Why does inflammation persist: a dominant role for the stromal microenvironment?

Michael R. Douglas, Karen E. Morrison, Michael Salmon and Christopher D. Buckley

Inflammatory responses occur within tissue microenvironments, with functional contributions from both haematopoietic (lymphocytic) cells and stromal cells (including macrophages and fibroblasts). These environments are complex – a compound of many different cell types at different stages of activation and differentiation. Traditional models of inflammatory disease highlight the role of antigen-specific lymphocyte responses and attempt to identify causative agents. However, recent studies have indicated the importance of tissue microenvironments and the innate immune response in perpetuating the inflammatory process. The prominent role of stromal cells in the generation and maintenance of these environments has begun to challenge the primacy of the lymphocyte in regulating chronic inflammatory processes. Sensible enquiries into factors regulating the persistence of inflammatory disease necessitate an understanding of the mechanisms regulating tissue homeostasis

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and remodelling during inflammation. This article highlights recent insights into the factors regulating dynamic aspects of inflammation, focusing particularly on mononuclear cell infiltrates, their interactions with stromal cells in tissues and the relevance of these interactions to existing and possible future therapies. A key feature of current research has been a growing appreciation that disordered spatial and temporal interactions between infiltrating immune cells and resident stromal cells lie at the heart of disease persistence.

Inflammatory responses resulting from tissue injury or infection generally result in a beneficial, self-limiting, healing process. The classical macroscopic features of inflammation as described 2000 years ago by the Roman physician Celsus are rubor (redness), tumour (swelling), colour (heat) and dolour (pain), and reflect the underlying molecular and cellular processes – specifically the release of inflammatory mediators leading to localised recruitment of immune effector cells including neutrophils, monocytes and lymphocytes. These responses can be defined by three important characteristics: spatial distribution (site specificity), the identity of the inflammatory infiltrate (cell type and magnitude of influx), and temporal pattern (resolving versus persistent).

Contrasting acute and chronic inflammation

Defining acute and chronic inflammation might seem at first a straightforward process: acute inflammation presents as a short-lived process with complete resolution; by contrast, chronic inflammation presents as a long-lasting phenomenon associated with tissue hyperplasia and scarring. In practice, this segregation is not always clear. Gout, for example, can manifest clinically as a recurrent acute inflammatory lesion, lasting many years, whereas a tuberculin PPD (purified protein derivative of tuberculin) skin test is a chronic inflammatory process that resolves completely within a few weeks.

A histological definition (acute inflammation characterised by a neutrophilic infiltrate; chronic inflammation characterised by a mainly mononuclear infiltrate), in combination with the clinical picture (resolution versus persistence), is probably more useful. Thus, inflammation can be seen as being either acute resolving, acute persistent, chronic resolving or chronic persistent. Recruitment of leukocytes in inflammation is characterised by an initial infiltration of neutrophils, present within an hour of the initiating stimulus. This phase is later replaced by a more sustained influx of mononuclear cells. One of the biological consequences of this perivascular accumulation of mononuclear cells is a change in the appearance of endothelial cells, which adopt a structure more like high endothelial venules, normally seen only in lymphoid tissue (Ref. 1).

The molecular mechanisms controlling the switch from acute to chronic inflammation are becoming clearer. Cytokines and chemokines – proteins that participate in the conversation between immune and stromal cells – appear to play a particularly important role in this process. The chemokines form a superfamily of structurally related proteins subdivided into four subfamilies based on the arrangement of N-terminal cysteine residues (C, CC, CXC and CX_3C families, respectively) (Table 1) (Ref. 2). They act functionally to regulate tissue homeostasis and direct responses in both haematopoietic and stromal cells. A study monitoring the evolution of the leukocytic infiltrate in peritoneal inflammation (Ref. 3) has suggested that the interaction between interleukin 6 (IL-6) and its soluble receptor sIL-6R forms one of the major determinants of this temporal switch (Switch 1, Fig. 1). sIL-6R, produced by the infiltrating neutrophils, forms a complex with IL-6 and has the capacity to activate cells lacking expression of the cognate IL-6 receptor. This mechanism was shown to modulate CC and CXC chemokine expression directly. CXC chemokine expression induced by proinflammatory cytokines [IL-1 and tumour necrosis factor α (TNF-α)] was suppressed, whereas expression of the CC chemokine monocyte chemoattractant protein 1 (MCP-1; CCL2) was promoted. This chemokine shift suppresses further neutrophil recruitment and promotes a sustained mononuclear cell influx. Similarly, a study investigating the dynamics of

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Table 1. Chemokine nomenclature[a] (tab001cbb)

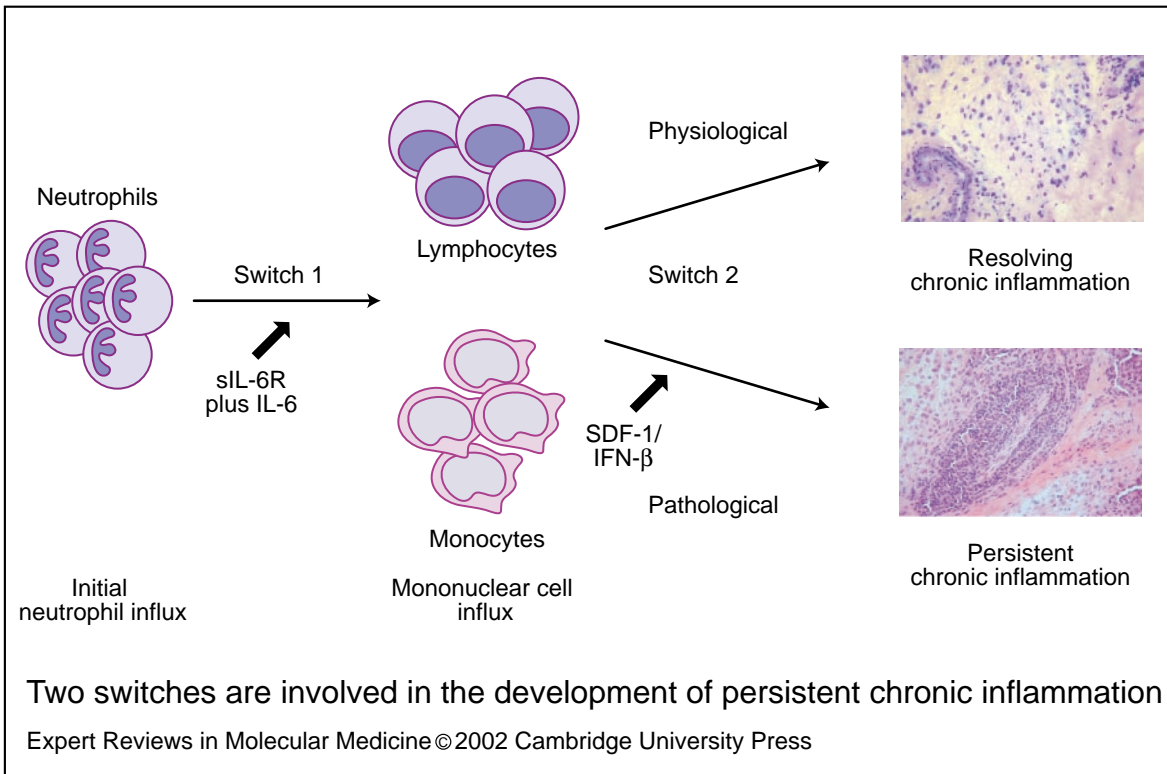| Systematic name	Original ligand name	Receptors
CXC chemokines		
CXCL1	GROα	CXCR2, CXCR
CXCL2	GROβ	CXCR2
CXCL3	GROγ	CXCR2
CXCL4	PF4	Unknown
CXCL5	ENA-78	CXCR2
CXCL6	GCP-2	CXCR1, CXCR2
CXCL7	NAP-2	CXCR2
CXCL8	IL-8	CXCR1, CXCR2
CXCL9	Mig	CXCR3
CXCL10	IP-10	CXCR3
CXCL11	I-TAC	CXCR3
CXCL12	SDF-1α/β	CXCR4
CXCL13	BCA-1	CXCR5
CXCL14	BRAK	Unknown
CXCL15	Unknown	Unknown
CXCL16	–	CXCR6
C chemokines		
XCL1	Lymphotactin/SCM-1α	XCR1
XCL2	SCM-1β	XCR1
CX$_3$C chemokines		
CX$_3$CL1	Fractalkine	CX$_3$CR1
CC chemokines		
CCL1	I-309	CCR8
CCL2	MCP-1	CCR2
CCL3	MIP-1α	CCR1, CCR5
CCL3L1	LD78β	CCR1, CCR5
CCL4	MIP-1β	CCR5
CCL5	RANTES	CCR1, CCR3, CCR5
CCL6	Unknown	Unknown
CCL7	MCP3	CCR1, CCR2, CCR3
CCL8	MCP-2	CCR3, CCR5
CCL9/CCL10	Unknown	CCR1
CCL11	Eotaxin	CCR3
CCL12	Unknown	CCR2
CCL13	MCP-4	CCR2, CCR3
CCL14	HCC-1	CCR1, CCR5
CCL15	HCC-2/Lkn-1/MIP-1δ	CCR1, CCR
CCL16	HCC-4/LEC/LCC-1	CCR1, CCR2
CCL17	TARC	CCR4
CCL18	DC-CK1	Unknown
CCL19	MIP-3β/ELC	CCR7
CCL20	MIP-3α/LARC	CCR6
CCL21	6Ckine/SLC	CCR7
CCL22	MDC	CCR4
CCL23	MPIF-1/CKb8	CCR1
CCL24	Eotaxin-2	CCR3
CCL25	TECK	CCR9
CCL26	Eotaxin-3	CCR3
CCL27	CTACK	CCR10
CCL28	MEC	CCR3/CCR10

[a] The new nomenclature for human cytokines is detailed. Adapted from Ref. 95.

(for abbreviations see next page)

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Abbreviations for Table 1 (tab001cbb)

BCA-1, B-cell-attracting chemokine 1; CTACK, cutaneous T-cell-attracting chemokine; DC-CK1, dendritic-cell-derived CC chemokine 1; ELC, EBL-1-ligand chemokine; ENA-78, epithelial-cell-derived neutrophil attractant 78; GCP, granulocyte chemotactic protein; GRO, growth-related oncogene; HCC, haemofiltrate CC chemokine; IL, interleukin; IP-10, interferon-inducible protein 10; I-TAC, interferon-inducible T-cell alpha chemoattractant; LARC, liver- and activation-regulated chemokine; LEC, liver-expressed chemokine; LCC-1, liver-specific CC chemokine-1; Lkn-1, leukotactin; MCP, monocyte chemoattractant protein; MDC, macrophage-derived chemokine; MEC, mammary-enriched chemokine; Mig, monokine induced by interferon γ; MIP, macrophage inflammatory protein; MPIF, myeloid progenitor inhibitory factor; NAP, neutrophil-activating peptide; PF4, platelet factor 4; RANTES, 'regulated on activation, normally T-cell-expressed and -secreted'; SCM-1α/β, single C motif-1 α/β; SDF, stromal-cell-derived factor; SLC, secondary lymphoid tissue chemokine; TARC, thymus- and activation-regulated chemokine; TECK, thymus-expressed chemokine.

Neutrophils

Lymphocytes

Physiological

Switch 1

sIL-6R plus IL-6

Switch 2

Resolving chronic inflammation

SDF-1/ IFN-β

Pathological

Monocytes

Initial neutrophil influx

Mononuclear cell influx

Persistent chronic inflammation

Two switches are involved in the development of persistent chronic inflammation

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Figure 1. Two switches are involved in the development of persistent chronic inflammation. Both acute and chronic inflammation are characterised by an initial infiltration of neutrophils, followed by a more sustained influx of mononuclear cells. Neutrophils produce soluble IL-6 receptor (sIL-6R), which binds IL-6 produced by haematopoietic and stromal cells in the vicinity. The change from a neutrophilic to a mononuclear population requires a switch from CXC to CC chemokines (Switch 1), and this is regulated by IL-6. (RANTES, also produced by haematopoietic and stromal cells, is an alternative regulator of this switch, but the exact molecular mechanism involved remains unclear.) In this way, the nature of the inflammatory infiltrate is tailored to the inflammatory stimulus, such that the appropriate quantity and quality of leukocyte subsets are recruited. For the inflammatory infiltrate to resolve completely, a second switch must occur that allows infiltrating cells to die and be cleared (Switch 2). This becomes disordered, and persistent chronic inflammation results, when cytokines such as interferon β (IFN-β) and chemokines such as stromal-cell-derived factor 1 (SDF-1) are ectopically produced by stromal cells such as macrophages and fibroblasts (see also Fig. 3). As shown by the histological sections, persistent inflammation is associated with an abnormal increase in the number and distribution of leukocytes within the tissue, classically as a perivascular infiltrate **(fig001cbb)**.

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the inflammatory infiltrate in a rat colitis model (Ref. 4) found that the CC chemokine RANTES (CCL5) is important in the progression to chronic disease. Markedly elevated levels of this chemokine were found in the chronic phase of the disease, with elevation of two of its key receptors (CCR1 and CCR5). Together, these studies suggest that the cellular switch from an acute to a chronic inflammatory process is partially chemokine mediated (Switch 1, Fig. 1), with a CXC to CC shift leading to a preferential influx of mononuclear cells at the site of inflammation. Furthermore, they suggest that cytokines and chemokines made by infiltrating leukocytes and resident stromal cells contribute to this switch. Other factors contribute to the segregation of a chronic resolving process from a chronic persistent inflammatory process (during Switch 2), and these are detailed later.

The anatomy of an inflammatory infiltrate

The role of the endothelium

To achieve efficient immune surveillance and longstanding immunity, lymphocytes continuously recirculate through tissues via the bloodstream, across resting endothelium and into efferent lymphatics (Ref. 5). On the basis of the environment in which they first encounter antigen, lymphocytes acquire a predilection to home to, and recirculate through, that same environment (Ref. 6). The mechanisms whereby such specificity is acquired are unclear, but probably depend on stromal factors. For example, it was recently shown that the expression of chemokine receptors defining tissue tropism is present within two days of immunisation and that site specificity is acquired by interactions with stromal elements present within secondary lymphoid tissue (Refs 7, 8).

Cellular recruitment to tissues is not random, but depends on a carefully choreographed sequence of molecular interactions, involving leukocyte activation, adhesion, chemoattraction and endothelial transmigration (see the article and video on the liver as a model of lymphocyte recruitment published recently in this journal: Ref. 9). Extensive experimental evidence supports the 'area-code' model of lymphocyte homing. This model proposes a cascade of sequential and combinatorial steps whereby appropriate leukocyte subsets leave the peripheral circulation and enter tissues via post-capillary venules (Ref. 10). Expression of adhesion molecules and

chemoattractant receptors on lymphocytes, and corresponding ligands for these receptors on tissue cells, plays a key role in positioning and retaining lymphocytes within tissues (Ref. 5).

Superimposed on this 'physiological' homing and recirculation of lymphocytes is the recruitment of immune cells to inflammatory sites – a key component of the inflammatory response. By contrast to the situation during leukocyte homing and recirculation, leukocyte recruitment during inflammation occurs across activated systemic vascular endothelium (Ref. 11). The anatomical location and nature of the inflammatory insult determine the recruitment pattern of leukocyte subsets and govern whether lymphocytes, monocytes, neutrophils or eosinophils predominate. The most striking examples of this are the marked accumulation of eosinophils at extravascular sites of allergic reaction in the lung in asthma (Ref. 12) and in the inflammatory diseases of the skin (dermatoses) (Ref. 13).

With the cloning of the molecules involved in lymphocyte homing during normal physiological responses and leukocyte recruitment during inflammation (Ref. 11), it became apparent that, at the molecular level, the regulation of these two distinct yet biologically related processes are strikingly similar. For example, E-selectin expressed by endothelial cells binds both neutrophils during acute inflammation [via E-selectin ligand 1 (ESL-1)] and skin-homing memory cells during T-cell homing to the skin [via cutaneous lymphocyte antigen (CLA)] (Ref. 14). Both processes rely on transient interactions between leukocytes and endothelium, a process termed 'rolling'. These contacts permit sampling for activating factors, particularly chemokines that bind to G-protein-coupled receptors on the rolling cell (Ref. 15). Reversible arrest, firm adhesion and migration across the endothelium into tissue then follow, mediated by additional adhesion molecules and chemokines (Ref. 16).

The role of stromal-cell-derived chemokines

Tissue-associated chemokine gradients also direct cellular localisation. Chemokines are important molecular signposts, playing an important role in cell exit from the circulation and retention within tissues (Ref. 5). The proinflammatory activities of chemokines have been appreciated for many years, but recent studies (Refs 5, 17) have

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Chemokine receptors and chemokine ligand specificity

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Figure 2. Chemokine receptors and chemokine ligand specificity *(see next page for legend)* **(fig002cbb)**.

Figure 2. Chemokine receptors and chemokine ligand specificity. Chemokine receptors are grouped according to their specificity for inflammatory chemokines (red boxes) or constitutive chemokines (blue boxes). Their cellular expression is shown by green boxes. Some constitutive chemokines or chemokine receptors have shown heterogeneous expression patterns (red/blue boxes). Some chemokine receptors are only expressed by subsets of certain cells (half-coloured boxes). The work summarised here is constantly being updated and is an intense area of investigation. Figure reproduced from Ref. 96, with permission from Elsevier Science (© Copyright 1998, Elsevier Science). Abbreviations: BCA-1, B-cell-attracting chemokine 1; CTACK, cutaneous T-cell-attracting chemokine; DC, dendritic cell; ELC, EBL-1-ligand chemokine; ENA, epithelial-cell-derived neutrophil attractant 78; GCP, granulocyte chemotactic protein; GRO, growth-related oncogene; HCC, haemofiltrate CC chemokine; IL, interleukin; IP-10, interferon-inducible protein 10; I-TAC, interferon-inducible T-cell alpha chemoattractant; LARC, liver- and activation-regulated chemokine; MCP, monocyte chemoattractant protein; MEC, mammary-enriched chemokine; Mig, monokine induced by interferon γ; MIP, macrophage inflammatory protein; MPIF, myeloid progenitor inhibitory factor; NAP, neutrophil-activating peptide; NK, natural killer; RANTES, 'regulated on activation, normally T-cell-expressed and -secreted'; SDF, stromal-cell-derived factor; SLC, secondary lymphoid tissue chemokine; TARC, thymus- and activation-regulated chemokine; TECK, thymus-expressed chemokine; Th, T helper **(fig002cbb)**.

demonstrated that chemokines also provide the molecular basis for many homeostatic non-inflammatory functions, including T- and B-cell development, lymphoid trafficking and T- and B-cell compartmentalisation within primary and secondary lymphoid tissues. This has led to a functional segregation of chemokines (Fig. 2) into 'inflammatory' (also called inducible) chemokines and 'homeostatic' (constitutive, housekeeping or lymphoid) chemokines (Ref. 18). The former group are produced following stimulation by proinflammatory cytokines or during direct pathogen contact, and promote the recruitment of effector cells (neutrophils, monocytes and effector T cells) (Ref. 18). The latter group are expressed constitutively at homing sites and act on receptors principally found on lymphocytes (Ref. 19). This functional segregation is not absolute, as several chemokines have overlapping functions, including macrophage-derived chemokine (MDC; CCL22), thymus- and activation-regulated chemokine (TARC; CCL17) and liver- and activation-regulated chemokine (LARC; CCL20) (Ref. 20). Nonetheless, the classification is conceptually useful.

The interaction of a particular chemokine, stromal-cell-derived factor 1 (SDF-1; CXCL12), with its receptor CXCR4 is important in regulating leukocyte development and retention within lymphoid tissue. Embryonic disruption of the genes for SDF-1 or CXCR4 results in death in utero, with evidence of defective red and white blood cell formation (Refs 21, 22). SDF-1 is a chemoattractant for T and B cells with important roles in the bone marrow (BM), thymus and secondary lymphoid organs. Production of

SDF-1 by BM stromal cells attracts B-cell precursors to the BM, where they mature under the influence of growth and differentiation factors (Ref. 23). Thymic production of SDF-1 also appears important, determining the distribution of particular thymocyte subsets (Ref. 24).

Lymphocyte migration into secondary lymph nodes and the generation of secondary lymphoid structures is regulated by B-cell-activating chemokine (BCA-1; CXCL13), which acts on CXCR5, and secondary lymphoid tissue chemokine (SLC; CCL21) and EBL-1-ligand chemokine (ELC; CCL19), which both act on CCR7 (Ref. 17). SLC is expressed by high endothelial venules and attracts CCR7-bearing lymphocytes. SLC and ELC present in the parafollicular area regulate T-cell migration, whereas CXCR5-expressing B cells migrate further to the BCA-1-expressing follicles (Ref. 17).

Less is known about the molecules that regulate monocyte trafficking, but recent evidence suggests that 'breast and kidney expressed chemokine' (BRAK; CXCL14), produced by a range of stromal tissues, is selectively chemotactic for activated monocytes (Ref. 25). Prostaglandin-induced activation modulates chemokine responsiveness: as BRAK responsiveness increases, the response to traditional monocyte chemoattractants MCP-1, RANTES and SDF-1 decreases. This mechanism might promote monocyte colocalisation with BRAK-producing stromal cells, providing factors important for monocytic differentiation (Refs 25, 26).

Combinations of adhesion molecules impart tissue tropism, with additional contributions

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from chemokine and chemokine receptor interactions (Ref. 26). Skin-homing T cells express CLA and leukocyte function-associated antigen 1 (LFA-1), which bind to E-selectin and intercellular cell adhesion molecules (ICAMs), respectively, on dermal venules of the skin (Ref. 27). Some circulating CLA[+] memory T cells express CCR4, and the respective ligands TARC and MDC are expressed predominately on the cutaneous vasculature (Ref. 28). These interactions contribute to the preferential recruitment of skin-homing memory T cells. By contrast, gut-homing cells lack CLA, but express α4β7, the receptor for mucosal addressin cell adhesion molecule 1 (MAdCAM-1) found on the intestinal vasculature; these cells also express CCR9, implicated in homing to intestinal tissues (Ref. 5).

Stromal determinants of inflammatory cell survival and retention at sites of inflammation

The supposition that the selective accumulation of distinct leukocyte subsets at sites of inflammation is a result of endothelial selection at the point of entry has largely been the prevailing paradigm (Ref. 29). Selection within the tissue, meditated by stromal determinants, has received relatively little attention, despite their well-defined role during lymphocyte development in the BM and thymus. However, in order to persist, an inflammatory infiltrate must result from an imbalance between cell recruitment, proliferation, emigration and death, and the stromal environment plays an important role in this. Resolution of the infiltrate depends on the dominance of factors depleting the infiltrating cell pool over factors increasing the infiltrating cell pool. By contrast, persistence of inflammation occurs when cell recruitment or proliferation is ongoing, and emigration and death are inhibited (Fig. 3).

After crossing post-capillary venules into the subendothelial compartment, leukocytes encounter a stromal microenvironment that is quite distinct from that found in the vascular compartment. It has emerged in recent years that, while providing the anatomical environment in which the immune response occurs, stromal cells also directly participate in the induction and effector phases of the response – particularly in the switch from the innate to the acquired immune response (Ref. 30). The T-cell expansion seen after antigenic stimulation is followed by a
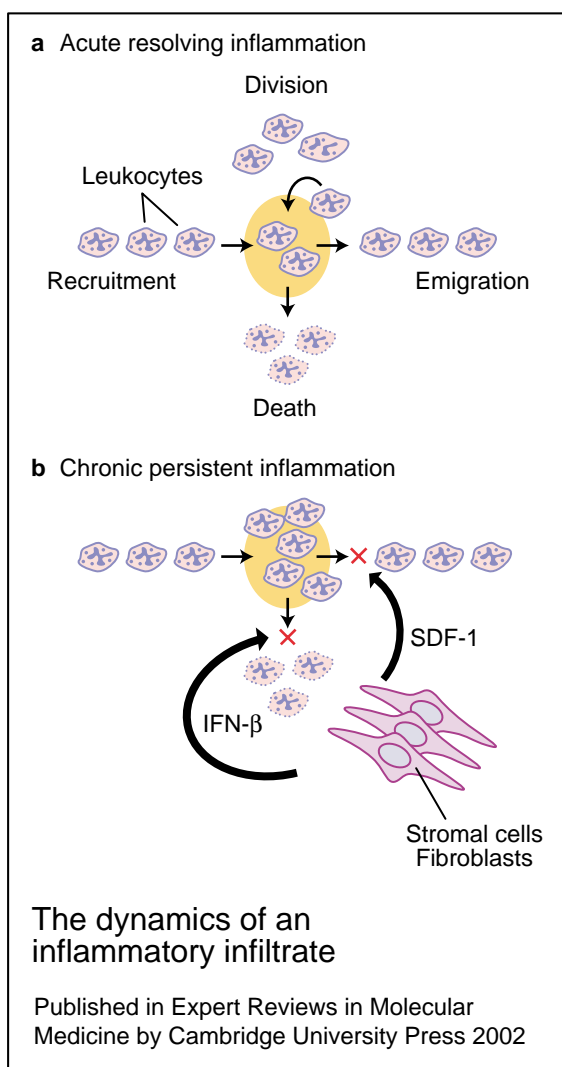

Figure 3. The dynamics of an inflammatory infiltrate. The accumulation of leukocytes in any tissue compartment depends on the dynamic balance between cell recruitment, division, emigration and death. (a) In the normal situation of acute resolving inflammation, homeostasis between these cell events is maintained, leading to resolution. (b) In chronic persistent inflammation, abnormal accumulation of leukocytes is caused by the inappropriate production by stromal cells and fibroblasts of factors that are either pro-retentive [e.g. stromal-cell-derived factor 1 (SDF-1)] or pro-survival [e.g. interferon β (IFN-β)] (see also Fig. 1). Figure reproduced (with modification) from Ref. 29, with permission from Elsevier Science (© Copyright 2001, Elsevier Science) **(fig003cbb)**.

significant elimination phase, during which cell numbers are restored to a near-basal state. These homeostatic mechanisms depend on the induction

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of apoptosis, either by Fas-induced cell death or by cytokine deprivation (Ref. 31). Cytokine deprivation appears to be a particularly important mechanism that ensures removal of lymphocytes during the resolution of inflammation (Ref. 32).

The microenvironment formed by stromal cells is bathed in cytokines, chemokines and growth factors that actively condition the cellular infiltrate (Refs 29, 33). Some of these mediators actively promote cell survival by a range of anti-apoptotic mechanisms, thereby contributing to the persistence of inflammation. In particular, cytokines of the IL-2 receptor common γ-chain family, such as IL-2, IL-4, IL-7 and IL-15, are able to inhibit apoptosis of activated T cells, most probably by Bcl-2 induction (Ref. 34). A second group, the type I interferons (IFN-α and IFN-β), protect against both Fas-induced and cytokine-deprivation-induced apoptosis by several mechanisms, including the induction of Bcl-x$_L$ expression and prevention of protein kinase C δ translocation (Ref. 33). These two survival mechanisms have quite different outcomes: survival and proliferation in the case of the common γ-chain cytokines, and survival and entry into cell cycle arrest in the case of the interferons.

Far less is known about stromal mediators of macrophage survival. In contrast to T cells, macrophages appear to be relatively resistant to survival factor deprivation, and active migration out of inflammatory sites has been demonstrated (Refs 35, 36). The molecular mechanisms mediating this process are unclear and are an area of active research.

Clinical examples of inflammation
Although the chronic inflammatory diseases rheumatoid arthritis, Sjögren's syndrome and multiple sclerosis show distinct pathologies and tissue responses, common processes are likely to underlie the inflammatory response since therapeutic intervention with steroids is helpful in many patients with these conditions. As discussed below, each of these diseases requires the recruitment of leukocytes, yet the way in which these infiltrating leukocytes are organised by the differing stromal microenvironment in the three diseases is quite distinct.

Rheumatoid arthritis: chronic inflammation in the joint
Rheumatoid arthritis is a chronic inflammatory disease of unknown aetiology, characterised by a disordered synovial microenvironment in which there is hyperplasia of resident stromal cells and a heavy infiltrate of haematopoietic cells such as T and B cells (Refs 37, 38). A characteristic feature of the inflammatory infiltrate is the accumulation of lymphocytes into distinctive micro-anatomical structures with architectural features that strongly resemble lymphoid tissue (Ref. 39). Lymphocytic activation is supposed to be a primary factor in this process, but it has not been possible to demonstrate direct evidence of a specific target for autoimmune T cells. Indeed, the heterogeneous antigenic reactivities observed in rheumatoid arthritis joints might instead reflect the occurrence of secondary, non-specific sensitisation. A better understanding of the underlying pathological processes in rheumatoid arthritis might be achieved by investigating the hypothesis that cellular recruitment to the joint occurs episodically. Using the concepts detailed above, we can ask (1) why the cells do not simply leave the joint and (2) whether there are local factors that maintain the architecture of an inflammatory infiltrate.

The synovial microenvironment promotes T-cell retention
The accumulation of T cells in the rheumatoid joint has been shown to be due to contributions from the active, chemokine-dependent retention of T cells. It has recently been demonstrated that synovial T cells highly express CXCR4, a receptor not normally found on highly differentiated CD45R0+ T cells in peripheral blood (Refs 40, 41). CXCR4 expression is dependent on factors present in the synovial microenvironment – particularly transforming growth factor β (TGF-β). SDF-1, the ligand for CXCR4, is found at high levels within the synovium and particularly on synovial endothelial cells (Refs 40, 42, 43). Interestingly, inhibiting the interaction between SDF-1 and CXCR4 in a mouse model of collagen-induced arthritis ameliorated the disease, suggesting that inhibitors of SDF-1–CXCR4 interactions might lead to clinical improvement in rheumatoid arthritis (Ref. 44).

The synovial stromal microenvironment prevents T-cell death
As mentioned above, removal of the vast majority of immune cells that were recruited and expanded during the active phase of disease is essential for the successful resolution of an inflammatory

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response. The persistent leukocyte infiltrate in the rheumatoid joint has been shown to be partly a consequence of the inhibition of apoptosis (Ref. 45). In rheumatoid arthritis, synovial T cells are highly differentiated (CD45R0^{+} CD45RB[dull]) and should therefore die easily. This process is partially inhibited by locally produced cytokines and growth factors such as IFN-α and IFN-β, produced by synovial fibroblasts and macrophages (Ref. 46). This mechanism is likely to be relevant for other cell types in other pathological conditions, as these type I IFNs are potent survival factors for a range of leukocyte subsets (Ref. 47).

The conclusion from present studies can be summarised as follows: the inflammatory infiltrate in rheumatoid arthritis appears to persist as a direct result of sustained recruitment, inappropriate retention and enhanced survival of cells, a process mediated by the abnormal expression of stromal factors associated with the local microenvironment (Switch 2, Fig. 1; Fig. 3).

Sjögren's syndrome: chronic inflammation in exocrine glands

The findings described above for rheumatoid arthritis provide a potential explanation for why rheumatoid tissues mimic many of the structural features of stable supportive stromal cell niches such as the BM and lymphoid tissue. Is this a unique feature of rheumatoid arthritis or a universal feature of many chronic inflammatory diseases, particularly those where epithelial tissues are inflamed?

Sjögren's syndrome is characterised by the accumulation of lymphocytes within salivary, lachrymal and other exocrine glands in the respiratory tract, gastrointestinal tract and vagina (Ref. 48). The inflammatory infiltrate consists predominantly of CD4^{+} T cells, with fewer CD8^{+} T cells, B cells and plasma cells. These first appear as small clusters around ductal tissue, later enlarging to form structures resembling ectopic germinal centres (GCs). The development of these ectopic lymphoid follicles has been implicated in the pathogenesis of Sjögren's syndrome, as large amounts of autoantibodies are a characteristic feature of the disease (Ref. 49). GCs classically arise in primary B-cell follicles of secondary lymphoid organs and provide a unique microenvironment for B-cell maturation into plasma cells (Ref. 50). Lymphoid aggregates with ectopic GC-like structures (sometimes called

tertiary lymphoid tissue) are found in several chronic inflammatory diseases. It remains unclear whether these ectopic structures contain all the necessary components required to generate a local B-cell-driven response or simply represent a focus point for the collection of autoantibody-producing B cells that migrate into inflamed tissue from nearby secondary lymphoid tissue (Refs 51, 52, 53, 54).

Why do ectopic GCs form in Sjögren's syndrome?

Recent studies have established a critical role for TNF and lymphotoxin (LT) in the development and maintenance of lymphoid tissue (Ref. 55). The lack of normal lymphoid organs in mice deficient in the lymphoid-homing chemokine receptors CXCR4 and CXCR5 has also implicated chemokines such as SDF-1 and BCA-1 in lymphoid neogenesis (Refs 17, 56). Elegant studies in transgenic mice overexpressing the constitutive lymphoid chemokine BCA-1 have confirmed that LT, TNF and BCA-1 act in a common pathway of lymphoid neogenesis (Ref. 57). Importantly, these studies have suggested that similar molecular mechanisms might be responsible for lymphoid development during embryogenesis and the formation of lymphoid aggregates in chronic inflammation, particularly with regard to the production of chemokines.

In Sjögren's syndrome, recent studies have now shown that the accumulation of lymphocytes in GC-like structures within inflamed tissue is also associated with the ectopic expression of the lymphoid-tissue homing chemokines BCA-1 and SDF-1 (Ref. 58). Inflamed glands (but not control tissue) from patients with Sjögren's syndrome expressed very high levels of BCA-1 on endothelial-like structures found abundantly throughout the inflamed tissue. In contrast to the situation in rheumatoid arthritis, SDF-1 was expressed on ductal epithelial tissue, rather than on fibroblasts and endothelium (Ref. 58).

Taken together, these findings suggest that the inappropriate temporal and spatial expression of chemokines plays an important role in determining the persistence and patterning of lymphoid aggregates within chronically inflamed tissues. They also provide strong support for the hypothesis that the ectopic expression of chemokines is a general feature that drives leukocyte accumulation in chronic inflammatory rheumatic diseases (Fig. 4).

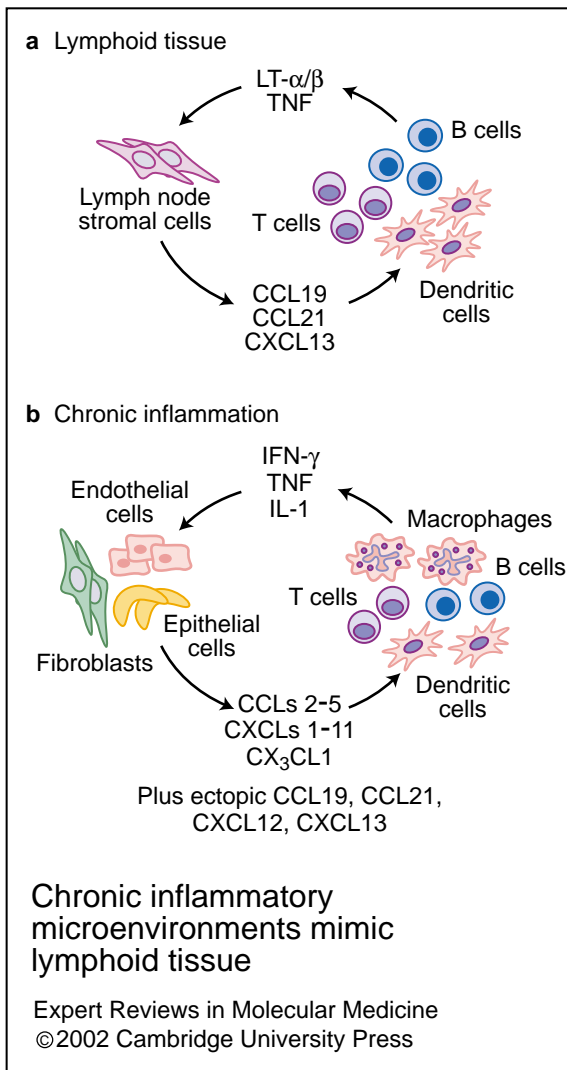**Why does inflammation persist: a dominant role for the stromal microenvironment?**

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a Lymphoid tissue

LT-α/β
TNF

B cells

Lymph node stromal cells

T cells

CCL19
CCL21
CXCL13

Dendritic cells

b Chronic inflammation

IFN-γ
TNF
IL-1

Endothelial cells

Macrophages

B cells

T cells

Epithelial cells

Fibroblasts

Dendritic cells

CCLs 2–5
CXCLs 1–11
CX_3CL1

Plus ectopic CCL19, CCL21, CXCL12, CXCL13

Chronic inflammatory microenvironments mimic lymphoid tissue

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Figure 4. Chronic inflammatory microenvironments mimic lymphoid tissue. Constitutive chemokines provide the link between lymphoid neogenesis and chronic inflammation. (a) In lymphoid tissue, tumour necrosis factor (TNF) family members, such as TNF and lymphotoxin α/β (LT- α/β), produced by infiltrating haematopoietic cells, lead to the production of constitutive chemokines (CCL19, CCL21, CXCL13) by stromal cells, driving the formation of lymphoid tissue by coordinating the further recruitment and distribution of T cells, B cells and dendritic cells. (b) During inflammation, other cytokines in addition to TNF, such as interleukin 1 (IL-1) and interferon γ (IFN-γ), are released by infiltrating haematopoietic cells, and this leads to the production of inflammatory chemokines (including CXCLs 2–5, CXCLs 1–11 and CX_3CL1) by the resident stromal cells such as fibroblasts, endothelial and epithelial cells. Constitutive chemokines such as CCL19, CCL21, CXCL12 and CXCL13 are not expressed during a normal, resolving inflammatory response. However, the inappropriate temporal and spatial production of constitutive chemokines by stromal cells is an intriguing feature of chronic persistent inflammatory microenvironments. Indeed, ectopic production of stromal-cell-derived factor 1 (SDF-1) and B-cell-activating chemokine (BCA-1) and their receptors CXCR4 and CXCR5 has been seen in the rheumatoid arthritis synovium and Sjögren's syndrome salivary gland. These chemokines have been demonstrated to be important in the formation of lymphoid tissue (Ref. 97). If the basal production of constitutive chemokines during inflammation is not tightly regulated, this might lead to the superimposition of lymphoid-like structures within inflamed tissue **(fig004cbb)**.

Multiple sclerosis: chronic inflammation in the brain parenchyma

Whereas rheumatoid arthritis and Sjögren's syndrome are characterised by the presence of large numbers of leukocytes within joints and exocrine glands, respectively, other inflammatory conditions, such as multiple sclerosis, often have a much more restricted accumulation of infiltrating inflammatory cells. Multiple sclerosis is a disease of unknown aetiology characterised by multifocal demyelination and polyphasic inflammation in the central nervous system (CNS) (reviewed in Ref. 59). Lymphocytic infiltration is likely to be important for the formation of multiple sclerosis plaques, but evidence of a specific target for autoimmune T cells is lacking despite strenuous attempts to define such targets.

Attention has therefore shifted to the mechanisms regulating lymphocytic accumulation in the CNS.

Difficulties with heterogeneous pathological features and lesion staging have made the interpretation of specific inflammatory patterns difficult (Ref. 60); nonetheless, it seems clear that the infiltrates are composed of T cells, some B cells, activated microglia and macrophages (Ref. 61). The origin of these cells has been the subject of some dispute: for a long time, the CNS was considered an immunologically privileged site, but research performed over the past decade has indicated that this notion no longer holds true (Ref. 62). Evidence of inflammatory cell trafficking from the periphery into the CNS in humans has been elegantly demonstrated in human studies performed on allogeneic BM transplantation

recipients (Ref. 63). These female recipients of male donor cells develop a Y-chromosome-bearing haematopoietic system. In situ hybridisation using specific probes demonstrated that all cells in the cerebrospinal fluid (CSF) and the perivascular compartment, as well as the infiltrating inflammatory cells, were donor derived. By contrast, the parenchymal microglia were host derived. These results closely mirror rat radiation BM chimaera studies (Ref. 59) and indicate that BM-derived cells continuously patrol the CNS, whereas the parenchymal microglial population appears very stable (Refs 63, 64). Thus, the brain parenchyma constitutes a quite different microenvironment to that formed by the CSF and meninges.

The CNS in inflammatory conditions promotes cellular retention

Little is known about the specific role of chemokines in cellular migration across the blood–brain barrier, and interpretation of observational data is therefore difficult. Most T cells in the CSF of both multiple sclerosis patients and normal controls express the chemokine receptor CXCR3, with some enrichment for CCR5-expressing cells (Ref. 65) Similar patterns are seen on perivascular lymphocytes in multiple sclerosis autopsy material, but rarely in control brain specimens. One of the ligands for CXCR3, IFN-γ-inducible protein 10 (IP-10; CXCL10), is produced by astrocytes in multiple sclerosis lesions and it is hypothesised that this interaction leads to the retention of CNS-infiltrating CXCR3+ cells (Ref. 66).

Chemokines also appear to play a role in monocyte accumulation in multiple sclerosis. Patients with neuroinflammatory disorders (including multiple sclerosis) have increased levels of macrophage inflammatory protein 1α (MIP-1α; CCL3) in the CSF (Ref. 67), and analysis of CNS-infiltrating monocytes reveals that a majority express the MIP-1α ligands CCR1 and CCR5, with CCR5 expression persisting in the multiple sclerosis lesion (Ref. 68). The importance of these findings is highlighted by the observation that T cells from multiple sclerosis patients display an enhanced chemotactic response to CCL3 and CCL5 but not to other chemokines (Ref. 69).

Prevention of T-cell death in the CNS?

Animal models of inflammatory disease in the CNS clearly demonstrate that apoptosis is an important factor in the resolution of the inflammatory infiltrate (Ref. 70). Despite this, lymphocyte apoptosis is not a prominent feature in multiple sclerosis lesions (Refs 70, 71). As lymphocytes persist in CNS infiltrates, it is likely that local factors antagonise apoptotic processes; however, the identity of such factors remains the subject of speculation. Osteopontin [also known as early T lymphocyte activation 1 (Eta-1)] has emerged as a likely important player in multiple sclerosis. This protein has multiple roles in the maintenance of tissue homeostasis during inflammatory processes, including macrophage recruitment and differentiation, inhibition of lymphocyte apoptosis and modulation of cytokine responses (Ref. 72). Two recent studies have demonstrated that osteopontin is present in the CNS lesions in multiple sclerosis and experimental autoimmune encephalomyelitis, and plays an important role in sustaining autoimmune destruction (Refs 73, 74). In view of the many physiological roles for this agent, the mechanism of action remains speculative. It is tempting to consider that the established anti-apoptotic actions of osteopontin also act to modulate lymphocyte survival in the CNS.

Research in progress and outstanding questions

Some common themes clearly emerge from these studies. Chronically inflamed tissues often contain lymphoid aggregates that share structural and functional features of secondary lymphoid tissues, with lymphoid follicles with GC reactions found in a range of conditions including rheumatoid arthritis and Sjögren's syndrome (Refs 58, 75, 76, 77). The development of tertiary lymphoid tissue shares common mechanisms with the development of lymphoid organs. Experiments using transgenic mice point to a pivotal role for LT-α and its interaction with the TNF receptor TNFR1 in the generation of lymph-node-like structures in non-lymphoid tissues (Ref. 78). This leads to the ectopic expression of SLC and BCA-1 and the formation of persistent inflammatory infiltrates (Refs 77, 79). As a result of this research, the inhibition of constitutive chemokines and their receptors is now providing a powerful new target for anti-inflammatory therapies (Refs 44, 80, 81).

The transition from an acute inflammatory response to long-lived acquired immunity is a critical time for the immune system. Two potentially competing processes occur in the

inflammatory microenvironment. To generate a productive response to antigen, immature dendritic cells must sample antigen within inflamed tissue and migrate to draining lymph nodes for antigen presentation to T cells (Ref. 82). Simultaneously, a range of stromal-tissue-derived tissue repair mediators bathe the inflammatory microenvironment. When these two processes become subverted, the wrong cells (dendritic cells / lymphocytes) accumulate in the wrong place (tissue) at the wrong time (during the resolution phase of inflammation). Chronically inflamed tissue might then act as a 'foster home' for leukocytes, leading to inappropriate retention and survival (Ref. 29). This might provide a molecular explanation for the powerful effects of anti-TNF-α therapy, since TNF-α is critically involved in the positioning of lymphocytes within tissue (Ref. 83).

Clinical implications

Large numbers of inflammatory mediators have now been identified, and many are attractive candidates for therapeutic manipulation in the treatment of chronic inflammatory diseases. Unfortunately, choosing which specific agent to target is difficult, as the dynamic environment makes it difficult to identify a specific hierarchy. It is easy to antagonise a specific cytokine or chemokine in vitro, when the assay read-out is yet another biological mediator. It is altogether more difficult to design an antagonist that produces predictable biological effects in complex microenvironments in vivo.

Changing the viewpoint and identifying specific architectural features in diseased tissues might be a more productive approach. The presence of lymphoid aggregates in the rheumatoid synovium with architectural features that closely mimic secondary lymphoid tissues implies that therapies should be designed to counteract the formation of such structures. This approach provides an attractive functional explanation for the success of anti-TNF therapy in rheumatoid arthritis, since it has recently been demonstrated that TNF family members are essential for lymph-node development (Refs 55, 84, 85). Anti-TNF therapy would therefore be expected to modulate the microenvironmental processes leading to lymphoid aggregate formation in the synovium.

It is unlikely that anti-TNF therapy will be useful for all chronic inflammatory conditions.

For example, multiple sclerosis forms an interesting therapeutic contrast to rheumatoid arthritis in that several attempts to treat multiple sclerosis by TNF-α blockade worsened disease rather than improved it (Refs 86, 87). The reason for this is unknown, as prior human and animal studies had suggested that TNF was an important proinflammatory mediator in multiple sclerosis (Refs 88, 89). The discrepancy might be explained by the important role of TNF-α in nitric oxide (NO) production, and the appreciation that NO inhibits the proliferation of CNS T cells (Ref. 90). Inhibition of TNF-α would therefore be proinflammatory in the CNS. By contrast, although IFN-β is a licensed immunomodulator in multiple sclerosis, elucidating its mechanism of action has proved difficult because the agent modulates a large number of genes that are potentially relevant to multiple sclerosis (Refs 91, 92). IFN-β certainly increases the number of IFN-γ-secreting cells and IFN-γ is an NO inducer, thus providing a potential microenvironmental explanation for the effect (Refs 93, 94).

These examples highlight how the interplay of complex microenvironmental controls found in tissues can account for apparently contradictory results during clinical trials. Further definition of the hierarchical structures controlling tissue homoeostasis in health and disease will provide numerous exciting avenues for the development of therapies to control chronic inflammatory conditions.

Acknowledgements and funding

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Further reading, resources and contacts

Two reviews highlighting the mechanisms of leukocyte accumulation in inflammatory diseases and possible therapeutic avenues:

Westermann, J., Engelhardt, B. and Hoffmann, J.C. (2001) Migration of T cells in vivo: molecular mechanisms and clinical implications. Ann Intern Med 135, 279-295, PubMed: 21402291

Pope, R.M. (2002) Apoptosis as a therapeutic tool in rheumatoid arthritis. Nat Rev Immunol 2, 527-535, PubMed: 22088851

Review covering many issues in lymphoid homeostasis:

Van Parijs, L. and Abbas, A.K. (1998) Homeostasis and self-tolerance in the immune system: turning lymphocytes off. Science 280, 243-248, PubMed: 98202600

The Chemokine Website (Kumamoto Univeristy School of Medicine, Japan) is frequently updated and provides links to database resources:

http://cytokine.medic.kumamoto-u.ac.jp/CFC/CK/chemokine.html

Some of the concepts in this article are highlighted at the Birmingham Department of Rheumatology website:

http://rheuma.bham.ac.uk/NewSite/department/site.htm

Features associated with this article

Figures
Figure 1. Two switches are involved in the development of persistent chronic inflammation (fig001cbb).
Figure 2. Chemokine receptors and chemokine ligand specificity (fig002cbb).
Figure 3. The dynamics of an inflammatory infiltrate (fig003cbb).
Figure 4. Chronic inflammatory microenvironments mimic lymphoid tissue (fig004cbb).

Table
Table 1. Chemokine nomenclature (tab001cbb)

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