

Inflammatory bowel disease

# Chemokines in inflammatory bowel disease

S Danese, A Gasbarrini

## Guilty of fatal attraction

Chemokines (chemotactic cytokines) are small (7–10 kDa) heparin binding proteins that govern the migration of circulating leucocytes to the sites of inflammation.<sup>1</sup> Chemokines, currently numbering more than 50, are classified into four supergene families based on cysteine residues: CXC, CC, C, and CX3C chemokines (table 1).<sup>2</sup> Chemokines are distinguished from other cytokines by acting on the G protein coupled serpentine receptors.<sup>2</sup>

Chemokines are classified into constitutively secreted and inducible.<sup>3</sup> Those that are constitutively secreted are homeostatic chemokines directing basal leucocyte trafficking and the organisation of the lymphoid tissue. Inducible chemokines are inflammatory molecules responsible for mediating the recruitment of leucocyte effector populations to the sites of immune reaction and tissue injury.<sup>3</sup>

“Aberrant leucocyte chemoattraction occurs in chronic inflammatory diseases and is characterised by an excessive recruitment of inflammatory cells into the injured tissue”

The biological effects of chemokines are achieved by their interaction with specific receptors on the surface of the target cells. There are a few receptors that bind a single ligand, whereas several chemokines can bind to more than one receptor (table 1).

Aberrant leucocyte chemoattraction occurs in chronic inflammatory diseases and is characterised by an excessive recruitment of inflammatory cells into the injured tissue. In such processes, chemokines tightly control the multistep paradigm of leucocyte adhesion and migration across the endothelium (fig 1).<sup>4</sup> Ligation of chemokines to their receptors increases the affinity/avidity of leucocyte integrins for cell adhesion molecules, resulting in the switch from leucocyte rolling to firm arrest on the endothelial surface.<sup>4</sup> Chemokines that regulate leucocyte firm adhesion are mainly produced by endothelial cells, interstitial cells, or rolling platelets.

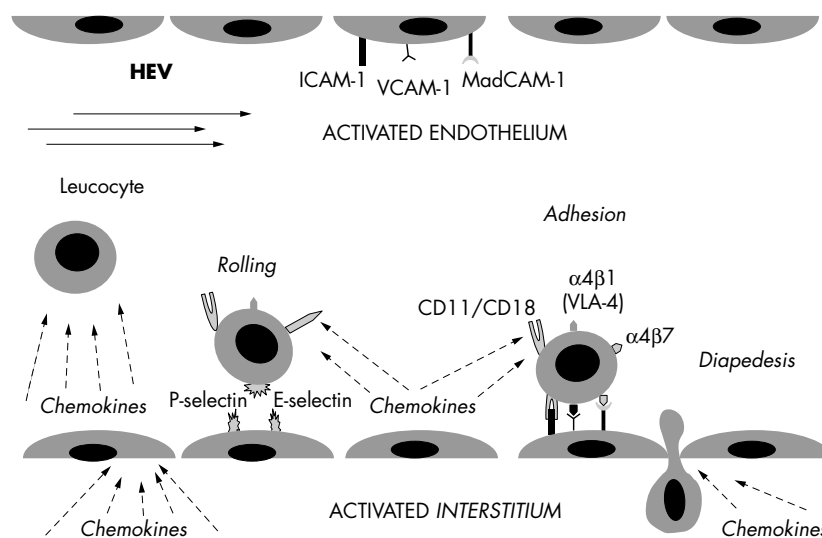
Subsequently, the adhering leucocytes move across the endothelial barrier following a chemokine gradient produced by interstitial cells, which act as a satellite system providing crucial driving directions out from the vascular bed.<sup>1, 4</sup>

Aberrant leucocyte chemoattraction probably occurs in all forms of tissue inflammation, including inflammation of the gut mucosa, because it is seen in Crohn’s disease (CD) and ulcerative colitis (UC), the two major forms of inflammatory bowel disease (IBD).<sup>5</sup> Although their aetiology is still unknown, in the past few years there have been great advances in the knowledge of the mediators that sustain chronic inflammation. In particular, it is now well established that chemokines play a central role in the pathogenesis of both forms of IBD, and are able to trigger multiple inflammatory actions including leucocyte activation and chemoattraction, granule exocytosis, production of metalloproteinases for matrix degradation, and upregulation of the oxidative burst.<sup>6, 7</sup>

Several chemokines have been investigated in both CD and UC, and their

expression is consistently increased during the active phases of the disease.<sup>6, 7</sup> In particular, interleukin 8 and its receptor are upregulated, as are monocyte chemoattractant proteins 1 and 3, epithelial neutrophil activating protein 78, macrophage inflammatory proteins 1 $\alpha$  and 1 $\beta$ , interferon inducible protein 10, stromal cell derived factor 1, and fractalkine.<sup>8–13</sup> Of particular interest is the demonstration that RANTES (regulated on activation normal T cell expressed and excreted) expression is not only increased in human IBD, but has also been shown to play a crucial role in the transition from acute to chronic disease in experimental models of colitis, and to trigger leucocyte adhesion to the inflamed intestinal microvasculature.<sup>14–16</sup> Moreover, some chemokines may be crucially relevant for regional specialisation of intestinal immunity. A clear example has been provided by the demonstration that thymus expressed chemokine is expressed exclusively in the small bowel but not in the colon.<sup>17</sup> Furthermore, only lamina propria mononuclear cells resident in the small intestine express its receptor CCR9, thus providing direct evidence of a small intestinal “address code” for memory T cell homing.<sup>18</sup>

Among the many chemokines studied in IBD, almost no information exists regarding the expression of Epstein-Barr virus induced molecule-1 ligand chemokine (ELC/CCL19) and secondary lymphoid organ chemokine (SLC/CCL21), both belonging to the CC chemokine family. In this issue of the *Journal of Clinical Pathology*, Kawashima *et al* investigate the expression of both molecules and their unique receptor CCR7 in CD and UC.<sup>19</sup> The authors find that CD



**Figure 1** Chemokines in the multistep process of leucocyte adhesion. ICAM-1, intercellular adhesion molecule 1; MadCAM-1, mucosal addressin cell adhesion molecule 1; VLA-4, very late antigen 4; VCAM-1, vascular cell adhesion molecule 1.

**Table 1** C, CC, CXC, and CX3C chemokine/receptor families

Systemic name	Classic name	Receptor
C chemokine family		
XCL1	Lymphotactin	XCR1
XCL2	SCM1- $\alpha$	XCR1
CC chemokine family		
CCL1	I-309	CCR8
CCL2	MCP-1	CCR2
CCL3	MIP-1 $\alpha$	CCR1, CCR5
CCL4	MIP-1 $\beta$	CCR5
CCL5	RANTES	CCR1, CCR3, CCR5
CCL6	Unknown	Unknown
CCL6	Unknown	Unknown
CCL7	MCP-3	CCR1, CCR2, CCR3
CCL8	MCP-2	CCR3
CCL9	Unknown	Unknown
CCL10	Unknown	Unknown
CCL11	Eotaxin	CCR3
CCL12	Unknown	CCR2
CCL13	MCP-4	CCR2, CCR3
CCL14	HCC-1	CCR1
CCL15	HCC-2	CCR1, CCR3
CCL16	HCC-4	CCR1
CCL17	TARC	CCR4
CCL18	DC-CK1	Unknown
CCL19	ELC	CCR7
CCL20	MIP-3 $\alpha$	CCR6
CCL21	SLC	CCR7
CCL22	MDC	CCR4
CCL23	MPIF-1	CCR1
CCL24	MPIF-2	CCR3
CCL25	TECK	CCR9
CCL26	Eotaxin-3	CCR3
CCL27	CTACK	CCR10
CCL28	MEC	CCR10
CXC chemokine family		
CXCL1	GRO $\alpha$	CXCR2
CXCL2	GRO $\beta$	CXCR2
CXCL3	GRO $\gamma$	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-1 $\alpha$ , SDF-1 $\beta$	CXCR4
CXCL13	BCA-1	CXCR5
CXCL14	BRAK	Unknown
CXCL15	Unknown	Unknown
CXCL16	Unknown	CXCR6
CX3C chemokine family		
CX3CL1	Fractalkine	CX3CR1

BCA-1, B cell attracting chemokine 1; BRAK, breast and kidney cell chemokine; CTACK, cutaneous T cell attracting chemokine; DC-CK1, dendritic cell derived chemokine 1; ELC, EB1 ligand chemokine; ENA-78, epithelial neutrophil activating protein 78; GCP-2, granulocyte chemotactic protein 2; GRO, growth regulated oncogene; HCC, hepatocellular carcinoma; IL-8, interleukin 8; IP-10, interferon inducible protein 10; I-TAC, interferon inducible T cell chemoattractant; MCP, monocyte chemotactic protein; MDC, macrophage derived chemokine; MEC, mammary enriched chemokine; MIG, monokine induced by interferon  $\gamma$ ; MIP, macrophage inflammatory protein; NAP-2, neutrophil activating protein 2; PF4, platelet factor 4; RANTES, regulated on activation normal T cell expressed and excreted; SCM1 $\alpha$ , single C motif 1 $\alpha$ ; SDF, stromal cell derived factor; SLC, secondary lymphoid tissue chemokine; TARC, thymus and activation regulated chemokine; TECK, thymus expressed chemokine.

mesenteric lymph nodes show increased expression of both SLC and ELC by immunohistochemistry. Furthermore, the cells displaying intense immunoreactivity were identified as high endothelial venules, dendritic cells, and lymphatic vessels, because of their colocalisation with the specific markers HECA452, CD83, and VEGFR3, respectively. In addition, Kawashima *et al* found a significant increase of the CCR7 receptor in CD but not in UC or

healthy subjects, consistent with their observation of augmented CC ligand expression in CD.<sup>19</sup> Although the function of ELC and SLC is not known, the authors show immunoreactivity for the two chemokines predominantly in CD T cell lymph node areas, thus suggesting a role for T helper type 1 polarisation in the lymph node through the interactions between ELC and SLC positive high endothelial venule or dendritic cells and positive CCR7 T cells.

"In Crohn's disease both SLC and ELC and their CCR7 receptor are significantly overexpressed, leading to the hypothesis of a pathological role of these mediators in intestinal inflammation"

SLC and ELC are classified as constitutive chemokines.<sup>2,20</sup> In particular, these two molecules are crucially relevant for the physiological development of lymph nodes and Peyer's patches.<sup>20,21</sup> Very recently, in addition to this classic task, a growing body of evidence has revealed that both SLC and ELC are significantly upregulated in chronic inflammatory conditions and may play a role in the pathogenesis of multiple diseases.<sup>20</sup> In particular, SLC is responsible for leucocyte chemoattraction during renal inflammation, and the administration of a specific blocking antibody directed against SLC improved the survival of mesangial cells, suggesting a crucial effect of SLC in modulating kidney inflammatory processes.<sup>22</sup> Similarly, SLC expression was found to be significantly increased in chronic liver disease and was selectively chemoattractive for CCR7 positive T cells, thus promoting the inflammatory response and fibrosis during chronic hepatitis.<sup>23</sup> In addition, both ELC and SLC are upregulated in the central nervous system and play a crucial role in the attraction of encephalitogenic T cells during experimental autoimmune encephalomyelitis and in various inflammatory diseases of the central nervous system.<sup>24</sup>

Consistent with these observations, in CD both SLC and ELC and their CCR7 receptor are significantly overexpressed, leading to the hypothesis of a pathological role of these mediators in intestinal inflammation. Because many chemokines and their receptors have been successfully targeted for therapeutic intervention in several chronic inflammatory diseases, it would be useful to evaluate the clinical impact of SLC and ELC blockade in CD.<sup>25</sup> Knowledge of the functional role of SLC and ELC and its potential relevance for IBD treatment would help us to understand whether their overexpression is just an epiphenomenon, or whether they play a key pathogenic role in gut inflammation, because they are guilty of the chemoattraction of pathogenic leucocytes into the gut.

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