Commentary

Homing chemokines in rheumatoid arthritis

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Abstract

In about 20% of patients with rheumatoid arthritis, B and T lymphocytes recruited into the inflamed synovium are organized into complex microstructures, which resemble secondary lymphoid organs. The development of such lymphoid aggregates with germinal centers appears to contribute to the pathogenesis of the disease. Growing evidence indicates that chemokines and their receptors control the recruitment and positioning of leukocytes as well as their organization into node-like lymphoid structures. Here, we comment on recent studies highlighting the importance of chemokines in rheumatoid arthritis, in particular of B-cell-activating chemokine-1 in lymphoid neogenesis in the inflamed synovium.

Keywords: BCA-1, chemokine receptors, chemokines, CXCR5, ectopic follicles

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation and destruction of the cartilage and bone in the joints [1]. Despite the large research effort, neither the initiating event nor the perpetuating factors are clearly understood. The characteristic features of the disease are synovial lining hyperplasia and chronic infiltration of inflammatory cells including T lymphocytes, B lymphocytes, monocytes/macrophages and granulocytes. The hyperplastic lining layer is mainly composed of highly activated macrophage-like cells and proliferating fibroblast-like cells. The infiltrating lymphocytes are localized in the sublining tissue and are found around the blood vessels and in the stroma. Frequently, lymph-node-like aggregates are observed. Today, it is generally accepted that chemokines and their receptors are critical for the recruitment and positioning of cells in the inflamed synovium [2].

The human chemokine system comprises about 50 chemokines and 18 receptors [3–6]. Depending on the number and spacing of cysteine residues in the NH_2-terminal region, chemokines are partitioned into four structural families (CXC, CC, CX3C and C), and depending on the their function in inflammation and immunity, they have recently been grouped into inflammatory (also called inducible) and homing (also called constitutive, lymphoid or housekeeping) chemokines. Inflammatory chemokines are expressed by many different tissue cells and by immigrating leukocytes on stimulation with proinflammatory cytokines and pathogens. The main function of these chemokines is to recruit effector cells of the innate and adaptive immune systems, including granulocytes, monocytes, natural killer cells and effector lymphocytes. Homing chemokines, by contrast, are constitutively expressed in discrete areas within lymphoid and non-lymphoid tissues. Such chemokines control the physiological traffic and homing of leukocytes, which mainly belong to the adaptive immune system. All chemokines act via seven transmembrane domain receptors that are coupled to guanosine-triphosphate-binding proteins [7].

Chemokines and their receptors in RA

Since it is well known that proinflammatory cytokines including tumour necrosis factor-α and IL-1β play a

BCA-1 = B cell-activating chemokine-1 (CXCL13); CCR = CC-chemokine receptor; CXCR = CXC-chemokine receptor; ENA-78 = epithelial–neutrophil activating protein-78 (CXCL5); FDC = follicular dendritic cell; GC = germinal centre; IL = interleukin; MCP-1 = monocyte-chemoattractant protein-1 (CCL2); MIP-1α = macrophage inflammatory protein-1α (CCL3); RA = rheumatoid arthritis; RANTES = regulated upon activation, normal T cell expressed and secreted (CCL5); RT-PCR = reverse-transcriptase-mediated polymerase chain reaction; SDF-1 = stromal cell-derived factor 1 (CXCL12); SLC = secondary lymphoid tissue chemokine (CCL21); Th = T helper cell.

crucial role in the pathogenesis of RA, it is not surprising that inflammatory chemokines are found to be abundantly expressed in the inflamed RA synovium [8,9]. Numerous studies have demonstrated that activated synovial fibroblasts and monocytes/macrophages are the main producers of chemokines, such as IL-8 (recently designated CXCL8 [10]), epithelial–neutrophil activating protein-78 (ENA-78 or CXCL5), monocyte-chemoattractant protein-1 (MCP-1 or CCL2), RANTES (regulated upon activation, normal T-cell expressed and secreted or CCL5) and macrophage inflammatory protein-1α (MIP-1α or CCL3) in RA synovial tissue, and that elevated levels of these chemokines are also detected in RA synovial fluids [9]. IL-8 and ENA-78, which act on granulocytes, and MCP-1, RANTES and MIP-1α, which act primarily on monocytes and lymphocytes, are involved in the selective recruitment and activation of these cells. Recent studies have focused on the analysis of chemokine receptor expression in RA synovial T lymphocytes. The marked expression of the chemokine receptors CXCR3, CXCR6 and CCR5 on memory $CD4^+$ T lymphocytes, which represent the predominant infiltrate the inflamed synovium, is consistent with their highly differentiated state [11–16]. These inflammatory chemokine receptors are prominently expressed on effector T lymphocytes (Th1 cells) that mediate a type 1 inflammation such as RA. Interestingly, it has also been demonstrated that the RA synovial memory $CD4^+$ T lymphocytes express high levels of the chemokine receptor CXCR4, and that the ligand stromal cell-derived factor 1 (SDF-1 or CXCL12) is produced by synovial fibroblasts and endothelial cells [17,18]. Since CXCR4 expression is enhanced by IL-15 and transforming growth factor-β, which are present in the inflamed joint, CXCR4 and SDF-1 have been suggested to be important in retaining the cells at this site [17,18].

In about 20% of patients with RA, infiltrating T and B lymphocytes accumulate underneath the synovial lining layer and organize into lymphocyte aggregates with germinal centres (GCs) [19–21]. These ectopic lymphoid structures share many features with secondary lymphoid tissue and are thought to contribute to the pathogenesis of the disease [22]. Some homing chemokines, which are mainly expressed in lymphoid tissues, have been implicated in the formation of lymphoid structures [5,23]. The first indication of their involvement came from studies of CXCR5 (formerly known as Burkitt's lymphoma receptor-1 [24]), which is highly selective for the single chemokine B cell-activating chemokine-1 (BCA-1) [25,26]. The chemokine receptor CXCR5 is expressed in all circulating mature B lymphocytes and a subset of memory $CD4^+$ T lymphocytes, whereas the expression of its ligand, BCA-1, is mainly confined to B-cell follicles [27–30]. Mice deficient in CXCR5 or B-lymphocyte chemoattractant (the murine homologue of human BCA-1) have a profound disturbance of follicle and GC formation in the spleen and Peyer's patches [31,32]. Transgenic expression of BCA-1 in pancreatic islets, on the other hand, was shown to promote the development of lymph-node-like structures suggesting that BCA-1 can induce extranodal formation of organized lymphoid tissue [33]. Lymphoid neogenesis is not only observed in RA, but also in several other chronic inflammatory diseases including *Helicobacter pylori* gastritis, Sjögren's syndrome, Hashimoto's thyroiditis and chronic hepatitis C [21]. It is interesting to note that BCA-1 expression has been detected in all instances where extranodal lymphoid structures were examined, including *H. pylori*-induced, gastric-mucosa-associated lymphoid tissue and gastric lymphomas [34] as well as Sjögren's syndrome [35,36]. Evidence for the critical involvement of BCA-1 in the formation of RA-associated follicular aggregates is summarized below.

BCA-1 in RA lymphoid follicle formation

Shi *et al.* [37] and Takemura *et al*. [38] have reported that BCA-1 is expressed in the RA synovium. In both studies, BCA-1 mRNA was detected in all RA samples by reverse-transcriptase-mediated (RT)-PCR, but the transcript level was markedly higher in tissues with GC-positive lymphoid follicles than in tissues with GC-negative lymphoid follicles or with a diffuse lymphoid infiltrate. Immunohistochemical analysis showed that BCA-1 was mainly expressed within the GC, and the follicular dendritic cells (FDCs) were identified as cellular source [37,38]. In addition, Takemura *et al.* [38] report that endothelial cells lining small arterioles and capillaries, and synovial fibroblasts in the lining and sublining tissue stained positive for BCA-1 in samples either with or without GC-positive follicles. The presence on the endothelial cells suggests that BCA-1 may also be involved in transendothelial migration of CXCR5-positive cells [39]. Evidence for a role of other homing chemokines in RA-associated lymphoid structure formation is less clear. For instance, ectopic lymphoid tissues were readily observed in mice carrying a transgene for secondary lymphoid tissue chemokine (SLC) [40]. In RA synovial tissue, Takemura *et al.* [38] detected SLC mRNA by RT-PCR, while Shi *et al.* [37] did not confirm these findings by immunohistochemical analysis of SLC protein expression. Further research is required to determine whether SLC is important in leukocyte aggregation within the RA synovium.

Intriguingly, a perfect correlation was found between the occurrence of FDCs and GC-positive follicles in rheumatoid synovitis [38]. GCs were observed only when FDCs, which produce BCA-1, were present in the follicle. Whether the FDCs develop locally from precursors or whether they are recruited to this area is not known. In either case, they are critical for lymphoid neogenesis in the synovium. Furthermore, the strict requirement of FDCs suggests that antigen recognition events play a major role.

Conclusion

Clearly, we do not yet understand the mechanisms of extranodal lymphoid follicle formation in RA. Recent studies provide evidence that chemokines have an inductive function in establishing these microstructures. The induction of BCA-1 and other lymphoid-tissue-inducing chemokines may convert the synovial lesion from an acute to a chronic state by amplifying antigen-specific responses. Blocking chemokine activity by means of chemokine receptor antagonists may thus have significant therapeutic value.

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