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The role of chemokines in B cell chronic lymphocytic leukaemia: pathophysiological aspects and clinical impact

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Abstract Chemokines are centrally involved in leukocyte migration, homing and haematopoiesis. Besides these physiological aspects, their role in pathological processes especially with respect to solid tumour and haematological neoplasias is well established. In this context, the focus was set here on disclosing their contribution in B cell chronic lymphocytic leukaemia (B-CLL), which is regarded as the most characteristic low-grade lymphoma. Up to now, it has been demonstrated that several chemokines are involved in migration of B-CLL cells to lymph nodes, secondary lymphoid organs and bone marrow. Moreover, some chemokines are known to have an anti-apoptotic effect and thus contribute to the survival of B-CLL cells. By interfering with both of these aspects, new therapeutic targets for this yet incurable disease may be developed. Furthermore, a correlation can be drawn between the concentration of some chemokines in patients' serum, the expression of their respective receptors on B-CLL cells and well-established predictive clinical parameters. Consequently, further systematic investigation of the chemokine network may lead to the identification of new diagnostic and prognostic markers. This review focuses on the impact of chemokines and their receptors on B-CLL pathophysiology and points out potential implications for both treatment and diagnosis.

Keywords B cell chronic lymphocytic leukaemia (B-CLL) · Chemokines · Pathophysiology · Clinical impact

Introduction

Chemokines constitute the growing family of chemotactic cytokines that are generally involved in leukocyte migration. According to a current classification based on their function, they are subdivided into three different groups: (1) the homeostatic chemokines regulating lymphocyte migration and homing processes under physiological conditions, (2) the inducible chemokines expressed during inflammation and (3) an overlapping group involved in both processes. Their expression can be induced by various stimuli, including growth factors and inflammatory cytokines [1, 2]. Besides these general aspects, chemokines are also associated to a variety of pathological processes. During tumourigenesis, they are known to play a crucial role in forming and modifying the tumour stroma by inducing the infiltration of various hematopoietic cells (e.g. macrophages, natural killer (NK) cells, eosinophils, B and T lymphocytes) as well as fibroblasts and endothelial cells. They also contribute to the neovascularisation, the growth and the spreading of tumours [2, 3]. Due to their decisive role in both haematopoiesis and haematopoietic cell migration, efforts have been made over the last years to uncover their role in haematological neoplasias [4–7]. In this context, a special focus was set here on B cell chronic lymphocytic leukaemia (B-CLL) which is the most common low-grade lymphoma in Europe and the USA. It is characterised by small monoclonal, mature, but functionally

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incompetent B cells that are not only detectable in the peripheral blood (PB) but also in secondary lymphoid organs and bone marrow (BM) [8, 9]. Besides supporting the proliferation and migration of these neoplastic cells to the BM and secondary lymphoid tissues, it has been demonstrated that chemokines can prevent B-CLL cells from undergoing spontaneous apoptosis, thus supporting their survival *in vitro*. For this reason, therapeutic targeting of chemokine activity has become the focus of extensive pharmaceutical research [10–12]. B-CLL cells possess a characteristic chemokine receptor profile; hence, receptor inhibition could function as a promising tool for treatment [13]. In addition, since the expression of some chemokines and chemokine receptors correlates with important and well-established predictive clinical parameters, they might be implemented as new diagnostic markers [14–18]. In the following, the different aspects of selected chemokine receptors and ligands and their involvement in B-CLL pathophysiology will be illustrated, including the support of homing, retention and survival in tissue microenvironments and the induction of resistance to spontaneous and chemotherapy-induced apoptosis. This review focuses on the impact of selected and most relevant chemokines and their respective receptors on the pathophysiology of B-CLL and points out clinical implications for both diagnosis and treatment.

CXCL12 (SDF-1) and its receptor CXCR4

The homeostatic chemokine CXCL12 is the sole ligand of the receptor CXCR4 [1]. CXCR4 is expressed on most haematopoietic cells (neutrophils, monocytes/macrophages, both mature and immature T and B lymphocytes, CD34⁺ progenitor cells from PB and BM, blood-derived dendritic cells (DC) and Langerhans cells) and various non-hematopoietic cells (e.g. neurons and vascular endothelial cells; for review [1]). It is known to be lethal in knockout mice, underlying its essential role in embryo development [19–21]. Its involvement in mediating the migration of hematopoietic cells and B cell development is well established. Since CXCR4 is expressed as a functional receptor on B-CLL cells, it is responsible for directing them to the BM environment (Fig. 1) [4, 10, 22–26]. Moreover, CXCL12 has been shown to have anti-apoptotic effects on B-CLL cells and therefore confers protection from spontaneous and chemotherapy (fludarabine)-induced apoptosis in a contact-dependent fashion via stromal cells or nurse-like cells. This effect can be inhibited by CXCR4 antagonists, suggesting a new therapeutic target (Table 1) [10, 27]. To date, various strategies, including small peptide (e.g. T140) and non-peptide CXCR4 antagonists (e.g. AMD3100) already being tested for hematopoietic stem cell mobilisa-

tion [28], anti-human CXCR4 or CXCL12 antibodies and modified CXCL12 peptides (e.g. CTCE-9908 or CTCE-0214), have been tested to inhibit this pathway [29–31]. Up to now, CXCR4 antagonism is the most relevant and advanced chemokine antagonism envisioned in B-CLL treatment. Although B-CLL cells are thought to be arrested at the G0/earlyG1 phase of the cell cycle, it was demonstrated that about 1% of all B-CLL cells are indeed in active stages. These cells are mostly found in specific microenvironmental structures, known as pseudofollicles or proliferation centres in the BM or the lymph nodes (LN). CXCR4 was shown to be down-regulated in the B-CLL cells entering the cell cycle. For this reason, Bennett et al. [32] suggested that CXCR4 inhibitors should be combined with agents that can target CLL cells already bound to stromal cells. Another interesting pathomechanism that could be targeted by CXCR4 antagonism was described by Redondo-Muñoz et al. [33]. They identified the metalloproteinase-9 (MMP-9), for which expression is up-regulated by CXCL12, as an important protein for trans-endothelial migration (TEM) of B-CLL cells through basement membranes. CXCR4 and CXCL12 have been correlated to established clinical parameters including Rai stages [15]. However, other groups did not find any correlation between CXCR4 or CXCL12 expression and clinical stage of disease or the pattern of BM infiltration, but were able to correlate CXCR4 expression to the leukocyte count [34, 35]. Interestingly, in one study, B-CLL patients showed lower CXCL12 plasma levels compared to those of healthy donors [34]. Moreover, Richardson et al. [36] reported that following co-culture with nurse-like cells, the survival of cells positive for the tyrosine kinase ZAP70, an established and reliable prognostic marker, was significantly enhanced by the addition of CXCL12 compared to cells lacking ZAP70. Taken together, CXCR4 and its ligand CXCL12 are promising targets for new therapeutic options that would inhibit both anti-apoptotic and migratory properties. With one antagonist already in use in another context, this chemokine receptor/ligand pair is also the most promising target for the near future. However, since CXCR4 is broadly expressed on B cells and the studies exposed here remain contradictory [15, 34], the use of CXCR4 as diagnostic or prognostic factor is still under evaluation.

CXCL8 (IL-8) and its receptors CXCR1 and CXCR2

CXCL8 is a potent inflammatory chemokine involved in the chemoattraction of polymorphonuclear leukocytes. CXCR1 and CXCR2, the two receptors for CXCL8, play important roles in acute inflammation and innate immunity. Both are mainly expressed by macrophages and neutro-

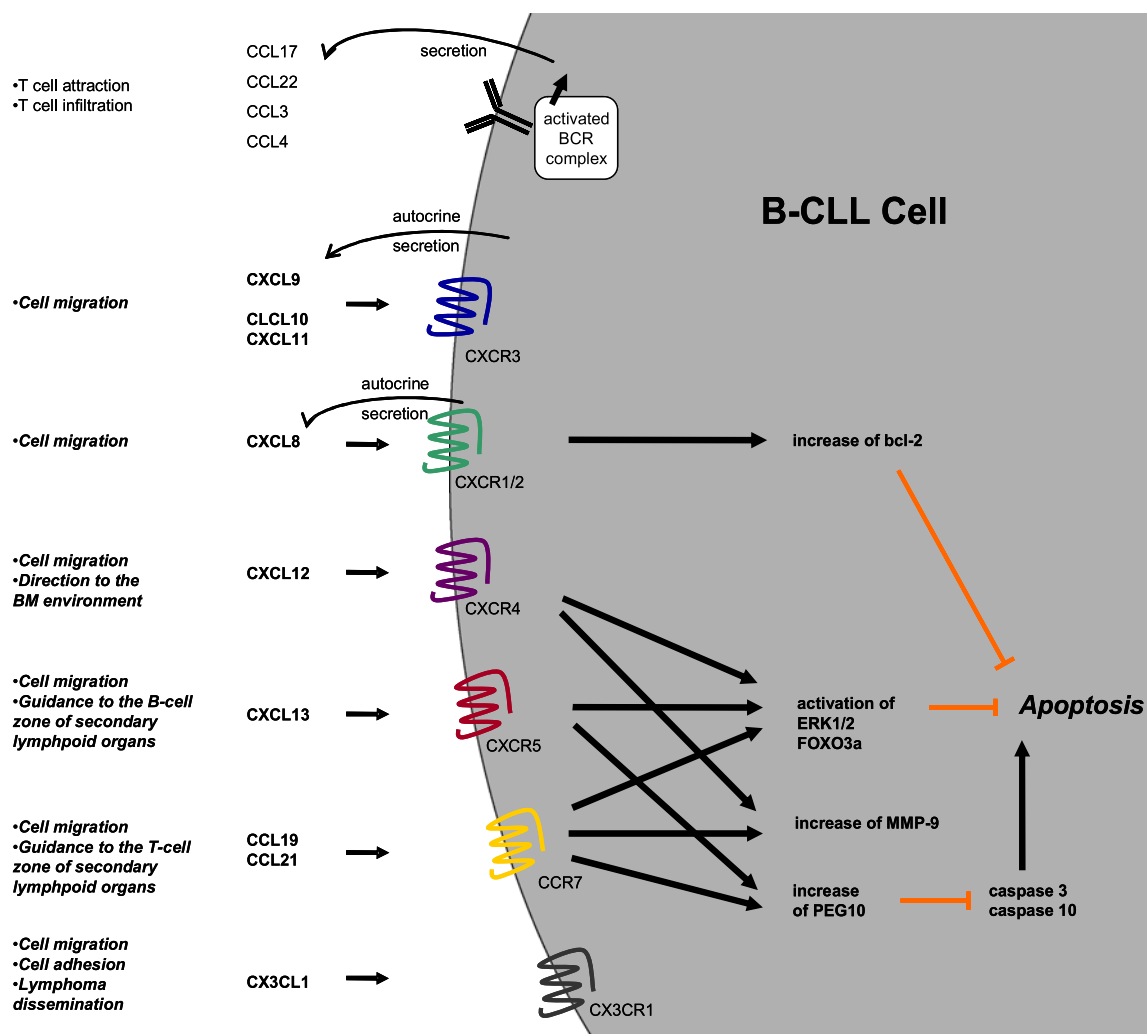


Fig. 1 Chemokines and their receptors known to be involved in B-CLL pathophysiology. CLL cells express the chemokine receptors shown, and the influence their activation has on the cells is shown on both the molecular level and on migration and positioning

phils, but can also be detected on cytokine-activated eosinophils, basophils, T lymphocytes, mast cells and DCs. Mediating cell migration might be the most important function of these receptors upon stimulation with their main ligand CXCL8. Di Celle et al. reported that B-CLL cells constitutively express CXCL8 as well as the corresponding receptors (Fig. 1). Therefore, a both autocrine and paracrine way of stimulation by CXCL8 is suggested. In addition, they compared the CXCL8 release of B-CLL cells with that of unstimulated CD5⁺ tonsillar B cells which are commonly seen as the normal counterparts of B-CLL cells. Since the CXCL8 release in B-CLL cells was significantly higher, they assumed that CXCL8 expression might be representative of the activation state of the leukemic clone. Furthermore (due to a lack of CXCL8 expression on other haematological neoplasias like hairy cell leukaemia and B cell lines NALM-6, K422, Daudi and Raji), they suggested a central role for this chemokine in the CD5⁺ cells [37, 38].

Up to now, various additional ways of stimulating CXCL8 release in B-CLL cells have been described: (1) activation of CD74 by its ligand macrophage migration inhibitory factor [11], (2) via the surface-expressed RANKL/RANK system (shown by induction by a RANK-Fc chimera) [39] and (3) via recombinant TRAIL [40]. Stimulation by CXCL8 leads to an increase of the expression of anti-apoptotic protein bcl-2 and thus contributes to the survival of B-CLL cells (Table 1) [38]. In fact, recombinant CXCL8 was shown to protect B-CLL cells from cytotoxic effects caused by the cytostatic drugs chlorambucil and fludarabine [39]. Several approaches to inhibit CXCR1 and CXCR2 have been undertaken, mostly in the context of inflammation in airway diseases, with proven efficacy in several animal models and ongoing phase II clinical trials for chronic obstructive pulmonary disease [41–45]. To date, there is no report on CXCR1/CXCR2 inhibition in B-CLL. Nevertheless, CXCL8 serum levels were found to correlate

Table 1 Pathophysiological aspects and therapeutic approaches

Chemokine	Corresponding receptors	Pathophysiological mechanism	Possible therapeutic target	References
CXCL8	CXCR1 and CXCR2	Inhibition of apoptosis by up-regulation of bcl-2	Inhibition of CXCL8 pathway Inhibition of RANK/RANKL dependent CXCL8 release Inhibition of CD74-dependent CXCL8 release	Binsky et al. [11] Secchiero et al. [39] Wierda et al. [47] Molica et al. [48] di Celle et al. [37, 38]
CXCL12	CXCR4	Contact-dependent inhibition of apoptosis B-CLL migration and homing	Inhibition of CXCL12/CXCR4 interaction	Bennett et al. [32] Zeng et al. [27] Burger et al. [10] Burger et al. [23] Ticchioni et al. [56]
		Infiltration by MMP-9	Inhibition of CXCL12/CXCR4 interaction	Redondo-Muñoz et al. [33]
CXCL13	CXCR5	Inhibition of apoptosis	Inhibition of CXCL13/CXCR5 interaction	Chunsong et al. [55] Hu et al. [12]
CCL21				Ticchioni et al. [56]
CCL19	CCR7	Inhibition of apoptosis	Inhibition of CCL21/CCR7 interaction	Redondo-Muñoz et al. [33] Ticchioni et al. [56] Gary-Gouy et al. [61]
		Enhanced responsiveness to the ligands after CD5 phosphorylation	Inhibition of CD5 phosphorylation Anti-CCR7 antibody	Alfonso-Perez et al. [13]
CX3CL1	CX3CR1	Involvement in lymphoma dissemination		Andreasson et al. [71]
CXCL8	CXCR1 and CXCR2	Inhibition of apoptosis by up-regulation of bcl-2	Inhibition of CXCL8 pathway Inhibition of RANK/RANKL-dependent CXCL8 release Inhibition of CD74-dependent CXCL8 release	Binsky et al. [11] Secchiero et al. [39] Wierda et al. [47] Molica et al. [48] di Celle et al. [37, 38]
CXCL12	CXCR4	Contact-dependent inhibition of apoptosis B-CLL migration and homing	Inhibition of CXCL12/CXCR4 interaction	Bennett et al. [32] Zeng et al. [27] Burger et al. [10] Burger et al. [23] Ticchioni et al. [56]
		Infiltration by MMP-9	Inhibition of CXCL12/CXCR4 interaction	Redondo-Muñoz et al. [33]
CXCL13	CXCR5	Inhibition of apoptosis	Inhibition of CXCL13/CXCR5 interaction	Chunsong et al. [55] Hu et al. [12]
CCL21				Ticchioni et al. [56]
CCL19	CCR7	Inhibition of apoptosis	Inhibition of CCL21/CCR7 interaction	Redondo-Muñoz et al. [33] Ticchioni et al. [56] Gary-Gouy et al. [61]
		Enhanced responsiveness to the ligands after CD5 phosphorylation	Inhibition of CD5 phosphorylation Anti-CCR7 antibody	Alfonso-Perez et al. [13]
CX3CL1	CX3CR1	Involvement in lymphoma dissemination		Andreasson et al. [71]

with important clinical features, such as β 2-microglobulin (β 2-MG) and the stages of the Rai classification (Table 2) [41, 42]. In contrast, another study performed by Molica et al. failed to correlate any of the clinico-biological features (like β 2-MG, BM involvement or clinical stage) with CXCL8 serum levels [46], although elevated CXCL8 serum levels were associated with significantly shorter survival, progress to a more advanced clinical stage of disease and increased activity of the leukemic clone [46–48]. Taken together, inhibiting the impact of CXCL8 on B-CLL cells could lead to novel concepts of therapeutic intervention with an expected impact on cell survival. However, CXCL8 will still have to be investigated in further going studies before being considered as a novel prognostic marker.

CXCL13 and its receptor CXCR5

Only one ligand, the homeostatic chemokine CXCL13, has been identified to bind to CXCR5 [1]. It is selectively and constitutively expressed in secondary lymphoid organs. The receptor CXCR5 plays an important role both in lymphocyte homing and lymphoid tissue development [1, 49, 50].

It is expressed in cord blood (CB), on haematopoietic cells, in BM B cells and PB B cells, but can also be detected on a small subset of PBT cells ($CD4^+$ and $CD8^+$). CXCL13 seems to have a major impact on guiding B cells into the B cell zone of secondary lymphoid tissues and, together with CCR7, ensures the close contact between T and B cells necessary for B cell activation (Fig. 1) [51]. CXCR5 is also expressed as a functional receptor on B-CLL cells. For this reason, the interaction of B-CLL with CXCL13 expressing cells (e.g. $CD68^+$ macrophages in lymphoid tissues, follicular dendritic cells or nurse-like cells) might have an impact on B-CLL cell positioning in lymphoid tissues. In addition, CXCL13 was found to be significantly elevated in serum of B-CLL patients and seems to correlate with β 2-microglobulin serum levels [52–54]. Furthermore, the CXCL13/CXCR5 axis has been demonstrated to be part of an interesting mechanism of apoptosis inhibition in B-CLL cells: CXCL13/CXCR5, together with CCL19/CCR7, enhance the expression of the paternally expressed gene 10 (PEG10) in $CD23^+ CD5^+ CB$ cells, B-CLL cells, as well as $CD19^+ CD34^+ B$ cells. By up-regulating this protein, caspase-3 and caspase-8 (which are normally pro-apoptotic proteins) are stabilised and thus prevented from degradation,

Table 2 Chemokine receptors and chemokines as diagnostic tools

Chemokines	Corresponding receptors	Prognostic marker	Correlation with clinical parameter	Possible diagnostic usage	Reference
CXCL8	CXCR1 and CXCR2	Ligand (CXCL8)	Correlation of elevated serum levels of CXCL8 with β 2-microglobulin serum levels, Rai stages	Prognostic marker Marker for disease progression in early stages	Kara et al. [17] Wierda et al. [47] Molica et al. [48]
CXCL9 CXCL10 CXCL11	CXCR3	Receptor (CXCR3)	Correlation of low CXCR3 expression with advanced Rai stages, high CD38, unmutated IgV_H , shorter overall survival	Prognostic marker	Ocaña et al. [16]
CXCL9		Receptor (CXCR3) Ligand (CXCL9)	Co-expression on B-CLL cells	Marker for differential diagnosis in small cell lymphomas	Ocaña et al. [16]
CXCL12	CXCR4	Receptor (CXCR4)	Correlation of CXCR4 expression with Rai stages	Prognostic marker	Ghobrial et al. [15]
CXCL13	CXCR5	Ligand (CXCL13)	Correlation of elevated serum levels of CXCL13 with β 2-microglobulin serum levels	Prognostic marker	Bürkle et al. [52]
CCL19 CCL21	CCR7	Receptor (CCR7)	Correlation of CCR7 expression with Rai stages	Prognostic marker	Ghobrial et al. [15]
CX3CL1	CX3CR1	Ligand (CX3CL1)	Detectable serum levels of CX3CL1 correlate with shorter time to treatment	Prognostic marker in early stages	Morabito et al. [14]
		Receptor (CX3CR1)	Correlation to ZAP70 expression and therefore to unmutated VH status	Prognostic marker	Ferrer et al. [70]

leading to an inhibition of TNF alpha-induced apoptosis (Table 1) [12, 55]. Ticchioni et al. [56] also demonstrated that CXCL13 is involved in inhibiting apoptosis by inducing ERK1/2 and Akt/GSK3 pathways.

CCL19, CCL21 and their common receptor CCR7

CCL19 and CCL21 are expressed in the T cell zone of secondary lymphoid, mucosa-associated lymphoid tissue and high endothelial venules, but not in the B cell areas or sinuses or blood-derived leukocytes [54]. They are the known ligands of the chemokine receptor CCR7 which is a crucial receptor for trafficking of B lymphocytes as well as T lymphocytes and DCs across high endothelial venules and for positioning in T cell zones of secondary lymphoid organs (Fig. 1) [57]. Although it is predominantly expressed on naïve T lymphocytes, CCR7 is also detectable on B lymphocytes (on which it was initially identified) [1, 58, 59]. CCR7 also has been demonstrated to have a great impact on the development of secondary lymphoid organs [60, 61]. Till et al. [60] demonstrated that due to increased CCR7 expression on B-CLL cells and CCL19 and CCL21 expression in high endothelial venules, TEM was significantly higher for malignant B cells of patients with LN involvement compared to those without this organomegaly. CCL21 binding to CCR7 activates the ERK1/2 and c-Fos pathway, leading to an increased expression of MMP-9 in infiltrating B-CLL cells (Fig. 1), which in turn facilitates TEM and invasion through basement membranes [33, 60]. Another interesting observation was reported by Richardson et al. [36] who identified an enhanced expression of CCR7 on ZAP70(+) B-CLL cells, leading to an increased responsiveness of CCR7 to its ligands CCL19 and CCL21. Gary-Gouy et al. [61] found that CD5 phosphorylation may lead to an additional expression increase of CCR7 on B-CLL cells. Furthermore, Ticchioni et al. [56] found that CCL19 and CCL21 contribute to prolonged survival of B-CLL cells by activating ERK1/2 and Akt. By inhibition of these pathways, B-CLL cells were no longer protected from undergoing apoptosis. Due to the high surface expression and tissue specificity of CCR7 in B-CLL cells, Alfonso-Perez et al. [13] proposed a murine anti-CCR7 monoclonal antibody as a new therapeutic agent. They report on a potent, complement-dependent cytotoxicity against B-CLL cells whilst sparing normal T lymphocytes from the same patient. These antibodies blocked the *in vitro* migration of CLL cells in response to CCL19, indicating that a chimeric or humanised anti-CCR7 antibody may also lead to a good clinical response in B-CLL treatment (Table 1). Ghobrial et al. [15] were able to correlate CCR7 expression levels with Rai stages, suggesting CCR7 as a novel prognostic marker in B-CLL (Table 2).

CXCL9, CXCL10, CXCL11 and their common receptor CXCR3

Three ligands bind to the chemokine receptor CXCR3: CXCL9, CXCL10 and CXCL11 [1, 50, 52]. Their best known function is the induction of the expression of Th1 cytokines. The chemokine receptor CXCR3 is expressed on activated T (Th1) cells and NK cells, but is also detected on a subset of circulating PB cells, macrophages and DCs [1, 35, 62, 63]. As a functional receptor expressed to a great extent on B-CLL cells (Fig. 1), CXCR3 supports the trafficking and spreading of malignant cells [18, 35, 63]. Interestingly, one ligand, CXCL9, was found to be expressed by the leukemic cells themselves, indicating an autocrine besides a paracrine way of neoplastic growth stimulation [18]. Conversely, CXCL9 and CXCL10 are also known to share some anti-tumour effects (e.g. inhibition of neovascularisation and progenitor cells) [64]. Antagonising CXCR3-dependent pathways has been shown to have therapeutic effects in different diseases (e.g. cardiovascular disorders, cancer) [65–67]. However, due to insufficient efficacy, some of the antagonists had to be withdrawn from active trials, and new antagonists are currently being developed [65]. There is no report on the application of CXCR3 antagonists in B-CLL so far. Ocaña et al. [16] were the first to correlate CXCR3 expression with clinical parameters. They found that low CXCR3 expression corresponded with advanced disease stages (Rai III and Rai IV), unmutated IgVH status, high CD38 expression and a shorter overall survival in these patients. In multivariate analyses, they could identify low CXCR3 expression as an independent predictor of poor outcome in B-CLL [16]. Since CXCR3 is expressed only by few haematological neoplasias, it could additionally function as an appropriate marker for haematological differential diagnosis (Table 2) [18]. However, the correlation of CXCR3 expression on B-CLL cells and Rai stages or leukocyte count could not be confirmed by Dao-Ung et al. [35]. The importance of CXCR3 involvement therefore remains controversial but definitely deserves further elucidation.

CX3CL1 and its receptor CX3CR1

CX3CL1 (fractalkine), which is expressed by neurons and endothelial cells, is the only known ligand for the receptor CX3CR1. CX3CR1 is unique among chemokine receptors since it functions directly as a cell–cell adhesion. It is expressed on neutrophils, monocytes, NK cells, T lymphocytes and B-CLL cells, but not on normal B lymphocytes [1, 68, 69]. This chemokine remains unique, being a transmembrane protein able to directly and firmly bind its receptor. According to the study performed by Morabito et

al. [14], CX3CL1 levels correlated with LN involvement measured by computed tomography surveys, and the time to treatment was found to be shorter in patients with detectable serum levels. CX3CL1 could also be used as a predictor of disease progression, especially in earlier stages of disease (Table 2) [14]. In addition, Ferrer et al. correlated CX3CR1 on B-CLL cells with ZAP70 expression [68]. Since ZAP70 is known to be closely correlated to unmutated VH status (which is an established prognostic marker), CX3CR1 might also be regarded as a novel prognostic tool [70]. Furthermore, Andreasson et al. [71] demonstrated that CX3CR1 is expressed on several lymphoma subtypes (including B-CLL cells) and therefore suggests a possible role for this receptor in lymphoma dissemination. CX3CR1 antagonists are currently being developed and may contribute to increasing insight into this chemokine/receptor complex in B-CLL pathophysiology [72, 73].

Other components of the B-CLL microenvironment

In addition to chemokines, there are other components in the B-CLL microenvironment known to play a crucial role in B-CLL pathogenesis and to interfere with chemokine expression. Some aspects dealing directly or indirectly with chemokines are addressed briefly in the following part.

–CD40 is a member of the tumour necrosis factor superfamily and is expressed on all mature B cells, monocytes and DC, but also on endothelial cells within blood vessels [74–76]. Its ligand CD40L (CD154) is a transmembrane protein expressed by various types of cells and tissues and can be detected as a soluble plasma protein (sCD40L). Upon CD40L stimulation, Łuczyński et al. [77] found that B-CLL cells produce the T cell-attracting chemokines CCL17 and CCL22 (detected on mRNA levels and as soluble plasma protein in the case of CCL22). The attracted T cells then induce a strong chemokine production initiated by the leukemic clone, leading to the progressive accumulation of neoplastic cells. According to Ghia et al. [78], T cell-mediated activation is necessary for the proliferation and production of T cell-attracting chemokines that will participate in the long-term support of B-CLL cells by stromal cells in the BM microenvironment. Moreover, recent reports emphasise this special role of T cell-attracting chemokines in the B-CLL context. For example, Burger et al. [79] demonstrated that co-culture with nurse-like cells as well as B cell receptor (BCR) activation induced high-level expression of B cell maturation antigen and the two T cell-specific chemokines CCL3 and CCL4. This was found to correlate with ZAP70 expression, a tyrosine kinase playing an important role in BCR signalling. Secretion of the mentioned chemokines can thus create a dynamic micro-

environment in the lymph nodes by initiating interactions of CLL cells with T cells that ultimately leads to propagation of the CLL clone.

–CD38 is a type II single-chain transmembrane molecule which exists both in a soluble and membrane-bound form. CD38 expression on B-CLL cells is assumed to be an independent and reliable marker for an unfavourable clinical course. It is functionally linked to the tyrosine kinase ZAP70. The interaction of CD38 with the cell-based CD31 ligand (which is expressed by stromal cells or nurse-like cells) has been shown to be crucial for initiating CD38-dependent signals. As a consequence, the CD100 receptor, involved in CLL growth and survival, is up-regulated [80–82]. Chemokines are assumed to play a crucial role in this mechanism, being the ones to guide CD38⁺ cells in the direction of CD31⁺ stromal cells. In line with this, Deaglio et al. [80] demonstrated enhanced migration of CD38⁺ ZAP70⁺ cells towards CXCL12.

Conclusion

It was illustrated here which chemokines play a decisive role in migration of B-CLL cells and contribute to the survival of these neoplastic B cells by maintaining various anti-apoptotic mechanisms (Fig. 1). Some chemokines and chemokine receptors correlate with clinical parameters and therefore may be used as diagnostic and prognostic tools themselves. CXCL12 and its receptor CXCR4 is the best studied chemokine/receptor pair in this respect, and inhibitors of CXCR4 are the only chemokine receptor inhibitors that are under investigation for therapeutic use in clinical trials in B-CLL so far. Inhibitors for other chemokine receptors are still being developed, but in which ways they will live up to the expectations is still under investigation.

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