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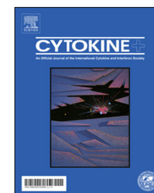

How post-translational modifications influence the biological activity of chemokines

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ABSTRACT

Chemokines are important proteins involved in the regulation of directed leukocyte migration during inflammation and the homeostatic homing of immune cells. In addition, they play a role in angiogenesis, hematopoiesis, organogenesis, tumor growth and metastasis. Therefore, the chemokine/chemokine receptor network is highly complex and needs to be tightly controlled. An important mechanism of fine-tuning chemokine activity and reducing its apparent redundancy is post-translational modification (PTM) of chemokines and their receptors. Under inflammatory conditions, enzymes such as matrix metalloproteinases (MMPs), plasmin, CD13, CD26, and peptidylarginine deiminases (PADs) and protein-modifying agents, such as peroxynitrite, are upregulated and released and may provoke truncation, degradation, nitration or citrullination of chemokines. Most modified chemokines show altered biological activity. This review reports how PTMs influence the biological functions of chemokines, with special attention for the impact beyond chemotaxis.

1. Introduction

1.1. Chemokines

Chemokines are small proteins (8–14 kDa) which mediate a great variety of functions, but are mainly involved in the regulation of leukocyte trafficking [1–4]. Chemokines are locally secreted by different cell types such as resident leukocytes, endothelial cells and fibroblasts. In total, about 50 human chemokine ligands have been identified and classified based on their function in homeostasis or housekeeping or as inducible inflammatory chemokines with a role in disease [5–7]. The latter subclass is locally secreted upon infection or tissue damage and requires prior induction by endogenous or exogenous stimuli. In contrast, homeostatic or housekeeping chemokines are expressed constitutively in lymphoid or other organs and mediate homeostatic migration and homing of various immune cells. Moreover, an emerging number of chemokines fullfils both homeostatic and inflammatory roles, illustrating that the functional classification is non-absolute (*vide infra*). In addition, chemokines can be classified into four families (CC, CXC, CX_3C and C chemokines) based on the pattern of two conserved cysteine residues in the NH_2-terminal region [3].

To exert their biological functions, chemokines need to interact with two major interaction partners namely (1) glycosaminoglycans (GAGs) and (2) seven transmembrane G protein-coupled receptors (GPCRs) designated CCR, CXCR, CX_3CR and XCR according to the nomenclature of the ligands [3,8]. GAGs are linear polysaccharides consisting of repeating disaccharide subunits with a molecular weight of 10–100 kDa. In brief, once inflammatory chemokines are secreted they create, through GAG binding, a gradient along which leukocytes can migrate from the blood vessel to the site of inflammation [9–12]. Subsequently, GAG-bound chemokines interact with their leukocyte-specific chemokine receptor resulting in adhesion to and extravasation of leukocytes through the endothelium [13–15]. This GAG binding of chemokines has been proven to be indispensable for chemokine activity *in vivo* [16–18]. The interaction between chemokines and GAGs occurs between basic amino acid motifs, frequently of the form BBXB or BBBXXBBX (in which B represents a basic and X represents any non-basic amino acid), and sulfated or carboxylated domains of GAGs [19]. On some chemokines, GAG binding motifs are located in the COOH-terminal region of the chemokine, at a site distant from the specific receptor-binding site. However, on a number of chemokines these sites are at least partially overlapping. For example, it was recently shown that interaction

Abbreviations: ACKR, atypical chemokine receptor; ADAM, a disintegrin and metalloprotease; $[Ca^{2+}]_i$, intracellular calcium concentration; CTAP-III, connective tissue-activating peptide III; DPP4, dipeptidyl peptidase 4; ERK, extracellular signal-regulated kinase; GAG, glycosaminoglycan; GPCR, G protein-coupled receptor; MMP, matrix metalloproteinase; PAD, peptidylarginine deiminase; PBP, platelet basic protein; PTM, posttranslational modification

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between CXCL13 and heparan sulfate relies on residues present in the COOH-terminal region and α helix of the chemokine, whereas CXCL13/CXCR5 binding depends on its NH_2-terminal domain [20]. Contrastingly, for several chemokines including CXCL10, mutation of specific residues was found to affect both the affinity for GAGs and GPCRs [21]. In line with these observations, we previously found that natural deimination of Arg5 of CXCL10 negatively affects its GAG binding and CXCR3 signaling potencies [22].

Chemokines can affect other cell types, thereby playing a role in angiogenesis, hematopoiesis, organogenesis, tumor growth and metastasis [23–25]. For example, CXCL4 and CXCL4L1 are known to shift the angiogenic/angiostatic balance in favor of angiostasis by inhibiting endothelial cell proliferation and migration. In addition, CXCL4L1 prevents the development and metastasis of various tumors [26]. In contrast, it has been shown that CXCL8 expression in humans correlates with an increase in tumorigenesis of bronchogenic carcinomas [27]. In addition, CXCL8 is associated with various cancers such as pancreatic cancer, prostate cancer and ovarian cancer [28–30]. Besides CXCL8, other CXC chemokines are involved in angiogenesis and metastasis [24]. For example, the CXCL12-CXCR4 axis has been shown to play a critical role in tumor metastasis, since it promotes the migration of tumor cells into metastatic sites. Moreover, CXCR4 is the chemokine receptor which is most often overexpressed in human tumors [31]. Finally, homeostatic chemokines control basal cell migration [32]. However, the relevance of homeostatic chemokines may extend beyond merely homeostatic processes. For example, a significant correlation was demonstrated between CXCL13 and its receptor CXCR5 – initially designated as homeostatic chemokine – chemokine receptor pair – and prostate cancer, with CXCL13 being a more reliable predictor of prostate cancer than prostate-specific antigen (PSA) [33]. In healthy peripheral tissues, homeostatic chemokines are responsible for leukocyte migration for immune surveillance and maintenance of mucosal immunity [34–36]. Furthermore, they navigate leukocytes during hematopoiesis in bone marrow and thymus, during initiation of adaptive immune responses in the spleen and lymph nodes and during organ development. Genetic deficiency of CCL21, for example, results in impaired dendritic cell migration and T cell priming in the lymph nodes [37]. Mice deficient for CXCL13 or CXCR5 show defective lymphoid tissue development [38]. Moreover, a defect in CXCR7/ACKR3 or its ligand CXCL12 even results in perinatal lethality due to disrupted cardiac development [39–42]. In addition, targeted mutation of CXCL12 and CXCR4 results in defective myelopoiesis and B cell lymphopoiesis. Noteworthy, some chemokines can fall into both categories depending on the biological context or pathological state, demonstrating that the initially proposed harsh distinction between inflammatory and homeostatic chemokines is rather non-absolute [43].

1.2. The regulation of chemokines

The availability and activity of chemokines are regulated at multiple levels to control the inflammatory response and physiological leukocyte homing [44–46]. Upon infection or tissue damage, it is essential to have an immediate up-regulation of chemokines and their receptors for the generation of a rapid influx of leukocytes. However, this influx also requires to be terminated upon resolution of the challenge. Otherwise, the persistence of an inflammatory response may lead to tissue damage and chronic inflammation. Therefore, several mechanisms of chemokine regulation are known [44,45]. As discussed before, the expression of, especially, inflammatory chemokines is upregulated by local transcription of chemokine mRNA by inflammatory stimuli. Chemokine mRNA is often highly unstable and a target for degradation [47,48]. Moreover, for some chemokines, different isoforms are generated from a single gene. This process of alternative splicing has been shown to have significant consequences for the biological activity and the tissue distribution of chemokines, such as CXCL12 [49–52]. Second, chemokines tend to synergize directly or indirectly with other chemokines thereby providing a powerful mechanism to strengthen leukocyte recruitment [53]. In contrast, chemokines can also counteract each other, thereby increasing the selectivity of cell recruitment or reducing the inflammatory responses. A third mechanism is the fine-tuning of chemokine availability by binding to atypical chemokine receptors (ACKRs), such as Duffy antigen receptor for chemokines (DARC) (ACKR1), D6 (ACKR2), CXCR7 (ACKR3), Chemocentryx chemokine receptor (CCX-CKR) (ACKR4) and CCRL2 (ACKR5) [54–56]. Due to the presence of a modified or missing canonical DRYLAIV motif and the resulting inability to couple to G proteins these atypical receptors are unable to induce conventional G protein-coupled signaling. In addition, chemokines have been shown to bind to GAGs which influences the chemokine availability by binding of the chemokines to the endothelium and presentation to their specific chemokine receptor [8]. Finally, different types of posttranslational modifications (PTMs) of chemokines, including proteolytic cleavage, glycosylation, citrullination and nitration, have been reported [57]. These PTMs have consequences on the chemokine activity and/or receptor selectivity, thereby decreasing, inactivating or potentiating the chemokine function.

In this review, we will give a summary of PTMs of chemokines and the functional consequences for their biological activity. Since chemokines contribute to a variety of functions on different cell types, we report the influence of the alterations by biological effect, namely chemotaxis, hematopoiesis, angiogenesis, tumor growth and metastasis and antiviral activity. In addition, part of this manuscript will be dedicated to the interaction of chemokines with GAGs, the influence of PTMs on GAG binding and PTMs of chemokine receptors.

2. General aspects of PTMs of chemokines

Emerging evidence points towards a potentially central role for PTMs in the regulation of protein activity [58–64]. Chemokine isoforms generated by PTM were isolated from natural sources including cell culture supernatants and body fluids [57,65]. The currently described chemokine modifications are proteolytic processing resulting in truncation or degradation, nitration, citrullination and glycosylation. Depending on the ligand and mode of processing, different isoforms of a specific chemokine can display dramatically altered biological activities and receptor interactions.

2.1. Truncation & degradation

Proteolytic truncation may occur at the NH_2- and COOH-terminal chemokine domain, and is the best studied and probably most common way of chemokine modification [57]. Additionally, certain endopeptidases cleave chemokines internally followed by subsequent degradation of the ligand involved. Inflammatory chemokines in particular seem most susceptible to proteolysis. Moreover, the abundance of chemokine-modifying proteases is especially high in an inflammatory environment [66–69]. Proteases such as CD13 and CD26 can be present as membrane-associated molecules or exist as soluble variants in body fluids, e.g. plasma [70,71]. Members of the matrix metalloproteinase (MMP) family, among others, are stored in intracellular vesicles and are rapidly released upon appropriate stimulation [66]. Consequently, one may speculate that proteolytic processing of chemokines may become predominantly relevant during inflammation. The consequences of truncation for chemokine functioning are highly complex, including increased or decreased biological activity, inactivation, change of receptor preference or generation of receptor antagonists [57]. An interesting example in this context is the prototype CXCR1/2 agonist and most potent neutrophil-attracting chemokine in humans, i.e. CXCL8. Upon its discovery, it left no doubt that natural CXCL8 displays an exceptional degree of NH_2-terminal heterogeneity, with most of the identified CXCL8 isoforms being characterized by loss of up to eight NH_2-terminal residues [72–78]. For CXCL8, NH_2-terminal shortening

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