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

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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 L_{929} 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 L_{929} 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 L_{929} 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 L_{929} 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 L_{929} 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 Fo 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 L_{929} 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 L_{929} 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 L_{929} 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 L_{929} cells [32]. Periodate treatment of influenza virus destroys its interferon-inducing ability in both L_{929} 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 L_{929} 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, L$_{929}$ 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 cytochalsin 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 europeus* 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], $\alpha2$ subunit of human VLA-2 for echoviruses 1 and 8 [5], erythrocyte P antigen for B19 Parvovirus

[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-ω) [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.

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