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Chemokine isoforms and processing in inflammation and immunity

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ABSTRACT

The first dimension of chemokine heterogeneity is reflected by their discovery and purification as natural proteins. Each of those chemokines attracted a specific inflammatory leukocyte type. With the introduction of genomic technologies, a second wave of chemokine heterogeneity was established by the discovery of putative chemokine-like sequences and by demonstrating chemotactic activity of the gene products in physiological leukocyte homing. In the postgenomic era, the third dimension of chemokine heterogeneity is the description of posttranslational modifications on most chemokines. Proteolysis of chemokines, for instance by dipeptidyl peptidase IV (DPP IV/CD26) and by matrix metalloproteinases (MMPs) is already well established as a biological control mechanism to activate, potentiate, dampen or abrogate chemokine activities. Other posttranslational modifications are less known. Theoretical N-linked and O-linked attachment sites for chemokine glycosylation were searched with bio-informatic tools and it was found that most chemokines are not glycosylated. These findings are corroborated with a low number of experimental studies demonstrating N- or O-glycosylation of natural chemokine ligands. Because attached oligosaccharides protect proteins against proteolytic degradation, their absence may explain the fast turnover of chemokines in the protease-rich environments of infection and inflammation. All chemokines interact with G protein-coupled receptors (GPCRs) and glycosaminoglycans (GAGs). Whether lectin-like GAG-binding induces cellular signaling is not clear, but these interactions are important for leukocyte migration and have already been exploited to reduce inflammation. In addition to selective proteolysis, citrullination and nitration/nitrosylation are being added as biologically relevant modifications contributing to functional chemokine heterogeneity. Resulting chemokine isoforms with reduced affinity for GPCRs reduce leukocyte migration in various models of inflammation. Here, these third dimension modifications are compared, with reflections on the biological and pathological contexts in which these posttranslational modifications take place and contribute to the repertoire of chemokine functions and with an emphasis on autoimmune diseases.

Contents

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1. Proteolysis of chemokines

1.1. Dipeptidyl peptidase IV/CD26

Dipeptidyl peptidase IV (DPP IV), alias CD26 is a serine type protease that cleaves off dipeptides from the N-terminus of peptide chains if the penultimate residue is Pro or Ala, though sometimes, other amino acids may be accepted [1,2]. Natural substrates of CD26 comprise peptide hormones, vasoactive peptides, neuropeptides, chemotactic cytokines (chemokines) and a few cytokines and growth factors [3–5]. Remarkably, many substrates activate G protein-coupled receptors (GPCRs), although their structural characteristics are quite diverse [4]. Inhibitors against CD26 were commercialized because the protease is a key regulator of glucose metabolism through cleavage of incretin hormones, but hematopoiesis, immunity, and cancer biology are also influenced by CD26. The role of CD26 within the immune system is a combination of its exopeptidase activity and its interactions with different molecules. This enables CD26 to regulate hematopoietic progenitor/stem cell (HPC/HSC) homing, engraftment, and growth; to serve as a costimulatory molecule influencing T cell activity [1,3]; to influence anti-viral defense (human immunodeficiency virus and hepatitis C virus) [1,6]; and to modulate leukocyte chemotaxis and mobilization [2,3,7].

1.1.1. CD26 expression

Cell-bound CD26 is rather ubiquitously expressed on leukocytes, fibroblasts, and epithelial, mesothelial, and endothelial cells and can be detected in placenta, pancreas, liver, gall bladder, intestine, kidney, and prostate [1,4]. Furthermore, modulated expression of CD26 on tumor cells has been reported [8]. Apart from its expression in solid tissues—either normal or malignant—CD26 is expressed by several leukocyte types, e.g., T cells, activated B cells, dendritic cells, NK cells and $CD34^+$ progenitor cells [1,4,9]. CD26 was characterized originally as a T cell subset marker, present on 10–60% of resting T cells [10]. Systematically higher CD26 levels were detected on $CD4^+$ T cells than on $CD8^+$ T cells [10]. CD26 expression increases after T cell activation [11] and therefore, is a suitable marker for activated T cells. T cells expressing high levels of CD26, constitute a subpopulation of $CD45RO^+$ memory T cells and produce IL-2 in response to mitogenic or alloantigenic stimulation [12]. Those $CD26^{high}$ subsets are the only $CD4^+$ cells that respond to recall antigens, induce synthesis of IgG in B cells, and activate MHC-restricted cytotoxic T cells [12].

In addition to the membrane-bound protease, a soluble form of CD26 exists, which is enzymatically fully active and occurs at high levels in seminal fluid; lower amounts are detected in plasma, urine, synovial fluid and cerebrospinal fluid [12]. For a long time, the enzyme releasing CD26 from cellular surfaces remained unknown. However, Röhrborn et al. [13] recently demonstrated that several MMPs can cleave CD26, setting free the extracellular catalytic domain. CD26 and its substrates highlighted in this review, namely chemokines, are often expressed under similar conditions. For instance in autoimmune diseases, such as multiple sclerosis (MS), Graves' disease, and rheumatoid arthritis (RA), large numbers of $CD26^+$ T cells have been detected in peripheral blood and/or inflamed tissues of patients [14–17].

1.1.2. CD26 inhibitors

Currently, at least 11 CD26 inhibitors have been approved by either the U.S. Food and Drug Administration, the European Medicines Agency or other Asian Agencies [18]. CD26 inhibitors are applied in diabetes to inhibit the proteolytic inactivation of the insulinotropic hormones (incretins), glucose-dependent insulinotropic polypeptide or gastric inhibitory polypeptide (GIP), and glucagon-like peptide-1 (GLP-1) and to normalize glucose homeostasis [1,18,19]. GIP and GLP-1 are released in response to food in the intestinal lumen and stimulate the production and release of insulin. Following evidence in animal models of type 2 diabetes for the therapeutic benefit of CD26 inhibitors stabilizing the incretins *in vivo*, CD26 inhibitors and CD26-resistant GLP-1 analogs are now approved therapeutics for diabetic patients. By prolonging the incretin effect, these therapeutics increase glucose tolerance. In addition, CD26 inhibitors (e.g., sitagliptin) improve pancreatic islet cell function in patients with type 2 diabetes, as prolonged activation of the β-cell GIP receptor induces proliferation and reduces apoptosis [20]. Currently, sitagliptin is also considered as add-on therapy for treating patients with autoimmune (type 1) diabetes, as inhibition of CD26 and its T cell-activating properties may preserve or increase β-cell mass [21]. The effect of CD26 inhibitors has also been evaluated in other pathologies in which CD26 is considered important. For instance, sitagliptin treatment was shown to reduce melanoma growth in mice because of delayed chemokine processing [22]. The latter study explores the possibility of

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