Host Defense Mechanisms with Special Reference to Chemokines and Viral Infections

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An important role for the mammalian body is to guard against infection by pathogenic micro-organisms. There are five main classes of pathogens, namely, viruses, bacteria, parasites, fungi, and worms. The complex relationships between these pathogenic micro-organisms and the vertebrate host are perhaps most clearly understood for viruses. The survival of viruses depends on the survival of susceptible hosts. In recent years, chemokines have been shown to play an integral role in the recruitment of cells to sites of infection, thus mediating the healing process. This review will provide an overview of immune responses with reference to viral infections and chemokines.

ABBREVIATIONS

ADCC	Antibody-dependent cell-mediated cytotoxicity
APCs	Antigen presenting cells
BCA	B cell-attracting
CHAK	Chemokine-activated killer cells
CMI response	Cell-mediated immune response
CMV	Cytomegalovirus
Crg	Cytokine responsive gene
CTL	Cytotoxic T lymphocyte
ELR-CXC	Glutamic acid-leucine-arginine-CXC
EMCV	Encephalomyocarditis virus
ENA	Epithelial derived neutrophil attractant
ER	Endoplasmic reticulum
EV	Ectromelia virus

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Introduction

A variety of factors, genetic and immunological, can influence the susceptibility of a host to viral infection. The immune system is composed of innate and adaptive components. Innate components include natural killer (NK) cells, mononuclear phagocytes (macrophages and blood monocytes), complements, and some cytokines. These form the first line of defense. Activation of the host immune system occurs as a result of invasion by microbes. This activation is of paramount importance for the elimination of foreign invaders. Innate immunity is the nonspecific arm of the immune system and comprises noninducible and inducible responses. Innate responses that are noninducible occur immediately after infection and are mediated mainly by unactivated NK cells.[1] Inducible responses also occur early after infection and are triggered by viral infections usually via the induction of interferons (IFNs).[1] Activated NK cells, mononuclear phagocytes, polymorphonuclear cells (PMNs), IFNs, and tumor necrosis factor (TNF), as well as the alternative complement pathway, constitute the immediate-early innate and inducible, but antigen nonspecific, antiviral pathways.[2]

Adaptive responses are elicited later and represent the more advanced arm of the immune response. They consist of B and T lymphocytes that are activated in a specific manner by antigens, resulting in their clonal expansion. This leads to triggering of effector mechanisms, such as the secretion of antigen-specific antibodies by B lymphocytes, and the production of cytolytic effector molecules and cytokines with antiviral and immunomodulatory properties by T lymphocytes. The activation of these responses also leads to the generation of immunological memory to specific antigens.

This review attempts to describe the various facets of the host immune responses in the context of a viral infection and the involvement of chemokines in these responses.

Innate Immunity

Natural Killer Cells

NK cells are large, granular leukocytes and account for up to 15% of human blood lymphocytes. These cells mediate lysis of tumor and virus-infected target cells in a nonmajor histocompatability complex (MHC)-restricted fashion.[3] The absence

ABBREVIATIONS

GKO	Gene knockout
HHV	Human herpes virus
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
ICAM	Intercellular adhesion molecule
IFN	Interferon
IL	Interleukin (e.g., IL-2, IL-12)
iNOS	Inducible nitric oxide synthase
KSHV	Kaposi's sarcoma-associated γ-herpes virus
IP-10	Inducible protein-10
LCMV	Lymphocytic choriom eningitis virus
LFA	Lymphocyte function-associated antigen
Lptn	Lymphotactin
mAB	Monoclonal antibody
MCMV	Murine cytomegalovirus
MCP	Monocyte chemotactic protein
MCV	Molluscum contagiosum virus
MDC	Macrophage-derived chemokine
MHC	Major histocompatibility complex
MHV	Murine hepatitis virus
Mig	Monokine induced by IFN-γ
MIP	Macrophage inflammatory protein
MRP	Macrophage inflammatory-related protein
MSV	Moloney Sarcoma virus
MuLV	Murine leukemia virus
NAP	Neutrophil activating peptide
NK cells	Natural killer cells
NO	Nitric oxide
ORF	Open reading frames
PMN cells	Polymorphonuclear cells
RANTES	Regulated on Activation, Normal T cell Expressed and Secreted
rVV	recombinant vaccinia virus
SDF	Stromal cell-derived factor
TAP	Transporter associated with antigen processing
TCR	T cell surface heterodimer receptor
TNF	Tumor necrosis factor
VCAM	Vascular cell adhesion molecule
VSV	Vesicular stomatitis virus
VV	Vaccinia virus

of B and T lymphocyte antigen receptors on NK cells distinguishes these cells from other lymphoid cells. NK cells usually carry Fc receptors and can be characterized by a number of cell markers. Murine NK cells are $CD3^-$, $CD2^+$, $CD16^+$, asialo$GM1^+$ and $NK1.1^+$.[4,5]

NK cells are activated early after a virus infection, and this activation is due partly to the production of IFNs α and β.[6,7] Interleukin (IL)-2 and IL-12 are also important factors in the activation of NK cells.[8-10] The importance of NK cells in antiviral immunity have been demonstrated in a number of viral infections, such as vaccinia virus (VV),[11,12] murine cytomegalovirus (MCMV),[13] human CMV,[14] and herpes simplex virus (HSV).[15] Intraperitoneally inoculated adult mice depleted of NK cells with antisera to asialoGM_1 or with monoclonal antibody (mAb) to the NK1.1 alloantigen showed enhanced virus growth in organs following infection with VV,[11,12] MCMV,[16] murine hepatitis virus (MHV),[11] influenza virus,[17] and ectromelia virus (EV).[18] Antiviral effects of NK cells are mediated through direct lytic activity of virus-infected cells, through antibody-dependent cell-mediated cytotoxicity[3] and by the production of antiviral cytokines such as IFN-γ or TNF.[19,20] Studies conducted at early times after lymphocytic choriomeningitis virus (LCMV) or MCMV infection demonstrate that NK cells express high levels of IFN-γ mRNA in murine spleen compartments.[21]

Recent studies have implicated a number of chemokines (see section "Factors Involved in the Immune Response to Virus Infections") in the recruitment and activation of NK cells. CC and CXC chemokines (refer to Table 2 for new nomenclature for chemokine system) can induce NK cell migration in vitro,[22] whereas several CC chemokines have been shown to augment NK-specific cytolytic responses in a dose-dependent fashion.[22] The IFN-inducible protein-10 (IP-10) and lymphotactin can induce the chemotaxis and calcium mobilization in CC chemokine-activated killer cells.[23] The presence of chemokine receptors specific for MCP-1 (monocyte chemotactic protein),[24] IP-10, and human Mig (monokine induced by IFN-γ) on IL-2-activated NK cell clones is consistent with a role for the corresponding chemokines in NK cell recruitment. It has been demonstrated that MCMV infection induces liver NK cell inflammation and protection through MIP-1 (macrophage inflammatory protein)-dependent pathways.[26] **INSERT REF NO. 25 BETWEEN 24 AND 26**Activated NK cells may be an important source of CC chemokines in human immunodeficiency virus type 1 (HIV-1)-infected individuals and may suppress HIV-1 replication by CC chemokine-mediated mechanisms, in addition to classic NK-mediated lytic mechanisms.[27]

Macrophages/Monocytes

Macrophages and blood monocytes are bone marrow–derived mononuclear phagocytic cells. These cells play a major role as antiviral effectors of both the innate and adaptive immune responses.

There are several ways in which macrophages promote the generation of antiviral immune responses. Production of cytokines, such as IFN-α and IL-12 by macrophages, enhances NK cell cytotoxicity and cytokine production and promotes generation of a cell-mediated immune (CMI) response.[28,29] Phagocytosed extracellular antigens presented by macrophages to $CD4^+$ T lymphocytes in association with MHC class II molecules can initiate antiviral immune responses. Macrophage expression of MHC class II molecules is up-regulated following activation with IFN-γ, which in turn may increase antigen presentation to $CD4^+$ T lymphocytes.[30] Macrophages can also be induced to express other cell surface molecules that are important in antigen presentation such as B7, ICAM-1 (intercellular adhesion molecule) and LFA-3 (lymphocyte function-associated antigen).[31-33] IFN-γ-activated macrophages can restrict replication of HSV-1, VV, and EV, and this is mediated substantially through the induction of iNOS (inducible nitric oxide synthase).[34,35] However, production of high levels of nitric oxide (NO) by macrophages can suppress T lymphocyte proliferation and antibody production.[36,37] Activated macrophages are also able to restrict virus replication in contiguous virus-infected epithelial or fibroblast cells in an NO-dependent fashion.[38]

Macrophages can be induced to produce chemokines such as Mig, Crg-2 (cytokine responsive gene), murine homologue to human IP-10, MCP-1, MDC (macrophage-derived chemokine),

and MRP-2 (macrophage inflammatory protein-related protein).[39-43] Thus, macrophages can also influence the outcome of an infection through recruitment of leukocytes. For instance, infection of human monocytes with influenza A virus results in a rapid expression of the mononuclear cell attracting CC chemokines.[44] Additionally, the T lymphocyte and NK cell chemoattractants MuMig (murine Mig) and Crg-2 are expressed in $CD11b^+$ cells, presumably macrophages, at the margin between the red and white pulps in the spleen after *Toxoplasma gondii* infection.[45] Chemokines are also produced by macrophages infected with *Listeria monocytogenes*, and their release is differentially regulated by different cytokines.[46] Neutralizing antibody studies have implicated MCP-1 as a major mediator of macrophage recruitment in several inflammatory models.[47] In MCP-1 transgenic mice, monocytes/macrophages are recruited to sites of MCP-1 expression.[48,49] In addition, mice deficient in MCP-1 or the receptor for MCP-1 (CCR2) were unable to recruit monocytes/macrophages 72 h after intraperitoneal administration of thioglycollate.[50] Other than MCP-1, CC chemokines, such as MIP-1α and MIP-1β, have also been shown to be potent monocyte chemoattractants.[51] In HIV-1 infection, it has been found that macrophage-tropic strains of this lentivirus utilize the chemokine receptor CCR5 for entry and fusion and that the natural ligands MIP-1α, MIP-1β, and RANTES (Regulated on Activation, Normal T cell Expressed and Secreted) inhibit viral entry (see section "Factors Involved in the Immune Response to Virus Infections").

Polymorphonuclear Cells

PMN cells are regarded primarily as a major component in natural immunity to bacteria. However, some evidence suggests that they may play an important role in the early nonspecific defense against viral infections. For instance, HSV-2 virions were found to be phagocytosed in vesicular lesions of penile skin.[52] In a study using influenza virus, it was found that PMN-like cells were important for early protection of mice.[53] In vitro studies have shown that PMNs are antiviral for VV, and this virucidal action is believed to be related to the induction of oxidative metabolism.[54] The most definitive evidence comes from studies with the mouse pathogen, EV. Acute depletion of neutrophils with specific mAb transformed the normally benign infection in genetically resistant C57BL/6 mice to fulminant disease with 100% mortality (Dr G. Karupiah, JCSMR, personal communication**PROVIDE MONTH AND YEAR**). PMNs can also be induced to produce NO, which also has antiviral properties.[55] Production of TNF and IFNs during viral infections has been shown to augment the phagocytic activities of PMN.[56]

IL-8, a product of virus-infected fibroblasts, is a chemokine and granule release stimulus for PMN and may mediate some of the immunomodulatory effects of TNF observed on these cells.[57] It was recently demonstrated that exposure of neutrophils to various microbial pathogens led to an increase in IL-8 and MIP-1α, suggesting the importance of neutrophils in the regulation of inflammation and the control of infection.[58,59] In MIP-2 (macrophage inflammatory protein) transgenic mice, it has been demonstrated that neutrophils are recruited to sites of MIP-2 expression.[60] Evidence also suggests that many or all of the ELR-CXC (glutamic acid-leucine-arginine-CXC) chemokines such as NAP-2 (neutrophil-activating-peptide) and ENA-78 (epithelial-derived neutrophil attractant) have neutrophil attractant capacity, possibly mediated through interaction with a shared CXC chemokine receptor, the so-called IL-8 receptor B now known as CXCR2.[61] In IL-8 receptor homologue gene knockout (GKO) mice, human IL-8 was unable to chemoattract neutrophils.[62] These mice demonstrate a paradoxical response to acute and chronic infection with *Listeria monocytogenes*.[63] Overexpression of IL-8 in IL-8 transgenic mice demonstrated a decrease in L-selectin expression on the neutrophil surface and impaired thioglycollate-mediated neutrophil extravasation.[64]

Adaptive Immunity

Antigen Presentation and T-Lymphocyte Activation

T lymphocytes recognize antigens (peptides) in association with host MHC molecules on antigen-presenting cells (APCs).[65] Antigen recognition by T lymphocytes is mediated via a T-cell surface heterodimer receptor (TCR).[66]

Two classes of MHC molecules exist, which differ in structure, composition, and the nature of the peptide they bind.[67] The MHC class I-restricted $CD8^+$ CTL (cytotoxic T lymphocyte) recognize antigenic peptides synthesized within target cells.[68,69] These antigens are degraded in the cytosol by proteosomes, and the resulting peptide fragments are translocated to the endoplasmic reticulum (ER) by TAP (transporter associated with antigen processing) molecules where the MHC molecules are present.[70,71] The peptides then bind to the class I MHC molecules and are ultimately transported to the cell surface. On the other hand, class II MHC-restricted $CD4^+$ helper T (Th) lymphocytes recognize peptides derived exogenously.[72] Upon binding of degraded peptides to the MHC class II molecules in the ER, the complex is then presented on the cell surface.[67]

Interaction between the TCR and peptide-MHC molecules, although essential, is insufficient to initiate activation of T lymphocytes.[73] A range of accessory molecules are required for costimulatory interactions between T lymphocytes and APC, including ICAM-1,[74] LFA-3,[75] and VCAM-1 (vascular cell adhesion molecule).[74-76] Additionally, B7-1 (CD 80), B7-2 (CD 86), or B7-3 on APC and CD28 on T lymphocytes have also been shown to be vital for T lymphocyte activation.[77] Interaction of CD28 with B7-1/B7-2 results in cell cycle progression and IL-2 production.[78] More recently, TCR and CD28 ligation have been shown to play an important role in the regulation of chemokine gene expression in T lymphocytes.[79,80] The requirement for T lymphocyte activation may vary among T lymphocyte subsets.[81]

Cytotoxic T Lymphocytes (CTLs)

The role of $CD8^+$, MHC-class I restricted cytotoxic T lymphocytes (CTLs), is important in the recovery from primary virus infection. CTL antiviral responses are at their peak following infection by EV, LCMV, HSV, or influenza virus.[82-85] The ability of CTLs to mediate recovery from poxvirus infection in vivo has been demonstrated by adoptive transfer experiments.[86,87]

CTL activity has usually been linked to class I MHC-restricted cytotoxicity. However, class II MHC-restricted $CD4^+$ CTL have also been described against LCMV, influenza virus, vesicular stomatitis virus (VSV), and MHV.[88-91]

Cytolytic activity of CTLs is mediated through perforin or through interactions with Fas antigen via calcium (Ca)-dependent or Ca-independent manner**CORRECT WORD CHOICE?**, respectively.[92] Results obtained from perforin GKO mice provide strong evidence that perforin-mediated cytotoxicity is important in the control of some virus infections such as LCMV,[93] EV (Dr. G. Karupiah, JCSMR, personal communication**PROVIDE MONTH AND YEAR**) but not VV.[94] Calcium-independent cytotoxicity is mediated through the binding of Fas molecule on target cells with its ligand (FasL) found on activated T lymphocytes, which result in apoptosis.[95]

Studies have shown that $CD8^+$ T lymphocytes can secrete a wide range of cytokines, including IFN-γ, IL-2, IL-3, TNF, and GM-CSF. There is some evidence to suggest that IFN-γ is involved in the antiviral action of $CD8^+$ CTL.[87]

Based on the findings described above, it has been proposed that cytokines are important in the control of cytopathic viruses (e.g., VV), whereas cytotoxicity is critical in the control of infection with noncytopathic viruses (e.g., LCMV).[96] However, findings made with EV, a cytopathic virus closely related to VV, question the simplicity of this proposition. Recovery from EV clearly requires the participation of perforin-dependent cytotoxicity and cytokine (IFN-γ) producing T lymphocytes.[97]

While lytic activity is regarded as an important component of $CD8^+$ T lymphocyte-mediated HIV-1 suppression, cell-free supernatants from cultures of activated $CD8^+$ T lymphocytes are able to dramatically inhibit HIV-1 infection and fusion in both T lymphocytes and macrophages. The elusive $CD8^+$ cell-derived HIV-suppressive factors were identified by Cocchi and colleagues who attributed the HIV-inhibitory activity of $CD8^+$ T lymphocyte to the combined actions of the CC chemokines MIP-1α, MIP-1β, and RANTES.[98] Furthermore, it was shown that these CC chemokines, together with granzyme A, are localized in the cytolytic granules of HIV-1-specific $CD8^+$ CTLs, and their secretion together facilitates lysis of virion-producing cells

and inhibition of free virus.[99] In addition, a recent report showed that one mechanism for the induction of HIV-1-specific cytotoxicity was mediated by RANTES via the chemokine receptor CCR3.[100]

Helper T Lymphocytes (CD4⁺)

$CD4^+$ T lymphocytes are activated during virus infections and can therefore influence the immune response to infection. This is regulated through their effect on antibody production, CTL, and macrophage activity, as well as production of antiviral cytokines.[101]

Varying results have been reported on the role of $CD4^+$ T lymphocyte in induction of antiviral CTL responses. For instance, $CD4^+$ T lymphocyte depletion studies in vivo indicate that help is important for induction of CTL responses to Moloney Sarcoma virus (MSV), LCMV, and EV.[102-104] On the other hand, other studies suggest that this may not be the case as demonstrated by similar depletion studies in vivo during EV and VV and LCMV infections.[105,106] The reasons for these differences are not clear but may be related to depletion protocols and the virus strain used.

$CD4^+$ T lymphocytes are also able to mediate antiviral activity through induction and secretion of antiviral cytokines, such as IFN-γ. $CD4^+$ T lymphocytes may also have direct antiviral cytotoxic effects, as is the case against influenza virus–infected cells.[107] Early during the course of virus infections, IgM antibody can be produced in the absence of $CD4^+$ T lymphocytes, but this cell population is critical for inducing a switch from IgM to IgG production in B lymphocytes.[108,109]

Th1 and Th2 Paradigm

The Th1/Th2 paradigm has dominated the interpretation of data obtained from in vitro and in vivo studies on T lymphocyte cytokine production. More than 10 years ago, Mosmann and Coffman first reported that long-term lines of murine $CD4^+$ T lymphocytes could be grouped into 2 subsets, which they termed T helper type 1 (Th1) and T helper type 2 (Th2), based on their distinctive cytokine production patterns.[110] Their activities have been correlated to types of cytokines secreted by Th lymphocytes. Th1 clones produce cytokines such as IFN-γ, IL-2 and these are associated with cell-mediated immunity, whereas Th2 clones produce cytokines associated with humoral immunity, for example, IL-4, IL-5, and IL-10.[110,111] Many T lymphocyte clones cannot be classified as either Th1 or Th2, as they produce both Th1 and Th2 cytokines, and these cells are described as Th0 lymphocytes.[112,113] It has been proposed that during a polarized Th1 or Th2 response, the spectrum of cytokine production of the T lymphocyte population is skewed toward Th1 or Th2.[114]

It is now clear that these patterns of cytokine production are not restricted to $CD4^+$ T lymphocytes, because NK cells and $CD8^+$ T lymphocytes can also produce Th1 and Th2 cytokines. Hence, a more appropriate terminology for the 2 profiles of cytokine production and the response generated is type 1 (T1) and type 2 (T2).[115]

Factors that favor the development of Th1 or Th2 lymphocytes include antigen concentration, the type of APC and accessory molecule that is expressed by the APC, and the type of cytokines present during initial priming of T lymphocytes.[116-119] The latter is believed to be the most important factor. For instance, IL-4 results in the development of Th2 lymphocytes, whereas IL-12 presence tends to favor the development of Th1 lymphocytes.[118,119] Both cytokines can inhibit the development of the alternative response.

In addition to effector function, activated T lymphocytes also acquire different migratory capacities, and this is critical to efficient regulation of the immune response. The regulation of leukocyte migration is an intricate process involving the participation of adhesion molecules such as ICAM-1, ICAM-2, ICAM-3, VCAM-1, selectins, and integrins, as well as chemokines and chemokine receptors.[120-122] Austrup and colleagues showed that P- and E-selectin mediate recruitment of Th1, but not Th2, lymphocytes into inflamed tissues.[123] Recently, it was reported that human Th1 and Th2 lymphocyte lines differentially express chemokine receptors and, accordingly, differentially migrate in response to different chemokines.[124,125] These studies indicate that chemokines are part of effector and amplification mechanisms of polarized Th1- and Th2-mediated immune responses, and their recep-

tors might serve as Th1 (T1) versus Th2 (T2) markers.

B Lymphocytes and the Humoral Immune Response

B lymphocyte-antigen recognition is mediated by membrane immunoglobulin antigen receptors, which mediates the internalization of antigen, which is then degraded and presented in association with class II MHC molecules. For the production of antibody, B lymphocytes require stimulatory signals from activated $CD4^+$ T lymphocytes.

Antibodies are important in preventing reinfection with many viruses.[126] Antibody-mediated mechanisms that are thought to control virus infections are the neutralization of virus particles and the cytolysis of antibody-coated infected cells. Although an antibody has little role in the recovery of a primary viral infection, it is important in the recovery from some viral infections like Sindbis virus, VSV, and EV.[97,127-129] Viruses producing systemic disease characterized by a plasma viremia appear to be controlled principally by circulating antibody.

The killing of virus-infected cells can also be mediated by the binding of a complement to an antibody on virus-infected cells. This triggers the classical pathway of complement-mediated cytotoxicity. Several studies have demonstrated that complement-mediated lysis may be important in the control of virus infections such as LCMV.[130] The importance of complement in virus infection is also reflected by the ability of some viruses to block the complement pathway.[131]

There is little information on chemokine activities and chemokine receptor expression on B lymphocytes. Two newly identified CC chemokine receptors, CCR6 and CCR7, were reported to be present on T and B lymphocytes, but no ligand was found that induces chemotaxis of B lymphocytes.[132,133] A CXC chemokine, SDF-1 (stromal cell-derived factor), that was originally described as a growth factor for progenitor B lymphocytes, is chemotactic for pre- and pro-B lymphocyte cell lines, but it does not attract mature B lymphocytes.[134] Another study showed that IL-8 and IP-10 induced a significant chemokinetic response of human B lymphocytes.[135] Recently, it was demonstrated that BCA-1 (B cell-attracting chemokine), a CXC chemokine expressed in lymphoid tissues, selectively attracts B lymphocytes via the chemokine receptor CXCR5.[136] With respect to regulation of antibody production, it was found that IL-8 selectively inhibited IgE and IgG4 production induced by IL-4, whereas RANTES and MIP-1α selectively enhanced production of these classes of antibodies.[137] More recently, a novel CC chemokine produced by activated murine B lymphocytes and that acts selectively on activated T lymphocytes has been identified.[138]

Factors Involved in the Immune Response to Virus Infections

Interferons (IFNs)

There are 3 distinct species in the IFN family: IFN-α, IFN-β (classified as type I IFN), and IFN-γ (classified as type II IFN). The IFNs are inhibitory against a number of DNA and RNA viruses. They mediate their antiviral effect through synergy with each other, as well as with the TNFs.

The antiviral activity of IFNs, the property that led to their discovery nearly 50 years ago, is mediated by a number of intracellular antiviral pathways that are activated by IFNs.[139] IFNs are able to induce antiviral mechanisms through the synthesis of a number of proteins that inhibit viral infection by interfering with the regulation of viral and cellular macromolecular synthesis and degradation (Table 1). In the presence of double-stranded RNA, 2,5 oligoadenylate synthetase, which is induced by IFN-α, -β, and -γ, activates a ribonuclease that degrades host and virus RNA.[140] The Mx protein, which is localized in the nucleus, blocks the replication of influenza virus in cultured cells as well as in mice without affecting the replication of other viruses.[141] Several studies have demonstrated that IFNs are able to induce changes in the membrane of cells, which may influence the adsorption and penetration of cells by certain viruses.[141] Other evidence suggests that inhibition of virus replication in macrophages by IFN-γ is mediated through production of NO.[35] The RNA-dependent protein kinase, PKR, is believed to be a key component in the control of protein synthesis in IFN-treated and virus-infected cells. Induction of protein kinase PKR by IFNs leads to phosphorylation of eukary-

Table 1 | **Interferon Inducible Proteins**

Proteins	Characteristics	Inducer
2´5´ $(A)_n$ synthetase families	2´5´ $(A)_n$ synthesis	α, β > γ
p68 kinase	Protein phosphorylation	α, β > γ
Indoleamine 2,3-dioygenase	Tryptophan degradation	γ > α, β
P56	Trp-tRNA synthetase	γ > α, β
GBP/g67	Guanylate binding	γ > α, β
Mx families	Anti-influenze virus	α, β > γ
IRF-1	Transcription factor	α, β, γ
IRF-2	Transcription factor	α, β
MHC class I	Immune system	α, β, γ
MHC class II	Immune system	γ
β2-microglobulin	Immune system	α, β, γ
IP-10/Crg-2	Chemokine	α, β, γ
Mig	Chemokine	γ
I-TAC	Chemokine	γ
IFN-β	Cytokine	γ
NOS2	NO synthase	γ

Abbreviations: GBP = Guanylate binding protein; IRF = Interferon regulatory factor; MHC = Major histocompatibility complex; NOS2 Inducible isoform of nitric oxide synthase; IP = IFN-inducible protein; Crg = cytokine response gene; MIG = monokine induced by IFN-; I-TAC = inteferon-inducible T cell alpha chemoattractant.

otic initiation factor 2α (eIF2α), which inhibits protein synthesis and protects cells from virus infection.[142] Induction of a number of chemokines by IFNs, such as Mig and IP-10/Crg-2, plays an important role in the inflammatory and healing process during infection. On the other hand, IL-8 can inhibit the antiviral action of IFN-γ through reduced 2′,5′-A oligoadenylate synthetase activity.[143,144] There are many more proteins that can be induced by IFNs and that can exert antiviral effects.

Several studies have shown that IFN-α and IFN-β contributed to antiviral function in vivo. It was demonstrated that administration of antibodies against these factors to mice during infection with HSV, MSV, VSV, Newcastle disease virus, EV, and influenza virus increased the intensity and severity of these infections, directly indicating a protective role of these factors.[145,146] Studies using mice that are deficient in type I IFN receptor (IFN-α/β R GKO) further support the importance of type I IFNs in the early defense against virus infection.[147] Despite being armed with the capacity to mount an otherwise normal immune response, the IFN-α/β R GKO mice are highly susceptible to several viruses.

Tumor necrosis factors (TNFs)

TNF-α and TNF-β, now known as TNF and lymphotoxin, respectively, have been reported to have antiviral activity against a number of RNA and DNA viruses in vitro, and this activity was found to be dependent on endogenous IFN-β.[148,149] On the other hand, others have demonstrated that the antiviral activity of the TNFs is independent of IFN-α, -β, and –γ.[150] TNF and lymphotoxin act synergistically with the antiviral activity of IFN-α, -β, and -γ on a variety of cell types against a number of RNA and DNA viruses. IFN-γ, a potent inhibitor of VV replication, also synergizes with TNF. The importance of TNF in recovery from viral infections has been demonstrated by the administration of recombinant TNF or antibodies against TNF. For instance, recombinant TNF inhibited the replication of encephalomyocarditis virus (EMCV) and HSV.[151,152] Although the mechanism(s) are still not known, a recombinant VV encoding TNF-α was found to be attenuated in vivo by a mechanism that was neither dependent on the induction of cell-mediated nor humoral immunity.[153]

Interleukin-12 (IL-12)

IL-12 is predominantly produced by macrophages and monocytes. This heterodimeric cytokine has a variety of effects on T lymphocytes and NK cells. These include its ability to induce IFN-γ secretion by T lymphocytes and NK cells, to act as a growth factor for activated T lymphocytes and NK cells, to enhance the lytic activity of NK cells, and to facilitate specific CTL responses. IL-12 plays a unique role in regulating the balance between the type 1 and type 2 subsets of T helper cells.[119]

Administration of recombinant IL-12 to mice results in protection against a number of viruses such as VSV, EMCV, murine leukaemia virus (MuLV), LCMV, and MCMV.[154,155] Elevated levels of IL-12 heterodimer proteins are observed during MCMV infection.[10] Studies in IL-12 GKO mice established the necessity for IL-12 to generate a T1 cytokine response that is often required for elimination of intracellular pathogens.[156] Furthermore, studies have shown that the antiviral activity of IL-12 is mediated through endogenous IFN-γ.[157]

In addition, IL-12 neutralization by antibody treatment in mice infected with MCMV or EV resulted in significantly higher virus titers recovered from mice organs (Dr. G. Karupiah, JCSMR, personal communication**PROVIDE MONTH AND YEAR**).[10]

Interleukin-4 (IL-4)

IL-4 is an immunoregulatory cytokine produced predominantly by Th2 cells. IL-4 is required for the optimal development of this cell subset, while it inhibits the growth of Th1 cells. This cytokine is also produced by mast cells and basophils. IL-4 is produced predominantly by T lymphocytes during virus infections in vivo.

This cytokine blocks IL-2-dependent proliferation of T lymphocytes in vitro by down-regulating IL-2 receptors.[158] IL-4 can inhibit the production of IFN-α and IFN-β, as well as blocking the capacity of IFNs to protect cells from virus infection.[159,160] IL-4 may also antagonize the actions of IL-12, which is an important factor for the establishment of type 1 responses.[161] Treatment of mice with recombinant IL-4 delays clearance of HSV-1 and influenza virus.[162,163] Recombinant VV encoding IL-4 exhibits enhanced virulence compared to a control virus, and this is associated with decreased expression of type 1 cytokines, as well as decreased CTL activity and NO production.[164]

Chemokines

Chemokines are low molecular weight chemoattractant cytokines secreted by a variety of cells, including leukocytes, epithelial cells, endothelial cells, fibroblasts, and numerous other cell types.[165] They are produced in response to exogenous stimuli such as viruses and bacterial LPS (lipopolysaccharide), and endogenous stimuli such as IL-1, TNF, and IFNs.[166] These factors mediate chemotaxis and leukocyte activation. They also regulate leukocyte extravasation from the blood and/or lymph vessel luminal surface to the tissue space, the site of inflammation. The release of chemokines and the matrix upon or through which the cells traverse governs the selective trafficking of leukocytes. As well as playing this early role in host defense, chemokines influence other leukocyte subsets, and so influence the composition of a cellular infiltrate, the outcome of infection, and the level of tissue damage.

To date, more than 60 different chemokines have been described (Table 2). A protein with 2 instead of 4 conserved cysteines, lymphotactin (C chemokine), and a chemokine-like structure with 3 amino acids between the 1st 2 cysteines (CX_3C chemokine) family containing a single member each (fractalkine/neurotactin) has recently been characterized.[167,168] AUTHOR: PLEASE CLARIFY THIS SENTENCE. ARE YOU IDENTIFYING A PROTEIN FAMILY?

Chemokine receptors belong to the 7 transmembrane spanning family of G protein-coupled receptors. Chemokines have 2 main sites of interaction with their receptors, one in the N-terminal region and the other within an exposed loop of the backbone that extends between the 2nd and 3rd cysteine.[169] The N-terminal binding site is essential for triggering of the receptor. The discovery of chemokine receptors appears to be growing rapidly. There are now 15 known chemokine receptors, many of which exhibit multiple ligand specificity, indicating that redundancy and versatility are characteristic for the chemokine system.

Table 2 | **Chemokine Nomenclature**

Systematic Name	Ligand	Receptor
CC Chemokine		
CCL1	I-309	CCR8
CCl2	MCP-1	CCR2
CCL3	MIP-1α	CCR1, CCR5
CCL4	MIP-1β	CCR5
CCL5	RANTES	CCR1, CCR3, CCR5
CCL7	MCP-3	CCR1, CCR2, CCR3
CCL8	MCP-2	CCR3
CCL11	Eotaxin	CCR
CCL13	MCP-4	CCR2, CCR3
CCL14	HCC-1	CCR1
CC	L15	MCC-2/Lkn-1/MIP-1γ
CCR1, CCR3		
CCL16	HCC-4/LEC	CCR1
CCL17	TARC	CCR4
CCL18	DC-CK1	Not known
CCL19	NIP-3β/ELC/exodus-3	CCR7
CCL20	NIP-3α/LARC/exodus-1	CCR6
CCL21	6Ckine/SLC/exodus-2	CCR7
CCL2	MDC/STCP-1	CCR4
CCL23	MPIF-1	CCR1
CCL24	MPIF-2/Eotaxin-2	CCR3
CCL25	TECK	CCR9
CCL26	Eotaxin-3	CCR3
CCL27	CTACK/ILC	CCR10
CXC Chemokine		
CXCL1	GROα/MGSA-α	CXCR2,CSCr1
CXCL2	GROβ/MGSA-β	CXCR2
CXCL3	GROγ/MGSA-γ	CXCR2
CXCL4	PF4	Not known
CXCL5	ENA78	CXCR2
CXCL6	GCP-2	CXCR1, CXCR2
CXCL7	NAP-2	CXCR2
CXCL8	IL-8	CXCR1, CXCR2
CXCL9	Mig	CXCR3
CXCL10	IP-10	CXCR3
CXCL11	I-TAC	CXCR3
CXCL12	SDF-1α/β	CXCR4
CXCL13	BLC/BCA-1	CXCR5
CXCL14	BRAK/bolekine	Not known
C Chemokines		
XCL1	Lymphotactin/SCM-1α	XCR1
XCL2	SCM-1β	SCR1
CX3C Chemokine		
CS3CL1	Fractalkine/neurotactin	CX3CR1

Table 3 | **Anticytokine Strategies Encoded by Viruses**

Function	Gene/Protein	Virus	Mechanism
VTNFR	M-T2	MV	binds rabbit TNF
	CrmB	CPV	binds rabbit TNF and LT-α
	CrmC	CPV, VV	binds TNF
	CrmD	CPV, EV	binds rabbit TNF and LT-α
	CrmE	CPV	binds TNF
	UL144	HCMV	TMFR homolog
VIL-1βR	B15R	VV	binds IL-1β
vIFN-γR	M-T7, B8R	MV, VV, CPV	binds IFN-γ
vIFN-α/βR	oBI8R	VV	binds type I IFNS
vCSF-1R	BARF-1	EBV	binds CSF-1
vGMCSF	GIF	OV	binds GMCSF
vIL-18BP	MC54	MCV	binds IL-18
	MC53	MCV	binds IL-18
	D7L	EV, VV, CPV	binds IL-18
VIL-10	BCRF-1	EBV	IL-10 activity down-regulates Th1 response

Abbreviations: CPV = cowpox virus: MV = myxoma virus; EV = ectromeila virus; EBV = epstein barr virus; VV = vaccinia virus; MCV = molluscum contagiosum virus.

Chemokines in Viral Infections

Chemokine Binding Proteins Encoded by Viruses

A number of viruses, particularly members of the poxvirus, herpesvirus, and retrovirus families, have adapted to the vertebrate immune responses by capturing and modifying cellular genes that regulate the host immune system (described below). Included among these host-derived virus genes are modified versions of receptors and ligands for cytokines and chemokines. The various cytokine receptor and ligand homologs encoded by viruses are listed in Table 3 and will not be discussed in this review.

Poxviruses

Poxvirus genomes encode several proteins that inhibit specific elements of the host immune system including a secreted protein with high affinity binding to virtually all known CC chemokines (Table 4).[170] The human cutaneous poxvirus, molluscum contagiosum viruses (MCV) types 1 and 2, contain chemokine-like genes that encode proteins that are able to antagonize the chemotactic activity of human chemokines.[171] Myxoma virus M-T7 protein binds many CC, CXC, and C chemokines and modulates the infiltration of leukocytes into infected tissues.[172] Alcami and colleagues reported that a soluble 35 kD protein encoded by VV strain Lister has chemokine-binding activity,[173] and similar proteins are produced by 11 orthopoxviruses representing 3 species: VV, cowpox, and camelpox.[170] It was reported that the virus chemokine-binding protein binds CC chemokines with high affinity and inhibits their ability to induce signal transduction and cell migration in vitro.[173]

Herpesviruses

Human herpesvirus 8 (HHV-8), which is a Kaposi's sarcoma-associated γ-herpesvirus (KSHV), synthesizes several vCks, namely, vMIPI, vMIPII, and vMIPIII. These molecules have similarity to the CC chemokine, MIP-1α.[174,175] vMIPII functions as a competitive antagonist as it binds with high affinity to both CC and CXC chemokine receptors and inhibits calcium mobilization upon subsequent chemokine stimulation.[176] vMIPI appears to be a selective agonist for CCR8, a receptor that is expressed primarily on T cells of the T helper 2 (Th2) phenotype.[177] HHV-8 also encodes a virus-encoded chemokine receptor homolog, termed ORF-74, which binds to a collection of CXC and CC chemokines.[178] ORF-74 activity is thought to contribute to the formation of highly vascularized tumors; however, the role of this molecule in this process is yet to be fully elucidated. Interestingly,

Table 4 | **ANTICHEMOKINE STRATEGIES ENCODED BY VIRUSES**

Membrane Chemokine Receptor-like Protein	
Swinepox	K2R
Sheepox	Q2/3I
Murine CMV	M33
Human CMV	US27, US28, UL-33
Herpesvirus Salmiri	ECRF-3
KSHV	ORF-74
Chemokien Homologue	
Molluscum contagiosum	MC1 48R
KSHV	K4, K6
Human herpesvirus-6	U83, DR1, DR6
Soluble Binding Protein	
Vaccinia	B29R, 35 kDa, CKBP
Myxoma	M-T7, M-T1
Various Orthopoxviruses	35kDa CKBP

Abbreviations: KSHV = Kaposi's Sarcoma herpesvirus; CKBP = chemokine binding protein.

CXC chemokines CXCL10 and CXCL12 each inhibit signaling by ORF-74.[179] This may have an important therapeutic application in inhibiting the effects of ORF-74.

Human cytomegalovirus (HCMV) is a species-restricted β-herpesvirus. HCMV has been linked with a variety of human syndromes, including pneumonitis, obliterative bronchiolitis, and vascular injury-associated atherosclerosis.[180,181] HCMV infects epithelial, smooth muscle, and white blood cells in vivo causing acute, latent, and chronic infections. HCMV has long been known to possess open reading frames (ORFs) encoding 7 transmembrane (7TM) proteins (US27, US28, UL33, and UL78).[182] The HCMV chemokine receptor homolog US28 induces second-messenger signaling, including calcium flux in response to the CC chemokines CCL2, CCL3, CCL4, and CCL5.[183] Thus, HCMV can alter the chemokine environment of infected cells through strong sequestering of CC chemokines, mediated principally by expression of the US28-encoded chemokine receptor. Therefore, US28 binding to chemokines inhibits both leukocyte chemotaxis and activation of effector function.

Human Cytomegalovirus (HCMV) Infection

Virus-induced alterations in the cellular expression of chemokines may be important in directing the migration of specific leukocyte subsets to sites of infection, thereby playing a pivotal role in viral pathogenesis. For instance, HCMV infection of human fibroblasts resulted in significantly increased expression of IL-8.[184] The increase in IL-8 production has functional consequences, as demonstrated by the ability of supernatants from HCMV-infected fibroblasts to significantly enhance neutrophil transendothelial migration. Neutrophils play an important role in the dissemination of HCMV throughout the body, and thus HCMV-induced neutrophil recruitment would be expected to enhance HCMV dissemination.

Human Immunodeficiency Virus (HIV) Infection

The CC-chemokines RANTES, MIP-1α, and MIP-1β have now been identified as soluble suppressors of macrophage-tropic, but not T lymphocyte cell line-tropic, HIV infection in vitro.[98] The molecular mechanism of HIV suppressor activity by chemokines has been revealed to occur at the level of chemokine receptors. The orphan chemokine receptor, designated fusin, is the co-receptor for fusion and entry of the T lymphocyte cell line-tropic form of HIV-1.[185] This receptor allowed for entry of T lymphocyte cell line-tropic form of HIV-1, but was not permissive for macrophage-tropic isolates. Subsequent studies have shown that fusin is a receptor for the CXC

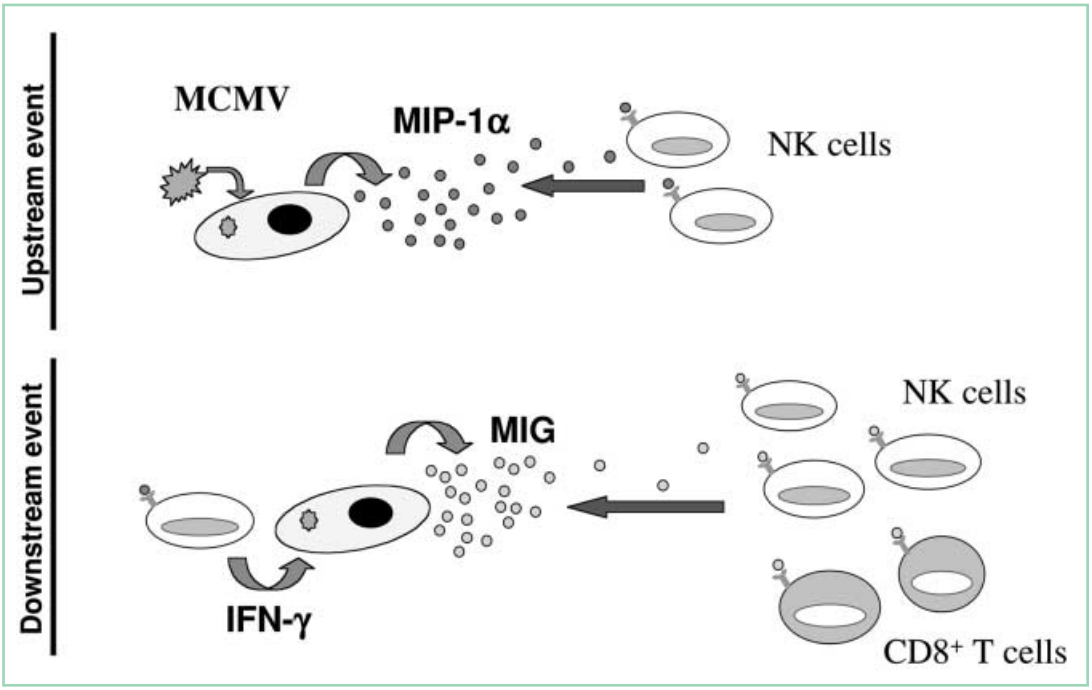

Figure 1. A model of chemokine function during a murine cytomegalovirus (MCMV) infection. During viral infection, chemokines perform two functions; the first is the recruitment of effector cells to the site of infection and the second is the activation of those effector cells. These activated cells can trigger the killing of virally infected cells through cytolytic activity, as well as a capacity to produce IFNs leading to a variety of anti-viral mechanisms as well as a secondary wave of chemokine release which recruit yet more effector cells.

chemokine SDF-1, hence its even more recent redesignation as CXCR4.[186] The co-receptor for macrophage-tropic HIV-1 has also been identified.[187,188] Here the chemokine receptors CCR5 and, for some HIV-1 strains, CCR3 are implicated. CCR5 has as its ligands RANTES, MIP-1α, and MIP-1β, the same chemokines that act as inhibitors of macrophage-tropic HIV-1.[98] Recent genetic evidence suggests that individuals homozygous for a CCR5 deletion mutant are resistant to HIV infection.[189]

Interferon-Inducible Chemokines in the Control of VV Infection

As described earlier, IFNs have been shown to play an important role in the control of poxvirus replication by mediating antiviral activity through the induction of several other proteins such as IP-10 and Mig. Both Mig and IP-10 are chemoattractant for NK cells and T lymphocytes. The delivery of cytokines using recombinant VV (rVV) has proved a favorable model for establishing their antiviral/biological activity in vivo, and such a strategy has been used to express a number of type 1 and type 2 cytokines. Using this expression system, IP-10 and Mig have been shown to exhibit antiviral activity in vivo.[190] In infected mice, rVV-encoded IP-10 or Mig enhanced the cytolytic activity of NK cells, mononuclear cell infiltration in livers, and IFN secretion by 2 to 3 times and resulted in significant viral clearance and survival in nude mice. In contrast, mice infected with a control virus (rVV-X) that does not express chemokines succumbed to generalized infection and died.

Chemokine to Cytokine to Chemokine Cascade in the Control of MCMV Infection

In humans, the liver is a common target organ of CMV infections. Similarly, MCMV can infect the liver and cause profound disease in mice. MIP-1α triggers NK cell inflammation in the liver during MCMV infections, and IFN-γ produced by NK

cells contributes to defense against MCMV infections.[191] **THERE IS NO REF NO. 191**MIP-1α deficiency profoundly decreases resistance to MCMV and is associated with dramatically reduced NK cell accumulation and IFN-γ production in the liver. MIP-1α-independent IFN-γ responses have been observed in serum and spleen, and infection-induced elevations in blood NK cell populations occur in absence of MIP-1α. Peak liver expression of Mig, however, depends upon the presence of MIP-1α, NK cells, and IFN-γ. The Mig response is also important for viral resistance. Therefore, MIP-1α is critical for NK cell migration and IFN-γ delivery to mediate protection; thus, Mig induction in tissues is a downstream protective response resulting from the process (Fig. 1).

Conclusion

In just a few years, there has been enormous understanding of what chemokines are and what they do in a number of functional settings. It is also clear that their role is not restricted just to cell attraction. As the specifics of chemokine biology become clear, this information should prove applicable to the design of therapies for a variety of autoimmune, inflammatory, and infectious disorders. The generation and use of transgenic and GKO mouse models of chemokines and/or chemokine receptor(s) should ultimately prove essential tools for filling the gaps in our knowledge on the precise functional importance of individual chemokines in modulating the immune response. One would only hope that as the discovery of more chemokines and their receptors continues rapidly, their understanding and functional relevance continue to progress at a comparable rate.

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