cell surface appears to be sufficient for interferon triggering in mouse spleen cells. Furthermore, UV-irradiated influenza virus can induce interferon in mouse spleen cells but not in L929 cells [32]. Periodate treatment of influenza virus destroys its interferon-inducing ability in both L929 cells and mouse spleen cells, but binding of the inactivated virus to erythrocytes restores its interferon-inducing activity in mouse spleen cells but not in L929 cells [32]. These results suggest that the mechanism of interferon induction by influenza virus in mouse spleen cells is similar to that by paramyxoviruses.
Furthermore, when mouse spleen cells are incubated with Sendai virus envelope with virus glycoprotein(s) such as HN + F or HN + Fo, interferon-α/β is induced [33]. Even when mouse spleen cells are incubated with membranes containing HN glycoprotein alone, they produce interferon [33]. However, L929 cells have no capacity for interferon production in response to any stimulation of subviral components [33]. It is concluded from these findings that HN glycoprotein is the active component of Sendai virus responsible for interferon induction in mouse spleen cells and that viral RNA and F glycoprotein are not required. The results confirm that the interaction between HN glycoprotein and receptors on the cell surface triggers production of interferon in lymphoid cells. When mice are given an intravenous injection of isolated viral glycoproteins of purified Sendai virus, circulating interferon is detected [31], indicating that isolated viral glycoproteins per se have the ability to induce interferon in vivo.

Viral glycoprotein expressed in cell lines transfected with a cloned cDNA have an ability to induce interferon in lymphoid cells

To further determine whether the actual inducer of interferon in mouse spleen cells was HN glycoprotein, a recombinant plasmid was constructed by inserting the cDNA of the HN gene of parainfluenza virus type 4 (PIV-4A) into pcDL-SRα expression vector. Interferon activity cannot be detected in culture fluids of COS7 cells expressing HN protein (COS/HN cells), mouse spleen cells or COS7 cells [39]. Mouse spleen cells produced interferon when cocultured with COS/HN cells, but do not produce it when cocultured with COS7 cells transfected within or without the vector alone [39]. In addition, we established HeLa cell lines constitutively expressing PIV-4A HN (HeLa-4aHN cells) or F protein (HeLa-4aF cells). Mouse spleen cells produce interferon-α/β when cocultured with HeLa-4aHN cells, but not when cocultured with HeLa-4aF cells [39]. Therefore, it is concluded that HN glycoproteins of paramyxovirus on the cell surface are sufficient for interferon induction in mouse lymphoid cells.

Francis and Meltzer [16] have recently reported that HIV-1 virions and HIV-1 infected cells both induce interferon-α production in monocytes through interaction between envelope gp120 and cell surface CD4 molecule and that induction of interferon-α by HIV-1 does not require virus replication. Interferon-α was induced by (a) heat-inactivated HIV-1, (b) virions from 8E5 cells, a cell line that releases noninfectious HIV-1, (c) HIV-1-infected cells fixed in paraformaldehyde, and (d) T cell-tropic HIV-1 that binds to but does not infect monocytes, indicating a similarity to induction of interferon by paramyxovirus in mouse spleen cells. Furthermore, Capobianchi et al. [7a] have recently reported that recombinant glycoprotein 120 is a potent interferon inducer.

Involvement of cytoskeletal system in triggering interferon induction

When mouse spleen cells are cocultured with BHK-SV cells for 1–2 h, and further incubated without BHK-SV cells, interferon is produced, indicating that
short-period stimulation is sufficient for interferon triggering and the following process of interferon production progresses without further stimulation [34, 35]. On the contrary, interferon-γ-producing cells adhere closely to target antigen until interferon production begins. Mouse spleen cells stimulated by virus-infected cells cannot produce interferon in the presence of either cytochalasin or colchicine [34]. However, when cytochalasin or colchicine is added to culture fluid of mouse spleen cells 1 or 2 h, respectively, after mix-culture with BHK-SV cells, these drugs show no inhibitory effect [34]. When mouse spleen cells are cocultured for 2 h with BHK-SV cells in the presence of cytochalasin and then mouse spleen cells are further incubated without BHK-SV cells and cytochalasin, interferon production is not found, showing that interferon induction is not triggered in the presence of cytochalasin [35]. On the other hand, BHK-SV cells show adsorption of spleen cells to their surfaces in the presence of cytochalasin [35]. These findings show that cytochalasin does not inhibit the cell-to-cell contact between spleen cells and BHK-SV cells and therefore contacts alone of spleen cells to HN proteins are not sufficient, but active interactions between these membranes are necessary for triggering interferon production. Intriguingly, neither cytochalasin nor colchicine suppresses interferon production of L_929_ cells stimulated with NDV [34]. From these findings, early steps (triggering) of interferon production by lymphoid cells stimulated with viral glycoprotein progresses as follows: binding of viral glycoproteins to lymphoid cells → cytochalasin sensitive step (microfilament-related step) → colchicine sensitive step (microtubulus-related step) → further steps unrequired for stimulation by viral glycoprotein. Further identification of the signals transduced by the viral glycoproteins-cellular receptor interaction is an obvious future goal.

**Interferon induction by plant lectins in mouse spleen cells**

The interferon induction system, in which attachment of virus glycoprotein to the cellular receptor on the cell surface triggers interferon induction in lymphoid cells, is similar to a system in which plant lectins such as concanavalin A (Con-A) and phytohemagglutinin (PHA) stimulate lymphocytes and consequently induce interferon. Con-A and PHA are mitogenic lectins that have an ability to stimulate DNA synthesis and to induce interferon-γ [17, 37]. However, glycoprotein of Sendai virus shows no mitogenic activity under our experimental conditions, although its low mitogenicity is reported by other investigators [42]. Therefore, it is very likely that non-mitogenic lectins are able to induce interferon in mouse spleen cells. When twenty-two sorts of lectin are tested for interferon-inducing ability in mouse spleen cells, all the mitogenic lectins, Con-A, Succinylated-Con-A (s-Con-A), *Lens culinaris* type A (LcH-A), LcH-B and Poke weed mitogen (PWM), induced interferon-γ, and 5 out of 17 non-mitogenic lectins, wheat germ agglutinin (WGA), *Ulex europaeus* II (UEA-II), *Lotus tetragonolobus* seed lectin, *Salanum tuberosame* (STA), and *Bandeiraea simplicifolia* II (BS-II) prove to be capable of inducing interferon-β [37]. When WGA, a non-mitogenic lectin, is administered intraperitoneally to mice,
interferon is induced in the circulation [37]. From these results, it is found that interferon inducing ability is not limited to mitogenic lectins. It is conceivable that virus glycoproteins induce interferon, one of the cytokines, through their interaction with the cellular receptors via lectin-like action.

**Virus glycoproteins as viral lectins**

A lectin is a sugar-binding protein or glycoprotein of non-immune origin that agglutinates cells (most commonly erythrocytes) [20]. Because we think of a conception that virus glycoproteins have a lectin-like function, we try to arrange functions of viral glycoproteins from this point of view. Significantly, the glycoproteins of parainfluenza and influenza viruses used mainly in the above studies bind to sialyl-oligosaccharides [62].

**Hemagglutinating activity of viral (glyco)proteins**

Since Hirst [25] discovered the hemagglutinating activity of influenza virus in 1941, a large number of viruses have been found to have hemagglutinating activity and a large number of virus glycoproteins have proved to possess this activity. When cells are infected with a virus, viral hemagglutinin functions as a viral attachment factor and its binding to cellular receptors is the first step of infection. Lectins were discovered in the form of hemagglutinin originating from plants and the most universal property of lectins is hemagglutinating activity [20]. The finding that hemagglutinating activity is detected in a large number of virus glycoproteins indicates a certain similarity in the properties of virus glycoproteins and lectins.

**Important cellular components are used for virus receptors**

Important components on cell surface membranes such as major histocompatibility complexes (MHC) act as lectin receptors. And important constituents of host cell membranes have been found to be also used as viral receptors. For example, sialyl-oligosaccharides are receptors for parainfluenza and influenza viruses [62], human membrane cofactor protein (CD46) for measles virus [13, 58], MHC class I for Semliki Forest virus (SFV) [24], MHC class II for lactose dehydrogenase virus (LDH virus) [26], phosphatidylserine and phosphatidylinositol for vesicular stomatitis virus (VSV) [51], the CD4 for human immunodeficiency virus (HIV) [11, 43], the C3d receptor CR2 for Epstein-Barr virus [15, 59, 69], acetylcholin receptor for rabies virus [47], the intercellular adhesion molecule-1 (ICAM-1) for the major subgroup of human rhinoviruses [23, 67, 69], another member of the immunoglobulin superfamily for poliovirus [45, 54], a basic amino acid transporter for gibbon ape leukemia virus and feline leukemia virus [1, 40, 68, 70, 71], aminopeptidase N [13, 75] or a member of the carcinoembryonic antigen family of proteins for the coronavirus virus [14], a high-affinity laminin receptor for sindbis virus [72], \( \alpha \)2 subunit of human VLA-2 for echoviruses 1 and 8 [5], erythrocyte P antigen for B19 Parvovirus
Viral glycoproteins and interferon induction

[6], and CD13 (human aminopeptidase N) for cytomegalovirus [66]. Most of these virus receptors are involved in cell-cell adherence and in cell-cell recognition. Therefore, it is highly probable that binding of viral (glyco)protein to the cellular receptor influences some cell functions.

**Suppression of cellular macromolecular synthesis by virus glycoproteins**

Infection with viruses often results in shut-off of cellular macromolecular syntheses, although degrees of the suppression are varied. In some cases (for example, reovirus [64], VSV [52], mumps virus [74] infection), attachment of virus glycoproteins to cellular receptors leads to suppression of cellular macromolecular synthesis. Intriguingly, binding of HIV-gp 160 to CD4 molecule suppresses various cellular functions [8, 49, 73]. These findings show that inhibition of the cellular macromolecular syntheses is mediated through an interaction at the cell surface.

**Mitogenic activity of virus glycoprotein**

In 1960 Nowell [60] found that when human lymphocytes were incubated with phytohemagglutinin (PHA), a lectin originating from *Phaseolus vulgaris*, lymphocytes transformed into lymphoblastoid cells. This mitogenic function is the most noteworthy property of lectins. Recently, some virus glycoproteins have been found to show a mitogenic effect, although the activity is rather weaker than that of plant lectins [2, 3, 19, 21, 22, 41, 42, 46, 56, 63]. HN glycoprotein of Sendai virus used in our studies shows weak mitogenic effect under some conditions [42]. Therefore, an interaction between viral virus glycoproteins and virus receptors of host cells at the cell surface can induce or enhance cellular macromolecular syntheses. The finding that some viral glycoproteins possess mitogenic activity is a basis of evidence that virus glycoprotein can be considered as a viral-lectin.

As demonstrated above, viral glycoproteins (cell attachment proteins) have a viral lectin-like property. In other words, some viral glycoproteins are simply lectins, so it is not surprising that stimulation of lymphocytes with the viral lectin triggers production of interferon, one of the cytokines.

**Interferon induction by other cell-to-cell interactions or by cytokines**

Interferon is induced by interaction between NK and tumor cells or by mixed-lymphocyte culture. This interferon induction is also triggered by the membrane-membrane interactions. Recently, some cytokines such as tumor necrosis factor (TNF) and platelet derived growth factor (PDGF) have been found to induce interferon [44, 61]. Furthermore, interferon *per se* has been reported to induce interferon [44, 61]. Binding of the cytokines to the cellular receptors triggers interferon induction. These findings show that interferon triggering mechanisms unrelated to double-stranded RNA function particularly in lymphoid cell systems.
What does interferon induction by viral glycoproteins mean?

In this review, I show clearly that there are two interferon induction systems in virus infection: one is that viral-nucleic acid is involved in interferon induction, and the other is that viral glycoproteins trigger interferon induction by the membrane-membrane interaction via a lectin-like activity. Some kinds of viral glycoproteins can be regarded as viral lectins and their attachment to the cellular receptors influences cellular functions, for instance, suppression or enhancement (induction) of cellular macromolecular synthesis and therefore stimulation of cellular gene expressions resulting in production of cellular factors including interferon. Cell-to-cell interactions are mediated by receptor-ligand (counter-receptor) system found on the cell surface membrane, that is, a membrane-membrane interaction. Most virus receptors are considered to be adhesion or adhesion-related molecules, and consequently interactions between lymphoid cells and virus-infected cells are similar to the cell to cell interactions mediated by adhesion molecules. Judging from this point of view, the recently reported embryonic interferon (interferon-c0) [9, 27] that is thought to be induced during differentiation and to play important roles in embryogenesis intrigues us. Although interferon was first discovered as an antiviral substance [28], it has since been shown to affect a wide variety of cellular functions such as cell-multiplication-inhibitory activity, immune regulatory function, and the enhancing activity of multiple cellular genes. Therefore, it is inferred that interferon may be originally regulatory-molecules that are induced by interaction between different cells and function in differentiation and maturation.

When we first discovered an interferon induction system triggered by virus glycoprotein in lymphoid cells [29], the meaning of this phenomenon remained obscure. However, when interferons and the interferon induction are interpreted as described here, the interferon induction triggered by viral glycoprotein can be categorized within general biological phenomena, though it appears puzzling at first sight.

References

1. Ablation LM, Testing L, Scanned D, Cunningham JM (1989) A putative murine ecotropic retrovirus receptor gene encodes a multiple membrane-spanning protein and confers susceptibility to virus infection. Cell 57: 659–666
2. Anders EM, Scalzo AA, Rogers GN, White DO (1986) Relationship between mitogenic activity of influenza viruses and the receptor-binding specificity of their hemagglutinin molecules. J Virol 60: 476–482
3. Armstrong RB, Butchko GM, Kiley SC, Phelan MA, Ennis FA (1981) Mitogenicity of influenza hemagglutinin glycoproteins and influenza viruses bearing H2-hemagglutinin. Infect Immun 34: 140–143
4. Atkins GJ, Johnston MD, Westmacott L, Burke DC (1974) Induction of interferon in chick cells by temperature-sensitive mutants of Sindbis virus. J Gen Virol 25: 381–390
5. Bergelson JM, John N St, Kawaguchi S, Chan M, Stubdal H, Modlin J, Finberg RW (1993) Infection by echoviruses 1 and 8 depends on the α2 subunit of human VLA-2. J Virol 67: 6847–6852
6. Brown KE, Anderson SM, Young NS (1993) Erythrocyte P antigen: cellular receptor for B19 parvovirus. Science 262: 114–117
7. Burke DC, Skehel JJ, Low M (1967) Interferon production and viral ribonucleic acid synthesis in chick embryo cells. J Gen Virol 1: 235–237
7a. Capobianchi M, Ansel H, Ameglio F, Paganelli P, Pizzoli P, Dianzani F (1992) Recombinant glycoprotein 120 of human immunodeficiency virus is a potent interferon inducer. AIDS Res Hum Retroviruses 8: 575–585
8. Chanh TC, Kennedy RC, Kanda P (1988) Synthetic peptides homologous to HIV transmembrane glycoprotein suppresses normal human lymphocyte blastogenic response. Cell Immunol 111: 77–86
9. Charpigny G, Reinaud P, Huet J-C, Guillomot M, Charlier M, Pernollet J-C, Martal J (1988) High homology between a trophoblastic protein (trophoblastin) isolated from ovine embryo and alpha-interferons. FEBS Lett 228: 12–16
10. Clavell LA, Bratt MA (1971) Relationship between the ribonucleic acid synthesizing capacity of ultraviolet-irradiated Newcastle disease virus and its ability to induce interferon. J Virol 8: 500–508
11. Dalgleish AG, Beverley PCL, Clapman PR, Crawford DH, Greaves MF, Weiss RA (1984) The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. Nature 312: 763–767
12. Delmas B, Gelfi J, L’Haridon R, Vogel LK, Sjostrom H, Noren O, Laude H (1992) Aminopeptidase N is a major receptor for the enteropathogenic coronavirus TGEV. Nature 357: 417–420
13. Dorig RE, Marcil A, Chopra A, Richardson CD (1993) The human CD46 molecule is a receptor for measles virus (Edomonston strain). Cell 75: 295–305
14. Dveksler JK, Pensiero MN, Cardellichio CB, Williams RK, Jiang G-S, Holmes KV, Dieffen Bach CW (1991) Cloning of the mouse hepatitis virus (MHV) receptor: expression in human and hamster cell lines confers susceptibility to MHV. J Virol 65: 6881–6891
15. Fingeroth JD, Weiss JJ, Tedder TF, Strominger JL, Biro PA, Fearon DT (1984) Epstein-Barr virus receptor of human B lymphocytes is the C3d receptor CR2. Proc Natl Acad Sci USA 81: 4510–4514
16. Francie ML, Meltzer MS (1993) Induction of IFN-a by HIV-1 in monocyte-enriched PBMC requires gp120-CD4 interaction but not virus replication. J Immunol 151: 2208–2216
17. Friedman RM, Cooper HL (1967) Stimulation of interferon production in human lymphocytes by mitogens. PSEBM 125: 901–905
18. Gandhi SS, Burk DC (1970) Virus RNA synthesis by ultraviolet-irradiated Newcastle disease virus and interferon production. J Gen Virol 9: 97–99
19. Gazzolo L, Dodon MD (1987) Direct activation of resting T lymphocytes by human T-lymphotropic virus type I. Nature 326: 714–717
20. Goldstein IJ, Hughes RC, Monsigny M, Osawa T, Sharon N (1980) What should be called a lectin? Nature 285: 66
21. Goodman-Snitkoff GW, Mannino RJ, McSharry JJ (1981) The glycoprotein isolated from vesicular stomatitis virus is mitogenic for mouse B lymphocytes. J Exp Med 153: 1489–1502
22. Goodman-Snitkoff GW, McSharry JJ (1982) Mitogenic activity of Sindbis virus and it's isolated glycoproteins. Infect Immun 38: 1242–1248
23. Greve JM, Davis G, Meyer AM, Forte CP, Yost SC, Marlor CW, Kamarck ME, McClelland A (1989) The major human rhinovirus receptor is ICAM-1. Cell 56: 839–847
24. Helenius A, Morein B, Fries E, Simons K, Robinson P, Schirrmacher V, Terhorst C, Strominger J (1978) Human (HLA-A and HLA-B) and murine (H-2K and H-2D) histocompatibility antigens are cell surface receptors for semliki forest virus. Proc Natl Acad Sci USA 75: 3846–3850
25. Hirsh GK (1941) Adsorption of influenza hemagglutinin and virus by red blood cells. J Exp Med 76: 196–209
26. Inada T, Mims CA (1984) Mouse Ia antigens are receptors for lactate dehydrogenase virus. Nature 309: 59–61
27. Imakawa K, Anthony RV, Kazemi M, Marotti KR, Polites HG, Roberts M (1987) Interferon-like substance of ovine trophoblast protein secreted by embryonic trophectoderm. Nature 330: 377–379
28. Isaacs A, Lindenmann J (1957) Virus interference: I. The interferon. Proc R Soc London Ser B 147: 258–263
29. Ito Y, Kimura Y, Nagata I, Kunii A (1974) Production of interferon-like substance by mouse spleen cells through contact with BHK cells persistently infected with HVJ. Virology 60: 73–84
30. Ito Y, Nishiyama Y, Shimokata K, Kimura Y, Nagata I, Shimizu K, Kunii A (1975) Interferon induction in mice by BHK cells persistently infected with HVJ. J Gen Virol 27: 93–95
31. Ito Y, Nishiyama Y, Shimokata K, Takeyama H, Kunii A (1978) Active component of HVJ (Sendai virus) for interferon induction in mice. Nature 274: 801–802
32. Ito Y, Nishiyama Y, Shimokata K, Nagata I, Takeyama H, Kunii A (1978) Mechanism of interferon induction in mouse spleen cells stimulated with HVJ. Virology 88: 128–137
33. Ito Y, Hosaka Y (1983) Component(s) of Sendai virus that can induce interferon in mouse spleen cells. Infect Immun 39: 1019–1023
34. Ito Y, Nishiyama Y, Shimokata K, Kimura Y, Nagata I, Kunii A (1976) The effects of cytochalasin and colchicine on interferon production. J Gen Virol 33: 1–5
35. Ito Y, Nishiyama Y, Shimokata K, Takeyama H, Kunii A (1978) Suppression of interferon production in mouse spleen cells by cytochalasin D. J Gen Virol 41: 129–134
36. Ito Y, Nishiyama Y, Shimokata K, Kimura Y, Nagata I, Kunii A (1976) Interferon-producing capacity of germfree mice. Infect Immun 13: 332–336
37. Ito Y, Tsurudome M, Yamada A, Hishiyama M (1984) Interferon induction in mouse spleen cells by mitogenic and nonmitogenic lectins. J Immunol 132: 2440–2444
38. Ito Y, Nagai Y, Maeno K (1982) Interferon production in mouse spleen cells and mouse fibroblasts (L cells) stimulated by various strains of Newcastle disease virus. J Gen Virol 62: 349–352
39. Ito Y, Bando H, Komada H, Tsurudome M, Nishio M, Kawano M, Matsumura H, Kusagawa S, Yuasa T, Ohta H (1993) HN proteins of human parainfluenza type 4A virus expressed in cell lines transfected with a cloned cDNA have an ability to induce interferon in mouse spleen cells. J Gen Virol 75: 567–572
40. Kim JW, Close EL, Albritton LM, Cunningham JM (1991) Transport of cationic amino acids by the mouse ecotropic retrovirus receptor. Nature 352: 5244–5249
41. Kirchner H, Darai G, Hirt M, Keyssner K, Munk K (1978) In vitro mitogenic stimulation of murine spleen cells by herpes simplex virus. J Immunol 120: 641–645
42. Kizaka S, Goodman-Snitzoff G, McSharry JJ (1983) Sendai virus glycoproteins are T cell-dependent B cell mitogens. Infect Immun 40: 592–600
43. Klazmann D, Champagne E, Chamaret S, Gruest J, Guetard T, Hercend T, Gluckman JC, Montagnier L (1984) T-lymphocytic T4 molecule behaves as the receptor for human retrovirus LAV. Nature 312: 767–768
Viral glycoproteins and interferon induction

44. Kohase M, May LT, Tamm L, Vilecek J, Segal PB (1987) A cytokine network in human diploid fibroblasts: Interaction of β-interferons, tumor necrosis factor, platelet-derived growth factor, and interleukin-1. Mol Cell Biol 7: 273–280

45. Koike S, Horie H, Ise I, Yoshida M, Iizuka N, Takeuchi K, Takegami T, Nomoto A (1990) The poliovirus receptor protein is produced both as membrane-bound and secreted forms. EMBO J 9: 3217–3224

46. Kornfeld H, Cruikshank WW, Pyles SW, Berman JS, Center DM (1988) Lymphocyte activation by HIV-1 envelope glycoprotein. Nature 335: 445–448

47. Lentz TL, Burrage TG, Smith AL, Crick J, Tignor GH (1982) Is the acetylcholine receptor a rabies virus receptor? Science 215: 182–184

48. Lockhart RZ, Bayliss NL, Toy ST, Yin FH (1968) Viral events necessary for the induction of interferon in chick embryo cells. J Gen Virol 2: 962–965

49. Mann DL, Lasane F, Popovic M, Arthur LO, Robey WG, Blattner WA, Newman MJ (1987) HTLV-III large envelope protein (gp 120) suppresses PHA-induced lymphocyte blastogenesis. J Immunol 138: 2640–2644

50. Marcus PI, Sekellick MJ (1977) Defective interfering particles with covalently linked [+ / −] RNA induce interferon. Nature 266: 815–819

51. Mastromarino P, Conti C, Goldoni P, Huthecoer B, Orsi N (1987) Characterization of membrane components of the erythrocyte involved in vesicular stomatitis virus attachment and fusion at acidic pH. J Gen Virol 68: 2359–2369

52. McSharry JJ, Choppin PW (1978) Biological properties of the VSV glycoprotein I. Effects of the isolated glycoprotein on host macromolecular synthesis. Virology 84: 172–182

53. Meager A, Burke DC (1972) Production of interferon by ultraviolet radiation inactivated Newcastle disease virus. Nature 235: 280–282

54. Mendelsohn CL, Wimmer E, Racaniello VR (1989) Cellular receptor for poliovirus: molecular cloning, nucleotide sequence, and expression of a new member of the immunoglobulin superfamily. Cell 56: 855–865

55. Miyamoto M, Fujita T, Kimura Y, Maruyama M, Harada H, Sudo Y, Miyata T, Taniguchi T (1988) Regulated expression of a gene encoding a nuclear factor, IRF-1, that specifically binds to IFN-β gene regulatory elements. Cell 54: 903–913

56. Mochizuki D, Hedrick S, Watson J, Kingsbury DT (1977) The interaction of herpes simplex virus with murine lymphocytes I. Mitogenic properties of herpes simplex virus. J Exp Med 146: 1500–1510

57. Nagata I, Kimura Y, Ito Y, Tanaka T (1973) Temperature-sensitive phenomenon of viral maturation observed in BHK cells persistently infected with HVJ. Virology 49: 453–461

58. Nanniche D, Varior-Krishnan G, Cervoni F, Wild TF, Rossi B, Raboudin-Combe C, Gerlier D (1993) Human membrane cofactor protein (CD46) acts as a cellular receptor for measles virus. J Virol 67: 6025–6032

59. Nemerow GR, Wolpert R, McNaughton ME, Cooper NR (1985) Identification and characterization of the Epstein-Barr virus receptor on human B lymphocytes and its relationship to the C3d complement receptor (CR2). J Virol 55: 347–351

60. Nowell PC (1960) Phytohaemagglutinin: An initiator of mitosis in cultures of normal human leukocytes. Cancer Res 20: 462–466

61. Onozaki K, Urawa H, Tamatani T, Iwamura Y, Hashimoto T, Baba T, Suzuki H, Yamada M, Yamamoto S, Oppenheim JJ, Matsushima K (1988) Synergistic interactions of interleukin 1 interferon-β, tumor necrosis factor in terminally differentiating a mouse myeloid leukemia cell line (M1). J immunol 140: 112–119
62. Paulson JC, Sadler JE, Hill RL (1979) Restoration of specific myxovirus receptors to asialoerythrocytes by incorporation of sialic acid with pure sialytransferases. J Biol Chem 254: 2120–2124

63. Poumbourios P, Anders EM, Scalzo AA, White DO, Hampson AW, Jackson DC (1987) Direct role of viral hemagglutinin in B-cell mitogenesis by influenza viruses. J Virol 61: 214–217

64. Sharpe AH, Fields BN (1981) Reovirus inhibition of cellular DNA synthesis: Role of the S1 gene. J Virol 38: 389–392

65. Skehel J, Burke DC (1968) A temperature-sensitive event in interferon production. J Gen Virol 3: 191–199

66. Soderberg C, Giugni, TD, Zaia JA, Larsson S, Wahlberg JM, Moller E (1993) CD13 (human aminopeptidase N) mediated human cytomegalovirus infection. J Virol 67: 6576–6585

67. Staunton DE, Merluzzi VJ, Rothlein R, Barton R, Marlin SD, Springer TA (1989) A cell adhesion molecule, ICAM-1, is the major surface receptor for rhinoviruses. Cell 56: 849–853

68. Takeuchi Y, Vile RG, Simpson G, O’Hara B, Collins MKL, Weiss RA (1992) Feline leukemia virus subgroup B uses the same cell surface receptor as gibbon ape leukemia virus. J Virol 66: 1219–1222

69. Tomassini JE, Graham D, DeWitt CM, Lineberger DW, Rodkey JA, Colomno RJ (1989) cDNA cloning reveals that the major group rhinovirus receptor on HeLa cells is intracellular adhesion molecule 1. Proc Natl Acad Sci USA 86: 4907–4911

70. Vile RG, Weiss RA (1991) Virus receptors as permeases. Nature 352: 666–667

71. Wang H, Kavanaugh MP, North RA, Kabat D (1991) Cell-surface receptor for ecotropic murine retroviruses is a basic amino-acid transporter. Nature 352: 729–731

72. Wang K-H, Kuhn RJ, Strauss EG, Ou S, Strauss JH (1992) High-affinity Laminin receptor is a receptor for Sindbis virus in mammalian cells. J Virol 66: 4992–5001

73. Weinhold KJ, Lyerly HK, Stanley SD, Austin AA, Matthews TJ, Bolognesi DP (1989) HIV-1 gp120 mediated immune suppression and lymphocyte destruction in the absence of viral infection. J Immunol 142: 3091–3097

74. Yamada A, Tsurudome M, Hishiyama M, Ito Y (1984) Inhibition of host cellular ribonucleic acid synthesis by glycoprotein of mumps virus. Virology 135: 299–307

75. Yeager CL, Ashmun RA, Williams RK, Cardellichio CB, Shapiro LH, Look AT, Holmes KV (1992) Human aminopeptidase N is a receptor for human coronavirus 229E. Nature 357: 420–422.

76. Yefenof E, Klein G, Jondal M, Oldstone MBA (1976) Two color immunofluorescence studies on the association between EBV receptor and complement receptor on the surface of lymphoid cell lines. Int J Cancer 17: 693–700

Authors’ address: Dr. Y. Ito, Department of Microbiology, Mie University School of Medicine, 2–174 Edobashi, Tsu-Shi, Mie 514, Japan.

Received October 22, 1993