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REVIEW PAPER

Cytokines and chemokines involved in the defense reaction against HIV-1 and hepatitis B virus: isn't it time to use a standardized nomenclature of the involved mediators?

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Abstract

Discovery of new mediators of immune cell activation and interaction facilitated elucidation of the various ways of defense against infectious agents and happened some 40 years ago. Each involved group of researchers named the mediators according to their scope of investigation; often the same molecules were published at the same time with different names. To avoid confusion resulting from using different names for the same mediators and to prevent a Babylonian confusion, standardization was implemented—as in the field of metrics, music, or science including virology. For cytokines and chemokines a standard nomenclature was proposed some 10 years ago and in conclusion it should be used. In this paper the most relevant biomarkers in HIV-1 and HBV infection and their contribution during viral pathogenesis are listed.

Keywords Cytokines · Chemokines · HIV · HBV · Infection · Biomarker

Historical aspects

According to accepted definition cytokines are bio-active molecules as tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), as the interleukins IL-2, IL-4, Il-6 and Il-10, whereas under chemokines mediators such as CXCL8, CXCL9, CXCL10, CCL2, and CCL5 are found that regulate cell activity and cell trafficking during viral infection [1]. Cytokines and chemokines—chemokines are defined as chemotactic cytokines—have been detected some 40 years ago and more than 100 different proteins were described with more than 400 different names. Chemokines were ranked as inflammatory as CCL2, CCL3, CXCL10 and further ones by the involvement of immune cells in, for example, the defense of a viral disease; while other chemokines involved in the migration of leukocytes were named homeostatic chemokines as CCL14, CCL19 and others. CC-chemokines have been named also β-chemokines [2].

In 2000 the American Society for Bone and Mineral Research discussed the nomenclature for new tumor necrosis factor family members [3]. In 2002 the IUIS (International Union of Immunological Societies)-WHO committee published a list of systematic names for the CC-, CXC-, and CX_3C- chemokine receptor family, including human and mouse ligands and the chemokine receptors [4]. In 2012, the chemokine superfamily and their receptors were revised, and the nomenclature updated [5]; a further comprehensive update was published in 2014 [6]. In 2015 Holdsworth and Gan made an effort for a fairly standardized ranking of those proteins involved in kidney diseases [7]. Jacobs et al. in their study of the activation of cytokines by HIV infection used the more recent designation of cytokines to support standardization [8], while Ehling et Tacke describing the HBV triggered pathways leading to hepatocellular carcinoma in 2016 used the proposed chemokine nomenclature and their alternative names [9].

An extended description of the bulk of cytokines is available by industry (Raybiotech, China) (https://www.raybiotech.cn/uploadfiles/2014/04/20140425153827.pdf- (upload list English—cytokinenomenclature-pdf) which can be downloaded; it was published in 2014. An extended chemokine nomenclature list (R&D, USA) can be opened (https://www.rndsystems.com/resources/technicalinformation/chemokinenomenclature) and gives the systematic names, chromosomal

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locus and alternate names; this list was actualized in 2019. The designation of the interleukins was less frequently changed, only interleukin 8 has two names: IL-8 and CXCL8; a review on interleukin structure, function and action was published in 2016 [10].

Per definition cytokines are signaling proteins made by various cell types including immune cells, while chemokines, as chemotactic cytokines, are a subfamily of cytokines made mainly by white immune cells—but nomenclature is partially overlapping. Cytokine action is by binding to a cellular receptor, usually a G-protein, followed by a cascade of protein activation and finally by inducing various reactions like cell proliferation, inflammation, apoptosis and antiviral activity, as seen by the multiple actions of interferons [11–13]. The molecular weight of cytokines is roughly between 10,000 and 90,000 Da. Most human chemokines have a functionally corresponding homolog in other primates [14], and species as mice [5] indicating a long evolutionary history.

General structure and action of cytokines

Chemokines are classified according to their first cysteine position in the protein as XC, CC, CXC and CXXXC; X can be any amino acid [15]. C chemokines have an amino acid sequence with one cysteine–cysteine disulfide bond, while CC have two cysteine–cysteines at different positions in the protein, and in CXC or CX_3C 1 or 3 further amino acids, respectively, are inserted between the two cysteine residues [6, 15]. According to their function cytokines may be divided in either two groups as homeostatic cytokines for immune cell trafficking and inflammatory chemokines produced under inflammation [15] or subdivided in four groups as proinflammatory/involving T cells, anti-inflammatory/involving Th2 cells, chemoattractant chemokines, and growth factors as epidermal growth factor (EGF), fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) [14]—a scheme is summarized in Table 1. Each of the growth factors is building up its own family, composed of several proteins with fairly modified function.

Chemokine receptors (CCR) are mostly structured as heterotrimers and are frequently G proteins spanning the plasma membrane of immune cells and further cells. A chemokine receptor may be used by several chemokines as for example CCR1 is used by CCL3, -5, -7, -8, -13, -14, -15, -16 and -23 (so called promiscuous receptors), while for example CCR10 is only co-used by CCL27 and CCL28 [5, 6]. CCR5 and CCR2 are structurally similar, sharing 70% amino acid identity. CCR5 can form oligomers and further conformational changes and thus influence distinct signaling responses on T cells and macrophages [2].

Antagonists of chemokine receptors

The function of chemokine receptors can be blocked by antagonists. An antagonist of CCR1 is for example CCL26, while for CCR10 no antagonist is known [5]. Chemokine receptors may be stimulated by antimicrobial peptides as known from beta-defensins, which are secreted from epithelial cells to attract dendritic cells and memory T cells via CCR6. Homing of dendritic cells and T cells in the lymph node is regulated by CCR7 [6]. An example of an atypical chemokine receptor is Duffy antigen receptor chemokine (DARC) which is involved in inflammation. Duffy protein is expressed on the erythrocyte surface of Europeans and is genetically deleted in indigenous people living in malaria endemic regions of Africa.

Monoclonal antibodies (mab) against chemokines and chemokine receptors

Besides therapy of unwanted inflammation the main interest using those mab is to support treatment of cancer. More than 20 different types of cancer have been selected for treatment using mab. Tumor size reduction was achieved by blocking various chemokine receptors and ligands as CCR2, CCL2, CXCR4 and further ones treating patients with multiple melanoma, colon carcinoma, pancreatic carcinoma and others [17]. Growth of hepatocellular carcinoma (HCC) could be reduced by CCR2 inhibition with a combination of Sorafenib, an inhibitor of Raf tyrosine kinase [17] of the VEGF complex in preclinical and clinical trials [17, 18]. Mab which suppress extensively inflammation are anti-IL-6 and anti-TNF-α, which are used in clinical trials for autoimmune diseases such as rheumatic arthritis, Crohn's disease and systemic lupus erythematosus [19].

Table 1 Proposed ranking of cytokines according to their function [16]

Proinflammatory/T cells	IL-6, IL-7, IL-8, IL-9; Il-12 p40; Il-15; IL-17, IFN-γ, TNF-α, GM-CSF
Anti-inflammatroy/Th2 cells	Il-1Rα, sIL2Rα; Il-4, IL-5, Il-10, Il-13
Chemoattractants	CXCL10; CCL2, CCL7, CCL22, CCL3, CCL4, CCL11
Growth factors	VEGF, EGF, FGF-2

Cytokine turnover during HIV-1 infection

After CD4 binding via gp120/gp41 HIV uses as coreceptor either CXCR4, or CCR5 or both chemokine receptors. Blocking of CCR5 by maraviroc or vicriviroc is one arm of the established antiretroviral treatment (ART) to reduce HIV replication [20]. Blocking CXCR4 has initially failed to improve HIV therapy, but is used as supplementary therapy for various cancers, as described above [16]. A new monoclonal antibody—Ibalizumab (Trogarzo®) has recently been licensed; application of this monoclonal antibody prevents HIV binding without blocking further functions linked to the CD4 receptor [21]. Interaction of gp120 with CCR5 occurs on various sites with a structural plasticity [22] and adaptation of HIV to low expression of CCR5 molecules on the cell surface [23]. Amino acid mutations in CXCR4 and CXCL12 that alter interactions between CXCR4 and gp120/gp41 and thus impair HIV-1 attachment have been identified by deep sequencing [24]. Gp120 binding to TNF-receptor 1 and 2 leads by a cascade of intracellular mediators as TRAF (tumor necrosis factor receptor-associated factor), RIPK (receptor-interacting protein kinases 1, 3) and NF-κB via LTR binding to accelerated HIV transcription [25].

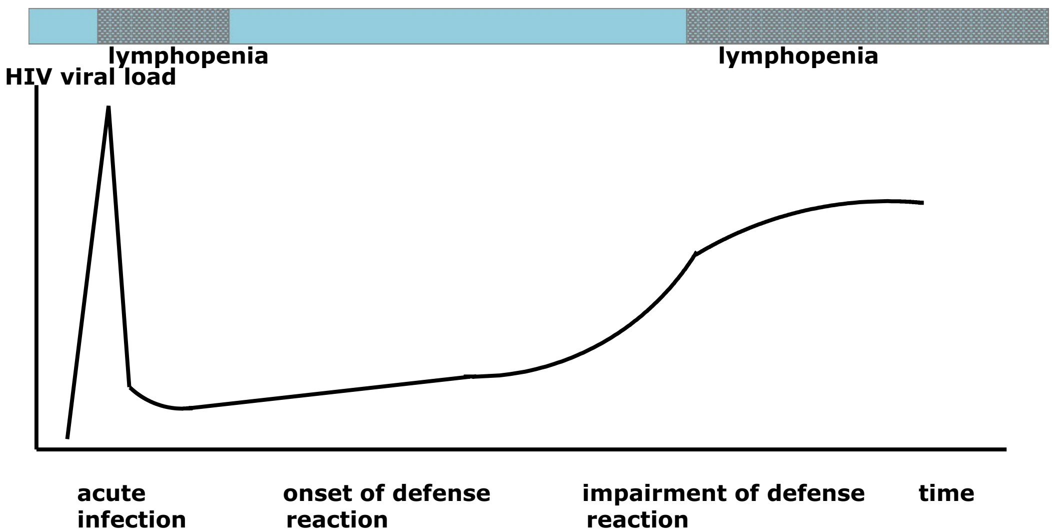
Viral Tat (trans-activator of transcription) causes impairment of macrophage autophagy, while Nef (negative regulatory factor) activates autophagy via IRGM (immunity related GTPase family M protein). Vpr (viral protein R), Tat and Nef contribute to apoptosis induced by CXCR4 and further mediators [25], thus regulating HIV release from cells. Binding of gp120 to CXCR4 forms a complex by which apoptosis of infected and uninfected T cells is mediated [26]. Chemokine levels of CCL14, -21, -27 and XCL1 and CXCL12 are higher in elite controllers [8]; they are as well involved in autophagy and apoptosis—which is summarized in Fig. 1. Th17 cells that express CCR6 are highly permissive to HIV; and HIV was found to be enriched in CCR6+ cells in gut and lymph node. When the studies describing the cytokine expression during HIV early infection are summarized the response to HIV induces the liberation of CCL2, CCL18, CCL19, CCL21 and additionally interleukin 6 and 10 (Fig. 1). A further aspect in the cytokine expression perturbation is microbial translocation from the damaged gut and bacterial components are further factors that influence the turnover and activity of cytokines such as CXCL13 and CCL20, and their receptors [27–29]. Blocking CCR6, and additionally CCR7 and CXCR3 might be a way to eliminate part of the latently HIV infected cell reservoir [30].

HIV neuropathogenesis is caused by viral gp120, Tat and Nef and host IFN-γ that induce the neurotoxic CXCL10 which is produced by macrophages and astrocytes, while PDGF (platelet derived growth factor) and CCL2 inhibit Tat toxicity [31]. Plasma CXCL10 levels correlate with HIV-associated neurocognitive disorders in women [32], indicating that gender related hormones might additionally influence cytokine expression.

Cytokine turnover during HBV infection

Following the infection of hepatocytes HBV is liberated in high amounts and after a week- or month-long delay an intensive immune response is following, leading in 90% to 95% of adult patients to clearance of HBV from the circulation—but the immune reaction is not sufficient to remove the ccc-DNA (circular covalently closed HBV-DNA) from the nucleus of the cell. During the peak of viraemia CXCL10 is increased roughly fivefold, CXCL9 twofold, while the levels of CCL5 and CXCL8 in serum remain roughly unchanged [1]. During the chronic course of HBV infection CXCL9, CXCL10, CXCL11 and IL-10 levels were highly elevated while GCSF (granulocyte colony stimulating factor), CCL7 and IFN-γ levels were found to be decreased, studying 69 patients in China [33]. A positive correlation between the IL-4 amount produced by CD4-cells and a high plasma level of HBV was found. There is as well a correlation between the IL-17 amount produced by CD4 cells and pre-core stop codon mutation and basal core promotor mutation [34]. Elevated IL-10 levels correlated to a hampered HBs protein response [32]. A slow reduction of the CXCL10 level was predictive to a pending HBe seroconversion in patients with chronic infection under entecavir treatment [35]; while in another study during entecavir treatment CCL22 levels were decreased and CXCL10 levels were increased [36]. IL-34 inhibited HBV replication [37]. HBV pathogenesis was enhanced by IL-17A generated by Th17 cells [38]. An increase of Tregs was inversely correlated to high HBV plasma levels; Tregs acted immune suppressive on CD4 and CD8 T cells by IL-2, IL-10, IL-35 and TGF-β release [39].

HBx protein increased TRAIL-induced apoptosis of renal tubular epithelial cells by enhancing the activation of NF-κB and upregulating death receptor 4 (DR4) [40]. Proinflammatory mediators released from Kupffer cells and monocytes/macrophages contribute to apoptosis of hepatocytes, and dying hepatocytes release mediators as TNF-α, RIPK1 (receptor-interacting protein kinase 1) or DRP1 (dynamin-related binding protein 1), hence establishing a hepatotoxic feedforward cycle of inflammation [40]. Most studies investigating cytokine reaction during acute HBV infection show that CXCL10 and IL-10 are highly increased, besides further chemokines [1, 33, 41–44]. HBV induced encephalopathy was associated by an elevated level of IL-6, IL-17a and IFNγ [45].

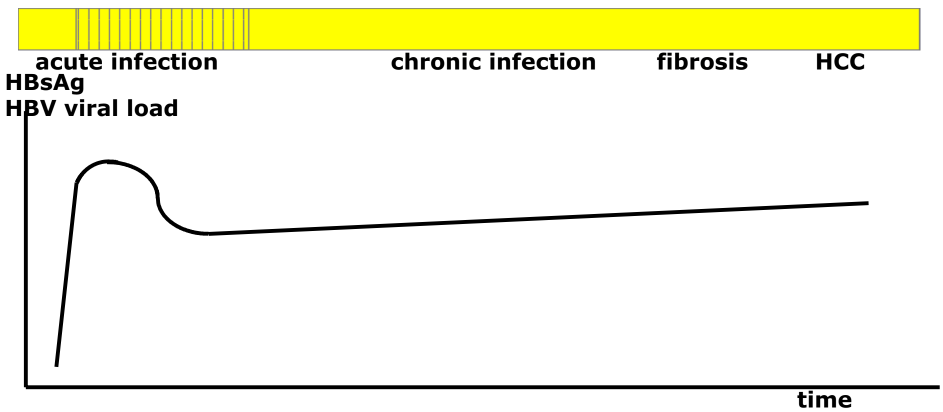


cytokine liberation			references
CCL2 ++ TNFSF13B + IFN alpha -	sCD23 ++ TNFSF13B -		Pastor et al [46]
	CCL21 ++ CXCL9 ++ CXCL12 ++ sEGF ++	CXCL10 ++	Jacobs et al [8]
	TNF-alpha ++ IL-12 p40 - CXCL10 -	TNF-alpha ++ IL-12 p40 - IL-15 - CXCL10 ++ FGF- 2	Keating et al [16]
CCL2+, CCL19+ sTNFR II, Il-10+		CCL13 CCL20	Teigler et al [29]
CCL2++, IL-6+			Kroeze et al [28]
CCL18++, CCL17 CCL22 ++			Malhota et al [30]

Fig. 1 Expression of various cytokine profiles during the course of an HIV-1 infection, ++ indicates a high level, + an elevated level and – a downregulated level compared to uninfected healthy control subjects. Time should be approximately 12 years. Viral load is initially and in the late stage of AIDS at high levels. The toxic action of HIV leads to lymphopenia which is indicated in the upper rectangle; the right column gives the references. *TNFSF 13B* tumor necrosis factor ligand superfamily, *EGF* epidermal growth factor, *IFN* interferon; *TNF* tumor necrosis factor

Relevant chemokines that are involved in the induction of hepatocellular carcinoma (HCC) are: CCL2, -3, -5, -20 and -22, and CXCL 5, -8 and -12; of major importance is the CXCL12–CXCR4 axis, of minor importance the CXCL8–CXCR2 and CXCL5–CXCR2 axis (Fig. 2). Chemokine action might be supported by oncogenes out of the Ras and Myc-family in the hepatic microenvironment [9].

A list of cytokines and their various names which are involved in the defense reaction against HIV-1 and HBV infection is shown in Table 2.



acute phase	chronic phase	reference
cytokine liberation		
IL-10++ CXCL10++, CXCL9+ IL-4+, IL-6+	CXCL10+ CXCL5-	Wu et al [1]
IL-12 p40++ IL-15++	IL-12 p40+, IL-2+, IL-6+ IL-7++, IL-29+	He et al [47]
	CXCL9+++, CXCL10++ CXCL11+, IL-10++, GCSF- CCL7-, IFN gamma -	Lian et al [33]
IL-6+, IFN alpha+		Xia et Protzer [48]
IL-4+, Il-10+ IL-17+	IFN gamma ± IL-4± , IL-10±, IL-17±	Gu et al [34]
CCL22--, CXCL10++		Kurihara et al [36] entecavir
IL-21+ CXCL9+, CXCL10+ CXCL11+, CXCL13+	IL-21+	Yoshio et al [43]
CXCL10+, IL-10+ CCL4+, sIL-2R alpha+		Keating et al [42]

Fig. 2 Scheme of the course of cytokine levels during acute HBV infection and in the following chronic phase. The acute phase occurs within 1–6 months after HBV acquisition, the chronic phase might last for more than 20 years or life long. ++ indicates a highly increased level, + an increased level and – a decreased level and ± no change compared to uninfected healthy control subjects. The right column gives the reference. The rectangle in the upper part indicates the various stages of HBV disease progression. *HCC* hepatocellular carcinoma, *GCSF* granulocyte colony stimulating factor, *IFN* interferon

Table 2 Chemokines/cytokines and receptors involved in the defense action against HIV and HBV (an alphabetical order is given, and only the most important are listed)

Chemokine cytokine	Original name and further names	Receptor	Antagonist
CCL2	MCP-1: monocyte chemotactic protein 1 SCYA2-small inducible cytokine A2	CCR2	
CCL3	MIP1α: macrophage inflammatory protein 1 alpha, LD78α	CCR1, CCR5	
CCL4	MIP1β: macrophage inflammatory protein 1 beta	CCR5	
CCL5	RANTES: regulated on activation normal T cells expressed and secreted	CCR1, CCR3, CCR5	
CCL7	MCP-3: monocyte chemotactic protein 3	CCR1, CCR2, CCR3	CCR5
CCL14	HCC-1: hemofiltrate CC chemokine 1, SCYA14: small inducible cytokine subfamily A	CCR1, CCR3, CCR5	
CCL20	MIP-3α: macrophage inflammatory protein 3 alpha, LARC: liver activation regulated cytokine, Exodus-1: beta chemokine Exodus 1	CCR6	IL-10
CCL21	SLC: secondary lymphoid tissue chemokine; 6C kine – 6 conserved cysteine residues chemokine	CCR7	
CCL22	MDC: macrophage derived chemokine, STCP-1: stimulated T cell chemotactic protein 1	CCR4	
CCL27	CTACK: cutaneous T cell attracting chemokine; ILC: IL-11 R alpha-locus chemokine	CCR10	
CXCL5	ENA78: epithelial derived neutrophil activating peptide	CXCR2	
CXCL8	IL-8: interleukin 8	CXCR1, CXCR2	
CXCL9	MIG: monokine induced by gamma interferon	CXCR3	CCR3
CXCL10	IP10: interferon gamma induced protein 10 SCYB10: small inducible cytokine B10	CXCR3	CCR3
CXCL11	I-TAC: interferon inducible T cell alpha attractant; IP-9: interferon gamma inducible protein 9	CXCR3, CXCR7	CCR5
CXCL12 a CXCL12 b	SDF-1: stromal cell derived factor 1 PBSF: pre B cell growth stimulating factor	CXCR4 (fusin), CXCR7	
CXCL13	BLC: B lymphocyte chemoattractant BCA-1: B cell attracting chemokine 1	CXCR5, CXCR3	
FGF-2	Basic fibroblast growth factor	FBGFR 1–4, heparin heparan sulfate	
GCSF	Granulocyte colony stimulating factor CSF3: colony stimulating factor 3		
PDGF	Platelet derived growth factor (4 isoforms)	PDGF receptor – tyrosine kinase	Anti-PDGF[a]
sCD23	Fc-epsilon-RII Lymphocyte IgE receptor	a: B lymphocyte b: monocyte	
sEGF	Soluble epidermal growth factor	ErbB1, HER1	Afatinib, … [a] Cetuximab, … [a]
TNF-alpha	Tumor necrosis factor alpha, cachexin, cachectin	TNFR 1 = CD120a = p55/60 TNFR 2 = CD120b = p75/80	Infliximab[a] Adalimumab[a] Certolizumab Etanercept[a]
TNFSF10	Tumor necrosis factor superfamily member 10; TRAIL—tumor necrosis factor-related apoptosis-inducing ligand; APO2L, CD253, TNF- SF10:	death receptor DR4, DR5	Mapatumumab[a]
TNFSF13B	Tumor necrosis factor ligand superfamily member 13B BAFF: B cell activating factor BLyS-B lymphocyte stimulator		Belimumab[a]
XCL1	Lymphotactin; ATAC: activation induced T cell derived and chemokine related cytokine; SCM-1α: single cysteine motif-1 alpha	XCR1	

[a]Monoclonal antibodies are given in this column as they act by blocking the receptors and are used for the treatment of autoimmune diseases as rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis [19] and cancer [17]

Compliance with ethical standards

Conflict of interest The author declares that they have no conflict of interest.

Research involving human participants and involving animal studies Not applicable since no original studies were done.

Informed consent The author takes all responsibilities for the content of this article.

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