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Review Article *Pathology*

The role of chemokines in vertebrate physiology and disease: a concise review

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ABSTRACT

Chemokines are classified as proteins with chemoattractant activities that have multiple crucial roles in health and disease, where they participate in the processes of development, angiogenesis, hematopoiesis and tumor metastasis. Multiple cells are involved in the production of chemokines. However, the main cells involved in such role are blood monocytes, macrophages and polymorphonuclear leukocytes, where they exert their role in the inflammatory reaction following antigen recognition by tissue phagocytes. Due to their important role in the establishment of successful immune response, several microbes are incriminated in the production of proteins that mimic chemokines. In addition, their receptors could be used by microbes as a portal of entry to host cells, e.g., human immunodeficiency virus. Chemokines showed significant involvement in the pathogenesis of multiple diseases, e.g., thyroid autoimmune diseases, Behçet's disease and atherosclerosis. Presented is a concise minireview on some of the documented roles of chemokines in several physiological and pathological conditions.

Keywords: Chemokines; chemokines receptors; Behçet's disease; thyroid autoimmune disease; cancer

1. Structure and classification

Chemokines can be defined as chemoattractant proteins, secreted by cells to act on other cells, either by attracting them to a specific site or changing their biological behavior [1, 2]. According to their amino acid structure, they are subdivided into either CXCL (16 members), CCL (28 members), XCL (2 members) or CX3CL (one member) chemokines [2]. They serve important roles in multiple physiological and pathological disciplines, development, angiogenesis, hematopoiesis and tumor metastasis [3–10].

2. Chemokine-secreting and chemokine-responsive cells

The main cells involved in chemokine release are blood monocytes, macrophages and polymorphonuclear leukocytes (PMN) with destined activity on PMN (CXCL1, 2, 3, 4, 5, 6, 7, 8, 12 and 15, CCL1, 2, 3, 4, 5, 7, 8, 13, 15, 24 and 24 and CX3CL1), fibroblasts (CXCL1, 2, 3, 4 and 7 and CCL26), endothelial cells (CXCL4, 5, 6, 7, 8, 8, 10, 11, 15 and 16 and CCL22), T cells (CXCL8, 9, 10, 11, 12, 13 and 14, CCL1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27 and 28, XCL1 and 2 and CX3CL1), monocytes (CXCL12 and 14, CCL1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14 and 15 and CX3CL1), macrophages (CXCL12, CCL3, 4, 5, 25 and CX3CL1), natural killer T cells (CXCL16), dendritic cells (CXCL12 and 13, CCL2, 3, 4, 5, 7, 8, 13, 15, 16, 17, 18, 19, 20, 21, 22, 25, XCL1 and 2 and CX3CL1), natural killer cells (CXCL10, 11 and 12, CCL2, 3, 4, 5, 6, 7, 8, 16, 21 and 22, XCL1 and 2 and CX3CL1) and B cells (CXCL10, 11, 12, 13 and 14 and CCL4, 6, 12, 18, 19, 20, 21 and 27) [2, 11]. The main regulatory pathway of chemokine release is the inflammatory cascade [2, 12]. Their function in angiogenesis, the initial primordial germ cell migration in the early embryo, trigeminal neuron migration and the attraction of hematopoietic stem cells to their bone marrow niche are exerted through CXCL12 [10]. They also serve in lymphoid tissue development [8]. Among the cells associated with chemokine function, platelets express both chemokines, CXCL4, ß-thromboglobulins, CCL5 and CCL17, and chemokine receptors, CCR (CCR1, 2, 3, 4, 5, 6, 7, 8, 9, and 10) and CXCR (CXCR1, 2, 3, 4, and 5), on their outer cell membrane [13, 14].

3. Chemokines role in B cell responses

CCL28, a ß-chemokine, is expressed by mucosal epithelial cells, showing high expression in the salivary gland, small intestine and colon, is specialized in the recruitment of IgA+ plasma cells to mucosal sites [15–19]. CCL28 expression and the associated B cell recruitment was also recorded in the mammary gland [16].

4. Chemokines function in wound healing

Wound healing regularly occurs at the end of the inflammatory process, following the eradication of the causative agent of cellular injury and/or noxious stimuli [20, 21]. In the preliminary stages of the inflammatory process, chemokines play a crucial role in directing leukocytes to the inflammatory site [1, 22], and hence guaranteeing the establishment of an inflammatory process. Chemokines are also essential for the closure of wounds [23], where CX3CR1, a receptor for CX3CL1 (also known as fractalkine), disruption caused a reduction of alpha-smooth muscle actin (a marker for myofibroblasts) and collagen deposition in skin wounds and reduced neovascularization. Similar effects on defective reepithelization were recorded in models of deficient CXCR2 [24]. In addition, CXC chemokine interleukin (IL)-8 stimulates

keratinocyte migration and proliferation in cutaneous injury [22, 25–28].

5. Chemokines and cancer

CXCL1 expression was detected in gastric, colonic, colorectal, and urinary bladder cancer patients, and it was associated with the expression of vascular endothelial growth factor (VEGF) and phospho-signal transducer and activator of transcription 3 (p-STAT3) in gastric cancers, stimulators for angiogenesis [29–34]. Its expression was an indication of an advanced cancer grade and it increased xenograft tumor growth with its microvasculature. An *in vitro* application of CXCL1 in gastric cancer cell line increased cellular migration and increased the VEGF signaling (which was suppressed by CXC receptor 2 blockage) and p-STAT3 expression. In a different work by Xu et al. [35], gastric cancer cells stimulated CXCL1 release from lymphatic endothelial cells in a co-culture system, which in turn stimulated lymphatic endothelial cell migration and tube formation. In addition, CXCL1/MGSA/GRO-1 (melanoma growth stimulatory activity/growth regulated oncogene) is involved in the mutagenesis or transformation of melanocytes and ovarian cells [36, 37]. CXCL1 was also expressed by ovarian cancer cell lines and increased their invasiveness [38]. Pancreatic ductal adenocarcinoma cells showed high expression of CXCL1 which had a role in tumor progression [39].

Murine CXCL2, expressed by oral squamous cell carcinoma, was incriminated in osteoclast activation and the resulting bone destruction in cases of oral cancers [40]. In addition, CXCL1 and CXCL2 produced from bone marrow adipocytes were incriminated in the osteolysis associated with prostate cancers [41]. Inhibition of CXCL1 and CXCL2 reduced the metastasis of breast and prostate cancers [42–44]. Mammary adenocarcinoma induced the expression of CCL2, CCL5, and CXCL2 chemokines and CCR1, CCR2, CCR3 and CXCR2 chemokine receptors in splenic murine T lymphocytes [45]. Murine CXCL2 was found to be involved in the translocation of calreticulin (surface marker on cancer cells to be identified and uptaken by phagocytes/antigen-presenting cells) to the outer leaflet of the plasma membrane of cancer cells [46–48].

6. Viral mimicry of chemokines, their receptors, or their binding proteins

Besides mimicry of cytokines, some viruses encode proteins that mimic chemokines (e.g. human immunodeficiency virus, respiratory syncytial virus, members of betaherpesvirus and gammaherpesvirus genera, and molluscum contagiosum virus), chemokine receptors (e.g. members of betaherpesvirus and gammaherpesvirus genera and members of poxviridae), or chemokine-binding proteins/chemokine scavengers (e.g. members of alphaherpesvirus, betaherpesvirus, and gammaherpesvirus genera and members of poxviridae) aiming towards modulating the immune response against the invading viral pathogen [49–62].

7. Chemokine receptors acting as a portal of entry for human immunodeficiency virus (HIV) infection

CD4 is considered the primary receptor for HIV, where gp 120 and gp 41 (envelope proteins) mediate virus binding to the target cell membrane followed by consequent interaction with chemokine receptors CCR3 and 5 CCR2B or CXCR4 leading to merging of the host cell membrane and HIV membrane [63–72]. Other chemokines, CCR2, 3, 8 and 9, STRL33, Gpr15, Gpr1, APJ, ChemR23 and CX3CR1, are also used by HIV for host cell entry during *in vitro* infection [64, 73–76]. In addition, highly exposed persistently seronegative individuals showed upregulated expression of chemokines, RANTES (Regulated upon activation, normal T Cell expressed and presumably secreted), MIP-1α (macrophage inflammatory protein) and MIP-1β when exposed to *gag* peptide from HIV [77].

8. Chemokine signaling in skin diseases

Being one of the most common skin diseases, psoriasis involves chronic dermatitis evidenced by leukocytic infiltration (T cells, neutrophils and macrophages) of the dermis and the subcutaneous tissue [78]. The most common chemokines incriminated in the recorded leukocytic recruitment are CXCL8 (IL-8) and 10, CX3CL1 (fractalkine), CCL2/MCP-1 (monocyte chemoattractant protein-1), 5 (RANTES), 20 (MIP-3α), 26 (eotaxin2) and 27 [79, 80].

9. Chemokines and arterial disease

9.1. Hypertension

Being a serious risk factor for cardiovascular disease, a chemokine-mediated immune response is incriminated in the established disease pathogenesis, including MCP-1/CCL2, IP-10/CXCL10 (interferon (IFN)-γ inducible protein), IL-8/CXCL8, RANTES/CCL5, fractalkine (CX3CL1) and their receptors CCR2, CCR5, CXCR1, CXCR2, CXCR3 and CX3CR1, acting mainly through the activation of macrophages and monocytes migration to the vascular wall and causing endothelial cell dysfunction and vascular smooth muscle cells proliferation [81–83].

9.2. Atherosclerosis

Being one of the established complications of arterial hypertension, chemokines also play important role in the pathogenesis of atherosclerosis through the induced IL-8, fractalkine, MCP-1 which cause vascular inflammation as indicated by the observed vascular leukocyte infiltration and endothelial cell dysfunction [81]. Plasmacytoid dendritic cells seem to play important role in the established pathogenesis through the production of IFN-α cytokine and chemokines (CXCL1, CXCL10) [84].

10. Thyroid autoimmune diseases

Chemokine, particularly CXCL9, 10, and 11, and chemokines receptors, CXCR3, mediate T cell responses that play important role in the pathogenesis of thyroid autoimmune

disorders, e.g. Graves' disease [85–89]. Other chemokines, e.g. CCL2 and CCL5 showed variable levels of expression [90].

11. Alzheimer's disease

Chemokines play an eminent role in the physiology of the nervous system [91]. Upon antigenic stimulation, neuroglial cells, endothelial cells, and neurons of the central nervous system, as well as Schwann cells of the peripheral nervous system can release chemokines. In Alzheimer's disease, a neurodegenerative disease caused by the extracellular deposition of amyloid protein, intracellular neurofibrillary tangles, and the lack of neurons and synapses, inflammatory chemokines may play a vital role in its occurrence and development [20, 21, 91]. They mostly induce immune cell migration to the inflammatory site and regulate the migration of neuroglial cells, neurons and neural progenitors to sites of nervous tissue inflammation (neuroinflammation) [91]. MCP-1/CCL2 and its receptor CCR2 (in the serum, the cerebrospinal fluid (CSF) and the brain tissue) are considered as markers for Alzheimer's disease progression and their levels were positively correlated with a rapid loss of cognition and developing dementia. IL-8 also showed a positive correlation with Alzheimer's disease progression in the serum, and the CSF [92]. IP-10/CXCL10 showed an increase in the CSF of Alzheimer's disease patients [93, 94]. In contrast, RANTES/CCL5 showed downregulation in the serum and upregulation in the brain tissue of Alzheimer's disease patients [95, 96]. On the other hand, CXCL12/SDF-1 (stromal cell-derived factor 1) was reduced in the serum and CSF of reported cases of Alzheimer's disease [97].

12. Brain injury

Chemokines are known to be expressed in the vasculature of the blood-brain barrier, e.g. CXCL12, CCL19, CCL20, CCL21 and CCL27, through which endothelial cells regulate leukocytes entry into the central nervous system (CNS), hence called homeostatic chemokines [98, 99]. They also sustain signals for migration, proliferation, or differentiation to neurons and glia cells [100]. In addition, CX3CL1 and CXCL14 are expressed by the CNS and it appears that they are mainly expressed by the neurons [99, 101–103]. CXCL12 appears to be also involved in the process of neurogenesis and neuronal survival, a function also shared by CX3CL1 chemokine [99, 100, 104, 105].

13. Hepatic disease

Upon liver injury or establishment of hepatic disease, activated Kupffer cells secrete immunoregulatory protein including CXCL1, 2, and 8 (IL-8) as chemoattractants for neutrophils to exert their role in the eradication of the injurious agent that usually culminates in the organ healing upon successful eradication [2, 20, 21, 106–109]. Chemokines, CXCL9, CXCL10 and CXCL11, also play fundamental roles in the recruitment of lymphocytes to sites of chronic hepatic inflammation [107, 109, 110].

14. Pulmonary disease

Chemokines, CXCL1, 2, 5 and 8 were revealed to participate in the pathogenesis of acute lung injury through urgent leukocyte recruitment to the inflammatory site [111]. On the other hand, CCL2, CXCL1, 2, 5, 7, 8, 9, 10, 11 and 16, with their respective receptors, seem to play important role in the pathogenesis of the chronic obstructive pulmonary disease, not only causing recruitment to innate immune cells, neutrophils and monocytes but also enhancing the migration of T cells and B cells to target areas of pulmonary inflammation [112–114]. In addition, it was revealed that the activation of chemokine receptors, CXCR3 on T helper 1 cells and CCR4 and 8 and CXCR4 on T helper 2 cells, through their respective chemokine ligands is responsible for the establishment of idiopathic pulmonary fibrosis [115]. Other chemokines, Eotaxin, Eotaxin-2, RANTES, MCP-3, MCP-1, MIP-1α and CCR3 have roles in allergic airway hyper-reactivity [116].

15. Diabetes

Being one of the leading reasons for chronic renal failure, diabetes culminates in a set of renal degenerative changes that include glomerular hypertrophy, thickening of basement membranes of renal tubules and glomeruli through the accumulation of extracellular matrix leading to renal fibrosis [117–119]. One of the genetic response towards diabetes-associated hyperglycemia is the enhanced transcription of CCL2 chemokines and other modulators of inflammation [120]. In addition, it was revealed that MCP-1 plays a crucial role in the diabetes-associated nephropathy through its known function of macrophage activation [121].

16. Host-microbe homeostasis

One of the recorded models of dysbiosis or disruption in the homeostasis between host and microbes is periodontitis, where regulatory T cells are involved, through the chemoattractant CCL22, in orchestrating the resulting immune response following antigen recognition to exert a balance between immune response and tolerance, controlling inflammation and helping in the establishment of repair mechanism [122–124]. Such regulatory function of regulatory T cells prevents the resulting tissue pathology if their function is otherwise prohibited.

17. Behçet's disease

Behçet's disease, a chronic recurrent systemic inflammatory disorder, is associated with multiple organ pathologies, oral and genital ulcerations, skin lesions, and uveitis [20, 21]. Multiple etiologies were implicated in the disease pathogenesis, microbial antigens, environmental causes, endothelial cell dysfunction, genetic susceptibility, and immunological aberrations [125]. T helper 1 cells play a crucial role in the pathogenesis of Behçet's disease [126, 127]. Also, the expression of T helper 1-related chemokine receptors seems to be crucial in the established pathogenesis

CCR5 and CXCR3 [128–130], where CXCR3 is considered a marker for IFN-γ-producing T cell population.

Conclusion

This review elucidated the roles of chemokines as chemoattractant proteins in various physiologic and pathologic states. They have protective roles in the blood-brain barrier and share in the process of neurogenesis and neuronal survival in CNS. On the other hand, chemokines served in the pathogenesis of the chronic obstructive pulmonary disease, Behçet's disease, thyroid autoimmune disease and chronic hepatic disease through recruitment of T cells. They also shared other cell receptors as viral receptors for HIV.

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