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VIRUSES AS NONSPECIFIC MODULATORS OF IMMUNOLOGICAL REACTIVITY

B. F. SEMENOV

Institute of Poliomyelitis and Viral Encephalitides, U.S.S.R. Academy of Medical Sciences, 142782 Moscow, U.S.S.R.

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Summary. — As shown experimentally and by examination of patients, numerous DNA and RNA viruses induce transitory nonspecific changes in the immune response of the host to heterologous antigens. Attenuation does not affect this property of the parent strains. Nonspecific immunomodulation is connected with disturbed functions of B and T lymphocytes, macrophages and haemopoietic cells. The actual mechanisms of immunomodulation differ in different infections.

Key words: virus infections; immunomodulation; immunological reactivity; lymphocytes; macrophages; heterologous antigens

Numerous data have accumulated showing that viruses are able to induce nonspecific modulation of the immunological reactivity (IR) of the host, depressing or enhancing the immune response to heterologous antigens (Notkins *et al.*, 1970; Virelizier, 1975; Semenov *et al.*, 1977).

This phenomenon was first described in 1908 by von Pirquet who observed a transitory disappearance of delayed type skin hypersensitivity to tuberculin in measles patients. But intensive studies on nonspecific modulation of the IR in other virus infections have been carried out only in the second half of the 20th century.

As shown in Table 1, over 40 viruses belonging to at least 13 families induce nonspecific changes of the immune response to heterologous antigens.

The actual forms of nonspecific modulation in viral infections of men and animals vary greatly.

Many viruses, e. g. lymphocytic choriomeningitis (LCM) (Oldstone *et al.*, 1973), tick-borne encephalitis (TBE), yellow fever (Semenov and Vargin, 1978), dengue 2 (Semenov and Vargin, 1978; Tandon *et al.*, 1979), Visna (Svennerholm *et al.*, 1978), mouse hepatitis (Tamura *et al.*, 1979) and mouse cytomegalovirus (Tinghitella and Booss, 1979) viruses, depress (less frequently enhance) the humoral response of the host to sheep erythrocytes and other heterologous antigens.

Table 1. Taxonomic groups of viruses which cause nonspecific modulation of the IR in experimental and human infections

Adenoviridae	Adenoviruses of man (various serotypes), monkeys and birds
Arenaviridae	Lymphocytic choriomeningitis and Junín viruses
Bunyaviridae	Ťahyňa virus
Coronaviridae	Mouse hepatitis virus
Herpesviridae	Human and mouse cytomegaloviruses, Epstein-Barr, herpes simplex, turkey herpesvirus, Marek's disease and varicella-zoster viruses
Orthomyxoviridae	Human influenza virus
Papovaviridae	SV 40
Paramyxoviridae	Measles, mumps, Newcastle disease and distemper viruses
Picornaviridae	Coxsackieviruses A and B, enterovirus type 71, polioviruses, rhinoviruses
Retroviridae	Visna, Friend leukaemia, Moloney leukaemia, Rauscher leukaemia and feline leukaemia viruses
Rhabdoviridae	Rabies and vesicular stomatitis viruses
Togaviridae	Tick-borne encephalitis, dengue, Langat, yellow fever (vaccine virus), rubella and lactic dehydrogenase viruses
Ungrouped viruses	Aleutian mink disease, hepatitis B and Gumbargo disease viruses

Compiled from materials reviewed by Semenov *et al.* (1977) and papers quoted in the present review.

Representatives of different taxonomic groups, including influenza (Massanari, 1979), rubella (Ueda *et al.*, 1979), Epstein-Barr (Richter *et al.*, 1979) and Visna (Svennerholm *el al.*, 1978) viruses have been reported to change the delayed type hypersensitivity to bacterial and fungal antigens and chemicals.

Experimental infections with LCM (Lehmann-Grube *el al.*, 1972), Newcastle disease (Woodruff and Woodruff, 1974) or mouse cytomegalovirus (Howard and Najarian, 1974) prolong the survival of allogenic transplants.

Street rabies virus and wild poliovirus suppress the development of cellular immunity in mice to influenza and coxsackie B3 viruses, respectively (Wiktor *et al.*, 1977; Khozinsky *et al.*, 1978).

Based on reports in the literature and own data the following features of nonspecific modulation of the immune response in viral infections can be outlined:

1. Nonspecific changes of the IR appear 2-96 hr after inoculation and persist for several days up to 2-3 weeks (Notkins *et al.*, 1970; Vargin and Semenov, 1976; Svennerholm *el al.*, 1978; Massanari, 1979).

2. In the course of infection, qualitative changes of the immune response to heterologous antigens are possible. Immunosuppression may be replaced by an adjuvant effect and vice versa (Okunewick *el al.*, 1978; Semenov and Vargin, 1978; Nazimov and Shuratov, 1979; Tinghitella and Booss, 1979).

3. The actual changes (enhancement or depression) of the nonspecific IR in viral infections depend on the time interval between the administration of virus and heterologous antigen as well as on the sequence of their admini-

stration (Notkins *et al.*, 1970; Svennerholm *et al.*, 1978; Semenov and Vargin, 1978); on the dose of inoculum (Howard and Najarian, 1974; Dunmire *et al.*, 1975; Svennerholm *et al.*, 1978); on the genetic basis (Oldstone *et al.*, 1973; Okunewick *et al.*, 1978); and on the species-specific properties of the host (Kavetsky *et al.*, 1977).

4. The nonspecific immunomodulating effect of viruses is not universal. Depression of the immune response to one antigen usually is accompanied by a normal response to other antigens (Oldstone *et al.*, 1973; Munyer *et al.*, 1975).

5. Nonspecific modulation of the IR proceeds on the background of developing antiviral antiviral immunity (Cappel, 1976; Ganquly *et al.*, 1976).

6. Attenuation usually does not change the ability of viruses to modify the IR (Berkovitch and Starr, 1966; Kantzler *et al.*, 1974; Munyer *et al.*, 1975; Ganquly *et al.*, 1976). Attenuated strains of rabies virus are an exception (Wiktor *et al.*, 1977).

7. Inactivation of virus infectivity usually is associated with a loss of the ability to modify the immune response to heterologous antigens (Cappel, 1976; Svennerholm *et al.*, 1978; Massanari, 1979). But in other instances administration of inactivated virus to mice (Semenov and Vargin, 1978) or man (Hooren, 1976) causes temporary immunosuppression. In several instances the immunomodulating activity is connected with concrete structures of the virion (Mathes *et al.*, 1979).

A general theory explaining the mechanisms of the nonspecific modulation of the IR in viral infections has not yet been proposed. But numerous data make it possible to conclude that the phenomenon is based on changes in various functions of B and T lymphocytes, cells of the mononuclear phagocyte system or cells of the haemopoietic series.

Reports on the response to mitogens of B and (or) T lymphocytes of infected animals or patients are rather contradictory. This fact has been stressed in the respective surveys concerning influenza (Dolin *et al.*, 1977), measles (Semenov *et al.*, 1977), rubella (Maller and Sören, 1977) and herpes simplex (Araby *et al.*, 1978). The discrepancies have been explained by the fact that the studies were carried out on different clinical forms and at various intervals (Jacobs and Cole, 1976; Kauffman *el al.*, 1976) and with the use of different methodical approaches (Dolin *et al.*, 1977).

Changes in the number of circulating lymphocytes have been described in men in TBE (Semenov, 1979), viral hepatitis B, influenza and multiple sclerosis (Santolli *et al.*, 1978). Disturbed recirculation of lymphocytes in animals was demonstrated experimentally with influenza and Newcastle disease viruses (Woodruff and Woodruff, 1976) and lactic dehydrogenase virus (Mongini and Rosenberg, 1978).

Depression of the primary recognition by T lymphocytes of target cells in vitro and in vivo was shown in experiments on mouse cytomegalovirus (Kelsey *et al.*, 1978), feline leukaemia (Mathes *et al.*, 1979), TBE, Langat, dengue 2 and vaccine strain of yellow fever virus (Semenov, 1979).

Modulation of the activity of T-helpers, but not T-suppressors, was described in mouse thymic infection (Morse *et al.*, 1976; Cross *et al.*, 1977). TBE and Langat (Semenov, 1979) and dengue 2 (Semenov, 1979; Tandon *et al.*, 1979) were shown to induce in mice the development of nonspecific T-suppresors, suppressing the development of the local graft versus host reaction.

Suppression of lymphocyte response to mitogens in experiments with poliovirus (van Loon *et al.*, 1979), LCM (Jacobs and Cole, 1976) and influenza (Roberts and Steigbigel, 1978) viruses has been connected with damaged function of macrophages. On the other hand the inhibitory action of measles, rubella and lactic dehydrogenase viruses on lymphocyte transformation proved to be independent of macrophage activity (Lucas *et al.*, 1978; Vesikari and Buimovici-Klein, 1975; Michaelides and Simms, 1979). It has been assumed that infected macrophages release enzymes causing destruction of immunocompetent cells (Virelizier, 1975). According to Allison (1978) disturbed interferon synthesis along with activation of macrophages causes suppression of the immune response to sheep erythrocytes and a response of lymphocytes to mitogens. But Lucas *et al.* (1978) showed that the immunomodulating action of measles is not connected with extracellular interferon.

Disturbances of several functions (chemotaxis, chemokinesis) of cells of the myelopoietic series were described in herpes simplex (Rabson *et al.*, 1977) and influenza (Ruutu, 1977) virus infections.

As mentioned above, nonspecific modulation of the IR has been found in many viral human infections. One of the consequences of the disturbed immune regulation can be a more severe course of concomitant disease or the development of increased susceptibility to subsequent infection of viral or bacterial aetiology.

There have been numerous reports on the aggravation of tuberculosis in acute measles infection (Semenov *et al.*, 1977) but absence of such an effect was also reported (Dunmire *et al.*, 1975).

The development of bacterial pneumonia in severe forms of influenza in men has been explained by a suppression of chemotaxis and phagocytic activity of cells of the mononuclear phagocyte system and of haemopoietic cells (Pike *el al.*, 1977; Ruutu, 1977).

Semenov and Vargin (1978) described activation of asymptomatic Langat virus infection in mice infected with Tahyňa virus which possesses a marked immunosuppressing activity.

It has been suggested that virus-induced temporary immunosuppression could support the development of neoplastic disease (Kantzler *et al.*, 1974).

In conclusion, the following facts should be stressed. All viruses pathogenic for man and animals are nonspecific modulators of the IR of the host. Apparently, changes in the immune response to heterologous antigens lend support to homeostasis of the organism in critical conditions of infection, preventing it from unnecessary antigenic loads. But disturbances in immune regulation may become a trigger mechanism of immunopathological processes and support the development of concomitant infections. Consequently, the

evaluation of the IR of patients and means of its correction should be taken into account in the therapy of viral diseases. The first results obtained with the use of levamisole for normalization of cellular immunity in influenza (Pike *el al.*, 1977) and herpes simplex patients (Rabson *et al.*, 1977) testify for the prospects of such approach.

References

Allison, A. C. (1978): Mechanisms by which activated macrophages inhibit lymphocyte responses. *Immunol. Rev.* **40**, 3—27.

Araby, J. J. E., Chernesky, M. A., Rawls, W. E., and Dent, P. B. (1978): Depressed herpes simplex virus-induced lymphocyte blastogenesis in individuals with severe recurrent herpes infections. *Clin. Immunol. Immunopath.* **9**, 253—263.

Berkovitch, S., and Starr, S. (1966): Effects of live type 1 poliovirus vaccine and other viruses on the tuberculin tests. *New Engl. J. Med.* **274**, 67—72.

Cappel, R. (1976): Comparison of the humoral and cellular immune responses after immunization with live, UV-inactivated herpes simplex virus and subunit vaccine and efficacy of these immunizations. *Arch. Virol.* **52**, 29—35.

Cross, S. S., Morse, H. C., and Asofsky, R. (1977); Neonatal infection with mouse thymic virus: differential effects on T cells mediating the graft-versus-host reaction. *J. Immunol.* **117**, 635—641.

Dolin, R., Richman, D. D., Murphy, B., and Fauci, A. S. (1977): Cell-mediated immune responses in humans after induced infection with influenza A virus. *J. infect. Dis.* **135**, 714—719.

Dunmire, C., Ruckdeschel, J. C., and Mardiney, M. R. (1975): Suppression of in vitro lymphocyte responsiveness to purified protein derivative by measles virus. *Cell. Immunol.* **20**, 205—217.

Ganguly, R., Cusumano, C. L., and Waldman, R. H. (1976): Suppression of cell-mediated immunity after infection with attenuated rubella virus. *Infect. Immun.* **13**, 464—469.

Hooren, J. van (1976): Influenza vaccine and PPD skin-test reactivity. *Lancet* **i**, 44.

Howard, R. J., and Najarian, J. S. (1974): Cytomegalovirus-induced immune suppression. *Clin. exp. Immunol.* **18**, 106—126.

Jacobs, R. P., and Cole, G. A. (1976): Lymphocytic choriomeningitis virus-induced immunosuppression: a virus-induced macrophage defect. *J. Immunol.* **117**, 1004—1009.

Kantzler, G. B., Lauteria, S. F., Cusumano, C. L., Lee, J. E., Ganguly, R., and Waldman, R. H. (1974): Immunosuppression during influenza virus infection. *Infect. Immun.* **10**,996—1002.

Kauffman, C. A., Linneman, C. C., Schiff, C. M., and Phair, J. P. (1976): Effect of viral and bacterial pneumonias on cell-mediated immunity in humans. *Infect. Immun.* **13**, 78—83.

Kavetsky, R. E., Savtsova, Z. D., Struk, V. J., Yakimenko, L. V., Umansky, Y. A. (1977): Effect of influenza virus on immune responsiveness of animals. *Acta virol.* **21**, 109—113.

Kelsey D. K. Oberall J. C. and Glasgow L. A. (1978): Correlation of the suppression of mitogen responsiveness and the mixed lymphocyte reaction with the proliferative response to viral antigen of splenic lymphocytes from cytomegalovirus-infected mice. *J. Immunol.* **121**, 464—470.

Khozinsky V. V. Vasilieva I. G. Semenov B. F. and Drozdov S. G. (1978): Delayed type hypersensitivity in experimental enteroviral infection (in Russian). *Vop. Virus.* **23**, 474—475.

Loon, A. M. van, Logt, J. T. M. van der, and Veen, J. van der (1979): Poliovirus-induced suppression of lymphocyte stimulation: a macrophage-mediated effect. *J. Immunology* **37**, 135—143.

Lehmann-Grube F. Niemeyer J. and Löhler J. (1972): Lymphocytic choriomeningitis of the mouse. IV. Depression of the allograft reaction. *Med. Microbiol.* **158**, 16—25.

Lucas, C. J., Ubels-Postma, J., Calama, J. M. D., and Rezee, A. (1978): Studies on the mechnism of measles virus-induced suppression of lymphocyte functions in vitro. *Cell. Immunol.* **37**, 448—458.

Massanari, R. M. (1979): Suppression of tuberculin hypersensitivity during influenza infection in mice. *Infect. Immun.* **24**, 501—507.

Maller, R., and Sörén, L. (1977): In vitro effects of rubella virus strain RA 27/3 on human lymphocytes. *Acta parth. microbiol. scand.* **85C**, 45—56.

Mathes, L. E., Olsen, R. G., Heberbrand, L. C., Hoover, E. A., Schaller, J. P., Adams, P. W., and Nichols, W. C. (1979): Immunosuppressive properties of a virion polypeptide, a 15,000-dalton protein, from feline leukemia virus. *Cancer Res.* **39**, 950—955.

Michalides, M. C., and Simms, E. C. (1979): Immune response in mice infected with lactic dehydrogenase virus. IV. Functional status of the macrophage during acute LDV infection. *Immunology* **36**, 241—246.

Mongini, P. K., and Rosenberg, L. (1978): Lactic dehydrogenase virus alternation of lymphocyte circulation. *J. Immunol.* **120**, 459—462.

Morse, H. C., Cross, S. S., and Baker, P. J. (1976): Neonatal infection with mouse thymic viruses: effects on cells regulating the antibody response to type III pneumococcal polysaccharide. *J. Immunol.* **116**, 1613—1617.

Munyer, T. P., Mangi, R. J., Dolan, T., and Kantor, F. S. (1975): Depressed lymphocyte function after measles-mumps-rubella vaccination. *J. infect. Dis.* **132**, 75—78.

Nazimov, V. S., and Shuratov, I. Kh. (1979): The effect of adenovirus type 3 on the contents of antibody-forming cells in the spleen of mice immunized with sheep erythrocytes (in Russian). *Vop. Virus.* **24**, 48—52.

Notkins, A. L., Mergenhagen, S. E., and Howard, R. J. (1970): Effect of virus infections on function of the immune system. *Ann. Rev. Microbiol.* **22**, 525—538.

Oldstone, M. B. A., Tishon, A., Chiller, J. M., Weigle, W. O., and Dixon, F. J. (1973): Effect of chronic viral infection on the immune system: I. Comparison of the immune responsiveness of mice chronically infected with LCM virus with that of non-infected mice. *J. Immunol.* **110**, 1268—1278.

Okunewick, J. P., Meredith, R. F., Brozovich, B., and Weaver, E. (1978): Stimulation of immune response in hybrid mice following Rauscher virus infection. *Proc. Soc. exp. Biol. Med.* **157**, 449—452.

Pike, M. C., Daniels, C. A., and Snyderman, R. (1977): Influenza-induced depression of monocyte chemotaxis: reversal by levamisole. *Cell. Immunol.* **32**, 234—238.

Pirkquet, C. E. (1908): Das Verhalten der kutanen Tuberculinreaktion während der Masern. *Dtsch. med. Wschr.* **34**, 1297—1300.

Rabson, A., Whiting. D. A., Anderson, R., Glover, A., and Koornhof, H. J. (1977): Depressed neutrophil motility in patients with recurrent herpes simplex virus infections: in vitro restoration with levamisole. *J. infect. Dis.* **135**, 113—116.

Richter, J., Švejda, J., and Král, V. (1979): Kožní testy po onemocnění infekční mononukleozou. *Čas. Lék. čes.* **133**, 56—58.

Roberts, N. J., and Steignigel, R. T. (1978): Effect of in vitro virus infection on response of human monocytes and lymphocytes to mitogen stimulation. *J. Immunol.* **121**, 1052—1058.

Ruutu, P. (1977): Depression of rat neutrophil exudation and motility by influenza virus. *Scand. J. Immunol.* **6**, 1113—1120.

Santoli, D., Moretta, L., Lisak, R., Gilden, D., and Koprowski, H. (1978): Imbalances in T cell subpopulations in multiple sclerosis patients. *J. Immunol.* **120**, 1369—1371.

Semenov, B. F. (1959): Immunopathology in the process of infection (in Russian). *Vest. Akad. med. Nauk* **1979** (11), 85—92.

Semenov, B. F., and Vargin, V. V. (1978): Nonspecific interaction of some toga and bunyaviruses and flaviviruses vaccines with immunocompetent cells, pp. 507—514. In E. Kurstak and K. Maramorosch (Eds): *Viruses and Environment*, Academic Press, New York-San-Francisco-London.

Semenov, B. F., Zschiesche, W., and Gavrilov, V. J. (1977): *Immunopathology of viral disease*, VEB Gustav Fischer Verlag, Jena.

Svennerholm, B., Strannegard, Ö., and Lycke, E. (1978): Immune reactivity of visna virus-infected mice. *Infect. Immun.* **20**, 412—417.

Tamura, T., Machii, K., Ueda, K., Fujiwara, K. (1979): Modification in immune response in nude mice infected with mouse hepatitis virus. *Microbiol. Immunol.* **22**, 557—564.

Tandon, P., Chaturvedi, U. C., and Matur, A. (1979): Differential depletion of T lymphocytes in the spleen of dengue virus-infected mice. *Immunology* **37**, 1—6.

Tinghitella, T. J., and Booss, J. (1979): Enhanced immune response late in primary cytomegalovirus infection of mice. *J. Immunol.* **122**, 2442—2446.

Ueda, K., Nishima, S., Sasaki, F., Yoshikawa, H., and Goya, N. (1979): Suppression of tuberculin reactivity during natural rubella: observations with 54 patients. *Clin. Pediatr.* **18**, 105—107.

Vargin, V. V., and Semenov, B. F. (1976): Changed immune response of the host to heterologous antigen under the action of togaviral infection (in Russian). *Vop. Virus.* **21**, 150—154.

Vesikari, R., and Buimovici-Klein, E. (1975): Lymphocyte responses to rubella antigen and phytohemagglutinin after administration of the Ra 27/3 strain of live attenuated rubella vaccine. *Infect. Immun.* **11**, 748—753.

Virelizier, J. L. (1975): Mechanisms in immunodepression induced by viruses: possible role of infected macrophages. *Biomedicine* **22**, 255—261.

Wiktor, T., Doherty, P. C., and Koprowski, H. (1977): Suppression of cell-mediated immunity by street rabies virus. *J. exp. Med.* **145**, 1617—1621.

Woodruff, J. F., and Woodruff, J. J. (1974): Prolonged allograft survival in Newcastle disease virus-treated mice. *Infect. Immunity* **9**, 969—970.

Woodruff, J. J., and Woodruff, J. F. (1976): Influenza A virus interaction with murine lymphocytes. *J. Immunol.* **117**, 852—864.