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Virus-Induced Modulation of Reticuloendothelial Function

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1. INTRODUCTION

The ability of viruses to modify the functions of cells of the lymphoreticular system has been extensively investigated and reviewed (Woodruff and Woodruff, 1975; Specter and Friedman, 1978; Nash, 1985; Friedman *et al.*, 1986; Rouse and Horohov, 1986). Frequently this information is amassed in such a manner that the importance of the interactions of viruses and macrophages receives little attention. In the present chapter these interactions are the focus of the discussion and review. The exception to inclusion of viruses in this chapter are the RNA tumor viruses, which are dealt with in Chapter 13 in this volume.

The interactions of viruses and the immune system are bidirectional, so that the immune cells can limit virus spread while the viruses might modify lymphoreticular cell function. In the sections that follow I examine these interactions and explain the mechanisms by which they occur as well as the ultimate outcome of infection on the macrophage and the host in general.

2. MACROPHAGES IN HOST DEFENSES AGAINST VIRUSES

The protection of the host against virus infection involves several interactions with macrophages (Mogensen, 1986). These host–virus encounters may involve nonspecific functions, such as phagocytosis and digestion of the virus particle, or may involve specific immune phenomena that require the stimulation of macrophages by products released from lymphocytes during immune sensitization. Ingestion and degradation of the virion results in antigenic components being presented on the macrophage surface, which is important for the triggering of lymphocytes. This process is referred to as accessory cell function.

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Another function that results in activation of lymphocytes is the production of interleukin 1 (IL-1). This monokine is most noted for the activation of T lymphocytes but has been demonstrated to have other important activities in inflammatory and immune responses (Dinarello, 1984). In addition, macrophages may be activated by lymphokines or interaction with T lymphocytes and then become capable of killing virus-infected cells directly (Cook and Lewis, 1984) or participating in antibody-dependent killing of virus-infected cells (Kohl *et al.*, 1977). Cook and Lewis have noted that macrophages activated by the mycobacterial vaccine BCG readily kill adenovirus 2–infected hamster cells but are less effective at killing adenovirus type 12–infected cells. This has been related to the oncogenic potential of type 12 and related to expression of viral T antigen on the surface of these cells. Expression of this antigen is associated with viral transformation of cells and may be a protective mechanism that prevents macrophage killing.

The most basic function of macrophages in resisting virus infections, i.e., phagocytosis and digestion, has been demonstrated to be determined by both genetics and the age of the host (Lopez, 1975; Stiehm, 1980; Mogensen, 1986). The genetics will determine whether the macrophage is resistant (nonpermissive) or susceptible (permissive) to virus replication. The nonpermissive macrophage readily destroys the virus and prevents or limits infection. Permissive macrophages may not only replicate virus, but also act as a vehicle to transmit virus to distant sites in the host (Mims, 1964). Culturing nonpermissive macrophages *in vitro* frequently results in their conversion to a permissive state (Lopez and Dudas, 1979; Morahan and Morse, 1979). Thus the intrinsic genetic restriction of replication can be overcome under culture conditions and possibly during immune suppression in the host.

Finally, macrophages may be important as regulatory cells for immune responses in virus infections. Suppressor macrophages have been demonstrated from infected hosts that can modify a variety of immune responses (Varesio, 1983). It is noted here that this may not always be detrimental to the host since inhibition of immunopathogenesis may limit damage of vital organs that are infected by viruses.

3. ALTERATION OF MACROPHAGE FUNCTIONS BY VIRUSES

The list of viruses capable of infecting monocytes/macrophages *in vivo* and/or *in vitro* is extensive (Table 1). The interactions of these viruses and macrophages often determine whether disease will ensue or the macrophage will be able to abort infection. The consequences of interaction between macrophage and virus may be without a general effect on the host or they may result in mild to severe manifestations affecting host immunity (Tables 2 and 3).

3.1. ADENOVIRUSES

There is no evidence that adenoviruses are capable of infecting macrophages. However, there are indications that macrophages are important in ade-

TABLE 1. VIRUSES CAPABLE OF INFECTING MONOCYTE/MACROPHAGES

- Arenaviruses
  - Lymphocytic choriomeningitis virus
  - Junin
  - Pichinde
- Coronaviruses
  - Mouse hepatitis virus
- Enteroviruses
  - Poliovirus
- Herpesviruses
  - Bovine herpesvirus
  - Cytomegalovirus
    - Human
    - Mouse
  - Guinea pig herpes like virus
  - Herpes simplex virus
  - Infectious laryngotracheitis virus
  - Pseudorabies virus
  - Varicella zoster virus
- Influenza
- Papovaviruses
- Paramyxoviruses
  - Measles
  - Mumps
  - Parainfluenza viruses (Sendai virus)
  - Respiratory syncytial virus
- Poxviruses
  - Ectromelia
  - Vaccinia
- Reoviruses
- Retroviruses (nononcogenic only)
  - Caprine arthritis encephalitis virus
  - Equine infectious anemia
  - Human immunodeficiency virus
  - Visna virus
- Rhabdoviruses
  - Vesicular stomatis virus
- Togaviruses
  - Dengue
  - Japanese encephalitis virus
  - Lactate dehydrogenase virus
  - Rubella
  - West Nile
  - Yellow fever

novirus-induced immunosuppression. Berensci and co-workers (1982, 1985) related suppressed antibody production against sheep erythrocytes to macrophages in adenovirus-infected mice. This was based on the observation that silica gel, which is selectively toxic for macrophages, when given to mice infected with adenovirus type 6 prevents the immunosuppression. Furthermore, although adenovirus does not replicate in macrophages, it can infect primate lymphocytes. Andiman and Miller (1982) suggest that macrophages from cord blood are responsible for the maintenance of persistent infection. The mechanism by which the macrophage is capable of this was not elaborated.

TABLE 2. TYPES OF INTERACTIONS BETWEEN MACROPHAGES AND VIRUSES

Type of infection	Alteration of cell function	Viruses involved
Attachment and penetration	None identified	Most viruses
Abortive (non-permissive)	None to slight impairment	HSV, influenza, measles
Productive (permissive)	Moderate to severe impairment	HIV, measles, polio, togaviruses
Persistence	None to moderate impairment	LDHV, MCMV, CAEV, parainfluenza

TABLE 3. MACROPHAGE FUNCTIONS REPORTED TO BE ALTERED BY VIRUS INFECTION

Accessory cell function (antigen processing and/or presentation)
Adherence to glass or plastic surfaces
Antibody-dependent cellular cytotoxicity
Degradation of viral particles, antigens
Direct cytotoxic/cytocidal activity
Microbicidal activity
Phagocytosis
Production of monokines/inflammatory molecules (e.g., IL-1, interferon-α, prostaglandins)
Suppressor cell activity
Suppressor/cytotoxic factor production

3.2. ARENAVIRUSES

Although these viruses are seldom the cause of infections in humans (at least in the "developed" nations), they can cause severe, life-threatening diseases. Macrophages are a major target for infection by arenaviruses, along with lymphocytes (Murphy *et al.*, 1976, 1977; Doyle and Oldstone, 1978; Laguens *et al.*, 1983a,b). The most frequently studied model of arenavirus infection is lymphocytic choriomeningitis (LCM) virus in mice. LCM has a unique relationship with the immune system, in that T lymphocytes mediate the acute symptoms of the disease in the central nervous system (Buchmeier *et al.*, 1980).

In vitro infection of murine macrophages by LCM virus minimally affects their function. Phagocytosis is normal and the level of hydrolytic enzymes in these cells is unaltered (Mims and Wainwright, 1968; Oldstone *et al.*, 1973; Schwartz *et al.*, 1970). Some reports do indicate that enzyme activity and dye uptake are altered (Allison, 1967; Yarborough *et al.*, 1967). These studies suggest that infection of macrophages by LCM causes only minimal changes. However, *in vitro* studies in mice suggest a more important role for macrophages in LCM infection. Gledhill *et al.* report a decrease in phagocytosis of colloidal carbon following infection (1965). Jacobs and Cole further support the importance of a macrophage defect by showing that depressed T- and B-lymphocyte blastogenic responses to mitogens can be reversed by addition of macrophages from normal mice (1976). It has been suggested that the macrophage function in these studies may only be enhancing viability of the lymphocytes (Bro-Jorgensen, 1978). If this is so, then the defect could be the inhibition of IL-1 production or some other monokine by virus-infected macrophages.

Two other arenaviruses, Junin virus and Pichinde virus, have been reported to alter mouse macrophage function (Gonzalez *et al.*, 1982; Laguens *et al.*, 1983b; Friedlander *et al.*, 1984). Pichinde has been noted to inhibit the ability of mouse macrophages to respond to macrophage growth factor, resulting in a failure of these cells to proliferate (Friedlander *et al.*, 1984). The ability of Junin virus to replicate in macrophages *in vitro* is directly related to virulence, with virulent strains replicating and attenuated strains being inhibited (Laguens *et al.*, 1983b).

This suggests that virulence may be related to the ability of the virus to inhibit macrophage function. However, the only macrophage function tested was phagocytosis, and this was unaltered when compared to uninfected macrophages (Gonzalez *et al.*, 1982).

3.3. AVIAN INFECTIOUS BURSAL DISEASE

Avian infectious bursal disease (IBDV) is a double-stranded RNA virus containing 32 capsomeres in a naked nucleocapsid. Thus, this is reminiscent of the Reoviridae. Experimentation using IBDV is performed in chickens that exhibit a profound immunodepression of B- and T-lymphocyte responses following infection. This disease progression appears to be age related, as chicks infected *in ovo* or at birth show greater immunodepressive effects than birds infected at 3 weeks of age (Sivanandan and Maheswaran, 1980). Immunodepressive effects related to phytohemagglutinin-induced lymphoblast transformation have been attributed to a "macrophagelike" suppressor cell found in the spleen of infected chicks (Sharma and Lee, 1983). These suppressor cells were not altered by anti-T- or anti-B-lymphocyte antisera but could be depleted from spleen cell suspensions by plastic adherence or ingestion of carbonyl iron.

There are no reports on the infectivity of chicken macrophages by IBDV, suggesting that the effect of the virus on these cells may be indirect. In addition, phagocytosis of *Staphylococcus aureus* is normal in circulating phagocytes from IBDV-infected animals (Santivatr *et al.*, 1981).

3.4. MOUSE HEPATITIS VIRUS (CORONAVIRUS)

Mouse hepatitis virus (MHV) readily replicates in macrophages (peritoneal and Kupffer cells) of susceptible mice. The ability to replicate in macrophages is genetically determined and is responsible for susceptibility or resistance of the host (Bang and Warwick, 1960; Taguchi *et al.*, 1976). Two or more recessive genes are involved in control of susceptibility, at least one of which is H-2 linked (Levy-LeBlond *et al.*, 1979). This resistance/susceptibility of mouse spleen cell cultures is readily reversed by *in vitro* manipulation. Resistance can be conferred on susceptible cells by stimulation with concanavalin A (Con A) (Weiser and Bang, 1977) while resistant cells can be rendered susceptible following treatment with silica, cortisone, or lymphokines (Weiser and Bang, 1976; Taguchi *et al.*, 1980; Taylor *et al.*, 1981).

MVH strains can cause acute or chronic infection which is related to persistent infection of macrophages. Chronically infected mice respond to antigenic challenge with a depressed antibody response to sheep erythrocytes and *Escherichia coli* lipopolysaccharide, presumably because of macrophage dysfunction in antigen processing or presentation (Leray *et al.*, 1982). However, antibody responses to MVH, per se, were detectable in both acute and chronic infection. These responses were limited to the IgM class (Virelizier *et al.*, 1975). Although

macrophage accessory cell function seems to be altered, phagocytic activity was normal when measured by yeast phagocytosis *in vitro* and sheep erythrocyte uptake *in vivo* (Krzystyniak and Dupuy, 1983).

3.5. HEPATITIS B VIRUS

Hepatitis B virus (HBV) has not been detected within macrophages, including attempts to measure HBV DNA in such cells (Korba *et al.*, 1986). The only activity related to macrophages that has been tested during HBV infection is interferon-α (IFN-α) production, and this was normal (Davis *et al.*, 1984). Nevertheless, it is not possible to entirely rule out a role for macrophages in HBV infection since virus particles persist in the liver, where they are in close contact with Kupffer cells. Furthermore, there is an important immunopathologic aspect to disease progression which could readily involve macrophages as well as lymphocytes.

3.6. HERPESVIRUSES

A number of herpesviruses of humans and animals have been reported to alter immune responses of the host. Most of these viruses, as described in the following sections, can interact with macrophages and have an effect on immune responsiveness. A few, however, including herpes sylvilagus in rabbits (Kramp *et al.*, 1985) and mouse thymic virus in mice (Cohen *et al.*, 1975), do not appear to infect macrophages.

3.6.1. Human Cytomegalovirus

Monocytes have been described as the primary target site for human cytomegalovirus (HCMV), although this may often be an abortive replication (Einhorn and Ost, 1984; Rice *et al.*, 1984). Nevertheless, infectious HCMV has been isolated from mononucleosis patients (Carney and Hirsch, 1981), and infected monocytes are capable of inhibiting autologous lymphocytes from responding to Con A (Rinaldo *et al.*, 1977, 1980). The mechanism of the depression of the Con A response by monocytes has not been ascertained, but recently Rodgers *et al.* (1985) demonstrated a 95-kd protein in human monocyte cultures infected with CMV strain AD 169, which specifically inhibits IL-1.

3.6.2. Epstein–Barr Virus

Monocytes do not become infected with Epstein–Barr virus (EBV) but are often in the microenvironment of infected B lymphocytes. Junker *et al.* (1986) have demonstrated that monocyte numbers remain normal in infectious mononucleosis due to EBV. In fact, macrophages seem to be activated during such infections in hematopoietic tissues, and often small granulomas are seen in the

bone marrow (Rothwell, 1975). Activated macrophages often produce increased levels of prostaglandins, which in turn can depress T-lymphocyte function. Thus, macrophages appear to be involved in EBV-induced immunosuppression, although they are not directly infected.

3.6.3. Herpes Simplex Virus

Herpes simplex virus (HSV) has been shown to readily infect macrophages of both humans and experimental animals. HSV can infect macrophages *in vivo*, but this is generally an abortive infection; however, *in vitro* they may replicate and cause destruction of the infected macrophages (Morahan *et al.*, 1985). These authors also report that macrophage surface receptors, phagocytosis, oxidative metabolism, phagosome–lysosome fusion, and microbial killing are all altered by HSV infection. Decreases in natural killer cell activity, ADCC, and Fc receptor expression have also been reported (Rhodes, 1985). These decreases in immune function can be related to increased PGE_2 production by macrophages and resulting increases in intracellular cAMP levels. In addition, susceptible monocyte–macrophage cultures treated with PGE yield higher titers of HSV1. Nick *et al.* reported the suppression of antibody responses to HSV1 or HSV2 when mice or rats were given HSV2 intraperitoneally (Nick *et al.*, 1986). HSV2-induced suppression could be abrogated if the animals were treated with silica. This implicates the macrophages as the cell population responsible for suppression, but a mechanism was not investigated. The studies just cited suggest that this may be due to increased cAMP and/or prostaglandins.

3.6.4. Varicella–Zoster Virus

Macrophages have been reported to be susceptible to infection by varicella–zoster virus (VZV). Macrophages infected with VZV are capable of inhibiting mixed lymphocyte reactions *in vitro* (Twomey *et al.*, 1974). Arneborn and Biberfeld also report suppressive activity of monocytes on T-cell responses during varicella (1983). In contrast, removal of phagocytic cells did not result in a loss of suppression, suggesting that either monocytes/macrophages were not responsible for suppression or the damage to T cells by the infected macrophages was irreversible.

3.6.5. Bovine Herpesvirus

Bovine herpesvirus type 1 (BHV-1) is noted for causing infectious bovine rhinotracheitis. In this infection model, defects in macrophage function are readily observed between 4 and 7 days postinfection. In addition, polymorphonuclear leukocyte and lymphocyte dysfunctions are observed. Macrophages infected *in vitro* by BHV-1 express very few Fc receptors and have a reduced uptake of erythrocytes or yeast (Forman and Babiuk, 1982). Mitogen-induced proliferation of lymphocytes is reduced in the presence of BHV-1-infected macrophages, even when these infected cells comprise only 1% of the cells in the reaction (Bendixen *et*

al., 1981). Suppression of lymphocytes is most notable 3–5 days postinfection and has been demonstrated to be due to a soluble factor. Several macrophage-produced soluble products have been linked to the possible reduction in lymphocyte function. These include IFN-α or PGE_2, as well as toxic oxygen radicals like H_2O_2 or superoxide, all of which are increased in BHV-1 infection (Babiuk *et al.*, 1987). Indeed, plasma from BHV-1-infected cattle suppressed lymphocyte blast transformation by 80%. The authors speculate that PGE_2 may work via inhibition of IL-1, and that toxic oxygen radicals may cause damage to cellular DNA, thus causing lymphocyte dysfunction.

3.6.6. Equine Herpesvirus

Equine herpesviruses have been reported to infect monocytes and lymphocytes (Scott *et al.*, 1983). Both lymphocyte blastogenesis and ADCC are suppressed in these animals (Dutta *et al.*, 1980; Coignoul *et al.*, 1984). There did not seem to be a soluble factor responsible for the suppression of either response, and the role of infected macrophages in immune suppression was not identified.

3.6.7 Pseudorabies Virus

Pseudorabies virus (PRV) infects swine, causing a variety of disorders including Aujesky's disease, which involves the central nervous system. PRV infects pig lung macrophages *in vitro* (Smid *et al.*, 1981) and seems to infect macrophages *in vivo* with a resulting immune suppression (Babiuk *et al.*, 1987). PRV infection of swine renders them susceptible to secondary bacterial infection with *Pasturella multocida*. Macrophages infected *in vitro* cease function within 2 hr and lyse shortly thereafter but with only a few virus particles present, suggesting a toxic lysis rather than viral replication.

3.6.8. Marek's Disease Virus

The susceptibility of chicken macrophages to Marek's disease virus has been described (Jakowski *et al.*, 1970; Lee *et al.*, 1978). Lee and co-workers have suggested that splenic macrophages from infected birds are capable of suppressing mitogenic responses of lymphoid cells (1978). No mechanism of action was identified for these suppressor macrophages.

3.6.9. Infectious Laryngotracheitis Virus

Infectious laryngotracheitis virus (ILT) readily infects chicken macrophages *in vitro* (Calnek *et al.*, 1986), but infection of macrophages from infected animals has been difficult to assess and is not reported. Replication of ILT in bone marrow macrophages has been recorded, although replication is restricted. This appears to be a failure in assembly since large quantities of virus-directed macromolecules are detected but there is little or no mature virus. Curiously, attenuated vaccine strains replicate more efficiently than virulent virus strains in mac-

rophages *in vitro*. This suggests that replication in macrophages is unrelated to virulence.

3.6.10. Guinea Pig Herpes-Like Virus

Guinea pig herpes–like virus, like most other herpesviruses, infects macrophages and lymphocytes during acute infection, often leading to latency (Gonzalez-Serva and Hsiung, 1978). There is a resulting lymphocytosis, mainly of T cells, but little else is reported regarding functional alterations.

3.7. PAPOVAVIRUSES

Macrophages appear to be resistant to papovaviruses. *In situ* studies of warts show an accumulation of macrophages at the base of the wart, but these cells do not infiltrate the wart per se (Oguchi *et al.*, 1981). These cells appear to be involved in wart repression, which suggests they may ingest and digest wart virus. Both monocytes and macrophages are also resistant to the BK virus, a polyomavirus. These cells have surface receptors for the virus and internalize the bound virus; however, there is no evidence of virus replication or persistence (Portolani *et al.*, 1985). Thus monocytes, regardless of their state of differentiation, are important for degradation of BK virus but not viral replication.

3.8. MYXOVIRUSES

The myxoviruses are composed of two major families, the Orthomyxoviruses and the Paramyxoviruses. Both families have representatives that replicate in leukocytes and are immunosuppressive.

3.8.1. Influenza Virus (Orthomyxovirus)

Macrophages of mice and humans have been reported to be infected by influenza virus both *in vivo* and *in vitro* (Kleinerman *et al.*, 1976; Warshauer *et al.*, 1977; Nugent and Pesanti, 1979). In certain instances, modulation of macrophage and lymphocyte functions is recorded but some activities are unaltered. Decreases in accessory cell function, chemotaxis, phagocytosis, and bactericidal activity are noted for macrophages (Kleinerman *et al.*, 1974, 1975, 1976; Warshauer *et al.*, 1977; Roberts and Steigbigel, 1978; Nugent and Pesanti, 1979; Roberts *et al.*, 1980; Gardner and Lawton, 1982). By contrast, mouse alveolar macrophages retained normal phagocytic function and human alveolar macrophages retained accessory cell functions (Nugent and Pesanti, 1979; Ettensohn and Roberts, 1984). Lymphocyte responses to mitogens were depressed in association with lost accessory cell function, but the response to influenza antigen was enhanced (Roberts, unpublished observations, 1982). These results suggest

that the host may focus on selective antigens which challenge the integrity of the host at the expense of other immune functions. Roberts *et al.* (1979) refer to this as "immunofocusing."

Macrophages are not readily permissive for influenza, inactivating the virus *in vivo*, but they are infected *in vitro*. The immunosuppressive effects of the virus are not attributable to the virion, since inactivated virus does not induce suppression (Roberts and Steigbigel, 1978; Roberts *et al.*, 1980). Roberts and co-workers have eliminated prostaglandins (Ettensohn and Roberts, 1984) and IFN-α (Roberts and Steigbigel, 1978; Roberts *et al.*, 1979) as probable mediators of immune suppression. These investigators have detected both IL-1 and an IL-1 inhibitor in human macrophages infected with influenza virus *in vitro* (Roberts *et al.*, 1986). The role of this inhibitor as an immune suppressive factor in influenza and other virus infections remains to be determined.

3.8.2. Paramyxoviruses

The paramyxoviruses reported to infect macrophages include measles, mumps, respiratory synctial virus, and Sendai virus. Replication of measles virus can be demonstrated in human monocytes *in vitro*, but this is limited when compared to replication in lymphocytes (Joseph *et al.*, 1975; Sullivan *et al.*, 1975). Infected monocytes/macrophages can suppress mitogen-induced T-lymphocyte proliferation (Rinehart *et al.*, 1979). This suppression occurs most notably when there is direct lymphocyte–macrophage contact. Antibody production or B-cell mitogen stimulation is also depressed by measles-infected macrophages and this is related to cell contact and/or release of INF-α from macrophages (Kadish *et al.*, 1980; Harfast *et al.*, 1981).

Mumps virus has been demonstrated to infect monocytes/macrophages *in vitro;* however, the virus clearly infects lymphocytes more readily (Duc-Nguyen and Henle, 1966; Fleischer and Kreth, 1982). No relationship between infection of macrophages and alteration of immune function was suggested. Likewise, animal paramyxoviruses, canine distemper virus, and bovine rinderpest virus infect lymphocytes and macrophages (Appel, 1978; Rossiter and Wardley, 1985). These authors related ability to infect these cells with virulence, suggesting that restriction of replication inhibited disease.

Respiratory syncytial virus infection of macrophages is documented both *in vivo* and *in vitro* (Domurat *et al.*, 1985). Similar to influenza virus, RSV stimulates both IL-1 and IL-1 inhibitor (Roberts *et al.*, 1986). The levels of inhibitor are considerably greater with RSV than influenza infection; the significance of this finding is not known. Borysiewicz and co-workers (1985) describe an inhibition of IL-2 release by cytotoxic T cells during RSV infection; the relationship to the presence of IL-1 inhibitor is not reported.

Infection of mouse alveolar macrophages by Sendai virus resulted in decreased phagocytic function, even in the presence of immune serum (Jakab and Warr, 1981). In addition, Silverberg and co-workers (1979) have demonstrated an inhibition of phagosome–lysosome fusion in Sendai virus–infected macrophages. Sendai virus infection of macrophages does stimulate tumor necrosis

factor production, signifying that these cells are activated (Aderka *et al.*, 1986). This type of activation, however, may enhance certain responses while limiting others. In this manner, Newcastle disease virus (NDV) infection results in a loss of cytotoxic T-cell activity associated with macrophage activation (Brenan and Zinkernagel, 1983). NDV is a potent IFN stimulant, and this and/or other soluble factors from macrophages could be responsible for the diminished T-cell activity.

3.9. PICORNAVIRUSES

The picornaviruses are comprised of the rhinoviruses, enteroviruses (polioviruses, coxsackieviruses, echoviruses, and hepatitis A virus), and cardioviruses. All of these have been demonstrated to modulate immune responsiveness to some extent (Garzelli *et al.*, 1987). Poliovirus has been demonstrated to infect human monocytes and mouse macrophages. The infected macrophages have been demonstrated to be responsible for inhibition of PHA-induced lymphocyte blastogenesis (Gresser and Chany, 1964; Kantoch and Dobrowolska, 1969; Soontiens and Van Der Veen, 1973; Van Loon *et al.*, 1979).

Murine peritoneal macrophages are resistant to encephalomyocarditis virus infection; however, they become susceptible *in vitro* when mice are treated with anti-IFN-α/β (Belardelli *et al.*, 1984). In addition, hepatitis A virus has been noted to primarily replicate in Kupffer cells (Mathiesen *et al.*, 1977) while feline picornavirus first infects kitten alveolar macrophages (Kahn and Gillespie, 1971). While these infections play an important part in the pathogenesis of the virus infections, their effect on the immune system is undetermined. Hepatitis A virus has been noted to depress immunity; thus the infection of Kupffer cells and possibly other macrophages may be important in this regard (Mella and Lang, 1967; Willems *et al.*, 1969; Aiuti *et al.*, 1973).

The most intensively studied picornaviruses relative to immunosuppression are the Coxsackie B viruses, especially B3 (CVB3) (Toniolo *et al.*, 1986). CVB3 infection of mouse spleen cells results in a depression of the antigen-presenting activity of macrophages (Matteucci *et al.*, 1985). It is not clear whether splenic or peritoneal macrophages can be infected by CVB3, and most evidence supports engulfment but not necessarily infection (Rager-Zisman and Allison, 1973; Gauntt *et al.*, 1979). Although the participation of macrophages in generalized immunosuppression by CVB3 is uncertain, it has been suggested that this is primarily due to the failure of antigen-presenting cells (APC). Splenic macrophages from CVB3-infected mice fail to restore APC responses to macrophage-depleted cultures, but normal macrophages can restore activity to infected cultures (Garzelli *et al.*, 1987).

3.10. POXVIRUSES

Smallpox (variola) and vaccinia have both been demonstrated to replicate within macrophages (Avila *et al.*, 1972; Buchmeier *et al.*, 1979; Moss, 1985). This

infection *in vivo* is associated with the dissemination of infection and the generation of IFN by macrophages. Replication of vaccinia in rabbit alveolar macrophages is abortive in previously infected rabbits and fails to penetrate macrophages from immune rabbits. Evidence of macromolecular synthesis and a few viral particles in these infected cells suggest that the blockage occurs late in replication. McLaren *et al.* (1976) reported that when lymphoproliferative responses developed during acute vaccinia infection, depressed responses to Con A were seen. As with other viruses noted previously in this chapter, there seems to be a selective immunity against the virus and a sacrifice of generalized responsiveness. The ability to develop antivaccinia immunity was related to macrophage resistance. Resistance to ectromelia (mouse pox) was also related to macrophages and in this study linked to production of IFN (Tsuru *et al.*, 1983; Cohen *et al.*, 1984). One might speculate from this evidence that IFN might be important in vaccinia infection and the depression of Con A-induced lymphocyte blastogenesis.

Malignant fibroma virus (MV) of rabbits has been reported to generate suppressor factor(s) which, at least in part, are related to prostaglandins (PG) (Strayer, 1987). Since macrophages are an important source of PG and macrophages are noted to ingest virus-infected lymphocytes, these cells might contribute to the immune depression seen in MV. The evidence presented by Strayer (1987) supports this concept by indicating that most, but not all, suppressive activity is associated with nonadherent cells.

3.11. REOVIRUSES

Reovirus types 1 and 3 have been demonstrated to infect a mouse macrophage cell line, P388D1, in culture. Little else has been reported regarding the interaction of these viruses with macrophages, except that uptake and replication of reovirus by P388D1 cells was facilitated by nonneutralizing antibodies to the virus (Burstein *et al.*, 1983).

3.12. RHABDOVIRUSES

Vesicular stomatitis virus (VSV) infection in mice is the model usually employed to study rhabdoviruses. VSV has been demonstrated to replicate in mouse peritoneal macrophages, but only a small percentage of the cells become infected (Belardelli *et al.*, 1984). Injection of mice with anti-IFN prior to harvesting peritoneal macrophages allows the virus to replicate to higher titer. Thus IFN is seen to have a critical role in protection of the host from VSV via activation of macrophages. Macrophages or T lymphocytes infected with VSV are capable of completely eliminating proliferative responses of antigen-primed T cells, suggesting a defect in the macrophages as APC (Sy and Finberg, 1987). This defect in macrophage function is somewhat questionable since the macrophages may have merely carried virus to T cells, which were subsequently infected and rendered incompetent.

3.13. TOGAVIRUSES

Macrophages have been demonstrated to be infected permissively by a variety of togaviruses, including dengue virus, lactate dehydrogenase virus, rubella, West Nile virus, and yellow fever, as well as other togaviruses that result in persistent infections (Chaturvedi, 1987). Macrophages are the principal site of replication for dengue virus (Halstead *et al.*, 1977). *In vivo* studies reveal a decrease in the number of macrophages in mouse spleen and peritoneal cavity, and degenerative changes were noted in many of the macrophages present (Chaturvedi *et al.*, 1983a,b; Nath *et al.*, 1983). Phagocytic activity, attachment to a glass surface, and random migration were all inhibited *in vitro* (Gulati *et al.*, 1982; Chaturvedi *et al.*, 1983b). In contrast to these results, Japanese encephalitis virus infection of macrophages did not inhibit phagocytosis (Chaturvedi *et al.*, 1979).

The infection of mice by dengue virus results in the production of cytotoxic factors (CF) that appear to have a central role in immune suppression *in vivo* or cultures *in vitro* (Gulati *et al.*, 1983, 1986). A cytotoxic factor is generated by T cells infected *in vitro* by dengue virus; this CF subsequently destroys two-thirds of all macrophages. Surviving macrophages produce a second cytotoxic factor (CF2), which in turn is capable of killing lymphoid cells and rendering cultures or mice imcompetent immunologically. In addition, macrophage-produced CF2 mimics dengue virus by suppressing phagocytosis and E-rosette formation by human T cells (Chaturvedi *et al.*, 1982; Gulati *et al.*, 1984). There is also a pathway of formation of soluble suppressor factors which inhibits immune responses. Suppressor T cells produce a factor, SF, that is transmitted by macrophages to recruit a second T-cell subpopulation to produce a second suppressor factor, SF2. This signal transmission requires direct cell–cell contact (Chaturvedi and Shukla, 1981; Chaturvedi *et al.*, 1981; Shukla and Chaturvedi, 1981, 1983; Shukla *et al.*, 1982). This suppressor system is further characterized in the review by Chaturvedi (1987).

Lactate dehydrogenase virus replicates exclusively in macrophages (Herman *et al.*, 1966; Porter *et al.*, 1968). Only 5–20% of mouse macrophages are susceptible to LDV (Stueckemann *et al.*, 1982). The Ia antigen has been identified as the receptor for LDV, which may explain why only a limited number of macrophages (those expressing Ia) are susceptible (Inada and Mims, 1984, 1985). LDV is reported to severely diminish antigen-presenting activity of macrophages, thus resulting in decreased immune functions (Isakov *et al.*, 1982a,b). These same cells have normal phagocytic function. LDV has represented a particularly difficult problem in laboratories studying immune responsiveness. This virus often infects mice without causing any overt symptoms. Therefore, when animals are studied for immune responsiveness after tumors are induced or following infection by other viruses, LDV can complicate the interpretation of induced immune suppression (Riley, 1974). To avoid this complication, it is advised that mice should be periodically checked for LDV infection by testing the levels of lactate dehydrogenase in peripheral blood serum.

Rubella infection of human monocytes/macrophages has been readily demonstrated, as well as infection of lymphocytes (Chantler and Tingle, 1980; Van Der Logt *et al.*, 1980). The functional alterations due to macrophage infection by

rubella are not delineated. Thus, it is possible that these infected cells may contribute to the suppression of migration inhibitory factor production, lymphocyte blastogenesis, and skin test reactions associated with rubella infection or vaccination (Midulla *et al.*, 1972; Ganguly *et al.*, 1976; Buimovici-Klein *et al.*, 1979).

3.14. NONONCOGENIC RETROVIRUSES

Infection of macrophages has been demonstrated for caprine/ovine lentiviruses and lentivirus infection of humans by human immunodeficiency virus (HIV), the etiologic agent of the acquired immune deficiency syndrome (AIDS). Caprine arthritis encephalitis virus (CAEV) replication does not occur within ovine monocytes; however, when they are activated to macrophages they are readily infected (Anderson *et al.*, 1983; Narayan *et al.*, 1983). Although macrophages readily replicate CAEV, the virus does not inhibit macrophage functions such as phagocytosis of latex particles, Fc, and complement receptors or production of hydrolytic enzymes (Narayan *et al.*, 1983). A second ovine lentivirus, visna-maedi, is also known to infect peripheral blood monocytes (Narayan *et al.*, 1982, 1985). The virus is reported to inhibit humoral and cell-mediated immune function of mouse lymphocytes (Svennerholm *et al.*, 1978). Narayan and co-workers (1985) have demonstrated a unique interferon produced in cultures of sheep lymphocytes and macrophages; however, its relationship to altered immune responsiveness is undetermined. Although there is no direct evidence that macrophages mediate immune suppression associated with ovine lentivirus infection, the fact that they are the primary (or only) infected cell suggests so.

HIV is known to be a lymphotropic virus; however, recent reports indicate that macrophages are also productively infected (Gartner *et al.*, 1986; Koenig *et al.*, 1986). Macrophage function in AIDS is normal until late in infection, when there is a degeneration of numerous host functions. More interesting is the role of macrophages as a disseminator of HIV. Recent evidence indicates that macrophages transmit HIV to the brain, with resulting neurologic infection (Koenig *et al.*, 1986). Thus, the failure of macrophages to control infection has a devastating influence on the degeneration of the host.

4. CONCLUSIONS

The importance of monocytes/macrophages in viral-induced immunosuppression is evident, as delineated in the preceding sections. The contribution to immune depression made by these phagocytic cells may be direct, e.g., loss of function, or it may be indirect, whereby macrophages render lymphocytes incompetent through cell–cell interactions or soluble factors. Tables 3 and 4 list the macrophage functions that can be altered by virus infection and some mechanisms by which this is known to occur.

TABLE 4. MECHANISMS OF ALTERATION OF MACROPHAGE FUNCTION BY VIRUSES

Infection of macrophage
Cell death due to productive infection
Persistence of virus—loss of function
Production of immunomodulatory substances by macrophages
IL-1
IL-1 Inhibitor
Interferon-α
Prostaglandins, especially PGE_2
Production of mediators by other cells that regulate macrophage function
Failure to produce lymphokines that regulate macrophage function

Studies on the contribution of macrophages to virus-induced immune suppression suggest that the host alterations and mechanisms by which they occur are almost as diverse as the number of viruses. However, much of the diversity may be attributed to the particular parameters of macrophage and/or lymphocyte functions tested. It is unfortunate that comprehensive studies have not been performed for many of these viruses regarding their effect on immune cell functions. Nevertheless, within the limitations of the studies performed, some generalizations can be deduced. For some virus infections, macrophage functions appear to be unaltered, but lymphoid cells are inhibited, clearly indicating that macrophages are only part of the suppressive mechanisms important in virus infections.

Accessory cell function, as either antigen-processing or -presenting activity, appears to be one of the most sensitive assays for loss of macrophage function. Several studies could demonstrate loss of antigen-presenting activity when phagocytosis was normal (Isakov *et al.*, 1982a,b; Krzystyniak and Dupuy, 1983; Sy and Finberg, 1987). Thus, it is important to test the accessory cell function of macrophages in any study that is valid, to ascertain that infection has "no effect" on macrophage function.

Another important conclusion from these diverse studies is the realization that several functions must be examined to determine whether viral infection is truly altering host function with regard to progression of the infection. Roberts *et al.* (1979) have clearly demonstrated that immunity, as measured by mitogen responses and antigenic stimulation unrelated to influenza, is depressed nonspecifically in influenza infection, while antiinfluenza responses are potent. The authors refer to this response as "immunofocusing." Certainly, the idea that the host concentrates its immune resources on the most threatening intruder for a short period of time until the "alien" is repelled is practical. This same phenomenon is seen for other virus infections, as indicated in Sections 3.4, 3.8.2, and 3.10. Also, the fact these depressed immune responses are transient and the host returns to normal supports this concept.

The immune system's ability to successfully repel virus infections is a good indication that to manipulate the immune system in any virus infection that is not life threatening might be unwise. Alteration of the delicate balance of host

immunity and viral infection might favor the virus as opposed to the host. Since many viruses multiply in cells of the immune system, stimulating that system may provide a better milieu for virus replication. However, in situations such as AIDS, where HIV infection leads to immune cell destruction and ultimately death, immune therapy, perhaps in conjunction with antiviral drugs, seems warranted.

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