Review

Discovery Medicine 2026; 38(204): 1–21
https://doi.org/10.24976/Discov.Med.202638204.1

The Role of C-X-C Motif Chemokine Receptor 3 Axis in Viral Hemorrhagic Fever Diseases

Nongthombam Boby[1], Bapi Pahar[2,*]

[1]Department of Developmental Biology and Genetics, Indian Institute of Science, 560012 Bengaluru, Karnataka, India
[2]Translational Health Engineering Research Center, Michigan Technological University, Grand Rapids, MI 49503, USA
*Correspondence: bpahar@mtu.edu (Bapi Pahar)

Submitted: 29 October 2025 Revised: 17 November 2025 Accepted: 29 November 2025 Published: 20 January 2026

This review presents evidence that the C-X-C motif chemokine receptor 3 (CXCR3) axis and its ligands, CXCL9, CXCL10, and CXCL11, serve as crucial coordinators of immune responses in viral hemorrhagic fever diseases. We delineated the biology of CXCR3 and its expression in Th1, Th17.1, T follicular helper, regulatory T, cytotoxic CD8 T, and natural killer cells. Additionally, we summarized the role of interferon-mediated gradients of CXCL9, CXCL10, and CXCL11 in the recruitment and programming of these effector cells within inflamed tissues. Research involving both human and animal subjects has consistently associated elevated CXCL9/10/11 signaling with disease activity, endothelial dysfunction, and clinical outcomes. Experimental models have further elucidated that these signals can exert both protective and detrimental effects depending on factors such as timing, tissue compartment, and cell type. Proof-of-concept interventions demonstrate the greatest efficacy in dengue disease models, where modulation of this pathway results in reduced viral replication, restoration of type I interferon functions, improvement in hematologic parameters, and limitation of vascular leakage. In various hemorrhagic fevers, convergent transcriptomic and proteomic signatures identify the pathway as a viable target and source of dynamic biomarkers for risk stratification and response monitoring. Collectively, the CXCR3 axis emerged as a unifying mechanism and is a promising intervention for controlling viral hemorrhagic fever.

Keywords: CXCR3; CXCL9; CXCL10; CXCL11; viral hemorrhagic fever

Introduction

Viral hemorrhagic fevers (VHFs) are severe, life-threatening systemic febrile illnesses caused by a diverse group of RNA viruses belonging to the *Arenaviridae* (e.g., Lassa virus), *Filoviridae* (e.g., Ebola and Marburg viruses), *Flaviviridae* (e.g., Dengue virus), *Hantaviridae* (e.g., Hantaan viruses), *Nairoviridae* (Crimean-congo hemorrhagic fever virus), *Paramyxoviridae* (Nipah virus), *Phenuiviridae* (Rift valley fever virus) families [1]. Despite their taxonomic differences, these viruses share common clinical features, such as fever, systemic inflammation, vascular leakage, coagulopathy, and multi-organ dysfunction, all of which contribute to their high mortality rates, particularly in the absence of timely supportive care [1–4]. While specific viral targets and clinical manifestations vary across different VHF viruses, they exhibit similar pathogenic mechanisms, including direct viral cytotoxicity, immune evasion strategies, and significant host immune dysregulation, which collectively contribute to the disease [4–9]. Upon entry into the host, these viruses typically infect immune cells such as monocytes, macrophages, dendritic cells [10–12], and, in some instances, endothelial cells [13], facilitating rapid viral replication and systemic dissemination [2,14]. Many of these viruses employ mechanisms to suppress or delay the host's early interferon response, thereby enabling unchecked viral replication and increasing the potential for widespread tissue damage [6,9,15].

A defining characteristic of severe VHFs is the dysregulated activation of the host immune system, resulting in the excessive production of pro-inflammatory cytokines and chemokines [16–18]. This excessive inflammatory response compromises vascular integrity, increases endothelial permeability, and results in plasma leakage, tissue edema, hypotension, and multiorgan dysfunction [19]. The ensuing coagulopathy, including disseminated intravascular coagulation, in conjunction with systemic viral dissemination, can result in multi-organ failure, hypovolemia, and shock [20–25]. In addition to the hyperinflammatory response, many VHFs are marked by significant lymphocyte depletion, particularly of CD4+ and CD8+ T cells, leading to immunosuppression and impaired viral clearance [26–29]. Lymphocyte apoptosis, particularly in the context of Ebola virus (EBOV) infection, is well-documented in severe cases, driven by both direct and indirect mechanisms [30–33]. In contrast, our recent study utilizing an EBOV-infected non-human primates (NHPs) model revealed that EBOV infection resulted in significant depletion of myeloid, erythroid, and megakaryocyte hematopoi-

etic cells in the bone marrow (BM). These depletions were inversely correlated with cell proliferation and were not associated with BM apoptosis during the progression of the disease [34].

Chemokine-mediated trafficking of immune cells is a critical component of the dysregulated immune response observed in VHFs. Elevated concentrations of interferon-inducible chemokines, notably CXCL9, CXCL10 (IP-10), and CXCL11 [28,33,35,36], have been consistently associated with severe outcomes in VHFs. C-X-C chemokine receptor 3 (CXCR3) plays a crucial role in antiviral immunity by guiding effector lymphocytes to inflamed tissues in response to the chemokines CXCL9, CXCL10, and CXCL11 [37–42]. Although this axis is crucial for effective antiviral responses, excessive or dysregulated CXCR3 signaling may lead to pathological immune infiltration, tissue damage, and vascular injury. A genetic association study suggested that CXCL10 and CXCL11, along with their receptor CXCR3, are significantly implicated in the severity of dengue disease. Furthermore, haplotype analysis revealed a significant association between CXCL10 and CXCL11 and vascular leakage. These findings highlight the role of CXCR3 and its ligands in immune-mediated endothelial dysfunction [43].

Our recent study demonstrated a significant reduction in circulating CXCR3+ CD8+ T cells in NHPs exposed to the EBOV, suggesting that the loss of these effector cells may compromise the antiviral T cell response in severe infections [44]. Supporting this, a separate study in humans and NHPs also reported a marked decrease in both CXCR3+ B and T cells following EBOV infection [25]. Collectively, these findings indicate that the disruption of CXCR3+ lymphocyte populations is a common feature of VHFs and may contribute to both immune suppression and uncontrolled viral dissemination. Given these observations, understanding the dynamics of CXCR3 expression and function in VHFs is essential for elucidating the mechanisms of immune dysfunction and exploring potential therapeutic interventions aimed at restoring effective antiviral immunity. In this review, we discuss the role of CXCR3 in the immunopathogenesis of VHFs, highlighting the emerging link between CXCR3-driven immune responses and disease severity. We also explored the potential of targeting this pathway as a novel therapeutic strategy.

Viral Hemorrhagic Fever Diseases (VHFDs)

Viral hemorrhagic fever diseases (VHFDs) include a varied collection of viruses that cause febrile illnesses with hemorrhagic symptoms, originating from families such as *Arenaviridae*, *Filoviridae*, *Flaviviridae*, *Hantaviridae*, *Nairoviridae*, *Paramyxoviridae*, and *Phenuiviridae*. These enveloped viruses can lead to a range of symptoms, from mild to severe and may even be life-threatening. The clinical manifestations may include hemodynamic instability, alterations in cognitive function, and coagulopathy. Most of these viruses depend on secondary hosts for transmission to humans, with many being spread by arthropods, rodents, and mammals. These diseases usually remain in areas where their animal hosts are located. However, due to increased human travel and global connectivity, these diseases can spread beyond their original geographic boundaries. Table 1 (Ref. [45–51]) provides a comprehensive enumeration of all VHFDs, detailing their primary and secondary hosts, their current treatments, and the treatment options approved to date.

Most VHFs lack an approved vaccine, with yellow fever, Ebola, and Junin being notable exceptions. For instance, individuals infected with the yellow fever virus (YFV) may exhibit no symptoms or only mild ones, such as sudden fever, chills, severe headache, back pain, vomiting, fatigue, and weakness. While the majority of symptomatic individuals recover within a week, a small percentage develop severe illness, with 30–60% of these cases resulting in mortality due to shock and organ failure. Although there is no medication to treat yellow fever, an effective 17D live attenuated vaccine is available [52]. Similarly, the EBOV, first identified in 1976 in Zaire, now the Democratic Republic of Congo, has experienced several outbreaks throughout Africa. Ebola initially presents with flu-like symptoms, including fever, loss of appetite, muscle pain, and headache, which may progress to more severe symptoms such as bleeding, diarrhea, rash, and black, tarry stool. In later stages, Ebola can be severe, including brain inflammation, seizures, and organ failure. Treatment encompasses supportive therapy and may also incorporate monoclonal antibody therapy. A highly effective vaccine is available to mitigate the transmission of this infection and is predominantly recommended for individuals who are at an elevated risk of contracting the virus [53]. The Junin virus (JUNV), responsible for Argentine hemorrhagic fever, initially presents with symptoms similar to the flu, including fever, malaise, and headache. Over time, the virus can lead to hemorrhagic and neurological complications, with a mortality rate reaching up to 20% among those infected. The primary treatment involved administering immune plasma from individuals who had recovered, which significantly lowered the mortality rate. Additionally, ribavirin has been approved as a treatment option alongside supportive care. Since the introduction of the live-attenuated Candid #1 vaccine in the 1990s, the disease has been brought under control, and its incidence has significantly decreased [54]. Although research into new vaccine platforms is ongoing for several VHFs, focusing on chemokine signaling pathways is a significant research area for developing alternative and preventive strategies. The role of the CXCR3 axis in each disease is discussed separately in the following sections, where relevant.

Table 1. Detailed list of all viral hemorrhagic fever diseases.

Virus family	Virus name	Enveloped and genome type	Diameter (nm)/Length (μm)	Incubation period (in days)	Geographic distribution	Primary host	Secondary host	Mode(s) of transmission	Approved vaccine	Antiviral or other treatment options
Arenaviridae [45]	Lassa virus (LASV)	ambisense ssRNA	50–300	2–21	Benin, Burkina Faso, Côte d'Ivoire, Ghana, Guinea, Liberia, Mali, Nigeria, Sierra Leone, Togo, imported cases in Europe, Japan, USA	*Mastomys natalensis*, *Hylomyscus pamfi*, *Mastomys erythroleucus*, *Mus baoulei*	Humans	Contaminated objects, food, and rodents exposed to infected urine or droppings	None	Supportive care
	Lujo virus (LUJV)	ambisense ssRNA	50–300	7–13	Zambia, South Africa	Still unknown, likely Rodents	Humans	Breathing in air with an infected rodent's urine, droppings, or nesting materials, contaminated objects, food, or being bitten or scratched by infected rodents	None	Supportive care
	Junin virus (JUNV)	ambisense ssRNA	110–300	6–14	Argentina	*Calomys musculinus*, also isolated from *C. laucha*, *Akodon azarae*, *and Oryzomys flavescens*	Humans	Mucosal exposure, aerosolized excretions or secretions, or by direct contact of broken skin with infectious material from infected rodents	Live-attenuated Candid#1 vaccine	Ribavirin is the only approved antiviral drug against arenaviruses in the USA; Supportive care
	Chapare virus (CHAPV)	ambisense ssRNA	110–130	4–21	Bolivia	*Oligoryzomys microtis*	Humans	Contact with the saliva, urine, and droppings of infected rodents, contaminated fine aerosol particles, or bitten or scratched by an infected rodent	None	Supportive care
	Sabia virus (SABV)	ambisense ssRNA	30–400	6–21	Brazil	Not yet identified, likely a Rodent species from the *Calomys* genus	Humans	Ingestion or exposure to aerosols generated from feces, urine, and saliva containing the virus	None	Ribavirin has shown efficacy in treating human SABV infections; ST-193, a benzimidazole derivative, showed *in vitro* activity against viral entry; Supportive care
	Machupo virus (MACV)	ambisense ssRNA	50–300	3–16	Bolivia	*Calomys callosus*	Humans	Exposure to chronically infected rodents, inhalation of aerosols generated from infected rodents	None	Supportive care
	Guanarito virus (GTOV)	ambisense ssRNA	50–200	3–19	Venezuela	*Zygodontomys brevicauda*	Humans	Contact with the excreta of its rodent reservoir, inhalation of virus in aerosolized droplets of saliva, respiratory secretions, urine, or blood from infected rodents, or by inhalation of virus-contaminated dust particles	None	Supportive care
	Lymphocytic choriomenin-gitis virus (LCMV)	ambisense ssRNA	110–130	7–14	Global	*Rodents*	Humans	Contact with infectious mouse feces, urine, or secretions	None	Supportive care

Table 1. Continued.

Virus family	Virus name	Enveloped and genome type	Diameter (nm)/Length (µm)	Incubation period (in days)	Geographic distribution	Primary host	Secondary host	Mode(s) of transmission	Approved vaccine	Antiviral or other treatment options
Filoviridae [46]	Ebola virus (EBOV)	negative-sense ssRNA	80/up to 14	2–21	The Democratic Republic of the Congo, Gabon, Guinea, and the Republic of the Congo	Suspected: *Eidolon helvum*, *Epomophorus gambianus*, *Lissonycteris angolensis*, *Micropteropus pusillus*, *Mops condylurus*, *Rousettus aegyptiacus*, *Epomops franqueti*, *Hypsignathus monstrosus*, and *Myonycteris torquata*	Non-human primates, humans	Contact with infected person, contaminated materials, infected body fluids, Direct contact with bushmeat or bats, rodents, primates, living or dead in or from affected areas	ERVEBO (rVSVΔ-ZEBOV-GP) 2 doses: Zabdeno (Ad26.ZEBOV) and Mvabea (MVA-BN-Filo)	Monoclonal antibodies (Inmazeb and Ebanga); Supportive care
	Sudan virus (SUDV)	negative-sense ssRNA	80/up to 14	2–21	Uganda, South Sudan		Humans	Contact with infected body fluids, contaminated objects or surfaces, physical contact, and nursing care	None	Supportive care
	Bundibugyo virus (BDBV)	negative-sense ssRNA	80/up to 14	2–21	Uganda, The Democratic Republic of the Congo		Humans	Contact with infected body fluids, infected animals, like a bat or primate	None	Supportive care
	Taï Forest virus (TAFV)	negative-sense ssRNA	80/upto 14	2–21	Côte d'Ivoire		Humans, non-human primates	Only a single human was reported to be infected after being exposed to the virus during a wild chimpanzee necropsy, contact with infected body fluids, or contact with an infected animal, like a bat or primate	None	Supportive care
	Marburg virus (MARV)	negative-sense ssRNA	80/upto 0.79–0.97	2–21	Angola, The Democratic Republic of the Congo, Equatorial Guinea, Ghana, Guinea, Kenya, Tanzania, Uganda, Zimbabwe	Egyptian fruit bat (*Rousettus aegyptiacus*); also detected in *M. inflatus* and *Rh. Eloquens*	Humans, non-human primates	Human infections happen after direct exposure to infected bats or after contact with infected people's body fluids and contaminated surfaces and materials	None	Supportive care
	Ravn virus (RAVV)	negative-sense ssRNA	80/upto 0.66–>1.0	2–21	The Democratic Republic of the Congo, Kenya, Uganda	Egyptian fruit bat (*Rousettus aegyptiacus*)	Humans, non-human primates	Direct contact (through broken skin or mucous membranes) with the blood, secretions, organs or other bodily fluids of infected people, and with contaminated surfaces and materials	None	Supportive care

Table 1. Continued.

Virus family	Virus name	Enveloped and genome type	Diameter (nm)/Length (μm)	Incubation period (in days)	Geographic distribution	Primary host	Secondary host	Mode(s) of transmission	Approved vaccine	Antiviral or other treatment options
Flaviviridae [47]	Yellow fever virus (YFV)	positive-sense ssRNA	50	3–6	Africa, South America	Non-human Primates and Humans	Humans	*Aedes aegypti*, *Haemagogus* and *Sabethes* genera of mosquitoes	17D live attenuated vaccine	Supportive care
	Dengue virus (DENV)	positive-sense ssRNA	50	5–7	Africa, the Americas, South and Southeast Asia, Western Pacific region	Humans, also detected in bats, non-human primates, birds, bovids, dogs, horses, pigs, rodents, marsupials	Humans	*Aedes aegypti*, *Aedes albopictus*	Live-attenuated Dengvaxia (3 doses); live-attenuated Qdenga (2 doses)	Supportive care
	Kyasanur forest disease virus (KFDV)	positive-sense ssRNA	40–65	3–8	India	Monkeys, small mammals like rodents and shrews, and Domesticated animals like cattle, buffaloes, and goats	Non-human primates, humans	Tick bites (*Haemaphysalis spinigera*)	Formalin-inactivated vaccine	Supportive care
	Omsk hem-orrhagic fever virus (OHFV)	positive-sense ssRNA	35–40	3–8	Western Siberia regions of Omsk, Novosibirsk, Kurgan, and Tyumen	Ticks like *Dermacentor reticulatus*, *Dermacentor marginatus;* mites belong to *Gamasidae* and *Hydracarinae;* Rodents like *Ondatra zibethicus*, *Stenocranius gregalis and Arvicola amphibius*	Rodents, humans	infected tick bite or by contact with biological material from an infected, sick, or deceased animal	None	Supportive care
	Alkhurma hemor-rhagic fever virus (AHFV)	positive-sense ssRNA	40	2–4	Saudi Arabia, Egypt	Unknown. Hard ticks (*Hyalomma sp.*) may act as both vector and reservoir	Humans, livestock animals	Transmitted from a domesticated animal by direct contact or through tick and mosquito bites	None	Supportive care
Hantaviridae [48]	Dobrava virus (DOBV)	segmented negative-sense ssRNA	80–120	2–42	Europe	*Apodemus flavicollis* and *Apodemus ponticus* rodents	Humans	inhalation of aerosols or dust particles contaminated with virus-containing rodent excreta	None	Supportive care
	Hantaan virus (HTNV)	segmented negative-sense ssRNA	80–120	7–56	Americas, Europe, Asia	Rodents (*Peromyscus sonoriensis*), Moles (*Talpa occidentalis*), Shrews and Bats	Humans	infected rodent or insectivore hosts and even bats, contaminated aerosolized rodent excreta; person-to-person transmission was reported with the Andes virus strain of Hantaan virus	Hantavax: licensed only for use in Korea	Supportive care
	Puumalavirus (PUUV)	segmented negative-sense ssRNA	80–160	7–35	Europe, Russia, Asia	*M. glareolus*	Humans	Inhalation of infected rodent excreta	None	Supportive care

Table 1. Continued.

Virus family	Virus name	Enveloped and genome type	Diameter (nm)/Length (µm)	Incubation period (in days)	Geographic distribution	Primary host	Secondary host	Mode(s) of transmission	Approved vaccine	Antiviral or other treatment options
	Saaremaa virus (SAAV)	segmented negative-sense ssRNA	80–120	7–35	Europe	*Apodemus agrarius*	Humans	inhalation of aerosolized virus-contaminated rodent excreta	None	Supportive care
	Sin Nombre virus (SNV)	segmented negative-sense ssRNA	112	7–39	North America	*Peromyscus maniculatus*, Rat	Humans	Inhalation of aerosolized excreta from infected rodents	None	Supportive care
	Tula virus (TULV)	segmented negative-sense ssRNA	120–160	14–21	Europe, Russia	*Microtus arvalis*	Humans	aerosolized excreta of rodents, bitten by a wild rodent	None	Supportive care
	Seoul virus (SEOV)	segmented negative-sense ssRNA	80–160	14–21	Asia, Europe, Africa, North America	*Rattus novergicus*, *Mus musculus*	Humans	inhalation of aerosolized virus-contaminated rodent excreta	None	Supportive care
Nairoviridae [49]	Crimean-Congo Hemorrhagic Fever virus (CCHFV)	segmented negative-sense ssRNA	100	1–14	Africa, Central Asia, the Middle East, and Southern and Eastern Europe	*Hyalomma marginatum*; also isolated from other ticks belonging to the genera *Amblyomma*, *Dermacentor*, *Haemaphysalis*, and *Rhipicephalus*	Livestock (cattle, goats, sheep)	tick bites or through contact with infected animal blood or tissues during and immediately after slaughter	None	Supportive care
Paramyxoviridae [50]	Hendra virus (HeV)	negative-sense ssRNA	280–300	9–16	Australia	Flying fox bat (genus Pteropus): *Pteropus alecto* and *P. Conspicillatus*	Horses, humans	Humans may be infected after contact with tissues or excretions of infected horses and domesticated animals, like blood, urine, or birthing materials. Horses may be infected after exposure to the virus in the urine, droppings, or saliva of infected flying foxes	Equivac® HeV for horse; None for human use	Supportive care
	Nipah virus (NiV)	negative-sense ssRNA	120–150	5–14	Bangladesh, India, Malaysia	Flying fox bat (genus *Pteropus*): *P. lylei*, *Pteropus medius*, *Pteropus vampyrus*, *Pteropus hypomelanus*, *Rousettus leschenaultii*, *Rousettus amplexicaudatus*, *and Hipposideros larvatus*	Pigs, humans	Contact with infected pigs, bats, or food contaminated with bat saliva or urine. Human to human transmission through respiratory droplets or bodily fluids	None	Supportive care

Table 1. Continued.

Virus family	Virus name	Enveloped and genome type	Diameter (nm)/Length (µm)	Incubation period (in days)	Geographic distribution	Primary host	Secondary host	Mode(s) of transmission	Approved vaccine	Antiviral or other treatment options
Phenuiviridae [51]	Rift Valley Fever virus (RVFV)	segmented negative-sense ssRNA	90–110	2–6	Eastern and Southern Africa	Rodents (*Muridae*, *Sciuridae*), Ruminantia (*Bovidae*, *Caprinae*, *Camelidae*), Mammalia (*Suidae*, *Elephantidae*, *Vespertilionidae*, *Equidae*, *Rhinoceros*), Non-human primates (*Cercopithecidae*, *Chimpanzee*)	Humans	Aedes and Culex bites, contact with infected livestock	None	Supportive care
	Severe fever and thrombo-cytopenia syndrome virus (SFTSV)	segmented negative-sense ssRNA	80–100	7–14	China, South Korea, Japan, Australia, United States, Thailand, Vietnam, Myanmar	Ticks (*Haemophysalis longicornis*, *Amblyomma testudinarium*, *Ixodes nipponensis*, *and Rhipicephalus microplus*)	Humans	Tick bite	None	Supportive care

ss, single-stranded; nm, nanometer; µm, micrometer.

CXCR3 Biology, Ligands and Function

The chemokine receptor CXCR3, a seven-transmembrane G protein-coupled receptor, is predominantly expressed on activated immune cells, including T helper 1 (Th1), cytotoxic CD8+, memory T, natural killer (NK), and dendritic cells [55]. It is also present in various non-immune cell types, such as epithelial, endothelial, smooth muscle, and fibroblast cells [42,56].

Three different forms of CXCR3 have been discovered in humans: CXCR3-A, CXCR3-B, and CXCR3-alt [57]. The most common variant, CXCR3-A, is associated with chemotactic and proliferative activities in leukocytes, marked by calcium influx and increased cell movement. CXCR3-B is mainly found on endothelial cells and has anti-proliferative, anti-migratory, and angiostatic properties [58,59]. The role of the third form, CXCR3-alt, is not well understood. IFN-induced CXCL9, CXCL10, and CXCL11, along with platelet-derived CXCL4 and its non-allelic variant CXCL4L1, bind to the IFN-inducible receptor CXCR3 to perform their biological functions [41,55,60]. Among these, CXCL11 has the strongest affinity and effectiveness towards CXCR3A, leading to significant calcium mobilization and chemotaxis. CXCL9 has the weakest binding affinity, whereas CXCL10 is regarded as the most adaptable and extensively researched ligand because of its inducibility by various stimuli and broader expression patterns [61,62].

CXCR3+ T Cell Function

The chemokine axis comprising CXCR3 and its ligands, CXCL9, CXCL10, and CXCL11, plays a pivotal role in directing T cell trafficking and function during infections, inflammation, and autoimmune responses [63]. Under normal physiological conditions, expression of these ligands is minimal. However, upon inflammatory stimulation, particularly with IFNγ and type I interferons, their expression increased significantly (Fig. 1). This results in the formation of chemotactic gradients that attract CXCR3-expressing T cells to the sites of inflammation [41]. The migration of CXCR3+ effector T cells to these sites is essential for pathogen clearance. However, persistent antigenic stimulation in the context of chronic infections or autoimmunity can lead to sustained chemokine expression and pathological tissue inflammation [63]. CXCR3 is predominantly expressed on Th1 cells, which are characterized by the transcription factor T-bet and a cytokine profile rich in IFNγ, TNFα, and IL-2 [64,65]. The differentiation of Th1 cells is driven by IL-12 and IL-27 through T-bet–dependent pathways, promoting the upregulation of CXCR3, which facilitates Th1 migration to inflamed tissues [37,66]. At these sites, Th1 cells enhance inflammation by producing IFNγ, which further induces the expression of CXCL9, CXCL10, and CXCL11 through STAT activation, thereby recruiting additional effector cells, including cytotoxic CD8+ T lymphocytes, and promoting M1 macrophage polarization [67–70].

Th17 cells represent a proinflammatory subset of T cells, distinct from Th1 and Th2 cells, and are characterized by the expression of retinoic acid receptor-related orphan receptor γt (RORγt) and IL-17. Th17.1 cells, which arise from the plasticity of Th17 cells, express both IFNγ and IL-17, and they share transcription factors with both Th1 and Th17 cells [71]. Two CXCR3-positive Th17 cell subsets play pivotal roles in inflammatory trafficking and effector functions. The first subset is the non-classical Th17.1 population, which is characterized by CCR4-CXCR3+ expression. These cells co-express T-bet and RORγt, exhibit rapid expansion following T-cell receptor stimulation, and secrete IFNγ and IL17-A, along with substantial amounts of GM-CSF, which facilitates neutrophil recruitment and macrophage activation [63,72]. These cells often exhibit high CXCR3 expression with reduced aryl-hydrocarbon receptors, and their transcripts are enriched with mediators such as CCL3, CCL4, CCL5, granzyme B, IL-3, IL-22, GM-CSF, STAT1, T-bet, and IL-23R, supporting a pathogenic role in chronic inflammation [71,73]. The second subset was characterized by CCR6+CCR4+CXCR3+ expression. This group produces relatively lower levels of IFNγ, IL-17A, TNFα, and IL-13 than other Th17 lineages yet expresses adhesion and homing receptors that facilitate entry into barrier sites, including β-7 integrin and CXCR3 in intestinal tissue, CCR2 and CCR4 in skin, and β-1 integrin in the genitourinary mucosa [74]. Within these CXCR3-positive Th17 compartments, CXCR3 facilitates positioning within IFN-rich inflammatory niches. Concurrently, the Th17.1 program exhibits robust effector activity, which is advantageous for rapid control of extracellular microbes. However, this activity also poses an increased risk of prolonged tissue inflammation when antigen exposure remains sustained.

CXCR3 also delineates T follicular helper (Tfh) cell subsets that regulate B cell differentiation. CXCR3+ Tfh1 cells, defined by T-bet expression and IFNγ secretion, differ from Tfh2 and Tfh17 subsets by limiting B-cell activation rather than promoting antibody production [75,76]. These cells exhibit a Th1-like phenotype and produce IFNγ, rather than IL-21, limiting their B cell-help capacity. In patients with Common Variable Immunodeficiency with reduced switched-memory B cells, CXCR3+ Tfh1 and CXCR3+CCR6+ (Tfh17.1) subsets increased, while CXCR3-CCR6+ Tfh17 cells decreased. This CXCR3+ Th1-dominant phenotype is associated with higher IFNγ production and reduced B cell maturation [75].

CXCR3 delineates a Th1-polarized regulatory T cell (Treg) program, which is characterized by unique developmental, trafficking, and functional properties (Fig. 1). Within memory Tregs and a subset of naïve Tregs, CXCR3 identifies cells that develop under the influence of IL-12, IFN, or IL-27, facilitated by STAT4- and STAT1-dependent induction of T-bet and its receptor [77,78]. Phenotypically, CXCR3+ Tregs retain their fundamental regulatory

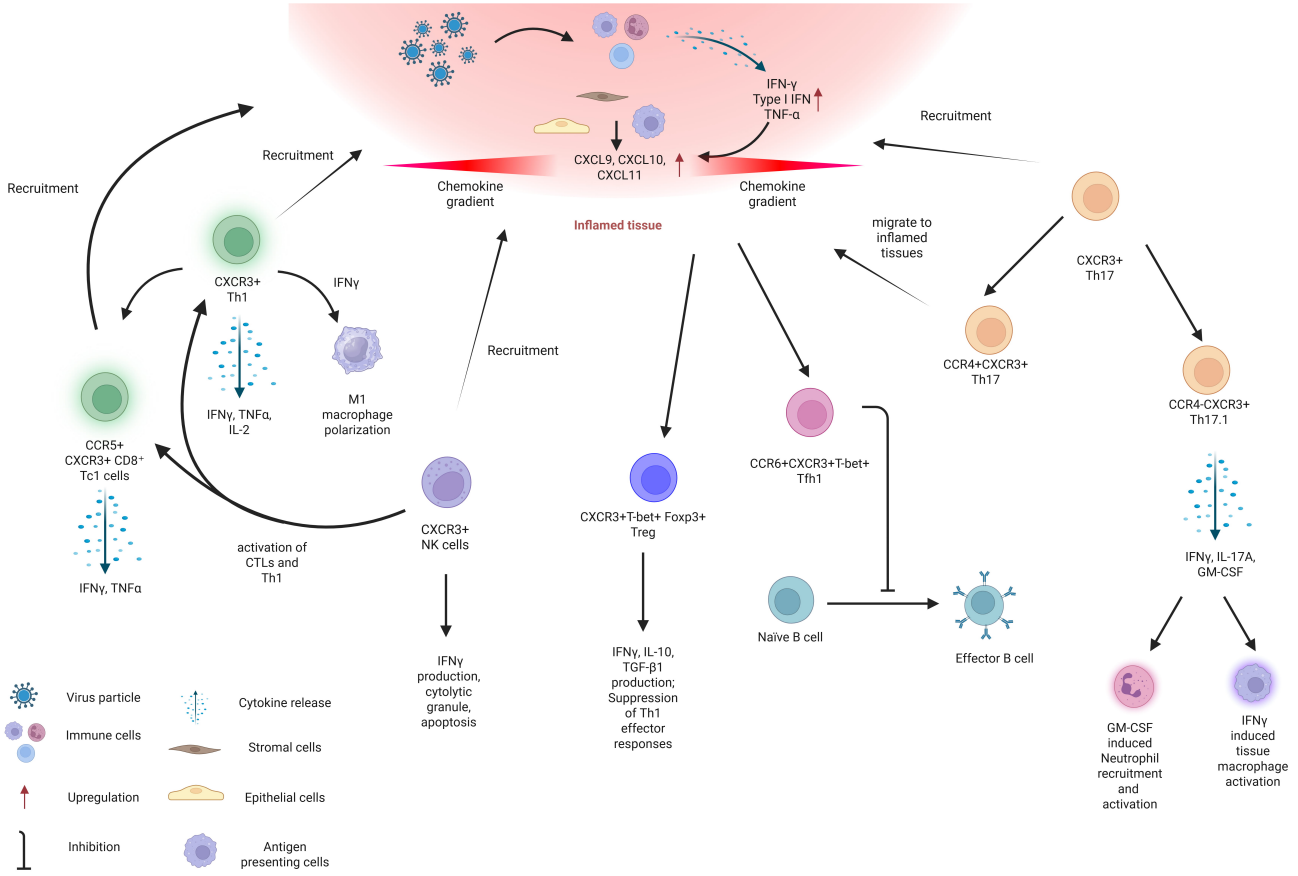

Fig. 1. CXCR3+ cells in host immunity. Viral infections prompt the secretion of inflammatory cytokines, such as IFNγ and TNFα, by immune cells. In response to IFNγ and type I interferons, cells within inflamed tissues post-viral infection—including stromal cells, epithelial cells, macrophages, and antigen-presenting cells—synthesize the CXCR3 ligands CXCL9, CXCL10, and CXCL11. This process establishes chemokine gradients that facilitate the recruitment of CXCR3+ T cell subsets. CXCR3+ Th1 (T helper 1) cells secrete IFNγ, TNFα, and IL-2, thereby augmenting chemokine production, promoting M1 macrophage polarization, and facilitating the recruitment of CD8+ Tc1 (T cytotoxic 1, CXCR3+CCR5+) cells. These recruited cells release IFNγ, TNFα, and cytotoxic molecules to effectively eliminate infected cells. T follicular helper 1 (Tfh1) cells, characterized by the markers CXCR3+CCR6+T-bet+, exert a negative regulatory effect on humoral immunity by inhibiting the differentiation of naive B cells into effector B cells. Concurrently, CXCR3-expressing Th17 (T helper 17) subsets contribute to tissue inflammation: CCR4+CXCR3+ Th17 cells migrate into inflamed tissues, whereas CCR4-CXCR3+ Th17.1 cells produce IFNγ, IL-17A, and GM-CSF, collectively facilitating macrophage activation and neutrophil recruitment. Th1-like regulatory T cells (CXCR3+T-bet+FoxP3+) play a crucial role in suppressing effector Th1 responses by producing IL-10, TGFβ, and IFNγ, thereby mitigating excessive inflammation. Interferon-induced chemokines CXCL9, CXCL10, and CXCL11, produced at sites of inflammation, also interact with CXCR3 receptors on NK cells, thereby facilitating their recruitment to infected tissues. Upon arrival, CXCR3+ NK cells initiate antiviral responses through cytokine production, activation of cytotoxic T lymphocytes (CTLs) and Th1 helper cells to enhance adaptive immunity, as well as cytolytic granule release and death receptor-mediated cytolysis of target cells. The figure was created using Biorender (http://biorender.com).

components, including FoxP3, CTLA-4, and Helios, similar to the other Treg subsets. Nevertheless, they display a Th1-oriented profile characterized by moderate production of IFNγ and IL-10, in conjunction with increased expression of CD73 and TGFβ1 [78,79]. Functionally, CXCR3 plays a crucial role in guiding Tregs along CXCL10 gradients, thereby directing them to sites of inflammation where they preferentially modulate Th1-driven effector responses *in vivo* [80,81]. Significantly, their program demonstrates plasticity, as substantial exposure to IL-12 can temporarily induce IFNγ production in CXCR3+ Tregs, accompanied by a reduction in their suppressive capacity. This alteration is reversible upon withdrawal of IL-12 or blockade of IFNγ [82].

CXCR3 is also expressed in the canonical T-cytotoxic (Tc) 1 subset of CD8+ T cells, which predominates in type-1 inflammation. These CXCR3+ CD8+ lymphocytes co-express CCR5 and lack CCR4, CCR6, and CXCR5,

which are characteristic of Tc2, Tc17, and follicular CD8 subsets. They execute direct cytolysis through perforin and granzymes while releasing IFNγ and TNFα, thereby shaping the inflammatory environment [83,84]. Functionally, these cells resemble a Th1-like program, as IFNγ-producing CD8+ cells frequently exhibit elevated IL-18R expression, thereby enhancing their responsiveness to innate cytokines during instances of infection or tissue stress [85]. Conversely, CXCR3-negative Tc2 and Tc17-like populations predominantly secrete cytokines with a limited cytolytic capacity. Clinical outcomes frequently reflect the balance between CXCR3+ Tc1 cytotoxicity and helper-skewed CD8 subsets in autoimmune and infectious contexts [86]. Consequently, CXCR3 functions as a trafficking receptor that guides CD8+ effector cells into IFN-rich environments and serves as a phenotypic marker of a cytotoxic IFN-high milieu. This environment aids in pathogen control but may lead to increased tissue damage if the regulation is insufficient.

Collectively, CXCR3+ T cells, including Th1, Th17, Tfh, Treg, and CD8+ lineages, form a cohesive chemokine-driven network that governs host defense, inflammation, and immune modulation. The synchronized induction of CXCL9–11 by IFNγ creates a self-sustaining recruitment and activation loop, which is essential for controlling pathogens but is potentially harmful in chronic or autoimmune situations. Thus, the CXCR3 axis acts as both a key orchestrator of protective immunity and a possible target for adjusting pathological inflammation.

CXCR3+ NK Cell Function

During viral infection, NK cells migrate to sites of infection via chemokine signaling, where CXCR3 plays a pivotal role in directing NK cells to inflamed tissues [87,88]. CXCR3 facilitates NK cell migration to the liver during Dengue virus (DENV) infection and, in conjunction with CD62L, enables NK cell homing to lymph nodes during inflammatory responses [89]. Upon recruitment, NK cells expressing CXCR3 exhibit antiviral properties by producing cytokines, releasing cytolytic granules, and inducing cytolysis via death receptors [90]. These cells release IFNγ, which inhibits viral replication, limits viral dissemination, and activates Tc and Th1 cells to enhance adaptive immunity [91] (Fig. 1).

CXCR3-positive NK cells migrate into inflamed or damaged tissues to amplify or resolve pathological conditions and infiltrate tumors to modulate anti-cancer responses. Gradients of CXCL9/10/11, driven by type-I IFN, engage CXCR3 to redirect NK cells from the splenic red pulp into T-cell zones. This relocation facilitates perforin-dependent pruning of activated antiviral T cells and modulates subsequent T- and B-cell responses [92].

Following an intracerebral hemorrhage, CXCR3-positive NK cells, which serve as tissue-trafficking effectors, are recruited to the injured brain. These cells accumulate in the perihematomal regions, where they produce IFNγ, thereby exacerbating white matter injury. The genetic deletion of CXCR3 or systemic antagonism with AMG487 has been demonstrated to reduce NK cell ingress, decrease the number of IFNγ-positive NK cells, preserve white matter, and improve motor outcomes [93]. This pattern suggests the involvement of a CXCR3-IFNγ axis in neuroinflammation, with IFNγ serving as a downstream effector of CXCR3-expressing cells, including NK cells [93].

Within the liver, a subset of human CD56^{bright} CXCR3+ NK cells exhibits notable anti-fibrotic cytotoxicity and IFNγ release targeting stellate cells. However, in the context of chronic hepatitis C, this subset becomes functionally impaired and paradoxically accumulates in advanced fibrosis, suggesting a context-dependent remodeling of CXCR3+ NK cell activity [94]. In a separate study utilizing a murine model of primary biliary cholangitis, liver-infiltrating NK cells exhibited elevated CXCR3 expression. The engagement of the Tim-3 pathway further enhances CXCR3 expression on liver-derived NK cells and modulates IFNγ release, indicating checkpoint control over CXCR3-guided trafficking and function [95].

Within tumors, IFNγ enhances the expression of CXCL9, CXCL10, and CXCL11, while the presence of CXCR3 on NK cells is essential for their effective accumulation within the tumor environment, with a preferential recruitment of the CD27 high subset. The administration of CXCL10 enhances the infiltration of NK cells and is correlated with improved survival outcomes, thereby establishing a CXCR3-mediated pathway for anti-tumor NK cell surveillance [96]. Recent review has delineated the phenotypes of CXCR3-positive tumor-infiltrating NK cells and have elucidated that CXCL9, CXCL10, and CXCL11, which are produced within the tumor microenvironment, recruit and program these cells to modulate anti-tumor immunity [97]. Collectively, these functions position CXCR3+ NK cells as a dynamic entity capable of detecting IFN-licensed chemokine environments to (a) regulate access to critical microanatomical sites for immune modulation, (b) execute cytotoxic and cytokine responses in damaged or infected tissues, and (c) influence anti-tumor immunity. Their effects can be either beneficial or detrimental, depending on the tissue context and the presence of checkpoint and chemokine signals.

The Role of CXCR3 and Its Ligand in VHFDs

Arenavirus

Lassa Virus (LASV)

When human macrophages infected with LASV were cocultured with NK cells, a significant increase in NK cell activation was observed, accompanied by a marked reduction in the surface expression of CXCR3 [98]. CXCR3 is instrumental in inducing CXCL9, 10, and 11, which are essential for the recruitment of activated T lymphocytes. This

observation suggests that the reduction in surface CXCR3 expression may be partially attributable to its internalization. The downregulation of CXCR3 may hinder the recruitment and trafficking of effector lymphocytes to infected tissues, thereby facilitating LASV-mediated immune evasion and persistence.

Serum levels of IL-8 and CXCL10 were significantly elevated in cases of acute nonfatal Lassa fever compared to controls. In contrast, these cytokines and chemokines were undetectable in fatal cases, suggesting that their reduced presence may be associated with adverse outcomes [99]. In cynomolgus monkeys infected with LASV, CXCL9 mRNA levels remained unchanged in peripheral blood and tissues relative to controls. However, increased mRNA levels of CXCL10 and CXCL11 were observed in PBMCs from infected monkeys 6 days post-infection and in lymph nodes 9 days post-infection. It is noteworthy that the mRNA levels of CXCL10 and CXCL11 were significantly higher in the lymph nodes of fatally infected monkeys compared to those of survivors, suggesting an elevated or dysregulated expression of CXCL10 and CXCL11 associated with severe LASV infection [28].

Filovirus

Ebola Virus (EBOV)

Our study [44], in conjunction with a prior investigation [25], revealed a decrease in CXCR3+ T cells within the mesenteric lymph nodes and peripheral circulation, respectively, in NHPs exposed to EBOV. This finding suggests that EBOV infection leads to the downregulation of CXCR3 expression in T cells. Additionally, several genes, including CXCL11, were found to be upregulated in EBOV-infected cynomolgus monkeys compared to those vaccinated with rVSV-ZEBOV-GP on day 7, indicating the significance of the innate immune response in EBOV infection [100].

The Ebola vaccine rVSV-ZEBOV induces an immune response in healthy adult humans and is associated with an increase in plasma CXCL10 as early as the first day post-vaccination. This finding suggests that the vaccine's efficacy may be mediated through the regulation of CXCL10 [101]. The concentrations of plasma CXCL10 and CXCL11 were observed to be significantly elevated on Day 1 post- rVSVG-ZEBOV-GP immunization and were correlated with initial vaccine adverse effects, such as headache and fatigue, as measured using a semi-quantitative proximity extension assay technology [102]. The replication-competent Ad26.ZEBOV vaccine also upregulates CXCL9, CXCL10, and CXCL11, which are implicated in the recruitment of monocytes and lymphocytes [103]. Conversely, infection with EBOV results in a delayed type I IFN response in hepatocyte-like cells derived from induced pluripotent stem cells. In these cells, the expression levels of CXCL10, CCL5, and ISG15 were elevated within 2–3 days post-infection across multiple donors, suggesting that this period is critical for the initiation of antiviral responses [104].

Flavivirus

Yellow Fever Virus (YFV)

The live attenuated 17D strain of YFV elicits the production of neutralizing antibodies and robust T cell responses in human clinical trials. These immune responses are associated with YFV-specific T cells expressing CXCR3, a marker indicative of a Th1 response [105]. Recent studies have identified marker-negative T cells (T_{MN}), which constitute approximately one-quarter of CD45RO-CCR7+ tetramer-labeled T cells that do not express CD95, CXCR3, CD11a, and CD49d in individuals vaccinated against YFV. These T_{MN} cells, which share TCR sequences with memory and effector T cells, exhibited minimal decline over time and maintained stability within the tetramer population, suggesting that long-lived memory T cells can be CXCR3 negative while producing IFNγ, TNFα, and/or IL-2 [106]. Notably, significant increases in CXCL10 protein expression were observed in individuals infected with YFV compared to those with cardiovascular conditions or sepsis, as demonstrated by analyses of frozen myocardial tissues [107]. Similarly, patients infected with YFV during the 2018 outbreak exhibited elevated CXCL10 expression during the acute phase of the infection [108].

Elevated concentrations of CXCL10 are inversely correlated with immune responses to the live-attenuated yellow fever 17D vaccine in healthy vaccinated individuals [109]. This finding suggests that increased levels of this chemokine may be associated with a less favorable prognosis. In contrast, another study involving the yellow fever 17D vaccine in healthy humans indicated that significantly elevated CXCL10 levels were positively correlated with the robustness of adaptive immune responses following vaccination [110].

Dengue Virus (DENV)

CXCL10 competes with DENV for binding to heparan sulfate on the cell surface, thereby reducing DENV uptake and subsequent infection. A notable feature of acute DENV infection is the upregulation of CXCR3 on T cells, a phenomenon not observed during the convalescent phase [36,111]. In co-culture studies, activated T cells interacting with DENV-infected dendritic cells demonstrated increased secretion of IFN-inducible chemokines CXCL9, CXCL10, and CXCL11. Elevated levels of CXCL10 have been detected in the plasma of patients with dengue hemorrhagic fever (DHF) grade II and other febrile illnesses [36,112]. Furthermore, a higher frequency of plasmablasts and plasma cells expressing CXCR3 was observed in patients with dengue compared to healthy individuals, suggesting their migration to inflamed tissues [113]. Individuals with both primary and secondary DENV infections exhibited elevated serum levels of CXCL9, CXCL10,

and CXCL11 [114–117], as well as increased CXCL10 concentrations in the cerebrospinal fluid of DENV patients with neurological manifestations [118], compared to healthy controls. This observation suggests that the enhanced CXCL9/CXCL10/CXCL11 signaling pathways play a critical role in DENV infection and are likely associated with increased vascular permeability [119–121]. Additionally, elevated plasma levels of CXCL9 were found in DENV-infected patients even when asymptomatic, compared to those who were not infected [122]. Individuals who later develop conditions such as DHF or dengue shock syndrome exhibit higher CXCL10 levels [115]. Patients with dengue presenting warning signs showed elevated plasma CXCL10, serving as potential markers to identify the risk of warning signs in early infection [123]. The tetravalent dengue vaccine TV005 has demonstrated enhanced efficacy against rDEN2Δ30 challenge, as evidenced by reduced CXCL10 expression and decreased incidence of viremia among patients. These findings suggest that CXCL10 may serve as a critical biomarker for evaluating the effectiveness of dengue vaccines [124].

Mouse models lacking CXCR3 demonstrated an increased vulnerability to intracerebral DENV infection, which resulted in hind limb paralysis. The reduced recruitment of effector T cells impairs the clearance of the virus from the brain, thereby increasing the risk of paralysis. Additionally, mice deficient in the CXCR3 ligand, CXCL10, when infected with DENV, exhibited higher mortality rates compared to CXCR3(-/-) mice. This suggests that both CXCR3 and CXCL10 contribute to resistance against primary DENV infection [125]. The increased susceptibility of CXCL10(-/-) mice to DENV infection is attributed to antiviral activity that promotes viral clearance, rather than defective lymphocytes recruitment [126].

The frequency of CXCR3+CD4+ T cells was elevated in patients with acute DENV infection compared to controls, irrespective of the severity of the infection, whereas the levels of CXCR3+CD8+ T cells remained consistent across all groups. Notably, CD107a expression increased in CXCR3+CD4+ T cells in patients with acute DENV infection. In contrast, the expression of CD38+ and CD107a+ expression was elevated in CXCR3+CD8+ T cells in patients with DENV-2 and DENV-3 who exhibited warning signs, as compared to controls [127]. This may suggest that CXCR3+CD4+ Th cells represent an activated Th1-like population with cytotoxic potential, contributing to antiviral effector responses during acute DENV infection.

Platelet activation is a hallmark of dengue infections. CXCL4, the ligand responsible for platelet activation, is synthesized by megakaryocytes and interacts with CXCR3-B in vascular endothelial cells, epithelial cells, fibroblasts, and leukocytes to modulate immune function and thrombosis. Monocytes deficient in CXCL4 exhibited reduced DENV2 replication and NS1 protein levels compared to wild-type mice monocytes. Treatment of DENV2-infected cells with CXCL4 resulted in increased viral replication by inhibiting lysosomal degradation and the synthesis of IFNα/β. Plasma CXCL4 levels were positively correlated with NS1-positive cells in patients with DENV and inversely correlated with autophagic rescue mechanisms [128–130].

Hantavirus

Hantaan Virus (HTNV)

Elevated serum levels of CXCL10 have been positively correlated with individuals infected with HTNV who exhibit severe, lethal hemorrhagic fever with renal syndrome (HFRS) [131]. CXCL10-CXCR3 signaling facilitates the recruitment of virus-specific T cells to sites of inflammation during infection [132]. The increased expression of CXCR3 on the CD14+ subset in the PBMCs of HFRS patients suggests that CXCL10 in acute HFRS may recruit CD14+ monocytes, potentially leading to excessive cytokine production and contributing to the “cytokine storm” [131]. In HTNV-infected HaCaT cells, there is a significant increase in CXCL10 levels, indicating an enhanced antiviral immune response [133]. Infected human lung microvascular endothelial cells demonstrate increased gene and protein expression of CXCL10 and CXCL11 when exposed to both pathogenic Andes and HTNV and non-pathogenic Prospect Hill viruses. This suggests that both types of viruses can enhance the recruitment of host immune cells in an *in vitro* infection setting [134]. Levels of CXCL9 and CXCL10 are consistently elevated in patients with HTNV disease. These chemokines increase during early stages and remain elevated throughout both HFRS and Hantavirus Pulmonary Syndrome (HPS), exhibiting broader and more pro-inflammatory profiles in HPS compared to HFRS. CXCL9 and CXCL10 are upregulated in the early phase, with CXCL9 remaining elevated in later stages of HPS [135].

Puumala Virus (PUUV)

PUUV is implicated in the etiology of a mild form of HFRS, exhibiting pathophysiological responses akin to those of other pathogenic hantaviruses, such as thrombocytopenia and disseminated intravascular coagulation. This makes it an exemplary model for studying hantavirus infections. During the acute phase of HFRS, patients demonstrated reduced platelet reactivity, affecting both degranulation and the activation of the fibrinogen receptor GPIIb/IIIa. The levels of CXCL4 corresponded with the platelet count, being lower during the acute phase compared to the recovery phase. Although CXCL4 exhibited a weak correlation with platelet count, it remained consistent throughout the disease when normalized. This observation challenges the hypothesis that latent platelet activation is responsible for thrombocytopenia in PUUV-HFRS [136]. The activation of the innate lymphoid cells 2 subset by PUUV is dependent on IFNβ, with an observed increase in CXCL10 expression *in*

vitro [137]. In patients with severe PUUV, serum CXCL10 levels are significantly elevated compared to those in patients with milder forms of the disease [138]. Conversely, among patients with severe conditions, CXCL10 levels were markedly lower than those experiencing less kidney dysfunction [139]. This suggests that elevated CXCL10 levels may exert a more substantial influence on the progression of severe thrombocytopenia than on kidney dysfunction.

Andes Orthohantavirus (ANDV)

Andes virus (ANDV) is a notable zoonotic pathogen and the primary etiological agent of hantavirus cardiopulmonary syndrome (HCPS) in South America, which is characterized by a high mortality rate. Research has indicated that individuals who have survived HCPS exhibit a reduction in Treg phenotypes (CXCR3+CCR6-) compared to healthy donors. This observation suggests that ANDV infection may alter the phenotype of memory CD4+ Treg cells post-infection, potentially influencing their trafficking to inflammatory sites [140].

Nairovirus

Crimean-Congo Hemorrhagic Fever Virus (CCHFV)

In patients infected with CCHFV, a significant positive correlation was identified between serum viral load and CXCL10 levels, suggesting that CXCL10 plays a crucial role in the pathogenesis of CCHFV [138, 141]. Whole-blood transcriptomic analysis of CCHFV-infected cynomolgus monkeys revealed an early and significant upregulation of CXCL10, beginning on the first day post-challenge and persisting throughout the initial week. Among the differentially expressed genes, CXCL10 demonstrated the most substantial cytokine fold-change and maintained the longest duration of elevation before diminishing as viremia and clinical scores decreased [142].

Paramyxoviruses

Nipah Virus (NiV)

Infection with NiV in primary human umbilical vein endothelial cells and *in vivo* using hamster models results in a significant upregulation of CXCL10 mRNA expression. Additionally, elevated CXCL10 protein expression levels were observed in patients infected with NiV from the 1999 outbreak in Malaysia, indicating that the overexpression of CXCL10 may play a critical role in the pathogenesis of NiV-associated encephalitis [143]. Moreover, NiV stimulates the production of inflammatory chemokines, such as CXCL10, which promote the chemotaxis of monocytes and T cells in primary human endothelial cells [144].

Hendra Virus (HeV)

In lung and spleen tissues infected with HeV, the expression of CXCL10 mRNA was significantly elevated 60 hours post-exposure compared to the levels observed in the lung and spleen tissues of healthy, uninfected controls. The enrichment of the T cell activation pathway in bats aligns with the upregulation of CXCL10, underscoring the importance of cell-mediated immunity in managing infection, as all bats remained clinically healthy throughout the study following viral infection [145]. This finding suggests a species-specific difference in the regulation of CXCL10 [145].

Phlebovirus

Rift Valley Fever Virus (RVFV)

Wild type or EGR1-/- U87MG cells were subjected to either mock-infection or viral infection at a multiplicity of infection of 5 for 1 hour. Post-infection with RVFV, there was a significant upregulation of CXCL10 expression, with its transcription being at least partially dependent on EGR1, as compared to mock-infected cells [146]. Levels of CXCL9 and CXCL10 were notably elevated in fatal cases compared to infected survivors and uninfected controls. Furthermore, these chemokines were increased in the infected patients compared to uninfected controls, suggesting their role as indicators of severe disease [35]. A significant positive correlation was observed between CXCL10 and plasma viral load in patients infected with RVFV. Additionally, CXCL4 levels were markedly elevated in RVFV-infected individuals compared to controls, indicating abnormalities in the coagulation pathway [147].

The Intricacies of the CXCR3 Axis Across VHFDs

The CXCR3 chemokine axis constitutes a dynamic, context-dependent immunoregulatory network during various VHFDs. Its activation, modulation, and distribution differ among viral families, reflecting variations in viral tropism, replication kinetics, immune evasion strategies, and host responses. In hemorrhagic fever–associated viruses such as LASV, EBOV, CCHFV, and RVFV, the CXCR3 axis exhibits a dual role. Early induction of CXCL9, CXCL10, and CXCL11 is associated with antiviral immune activation and survival, whereas their suppression or dysregulated overexpression correlates with fatal outcomes [28,99,101,138,146]. LASV infection reduces CXCR3 surface expression on macrophages and NK cells, thereby limiting effector T-cell trafficking to infected tissues. Conversely, EBOV infection downregulates CXCR3+ T-cell subsets while upregulating CXCL10 and CXCL11 transcripts during acute inflammation. These findings underscore the axis's role in both protective immunity and immune paralysis, contingent on the timing and location of infection.

In flaviviral infections such as DENV and YFV, the CXCR3 axis promotes antiviral Th1 polarization but can lead to immunopathology when hyperactivated. Elevated

levels of CXCL10 and CXCL11 during acute dengue correlate with vascular leakage, plasma cell recruitment, and disease severity [114–117]. YFV-17D vaccination induces CXCR3+ T-cell responses, highlighting its role in protective immunity [109]. Long-lived YFV-specific memory T cells maintain functional cytokine production even in the absence of CXCR3 expression, suggesting that CXCR3 expression defines effector localization rather than memory potential. CXCL10 upregulation is a hallmark of HTNV and PUUV infections, mediating the recruitment of monocytes and virus-specific T cells. However, excessive CXCL10/CXCR3 signaling contributes to endothelial activation and cytokine storm, linking chemokine dysregulation to renal and pulmonary syndromes. The persistence of elevated CXCL9/CXCL10 throughout the disease course underscores the chronic inflammatory imprint of these infections.

Paramyxoviruses (NiV and HeV) and Phleboviruses (RVFV) demonstrate CXCL10 induction in endothelial and neuronal tissues, indicating tissue-specific chemokine-driven inflammation [144,146]. In NiV infection, CXCL10 elevation in brain endothelium and sera is associated with encephalitis, while HeV-infected bats exhibit controlled CXCL10 expression linked to asymptomatic outcomes, highlighting a species-specific balance between antiviral signaling and tolerance.

These findings illustrate that the CXCR3 axis functions as a finely tuned sensor-effector module, whose spatiotemporal regulation determines viral clearance or immunopathology. Early, localized induction supports antiviral defense and vaccine efficacy, whereas prolonged or systemic expression drives immune-mediated tissue damage. Tissue tropism (endothelial, hepatic, neural, or lymphoid) and infection stage critically dictate the nature of CXCR3–ligand interactions. This complexity positions the CXCR3 axis as both a biomarker of disease progression and a potential target for immunomodulatory intervention across RNA viral infections.

Chemokine Receptors and Chemokine Ligands as Therapeutic Targets

Numerous preclinical studies utilizing animal models have underscored the potential therapeutic advantages of small molecule CXCR3 antagonists. Notably, piperazine-based piperidine has demonstrated promise in the treatment of autoimmune diseases, while Azaquinazolinone (AMG487) has shown efficacy in managing psoriasis and inflammatory conditions. Furthermore, derivatives of 1-phenyl-3-piperidin-4-ylurea have been identified as promising candidates for addressing inflammatory disorders [148]. In a similar vein, CXCR3 agonists like VUF11222, VUF11418, and FAUC1036 have been developed. The peptidomimetic PS372424, a CXCR3 agonist, has been effective in reducing the chemotaxis of activated T cells in a rheumatoid arthritis model [149]. Additionally, blocking CXCR3 with anti-CXCR3 antibodies has been found to effectively decrease the migration of cardiac CD8+ T cells towards macrophages, thereby preventing cardiac inflammation in an immune checkpoint inhibitors myocarditis animal model [150]. These findings suggest that regulating CXCR3 in specific disease conditions is crucial and may lead to favorable outcomes. However, for VHFDs, the study of CXCR3 regulation through agonists, antagonists, or anti-CXCR3 antibodies is limited, with most research conducted in the DENV model.

Research efforts at developing strategies to prevent DENV infection have focused on the application of various pharmacological agents and antibody-based methodologies. Mice deficient in the CXCR3 receptor exhibit increased mortality and hind limb paralysis, highlighting the protective role of this pathway during infection. These mice showed elevated viral loads and impaired T cell recruitment, particularly of CD8 T cells, thereby establishing a link between CXCR3 and antiviral control. CXCL10 has been identified as the principal ligand, as mice deficient in this chemokine display greater susceptibility than those lacking CXCR3, thus demonstrating CXCL10's protective role in DENV infection [125]. CXCL10 is rapidly induced in the liver following dengue infection. Neutralization of this chemokine reduces the recruitment of activated NK cells and the hepatic expression of their effector molecules [89]. Additionally, CXCL10 directly affects the virus by inhibiting dengue attachment to target cells through competition for heparan sulfate. Mutants unable to bind heparan sulfate lose their inhibitory capacity. Plaque assays reveal that this attachment blockade prevents viral uptake, indicating that CXCL10 contributes to host defense by recruiting antiviral NK cells and inhibiting viral entry [89]. Antibodies targeting CXCL4 or the inhibition of CXCR3 with AMG487 restored IFNα production and suppressed DENV replication in monocytes. These findings suggest that a deficiency in CXCL4 or inhibition of the CXCL4:CXCR3:IFN pathway can prevent DENV infection [128,129]. Compound 7D, acting as a CXCR3 antagonist, binds to CXCR3 and prevents CXCL4-driven DENV replication in monocytes, thereby enhancing IFNα/β and the expression of IFN-stimulated genes. Furthermore, 7D alleviates dengue symptoms by reducing DENV2 replication in tissues, enhancing platelet and monocyte counts, and increasing IFN production and antibody generation in mice [151]. These findings collectively support two complementary strategies for managing dengue. The first strategy involves maintaining beneficial CXCR3 signaling through the addition of CXCL10 or its mimetics. The second strategy seeks to counteract the harmful effects of platelet factor 4 by utilizing CXCR3 antagonists, such as AMG487 or 7D, or by inhibiting platelet factor 4 activity. Both approaches have demonstrated the ability to enhance antiviral IFN responses and improve disease outcomes in preclin-

ical models. The peptides COOH-terminal CXCL9 (74–103), acetyl-CXCL9 (74–103)-amide, and CXCL9 (74–93) have shown significant antiviral activity against DENV2, with EC_{50} values ranging from 23 to 115 µM. These peptides may play a critical role in inhibiting the virus's ability to bind to target cells, functioning independently of chemokine receptors [152]. Furthermore, a study on α-mangostin has demonstrated its efficacy in suppressing DENV replication in primary monocyte-derived dendritic cells, thereby reducing virus infection-induced cytokine production [153].

The findings related to changes in CXCR3 and its ligands during the development of VHFDs align with the well-known concept that CXCL9, CXCL10, and CXCL11 have a strong affinity for CXCR3, guiding T- and NK cells to areas of inflammation. Therefore, exploring small-molecule antagonists, neutralizing antibodies, or decoy strategies that target this pathway could be beneficial for these VHFDs, much like their use in other medical conditions. Recent progress in modulating the CXCR3 axis in DENV infection has shown promise in preclinical models, highlighting its potential as a therapeutic target. However, to successfully apply these strategies to other VHFDs, it is crucial to thoroughly understand the role of CXCR3 signaling in each specific infection. The use of agonists or antagonists may differently enhance the host immune response, depending on the viral pathogenesis and immune dynamics involved.

Discussion

Research on CXCR3-mediated immune regulation employs various methodologies, including the use of knockout mice, protein antagonists, small molecule inhibitors, and antibodies, to either inhibit or activate receptor-ligand interactions. These approaches elucidate the role of CXCR3 in the trafficking, activation, and response of immune cells within both innate and adaptive immunity, with significant implications for understanding inflammation, autoimmune diseases, cardiovascular diseases, neuronal diseases, infectious diseases, and cancer. The CXCR3 signaling pathway, which includes the receptor CXCR3 and the IFN-induced ligands CXCL9, CXCL10, and CXCL11, plays a crucial role in balancing protective and pathological responses in VHFDs. This pathway enhances antiviral control and aids in the clearance of infected cells by directing activated T-, NK-, and other effector cells to infection sites. However, if the response is excessive or poorly timed, these signals can worsen endothelial injury, vascular leakage, and organ dysfunction, which are characteristic of severe disease. In diseases such as Dengue, Ebola, Lassa, Crimean-congo hemorrhagic fever, HFRS, HPS, Rift valley fever, and yellow fever, the levels of CXCR3 ligands increase with disease activity and often correlated viral load and tissue damage. This consistent pattern presents two practical opportunities. Firstly, the pathway facilitates the identification of measurable biomarkers for patient monitoring and the assessment of potential therapeutic interventions. Secondly, it serves as a therapeutic mechanism that can be adjusted to meet the specific requirements of each disease. The aim is to achieve selective modulation that preserves beneficial trafficking and IFN-driven processes while minimizing excessive inflammation and microvascular damage.

Future research endeavors should prioritize the investigation of the timing and compartmentalization of immune responses. The initial IFN response may provide early defense, whereas prolonged chemokine signaling could exacerbate tissue damage and inflammation. While plasma analyses are indispensable for understanding systemic inflammation, the examination of tissue and endothelial cells is crucial for identifying specific sites of injury. Various methodologies can be employed to explore cytokine timing and compartmentalization, including longitudinal cytokine profiling in serum and tissues, single-cell RNA sequencing, flow cytometry-based cytokine analysis, immunohistochemistry or immunofluorescence imaging, the use of cytokine reporter mice, cytokine inhibition or blockade studies in animal models, virus tracking with cytokine profiling, cell-specific knockout mice, and spatiotemporal transcriptomics. Collectively, these complementary techniques offer a comprehensive evaluation of cytokine dynamics across different tissue compartments, immune cell subsets, and stages of infection.

Conclusion

Evidence from VHFs collectively suggests that precise, disease-specific modulation of the CXCR3 axis could enhance existing therapeutic strategies and improve patient outcomes. By employing clear biomarker strategies, considering timing and compartmentalization, and conducting mechanistically informed trials, the CXCR3 pathway could transition from observational studies to actionable interventions in future outbreaks.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization was undertaken by BP. The initial draft was written by NB and BP. Critical revisions were made by both NB and BP. The figure was prepared by NB. Both authors have reviewed and approved the final manuscript and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors assert that their research was conducted without any conflict of interest. BP is serving as one of the Editorial Board members of this journal. We declare that BP had no involvement in the peer review of this article and has no access to information regarding its peer review. Fig. 1 was created using BioRender. The authors have no financial or personal relationship with BioRender, and the use of this tool does not imply any endorsement.

References

[1] Flórez-Álvarez L, de Souza EE, Botosso VF, de Oliveira DBL, Ho PL, Taborda CP, *et al*. Hemorrhagic fever viruses: Pathogenesis, therapeutics, and emerging and re-emerging potential. Frontiers in Microbiology. 2022; 13: 1040093. https://doi.org/10.3389/fmicb.2022.1040093.

[2] Basler CF. Molecular pathogenesis of viral hemorrhagic fever. Seminars in Immunopathology. 2017; 39: 551–561. https://doi.org/10.1007/s00281-017-0637-x.

[3] Paessler S, Walker DH. Pathogenesis of the viral hemorrhagic fevers. Annual Review of Pathology. 2013; 8: 411–440. https://doi.org/10.1146/annurev-pathol-020712-164041.

[4] Messaoudi I, Basler CF. Immunological features underlying viral hemorrhagic fevers. Current Opinion in Immunology. 2015; 36: 38–46. https://doi.org/10.1016/j.coi.2015.06.003.

[5] Mahanty S, Hutchinson K, Agarwal S, McRae M, Rollin PE, Pulendran B. Cutting edge: impairment of dendritic cells and adaptive immunity by Ebola and Lassa viruses. Journal of Immunology (Baltimore, Md.: 1950). 2003; 170: 2797–2801. https://doi.org/10.4049/jimmunol.170.6.2797.

[6] Muñoz-Jordán JL, Laurent-Rolle M, Ashour J, Martínez-Sobrido L, Ashok M, Lipkin WI, *et al*. Inhibition of alpha/beta interferon signaling by the NS4B protein of flaviviruses. Journal of Virology. 2005; 79: 8004–8013. https://doi.org/10.1128/JVI.79.13.8004-8013.2005.

[7] Engelmann F, Josset L, Girke T, Park B, Barron A, Dewane J, *et al*. Pathophysiologic and transcriptomic analyses of viscerotropic yellow fever in a rhesus macaque model. PLoS Neglected Tropical Diseases. 2014; 8: e3295. https://doi.org/10.1371/journal.pntd.0003295.

[8] Jiang X, Huang Q, Wang W, Dong H, Ly H, Liang Y, *et al*. Structures of arenaviral nucleoproteins with triphosphate dsRNA reveal a unique mechanism of immune suppression. The Journal of Biological Chemistry. 2013; 288: 16949–16959. https://doi.org/10.1074/jbc.M112.420521.

[9] Le May N, Mansuroglu Z, Léger P, Josse T, Blot G, Billecocq A, *et al*. A SAP30 complex inhibits IFN-beta expression in Rift Valley fever virus infected cells. PLoS Pathogens. 2008; 4: e13. https://doi.org/10.1371/journal.ppat.0040013.

[10] Schmid MA, Diamond MS, Harris E. Dendritic cells in dengue virus infection: targets of virus replication and mediators of immunity. Frontiers in Immunology. 2014; 5: 647. https://doi.org/10.3389/fimmu.2014.00647.

[11] Schönrich G, Raftery MJ. Dendritic Cells (DCs) as "Fire Accelerants" of Hantaviral Pathogenesis. Viruses. 2019; 11: 849. https://doi.org/10.3390/v11090849.

[12] Feldmann H, Geisbert TW. Ebola haemorrhagic fever. Lancet (London, England). 2011; 377: 849–862. https://doi.org/10.1016/S0140-6736(10)60667-8.

[13] Zaki SR, Shieh WJ, Greer PW, Goldsmith CS, Ferebee T, Katshitshi J, *et al*. A novel immunohistochemical assay for the detection of Ebola virus in skin: implications for diagnosis, spread, and surveillance of Ebola hemorrhagic fever. Commission de Lutte contre les Epidémies à Kikwit. The Journal of Infectious Diseases. 1999; 179: S36–S47. https://doi.org/10.1086/514319.

[14] Odendaal L, Davis AS, Venter EH. Insights into the Pathogenesis of Viral Haemorrhagic Fever Based on Virus Tropism and Tissue Lesions of Natural Rift Valley Fever. Viruses. 2021; 13: 709. https://doi.org/10.3390/v13040709.

[15] Basler CF, Wang X, Mühlberger E, Volchkov V, Paragas J, Klenk HD, *et al*. The Ebola virus VP35 protein functions as a type I IFN antagonist. Proceedings of the National Academy of Sciences of the United States of America. 2000; 97: 12289–12294. https://doi.org/10.1073/pnas.220398297.

[16] Srikiatkhachorn A, Mathew A, Rothman AL. Immune-mediated cytokine storm and its role in severe dengue. Seminars in Immunopathology. 2017; 39: 563–574. https://doi.org/10.1007/s00281-017-0625-1.

[17] Fritz EA, Geisbert JB, Geisbert TW, Hensley LE, Reed DS. Cellular immune response to Marburg virus infection in cynomolgus macaques. Viral Immunology. 2008; 21: 355–363. https://doi.org/10.1089/vim.2008.0023.

[18] Bente DA, Alimonti JB, Shieh WJ, Camus G, Ströher U, Zaki S, *et al*. Pathogenesis and immune response of Crimean-Congo hemorrhagic fever virus in a STAT-1 knockout mouse model. Journal of Virology. 2010; 84: 11089–11100. https://doi.org/10.1128/JVI.01383-10.

[19] Feldmann H, Bugany H, Mahner F, Klenk HD, Drenckhahn D, Schnittler HJ. Filovirus-induced endothelial leakage triggered by infected monocytes/macrophages. Journal of Virology. 1996; 70: 2208–2214. https://doi.org/10.1128/JVI.70.4.2208-2214.1996.

[20] Zapata JC, Cox D, Salvato MS. The role of platelets in the pathogenesis of viral hemorrhagic fevers. PLoS Neglected Tropical Diseases. 2014; 8: e2858. https://doi.org/10.1371/journal.pntd.0002858.

[21] Khan SH, Goba A, Chu M, Roth C, Healing T, Marx A, *et al*. New opportunities for field research on the pathogenesis and treatment of Lassa fever. Antiviral Research. 2008; 78: 103–115. https://doi.org/10.1016/j.antiviral.2007.11.003.

[22] Gould EA, Solomon T. Pathogenic flaviviruses. Lancet (London, England). 2008; 371: 500–509. https://doi.org/10.1016/S0140-6736(08)60238-X.

[23] Gardner CL, Ryman KD. Yellow fever: a reemerging threat. Clinics in Laboratory Medicine. 2010; 30: 237–260. https://doi.org/10.1016/j.cll.2010.01.001.

[24] Ranjit S, Kissoon N. Dengue hemorrhagic fever and shock syndromes. Pediatric Critical Care Medicine: a Journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2011; 12: 90–100. https://doi.org/10.1097/PCC.0b013e3181e911a7.

[25] Stein SR, Platt AP, Teague HL, Anthony SM, Reeder RJ, Cooper K, *et al*. Clinical and Immunologic Correlates of Vasodilatory Shock Among Ebola Virus-Infected Nonhuman Primates in a

Critical Care Model. The Journal of Infectious Diseases. 2023; 228: S635–S647. https://doi.org/10.1093/infdis/jiad374.

[26] Reed DS, Hensley LE, Geisbert JB, Jahrling PB, Geisbert TW. Depletion of peripheral blood T lymphocytes and NK cells during the course of ebola hemorrhagic Fever in cynomolgus macaques. Viral Immunology. 2004; 17: 390–400. https://doi.org/10.1089/vim.2004.17.390.

[27] Kalabamu FS, Maliki S. Use of Haematological Changes as a Predictor of Dengue Infection among Suspected Cases at Kairuki Hospital in Dar Es Salaam, Tanzania: A Retrospective Cross Sectional Study. The East African Health Research Journal. 2021; 5: 91–98. https://doi.org/10.24248/eahrj.v5i1.655.

[28] Baize S, Marianneau P, Loth P, Reynard S, Journeaux A, Chevallier M, *et al*. Early and strong immune responses are associated with control of viral replication and recovery in lassa virus-infected cynomolgus monkeys. Journal of Virology. 2009; 83: 5890–5903. https://doi.org/10.1128/JVI.01948-08.

[29] Liu DX, Pahar B, Cooper TK, Perry DL, Xu H, Huzella LM, *et al*. Ebola Virus Disease Features Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome in the Rhesus Macaque Model. The Journal of Infectious Diseases. 2023; 228: 371–382. https://doi.org/10.1093/infdis/jiad203.

[30] Kortepeter MG, Dierberg K, Shenoy ES, Cieslak TJ, Medical Countermeasures Working Group of the National Ebola Training and Education Center's (NETEC) Special Pathogens Research Network (SPRN). Marburg virus disease: A summary for clinicians. International Journal of Infectious Diseases: IJID: Official Publication of the International Society for Infectious Diseases. 2020; 99: 233–242. https://doi.org/10.1016/j.ijid.2020.07.042.

[31] Bradfute SB, Swanson PE, Smith MA, Watanabe E, McDunn JE, Hotchkiss RS, *et al*. Mechanisms and consequences of ebolavirus-induced lymphocyte apoptosis. Journal of Immunology (Baltimore, Md.: 1950). 2010; 184: 327–335. https://doi.org/10.4049/jimmunol.0901231.

[32] Iampietro M, Younan P, Nishida A, Dutta M, Lubaki NM, Santos RI, *et al*. Ebola virus glycoprotein directly triggers T lymphocyte death despite of the lack of infection. PLoS Pathogens. 2017; 13: e1006397. https://doi.org/10.1371/journal.ppat.1006397.

[33] Wauquier N, Becquart P, Padilla C, Baize S, Leroy EM. Human fatal zaire ebola virus infection is associated with an aberrant innate immunity and with massive lymphocyte apoptosis. PLoS Neglected Tropical Diseases. 2010; 4: e837. https://doi.org/10.1371/journal.pntd.0000837.

[34] Liu DX, Pahar B, Perry DL, Xu H, Cooper TK, Huzella LM, *et al*. Depletion of Bone Marrow Hematopoietic Cells in Ebolavirus-Infected Rhesus Macaques: A Possible Cause of Hematologic Abnormalities in Ebolavirus Disease. The American Journal of Pathology. 2023; 193: 2031–2046. https://doi.org/10.1016/j.ajpath.2023.08.010.

[35] Jansen van Vuren P, Shalekoff S, Grobbelaar AA, Archer BN, Thomas J, Tiemessen CT, *et al*. Serum levels of inflammatory cytokines in Rift Valley fever patients are indicative of severe disease. Virology Journal. 2015; 12: 159. https://doi.org/10.1186/s12985-015-0392-3.

[36] Dejnirattisai W, Duangchinda T, Lin CLS, Vasanawathana S, Jones M, Jacobs M, *et al*. A complex interplay among virus, dendritic cells, T cells, and cytokines in dengue virus infections. Journal of Immunology (Baltimore, Md.: 1950). 2008; 181: 5865–5874. https://doi.org/10.4049/jimmunol.181.9.5865.

[37] Groom JR, Luster AD. CXCR3 in T cell function. Experimental Cell Research. 2011; 317: 620–631. https://doi.org/10.1016/j.yexcr.2010.12.017.

[38] Qin S, Rottman JB, Myers P, Kassam N, Weinblatt M, Loetscher M, *et al*. The chemokine receptors CXCR3 and CCR5 mark subsets of T cells associated with certain inflammatory reactions. The Journal of Clinical Investigation. 1998; 101: 746–754. https://doi.org/10.1172/JCI1422.

[39] Thomas SY, Hou R, Boyson JE, Means TK, Hess C, Olson DP, *et al*. CD1d-restricted NKT cells express a chemokine receptor profile indicative of Th1-type inflammatory homing cells. Journal of Immunology (Baltimore, Md.: 1950). 2003; 171: 2571–2580. https://doi.org/10.4049/jimmunol.171.5.2571.

[40] Cella M, Jarrossay D, Facchetti F, Alebardi O, Nakajima H, Lanzavecchia A, *et al*. Plasmacytoid monocytes migrate to inflamed lymph nodes and produce large amounts of type I interferon. Nature Medicine. 1999; 5: 919–923. https://doi.org/10.1038/11360.

[41] Tokunaga R, Zhang W, Naseem M, Puccini A, Berger MD, Soni S, *et al*. CXCL9, CXCL10, CXCL11/CXCR3 axis for immune activation - A target for novel cancer therapy. Cancer Treatment Reviews. 2018; 63: 40–47. https://doi.org/10.1016/j.ctrv.2017.11.007.

[42] Altara R, Manca M, Brandão RD, Zeidan A, Booz GW, Zouein FA. Emerging importance of chemokine receptor CXCR3 and its ligands in cardiovascular diseases. Clinical Science (London, England: 1979). 2016; 130: 463–478. https://doi.org/10.1042/CS20150666.

[43] Hoh BP, Umi-Shakina H, Zuraihan Z, Zaiharina MZ, Rafidah-Hanim S, Mahiran M, *et al*. Common variants of chemokine receptor gene CXCR3 and its ligands CXCL10 and CXCL11 associated with vascular permeability of dengue infection in peninsular Malaysia. Human Immunology. 2015; 76: 421–426. https://doi.org/10.1016/j.humimm.2015.03.019.

[44] Platt AP, Barr B, Marketon A, Bernbaum R, Rivera DF, Munster VJ, *et al*. Cellular immunophenotyping in human and primate tissues during healthy conditions and Ebola and Nipah infections. JCI Insight. 2025; 10: e185861. https://doi.org/10.1172/jci.insight.185861.

[45] Hastie KM, Melnik LI, Cross RW, Klitting RM, Andersen KG, Saphire EO, *et al*. The Arenaviridae Family: Knowledge Gaps, Animal Models, Countermeasures, and Prototype Pathogens. The Journal of Infectious Diseases. 2023; 228: S359–S375. https://doi.org/10.1093/infdis/jiac266.

[46] Biedenkopf N, Bukreyev A, Chandran K, Di Paola N, Formenty PBH, Griffiths A, *et al*. ICTV Virus Taxonomy Profile: *Filoviridae* 2024. The Journal of General Virology. 2024; 105: 001955. https://doi.org/10.1099/jgv.0.001955.

[47] Postler TS, Beer M, Blitvich BJ, Bukh J, de Lamballerie X, Drexler JF, *et al*. Renaming of the genus Flavivirus to Orthoflavivirus and extension of binomial species names within the family Flaviviridae. Archives of Virology. 2023; 168: 224. https://doi.org/10.1007/s00705-023-05835-1.

[48] Bradfute SB, Calisher CH, Klempa B, Klingström J, Kuhn JH, Laenen L, *et al*. ICTV Virus Taxonomy Profile: *Hantaviridae* 2024. The Journal of General Virology. 2024; 105: 001975. https://doi.org/10.1099/jgv.0.001975.

[49] Kuhn JH, Alkhovsky SV, Avšič-Županc T, Bergeron É, Burt F, Ergünay K, *et al*. ICTV Virus Taxonomy Profile: *Nairoviridae* 2024. The Journal of General Virology. 2024; 105: 001974. https://doi.org/10.1099/jgv.0.001974.

[50] Rima B, Balkema-Buschmann A, Dundon WG, Duprex P, Easton A, Fouchier R, *et al*. ICTV Virus Taxonomy Profile: *Paramyxoviridae*. The Journal of General Virology. 2019; 100: 1593–1594. https://doi.org/10.1099/jgv.0.001328.

[51] Sasaya T, Palacios G, Briese T, Di Serio F, Groschup MH, Neriya Y, *et al*. ICTV Virus Taxonomy Profile: *Phenuiviridae* 2023. The Journal of General Virology. 2023; 104: 001893. https://doi.org/10.1099/jgv.0.001893.

[52] Douam F, Ploss A. Yellow Fever Virus: Knowledge Gaps Impeding the Fight Against an Old Foe. Trends in Microbiology. 2018; 26: 913–928. https://doi.org/10.1016/j.tim.2018.05.012.

[53] Tomori O, Kolawole MO. Ebola virus disease: current vaccine solutions. Current Opinion in Immunology. 2021; 71: 27–33. https://doi.org/10.1016/j.coi.2021.03.008.

[54] Enria DA, Barrera Oro JG. Junin virus vaccines. Current Topics in Microbiology and Immunology. 2002; 263: 239–261. https://doi.org/10.1007/978-3-642-56055-2_12.

[55] Van Raemdonck K, Van den Steen PE, Liekens S, Van Damme J, Struyf S. CXCR3 ligands in disease and therapy. Cytokine & Growth Factor Reviews. 2015; 26: 311–327. https://doi.org/10.1016/j.cytogfr.2014.11.009.

[56] Groover MK, Richmond JM. Potential therapeutic manipulations of the CXCR3 chemokine axis for the treatment of inflammatory fibrosing diseases. F1000Research. 2020; 9: 1197. https://doi.org/10.12688/f1000research.26728.1.

[57] Boyé K, Billottet C, Pujol N, Alves ID, Bikfalvi A. Ligand activation induces different conformational changes in CXCR3 receptor isoforms as evidenced by plasmon waveguide resonance (PWR). Scientific Reports. 2017; 7: 10703. https://doi.org/10.1038/s41598-017-11151-x.

[58] Reynders N, Abboud D, Baragli A, Noman MZ, Rogister B, Niclou SP, *et al*. The Distinct Roles of CXCR3 Variants and Their Ligands in the Tumor Microenvironment. Cells. 2019; 8: 613. https://doi.org/10.3390/cells8060613.

[59] Amabebe E, Anumba DO. The transmembrane G protein-coupled CXCR3 receptor-ligand system and maternal foetal allograft rejection. Placenta. 2021; 104: 81–88. https://doi.org/10.1016/j.placenta.2020.11.003.

[60] Metzemaekers M, Vanheule V, Janssens R, Struyf S, Proost P. Overview of the Mechanisms that May Contribute to the Non-Redundant Activities of Interferon-Inducible CXC Chemokine Receptor 3 Ligands. Frontiers in Immunology. 2018; 8: 1970. https://doi.org/10.3389/fimmu.2017.01970.

[61] Weng Y, Siciliano SJ, Waldburger KE, Sirotina-Meisher A, Staruch MJ, Daugherty BL, *et al*. Binding and functional properties of recombinant and endogenous CXCR3 chemokine receptors. The Journal of Biological Chemistry. 1998; 273: 18288–18291. https://doi.org/10.1074/jbc.273.29.18288.

[62] Cole KE, Strick CA, Paradis TJ, Ogborne KT, Loetscher M, Gladue RP, *et al*. Interferon-inducible T cell alpha chemoattractant (I-TAC): a novel non-ELR CXC chemokine with potent activity on activated T cells through selective high affinity binding to CXCR3. The Journal of Experimental Medicine. 1998; 187: 2009–2021. https://doi.org/10.1084/jem.187.12.2009.

[63] Rubinstein A, Kudryavtsev I, Arsentieva N, Korobova ZR, Isakov D, Totolian AA. CXCR3-Expressing T Cells in Infections and Autoimmunity. Frontiers in Bioscience (Landmark Edition). 2024; 29: 301. https://doi.org/10.31083/j.fbl2908301.

[64] Yang Y, Ochando JC, Bromberg JS, Ding Y. Identification of a distant T-bet enhancer responsive to IL-12/Stat4 and IFNgamma/Stat1 signals. Blood. 2007; 110: 2494–2500. https://doi.org/10.1182/blood-2006-11-058271.

[65] Mousset CM, Hobo W, Woestenenk R, Preijers F, Dolstra H, van der Waart AB. Comprehensive Phenotyping of T Cells Using Flow Cytometry. Cytometry. Part a: the Journal of the International Society for Analytical Cytology. 2019; 95: 647–654. https://doi.org/10.1002/cyto.a.23724.

[66] Hölscher C. The power of combinatorial immunology: IL-12 and IL-12-related dimeric cytokines in infectious diseases. Medical Microbiology and Immunology. 2004; 193: 1–17. https://doi.org/10.1007/s00430-003-0186-x.

[67] Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, Goerdt S, *et al*. Macrophage activation and polarization: nomenclature and experimental guidelines. Immunity. 2014; 41: 14–20. https://doi.org/10.1016/j.immuni.2014.06.008.

[68] Nakanishi Y, Lu B, Gerard C, Iwasaki A. CD8(+) T lymphocyte mobilization to virus-infected tissue requires CD4(+) T-cell help. Nature. 2009; 462: 510–513. https://doi.org/10.1038/nature08511.

[69] Mikhak Z, Fleming CM, Medoff BD, Thomas SY, Tager AM, Campanella GS, *et al*. STAT1 in peripheral tissue differentially regulates homing of antigen-specific Th1 and Th2 cells. Journal of Immunology (Baltimore, Md.: 1950). 2006; 176: 4959–4967. https://doi.org/10.4049/jimmunol.176.8.4959.

[70] McLachlan JB, Catron DM, Moon JJ, Jenkins MK. Dendritic cell antigen presentation drives simultaneous cytokine production by effector and regulatory T cells in inflamed skin. Immunity. 2009; 30: 277–288. https://doi.org/10.1016/j.immuni.2008.11.013.

[71] Ramesh R, Kozhaya L, McKevitt K, Djuretic IM, Carlson TJ, Quintero MA, *et al*. Pro-inflammatory human Th17 cells selectively express P-glycoprotein and are refractory to glucocorticoids. The Journal of Experimental Medicine. 2014; 211: 89–104. https://doi.org/10.1084/jem.20130301.

[72] Annunziato F, Cosmi L, Santarlasci V, Maggi L, Liotta F, Mazzinghi B, *et al*. Phenotypic and functional features of human Th17 cells. The Journal of Experimental Medicine. 2007; 204: 1849–1861. https://doi.org/10.1084/jem.20070663.

[73] Hu D, Notarbartolo S, Croonenborghs T, Patel B, Cialic R, Yang TH, *et al*. Transcriptional signature of human pro-inflammatory T_H17 cells identifies reduced IL10 gene expression in multiple sclerosis. Nature Communications. 2017; 8: 1600. https://doi.org/10.1038/s41467-017-01571-8.

[74] Wacleche VS, Goulet JP, Gosselin A, Monteiro P, Soudeyns H, Fromentin R, *et al*. New insights into the heterogeneity of Th17 subsets contributing to HIV-1 persistence during antiretroviral therapy. Retrovirology. 2016; 13: 59. https://doi.org/10.1186/s12977-016-0293-6.

[75] Cunill V, Clemente A, Lanio N, Barceló C, Andreu V, Pons J, *et al*. Follicular T Cells from smB$^-$ Common Variable Immunodeficiency Patients Are Skewed Toward a Th1 Phenotype. Frontiers in Immunology. 2017; 8: 174. https://doi.org/10.3389/fimmu.2017.00174.

[76] Morita R, Schmitt N, Bentebibel SE, Ranganathan R, Bourdery L, Zurawski G, *et al*. Human blood CXCR5(+)CD4(+) T cells are counterparts of T follicular cells and contain specific subsets that differentially support antibody secretion. Immunity. 2011; 34: 108–121. https://doi.org/10.1016/j.immuni.2010.12.012.

[77] Zhang Z, Guo J, Jia R. Treg plasticity and human diseases. Inflammation Research. 2023; 72: 2181–2197. https://doi.org/10.1007/s00011-023-01808-x.

[78] Duhen T, Duhen R, Lanzavecchia A, Sallusto F, Campbell DJ. Functionally distinct subsets of human FOXP3+ Treg cells that phenotypically mirror effector Th cells. Blood. 2012; 119: 4430–4440. https://doi.org/10.1182/blood-2011-11-392324.

[79] Zhang R, Miao J, Zhang K, Zhang B, Luo X, Sun H, *et al*. Th1-Like Treg Cells Are Increased But Deficient in Function in Rheumatoid Arthritis. Frontiers in Immunology. 2022; 13: 863753. https://doi.org/10.3389/fimmu.2022.863753.

[80] Koch MA, Tucker-Heard G, Perdue NR, Killebrew JR, Urdahl KB, Campbell DJ. The transcription factor T-bet controls regulatory T cell homeostasis and function during type 1 inflammation. Nature Immunology. 2009; 10: 595–602. https://doi.org/10.1038/ni.1731.

[81] Tan TG, Mathis D, Benoist C. Singular role for T-BET+CXCR3+ regulatory T cells in protection from autoimmune diabetes. Proceedings of the National Academy of Sciences of the United States of America. 2016; 113: 14103–14108. https://doi.org/10.1073/pnas.1616710113.

[82] Dominguez-Villar M, Baecher-Allan CM, Hafler DA. Identification of T helper type 1-like, Foxp3+ regulatory T cells in human autoimmune disease. Nature Medicine. 2011; 17: 673–675. https://doi.org/10.1038/nm.2389.

[83] Loyal L, Warth S, Jürchott K, Mölder F, Nikolaou C, Babel N, *et al*. SLAMF7 and IL-6R define distinct cytotoxic versus helper memory CD8$^+$ T cells. Nature Communications. 2020; 11: 6357. https://doi.org/10.1038/s41467-020-19002-6.

[84] Annunziato F, Romagnani C, Romagnani S. The 3 major types of innate and adaptive cell-mediated effector immunity. The Journal of Allergy and Clinical Immunology. 2015; 135: 626–635. https://doi.org/10.1016/j.jaci.2014.11.001.

[85] Chan WL, Pejnovic N, Lee CA, Al-Ali NA. Human IL-18 receptor and ST2L are stable and selective markers for the respective type 1 and type 2 circulating lymphocytes. Journal of Immunology (Baltimore, Md.: 1950). 2001; 167: 1238–1244. https://doi.org/10.4049/jimmunol.167.3.1238.

[86] Mittrücker HW, Visekruna A, Huber M. Heterogeneity in the differentiation and function of CD8+ T cells. Archivum Immunologiae et Therapiae Experimentalis. 2014; 62: 449–458. https://doi.org/10.1007/s00005-014-0293-y.

[87] Brandstadter JD, Yang Y. Natural killer cell responses to viral infection. Journal of Innate Immunity. 2011; 3: 274–279. https://doi.org/10.1159/000324176.

[88] Grégoire C, Chasson L, Luci C, Tomasello E, Geissmann F, Vivier E, *et al*. The trafficking of natural killer cells. Immunological Reviews. 2007; 220: 169–182. https://doi.org/10.1111/j.1600-065X.2007.00563.x.

[89] Chen JP, Lu HL, Lai SL, Campanella GS, Sung JM, Lu MY, *et al*. Dengue virus induces expression of CXC chemokine ligand 10/IFN-gamma-inducible protein 10, which competitively inhibits viral binding to cell surface heparan sulfate. Journal of Immunology (Baltimore, Md.: 1950). 2006; 177: 3185–3192. https://doi.org/10.4049/jimmunol.177.5.3185.

[90] Lee SH, Miyagi T, Biron CA. Keeping NK cells in highly regulated antiviral warfare. Trends in Immunology. 2007; 28: 252–259. https://doi.org/10.1016/j.it.2007.04.001.

[91] Lee SH, Biron CA. Here today–not gone tomorrow: roles for activating receptors in sustaining NK cells during viral infections. European Journal of Immunology. 2010; 40: 923–932. https://doi.org/10.1002/eji.201040304.

[92] Ali A, Canaday LM, Feldman HA, Cevik H, Moran MT, Rajaram S, *et al*. Natural killer cell immunosuppressive function requires CXCR3-dependent redistribution within lymphoid tissues. The Journal of Clinical Investigation. 2021; 131: e146686. https://doi.org/10.1172/JCI146686.

[93] Ng ACK, Zhang C, Lam TL, Kiang KM, Ng VNC, Zhu Z, *et al*. CXCR3-mediated natural killer cell infiltration exacerbates white matter injury after intracerebral haemorrhage. Brain: a Journal of Neurology. 2025; 148: 3121–3136. https://doi.org/10.1093/brain/awaf108.

[94] Eisenhardt M, Glässner A, Krämer B, Körner C, Sibbing B, Kokordelis P, *et al*. The CXCR3(+)CD56Bright phenotype characterizes a distinct NK cell subset with anti-fibrotic potential that shows dys-regulated activity in hepatitis C. PloS One. 2012; 7: e38846. https://doi.org/10.1371/journal.pone.0038846.

[95] Xu J, Fu H, Yang Y, Yu H, Ai X, Lei Y, *et al*. Modulation of CXCR1 and CXCR3 expression on NK cells via Tim-3 in a murine model of primary biliary cholangitis. Molecular Immunology. 2021; 135: 342–350. https://doi.org/10.1016/j.molimm.2021.04.014.

[96] Wendel M, Galani IE, Suri-Payer E, Cerwenka A. Natural killer cell accumulation in tumors is dependent on IFN-gamma and CXCR3 ligands. Cancer Research. 2008; 68: 8437–8445. https://doi.org/10.1158/0008-5472.CAN-08-1440.

[97] Wang X, Zhang Y, Wang S, Ni H, Zhao P, Chen G, *et al*. The role of CXCR3 and its ligands in cancer. Frontiers in Oncology. 2022; 12: 1022688. https://doi.org/10.3389/fonc.2022.1022688.

[98] Russier M, Reynard S, Tordo N, Baize S. NK cells are strongly activated by Lassa and Mopeia virus-infected human macrophages in vitro but do not mediate virus suppression. European Journal of Immunology. 2012; 42: 1822–1832. https://doi.org/10.1002/eji.201142099.

[99] Mahanty S, Bausch DG, Thomas RL, Goba A, Bah A, Peters CJ, *et al*. Low levels of interleukin-8 and interferon-inducible protein-10 in serum are associated with fatal infections in acute Lassa fever. The Journal of Infectious Diseases. 2001; 183: 1713–1721. https://doi.org/10.1086/320722.

[100] Caballero IS, Honko AN, Gire SK, Winnicki SM, Melé M, Gerhardinger C, *et al*. In vivo Ebola virus infection leads to a strong innate response in circulating immune cells. BMC Genomics. 2016; 17: 707. https://doi.org/10.1186/s12864-016-3060-0.

[101] Rechtien A, Richert L, Lorenzo H, Martrus G, Hejblum B, Dahlke C, *et al*. Systems Vaccinology Identifies an Early Innate Immune Signature as a Correlate of Antibody Responses to the Ebola Vaccine rVSV-ZEBOV. Cell Reports. 2017; 20: 2251–2261. https://doi.org/10.1016/j.celrep.2017.08.023.

[102] Martinez-Murillo PA, Huttner A, Lemeille S, Medaglini D, Ottenhoff THM, Harandi AM, *et al*. Refined innate plasma signature after rVSVΔG-ZEBOV-GP immunization is shared among adult cohorts in Europe and North America. Frontiers in Immunology. 2024; 14: 1279003. https://doi.org/10.3389/fimmu.2023.1279003.

[103] Blengio F, Hocini H, Richert L, Lefebvre C, Durand M, Hejblum B, *et al*. Identification of early gene expression profiles associated with long-lasting antibody responses to the Ebola vaccine Ad26.ZEBOV/MVA-BN-Filo. Cell Reports. 2023; 42: 113101. https://doi.org/10.1016/j.celrep.2023.113101.

[104] Scoon WA, Mancio-Silva L, Suder EL, Villacorta-Martin C, Lindstrom-Vautrin J, Bernbaum JG, *et al*. Ebola virus infection induces a delayed type I IFN response in bystander cells and the shutdown of key liver genes in human iPSC-derived hepatocytes. Stem Cell Reports. 2022; 17: 2286–2302. https://doi.org/10.1016/j.stemcr.2022.08.003.

[105] James EA, LaFond RE, Gates TJ, Mai DT, Malhotra U, Kwok WW. Yellow fever vaccination elicits broad functional CD4+ T cell responses that recognize structural and nonstructural proteins. Journal of Virology. 2013; 87: 12794–12804. https://doi.org/10.1128/JVI.01160-13.

[106] Pan YG, Bartolo L, Xu R, Patel BV, Zarnitsyna VI, Su LF. Preservation of naive-phenotype CD4+ T cells after vaccination contributes to durable immunity. JCI Insight. 2024; 9: e180667. https://doi.org/10.1172/jci.insight.180667.

[107] Giugni FR, Aiello VD, Faria CS, Pour SZ, Cunha MDP, Giugni MV, *et al*. Understanding yellow fever-associated myocardial injury: an autopsy study. EBioMedicine. 2023; 96: 104810. https://doi.org/10.1016/j.ebiom.2023.104810.

[108] Gonçalves ANA, Costa PR, Thomazella MV, Correia CA, Marmorato MP, Dias JZC, *et al*. Systems Immunology Approaches to Understanding Immune Responses in Acute Infection of Yellow Fever Patients. Journal of Medical Virology. 2024; 96: e70099. https://doi.org/10.1002/jmv.70099.

[109] Santos-Peral A, Zaucha M, Nikolova E, Yaman E, Puzek B, Winheim E, *et al*. Basal T cell activation predicts yellow fever vaccine response independently of cytomegalovirus infection and sex-related immune variations. Cell Reports. Medicine. 2025; 6: 101946. https://doi.org/10.1016/j.xcrm.2025.101946.

[110] Querec TD, Akondy RS, Lee EK, Cao W, Nakaya HI, Teuwen D, *et al*. Systems biology approach predicts immunogenicity of the yellow fever vaccine in humans. Nature Immunology. 2009; 10: 116–125. https://doi.org/10.1038/ni.1688.

[111] Rivino L, Kumaran EA, Thein TL, Too CT, Gan VCH, Hanson BJ, *et al*. Virus-specific T lymphocytes home to the skin during natural dengue infection. Science Translational Medicine. 2015; 7: 278ra35. https://doi.org/10.1126/scitranslmed.aaa0526.

[112] Chau TNB, Quyen NTH, Thuy TT, Tuan NM, Hoang DM,

Dung NTP, *et al*. Dengue in Vietnamese infants–results of infection-enhancement assays correlate with age-related disease epidemiology, and cellular immune responses correlate with disease severity. The Journal of Infectious Diseases. 2008; 198: 516–524. https://doi.org/10.1086/590117.

[113] Pattanapanyasat K, Khowawisetsut L, Chuansumrit A, Chokephaibulkit K, Tangnararatchakit K, Apiwattanakul N, *et al*. B cell subset alteration and the expression of tissue homing molecules in dengue infected patients. Journal of Biomedical Science. 2018; 25: 64. https://doi.org/10.1186/s12929-018-0467-8.

[114] Huang J, Liang W, Chen S, Zhu Y, Chen H, Mok CKP, *et al*. Serum Cytokine Profiles in Patients with Dengue Fever at the Acute Infection Phase. Disease Markers. 2018; 2018: 8403937. https://doi.org/10.1155/2018/8403937.

[115] Fallahi P, Elia G. Interferon-γ-induced protein 10 in Dengue Virus infection. La Clinica Terapeutica. 2016; 167: e186–e191. https://doi.org/10.7417/CT.2016.1966.

[116] Her Z, Kam YW, Gan VC, Lee B, Thein TL, Tan JJL, *et al*. Severity of Plasma Leakage Is Associated With High Levels of Interferon γ-Inducible Protein 10, Hepatocyte Growth Factor, Matrix Metalloproteinase 2 (MMP-2), and MMP-9 During Dengue Virus Infection. The Journal of Infectious Diseases. 2017; 215: 42–51. https://doi.org/10.1093/infdis/jiw494.

[117] Coutinho-da-Silva MS, Sucupira PHF, Bicalho KA, Campi-Azevedo AC, Brito-de-Sousa JP, Peruhype-Magalhães V, *et al*. Serum Soluble Mediator Profiles and Networks During Acute Infection With Distinct DENV Serotypes. Frontiers in Immunology. 2022; 13: 892990. https://doi.org/10.3389/fimmu.2022.892990.

[118] Puccioni-Sohler M, da Silva SJ, Faria LCS, Cabral DCBI, Cabral-Castro MJ. Neopterin and CXCL-10 in Cerebrospinal Fluid as Potential Biomarkers of Neuroinvasive Dengue and Chikungunya. Pathogens (Basel, Switzerland). 2021; 10: 1626. https://doi.org/10.3390/pathogens10121626.

[119] Mustafa Z, Manzoor Khan H, Ghazanfar Ali S, Sami H, Almatroudi A, Alam Khan M, *et al*. Distinct inflammatory markers in primary and secondary dengue infection: can cytokines CXCL5, CXCL9, and CCL17 act as surrogate markers? Pathogens and Global Health. 2024; 118: 408–417. https://doi.org/10.1080/20477724.2024.2365581.

[120] Patra G, Mallik S, Saha B, Mukhopadhyay S. Assessment of chemokine and cytokine signatures in patients with dengue infection: A hospital-based study in Kolkata, India. Acta Tropica. 2019; 190: 73–79. https://doi.org/10.1016/j.actatropica.2018.10.017.

[121] Dalrymple NA, Mackow ER. Endothelial cells elicit immune-enhancing responses to dengue virus infection. Journal of Virology. 2012; 86: 6408–6415. https://doi.org/10.1128/JVI.00213-12.

[122] Fares-Gusmao R, Rocha BC, Sippert E, Lanteri MC, Áñez G, Rios M. Differential Pattern of Soluble Immune Markers in Asymptomatic Dengue, West Nile and Zika Virus Infections. Scientific Reports. 2019; 9: 17172. https://doi.org/10.1038/s41598-019-53645-w.

[123] Jusof FF, Lim CK, Aziz FN, Soe HJ, Raju CS, Sekaran SD, *et al*. The Cytokines CXCL10 and CCL2 and the Kynurenine Metabolite Anthranilic Acid Accurately Predict Patients at Risk of Developing Dengue With Warning Signs. The Journal of Infectious Diseases. 2022; 226: 1964–1973. https://doi.org/10.1093/infdis/jiac273.

[124] Hou R, Tomalin LE, Silva JP, Kim-Schulze S, Whitehead SS, Fernandez-Sesma A, *et al*. The innate immune response following multivalent dengue vaccination and implications for protection against dengue challenge. JCI Insight. 2022; 7: e157811. https://doi.org/10.1172/jci.insight.157811.

[125] Hsieh MF, Lai SL, Chen JP, Sung JM, Lin YL, Wu-Hsieh BA, *et al*. Both CXCR3 and CXCL10/IFN-inducible protein 10 are required for resistance to primary infection by dengue virus. Journal of Immunology (Baltimore, Md.: 1950). 2006; 177: 1855–1863. https://doi.org/10.4049/jimmunol.177.3.1855.

[126] Ip PP, Liao F. Resistance to dengue virus infection in mice is potentiated by CXCL10 and is independent of CXCL10-mediated leukocyte recruitment. Journal of Immunology (Baltimore, Md.: 1950). 2010; 184: 5705–5714. https://doi.org/10.4049/jimmunol.0903484.

[127] de-Oliveira-Pinto LM, Marinho CF, Povoa TF, de Azeredo EL, de Souza LA, Barbosa LDR, *et al*. Regulation of inflammatory chemokine receptors on blood T cells associated to the circulating versus liver chemokines in dengue fever. PloS One. 2012; 7: e38527. https://doi.org/10.1371/journal.pone.0038527.

[128] Singh A, Ghosh R, Asuru TR, Prajapat SK, Joshi G, Gaur KK, *et al*. Inhibition of cellular activation induced by platelet factor 4 via the CXCR3 pathway ameliorates Japanese encephalitis and dengue viral infections. Journal of Thrombosis and Haemostasis: JTH. 2024; 22: 818–833. https://doi.org/10.1016/j.jtha.2023.11.015.

[129] Ojha A, Bhasym A, Mukherjee S, Annarapu GK, Bhakuni T, Akbar I, *et al*. Platelet factor 4 promotes rapid replication and propagation of Dengue and Japanese encephalitis viruses. EBioMedicine. 2019; 39: 332–347. https://doi.org/10.1016/j.ebiom.2018.11.049.

[130] Singh A, Bisht P, Bhattacharya S, Guchhait P. Role of Platelet Cytokines in Dengue Virus Infection. Frontiers in Cellular and Infection Microbiology. 2020; 10: 561366. https://doi.org/10.3389/fcimb.2020.561366.

[131] Zhang Y, Liu B, Ma Y, Yi J, Zhang C, Zhang Y, *et al*. Hantaan virus infection induces CXCL10 expression through TLR3, RIG-I, and MDA-5 pathways correlated with the disease severity. Mediators of Inflammation. 2014; 2014: 697837. https://doi.org/10.1155/2014/697837.

[132] Lindell DM, Lane TE, Lukacs NW. CXCL10/CXCR3-mediated responses promote immunity to respiratory syncytial virus infection by augmenting dendritic cell and CD8(+) T cell efficacy. European Journal of Immunology. 2008; 38: 2168–2179. https://doi.org/10.1002/eji.200838155.

[133] Ye W, Xu Y, Wang Y, Dong Y, Xi Q, Cao M, *et al*. Hantaan virus can infect human keratinocytes and activate an interferon response through the nuclear translocation of IRF-3. Infection, Genetics and Evolution: Journal of Molecular Epidemiology and Evolutionary Genetics in Infectious Diseases. 2015; 29: 146–155. https://doi.org/10.1016/j.meegid.2014.11.009.

[134] Williams EP, Nandi A, Nam V, Allen LJS, Trindade AA, Kosiewicz MM, *et al*. Modeling the Immune Response for Pathogenic and Nonpathogenic *Orthohantavirus* Infections in Human Lung Microvasculature Endothelial Cells. Viruses. 2023; 15: 1806. https://doi.org/10.3390/v15091806.

[135] Khaiboullina SF, Levis S, Morzunov SP, Martynova EV, Anokhin VA, Gusev OA, *et al*. Serum Cytokine Profiles Differentiating Hemorrhagic Fever with Renal Syndrome and Hantavirus Pulmonary Syndrome. Frontiers in Immunology. 2017; 8: 567. https://doi.org/10.3389/fimmu.2017.00567.

[136] Schrottmaier WC, Schmuckenschlager A, Thunberg T, Wigren-Byström J, Fors-Connolly AM, Assinger A, *et al*. Direct and indirect effects of Puumala hantavirus on platelet function. Thrombosis Research. 2024; 233: 41–54. https://doi.org/10.1016/j.thromres.2023.11.017.

[137] García M, Carrasco García A, Weigel W, Christ W, Lira-Junior R, Wirth L, *et al*. Innate lymphoid cells are activated in HFRS, and their function can be modulated by hantavirus-induced type I interferons. PLoS Pathogens. 2024; 20: e1012390. https://doi.org/10.1371/journal.ppat.1012390.

[138] Korva M, Rus KR, Pavletič M, Saksida A, Knap N, Jelovšek M, *et al*. Characterization of Biomarker Levels in Crimean-Congo Hemorrhagic Fever and Hantavirus Fever with Renal Syndrome. Viruses. 2019; 11: 686. https://doi.org/10.3390/v11080686.

[139] Noack D, Travar M, Mrdjen V, Voermans JJC, van de Vijver D, Molenkamp R, *et al*. Serum Markers Associated with Disease Severity in a Bosnian Hemorrhagic Fever with Renal Syndrome Cohort. Viruses. 2022; 14: 1377. https://doi.org/10.3390/v14071377.

[140] Saavedra F, Garrido JL, Fuentes-Villalobos F, Calvo M, Riquelme R, Rioseco ML, *et al*. Differential CD4 T Regulatory Cell Phenotype Induced by Andes Hantavirus Glycoprotein. Frontiers in Cellular and Infection Microbiology. 2020; 10: 430. https://doi.org/10.3389/fcimb.2020.00430.

[141] Papa A, Yagci Caglayık D, Christova I, Tsergouli K, Koruklu-oglu G, Uyar Y. Crimean-Congo hemorrhagic fever: CXCL10 correlates with the viral load. Journal of Medical Virology. 2015; 87: 899–903. https://doi.org/10.1002/jmv.24141.

[142] Arnold CE, Shoemaker CJ, Smith DR, Douglas CE, Blancett CD, Graham AS, *et al*. Host response transcriptomic analysis of Crimean-Congo hemorrhagic fever pathogenesis in the cynomolgus macaque model. Scientific Reports. 2021; 11: 19807. https://doi.org/10.1038/s41598-021-99130-1.

[143] Mathieu C, Guillaume V, Sabine A, Ong KC, Wong KT, Legras-Lachuer C, *et al*. Lethal Nipah virus infection induces rapid overexpression of CXCL10. PloS One. 2012; 7: e32157. https://doi.org/10.1371/journal.pone.0032157.

[144] Lo MK, Miller D, Aljofan M, Mungall BA, Rollin PE, Bellini WJ, *et al*. Characterization of the antiviral and inflammatory responses against Nipah virus in endothelial cells and neurons. Virology. 2010; 404: 78–88. https://doi.org/10.1016/j.virol.2010.05.005.

[145] Woon AP, Boyd V, Todd S, Smith I, Klein R, Woodhouse IB, *et al*. Acute experimental infection of bats and ferrets with Hendra virus: Insights into the early host response of the reservoir host and susceptible model species. PLoS Pathogens. 2020; 16: e1008412. https://doi.org/10.1371/journal.ppat.1008412.

[146] Lehman CW, Smith A, Kelly J, Jacobs JL, Dinman JD, Kehn-Hall K. EGR1 Upregulation during Encephalitic Viral Infections Contributes to Inflammation and Cell Death. Viruses. 2022; 14: 1210. https://doi.org/10.3390/v14061210.

[147] de St Maurice A, Harmon J, Nyakarahuka L, Balinandi S, Tumusiime A, Kyondo J, *et al*. Rift valley fever viral load correlates with the human inflammatory response and coagulation pathway abnormalities in humans with hemorrhagic manifestations. PLoS Neglected Tropical Diseases. 2018; 12: e0006460. https://doi.org/10.1371/journal.pntd.0006460.

[148] Yuan Z. Research progress of CXCR3 inhibitors. Anti-cancer Drugs. 2024; 35: 36–45. https://doi.org/10.1097/CAD.0000000000001543.

[149] Jiao H, Pang B, Liu A, Chen Q, Pan Q, Wang X, *et al*. Structural insights into the activation and inhibition of CXC chemokine receptor 3. Nature Structural & Molecular Biology. 2024; 31: 610–620. https://doi.org/10.1038/s41594-023-01175-5.

[150] Huang YV, Sun Y, Chou H, Wagner N, Vitale MR, Bayer AL, *et al*. Novel Therapeutic Approach Targeting CXCR3 to Treat Immunotherapy Myocarditis. Circulation Research. 2025; 136: 473–490. https://doi.org/10.1161/CIRCRESAHA.124.325652.

[151] Gaur KK, Asuru TR, Srivastava M, Singh N, Purushotham N, Poojary B, *et al*. 7D, a small molecule inhibits dengue infection by increasing interferons and neutralizing-antibodies via CXCL4:CXCR3:p38:IRF3 and Sirt1:STAT3 axes respectively. EMBO Molecular Medicine. 2024; 16: 2376–2401. https://doi.org/10.1038/s44321-024-00137-8.

[152] Vanheule V, Vervaeke P, Mortier A, Noppen S, Gouwy M, Snoeck R, *et al*. Basic chemokine-derived glycosaminoglycan binding peptides exert antiviral properties against dengue virus serotype 2, herpes simplex virus-1 and respiratory syncytial virus. Biochemical Pharmacology. 2016; 100: 73–85. https://doi.org/10.1016/j.bcp.2015.11.001.

[153] Yongpitakwattana P, Morchang A, Panya A, Sawasdee N, Yenchitsomanus PT. Alpha-mangostin inhibits dengue virus production and pro-inflammatory cytokine/chemokine expression in dendritic cells. Archives of Virology. 2021; 166: 1623–1632. https://doi.org/10.1007/s00705-021-05017-x.