Motility and trafficking in B-cell non-Hodgkin's lymphoma (Review)

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Abstract. B cell non-Hodgkin's lymphomas (B-NHLs) consist of a wide spectrum of entities and consequently have varied clinical courses. Like many other malignancies, each of the B-NHL depend on their microenvironment for growth and survival; therefore, understanding the factors involved in their tissue localisation is likely to have implications for therapies designed to treat B-NHL. This review summarises the chemokines, integrins and sphingosine-1 phosphate receptors involved in normal B cell location and distribution within the lymphoid tissues (lymph nodes, spleen and bone marrow). It also provides a précis of what is known about these factors in the disease state: i.e., in some subtypes of B-NHL.

Contents

1. Introduction

Lymphocytes are by nature motile cells owing to their pivotal role in immune surveillance. They traffic through the immune tissues in search of the specific antigen that binds to their unique antigen receptor. Binding of antigen to receptor initiates an immune response designed to eliminate the pathogen bearing the antigen. In the case of B cells, when antigen-naïve lymphocytes encounter specific antigens they remain in the lymphoreticular tissues for 2-3 days in order to differentiate into mature effector cells. However, if they do not encounter antigen, they exit the tissues within a matter of hours and continue their search (1,2). The lymphocytes of B-cell lymphomas mostly reside within the tissues and therefore differ from normal B cells in their ability to traffic. Understanding the mechanisms by which these cells are retained in the tissues may therefore open up new avenues for novel therapy aimed at releasing the malignant lymphocytes from their tissue microenvironment and, in doing so deprive them of stimuli required for their growth and survival.

2. Normal B cells

The factors controlling the trafficking of normal B lymphocytes into, within and out of tissues have been extensively studied (Fig. 1; Table I). Entry of lymphocytes into the tissues is under the control of chemokines (3,4) and adhesion molecules, whereas exit (egress) is dependent on the sphingolipid, sphingosine-1-phosphate and its receptors S1PR1 and S1PR3 and is independent of adhesion molecules (5,6). Whether or not a lymphocyte remains in or exits the lymphoreticular system, as well as its localisation within lymphoreticular tissues, is determined by the balance of chemokines, S1P receptors and adhesion molecules. With regard to chemokines involved in the trafficking of normal B cells, CCR7 and its ligand CCL21 control entry into lymph nodes (7), whereas CXCR5 and its ligand CXCL13 direct B lymphocytes into the follicular area of LNs (7,8) and the white pulp of the spleen (8) and contributes to the retention of B cells at these sites. Finally, CXCR4 and its ligand CXCL12 are involved in the homing and retention of B lymphocytes in the bone marrow (BM) (9,10). With regard to adhesion molecules, binding of α4β1 (VLA-4) on lymphocytes to VCAM-1 on HEV contributes to the initial interaction of lymphocytes with HEV (11,12), whereas binding of αLβ2 (LFA-1) on lymphocytes to its ligand ICAM-1 on the surface of HEV is essential for entry of lymphocytes into LNs (13,14). Both α4β1 and αLβ2 are required for entry of lymphocytes into the splenic white pulp (15), whereas α4β1 is also involved in the motility and retention of B lympho-

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cytes within the spleen (16) and BM (10,17). α4 can also form heterodimers with β7; β7 integrins are responsible for efficient trafficking and retention of lymphocytes in the gut (18). When complexed with α4, β7 binds to MadCAM-1 on the HEVs of the mucosa-associated lymphoid tissue (MALT) of the gut (19) where it allows the entry of α4β7-expressing lymphocytes. Whereas $\alpha_E\beta7$ binds to E-cadherin and facilitates the retention of effector and memory lymphocytes in the gut epithelium (18). Exit of lymphocytes from the LNs is regulated by S1PR1, whereas S1PR3 regulates egress from the spleen (20) and BM (21).

Compared to normal B lymphocytes, much less is known about the trafficking of lymphoma cells. This review outlines the chemokine receptors and integrins that are known to be expressed on lymphoma cells, summarises the evidence supporting their role in lymphoma biology and speculates on how this understanding might translate into novel therapy.

3. Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is the most extensively studied of the B-cell lymphomas with regard to the factors involved in cell trafficking (Table II). This probably reflects its high prevalence and almost universal blood involvement. CLL cells migrate into and infiltrate all organs of the lymphoreticular system including the BM, LNs, white pulp of the spleen and liver. Invasion of LNs by CLL results in the complete destruction of the normal architecture, with the malignant lymphocytes occupying both the follicular and interfollicular areas (22).

CLL cell entry into lymph nodes resembles that of normal B cells in that it requires CCL21 and αLβ2 (23). However, CLL cells differ from normal B cells in that they also require α4β1 for transendothelial cell migration (TEM). In keeping with this observation, lymphadenopathy in CLL is associated with high levels of α4β1 and CCR7 (23). Furthermore, high expression of α4 (CD49d) has been observed to be an independent adverse prognostic factor (24,25). The dependence of CLL cells on α4β1 for TEM can be explained by a defect in the polar clustering of αLβ2 that is overcome by α4β1 expression (24,25).

The role of CXCR4 and its potential involvement in the accumulation of CLL cells in the BM has also been investigated. CXCR4 mediates the migration of CLL cells through BM stromal cells, which secrete its ligand CXCL12 (26), and the retention of CLL cells within the BM (27). Furthermore, high CXCR4 expression correlates with extensive tissue invasion and adverse outcome (28). It is unclear whether other chemokine receptors play a role in regulating the migration of CLL cells into and within tissues. For example, although CXCR5 has been reported to be overexpressed by CLL cells (29), this chemokine receptor is predominantly expressed in the follicles and is associated with homing to this site (7,8). Since CLL cells do not accumulate in the follicles, the role of CXCR5 in CLL-cell homing is unclear.

There is emerging evidence that novel therapeutic agents that target components of the B-cell receptor signalling pathway may act at least in part by interfering with CLL-cell trafficking. For example, the phosphotidylinositol 3-kinase (PI3K) δ inhibitor, idelalisib (CAL-101), has been reported to downregulate the expression of CXCL13 and reduce chemotaxis towards CXCL12 and CXCL13 without affecting the expression of chemokine receptors (30). These observations are in keeping with the established role of PI3K in the directional movement of lymphocytes (31,32). Furthermore, administration of idelalisib to patients with CLL results in a rapid reduction in LN size and a simultaneous increase in blood involvement which subsequently declines over a period of several months, suggesting an effect on the trafficking of CLL cells into or out of lymph nodes (30). Administration of the SYK inhibitor fostamatinib to patients with CLL also results in an transient lymphocytosis (33), likely reflecting the established role of SYK in signalling mediated through integrins and chemokines (34). Furthermore, the BTK inhibitor ibrutinib which also induces lymphocytosis inhibits chemokine and BCR-mediated adhesion of the malignant lymphocytes via α4β1 (35). In summary, disruption of CLL trafficking appears to be a consistent effect of these kinase inhibitors, and it is intriguing to speculate that this might account for at least some of their therapeutic activity. In theory, CLL-cell trafficking could be targeted more directly by targeting molecules such as α4β1 and CXCR4 (36,37) which are known to play a crucial role in the migration and survival of CLL cells. Indeed, inhibitors of both molecules have already shown activity in other diseases including multiple sclerosis, Crohn's disease and chronic myeloid leukaemia (38,39).

4. Hairy cell leukaemia

Similar to CLL, the neoplastic lymphocytes of hairy cell leukaemia (HCL) are usually found in the circulation as well as in the tissues. Thus, despite its rarity (<1% of all leukaemias), the factors involved in the trafficking and organ involvement in HCL have been more extensively studied than in other, more common, lymphoid malignancies (Table II) (40). The pattern of tissue involvement in HCL differs from that of CLL. In particular, HCs do not infiltrate the lymph nodes but are instead localised to the red pulp of the spleen (41). The malignant lymphocytes also infiltrate the BM where they secrete fibronectin resulting in BM fibrosis (42). In keeping with the absence of lymphadenopathy in HCL, HCs express CCR7 at extremely low levels (43). In addition, the low expression of CCR7 and CXCR5 (43), which are required for entry into the splenic white pulp (44) and lymphoid follicles, respectively, likely explains why HCs are not founds at these sites. The homing of HCs to the BM can be attributed to their high expression of CXCR4 (45).

With regard to adhesion molecules, HCs express α4β1, whereas αLβ2 is either absent or expressed at very low levels (46). Since αLβ2 is required for TEM into LN, the low expression of this integrin, together with the low expression of CCR7, provides an explanation for the absence of LN involvement in HCL. In contrast, high expression of α4β1 (together with CXCR4 and CXCR5) would explain the homing of HCL cells to, and their retention in, the spleen and BM. In addition, the expression of $\alpha_E\beta7$ characterises HCL, although as HCs do not home to the gastointestinal tract, it is unclear why the neoplastic B-cells express this integrin (47). In summary, the chemokine and integrin receptor profile of HCs (with the exception of $\alpha_E\beta7$) fits perfectly with the unique tissue distribution of HCL.

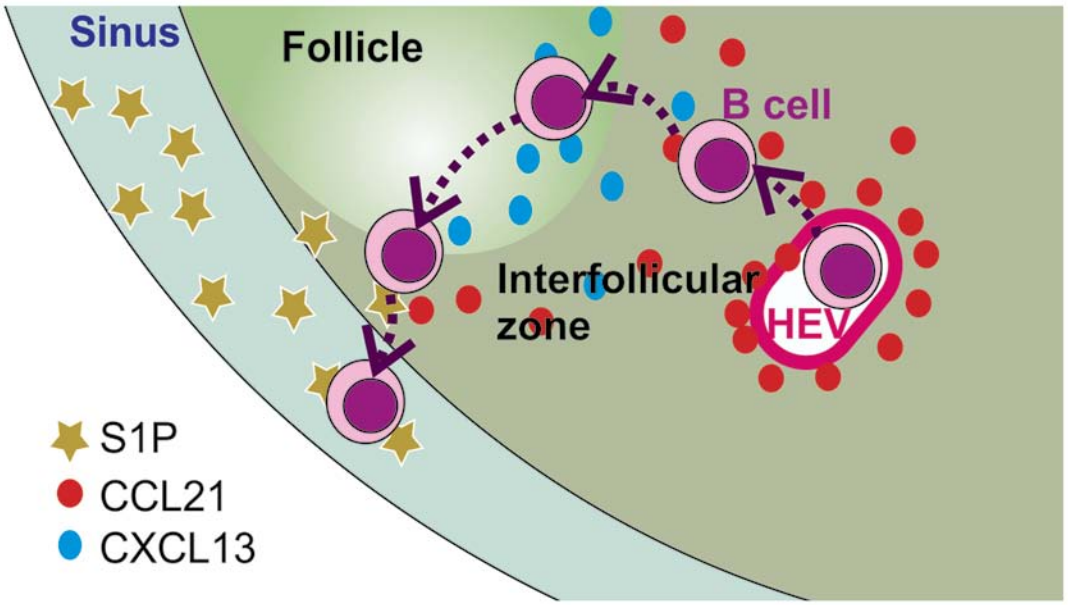

Figure 1. Chemotactic signals involved in the recirculation of normal B cells into tissues. B lymphocytes enter the lymph nodes through the HEV in the T cell zones in response to CCL21 and move towards the follicle in the search for antigen in response to a gradient of CXCL13. In the absence of an antigen encounter B cells up-regulate CCR7, and migrate back towards the high concentration of CCL21 in the T cell zone. S1PR1 is up regulated and the B cells exit the nodes through the cortical sinuses along the S1P gradient. However, if the B cells encounter an antigen the transit time is increased to approximately 3 days due to a reduced expression of S1PR1. For ease, the route of lymphocytes travel is shown as linear path; however it is clear that lymphocytes randomly walk within tissues along chemokine gradients and visit the follicular and interfollicular areas more than once during their visit to the node.

Table I. Molecules involved in normal B cell homing to, and egress from, lymphoreticular tissues.

A, Chemokines and integrin ligands involved in homing.

	Chemokine/Ligand			Ligand/Integrin		
Organ	CCL21/**CCR7**	CXCL12/**CXCR4**	CXCL13/**CXCR5**	VCAM-1/**α4β1**	MadCam-1/**α4β7**	ICAM-1/**αLβ2**
Peripheral LN						
HEV entry	√			√		√
Follicle			√			
Mucosal LN						
HEV entry	√				√	
Spleen (white pulp)			√	√		√
BM		√				

Receptors on lymphocytes are indicated by bold type.

B, SIP receptors involved in egress from lymphoreticular tissues.

Organ	$S1P_1$	$S1P_3$
Peripheral LN	√	
Mucosal LN	√	
Spleen (white pulp)		√
BM		√

Table II. The expression of chemokine receptors and adhesion molecules involved in lymphocyte homing by B cell lymphomas.

Disease	CCR7	CXCR4	CXCR5	α4β1	α4β7	αLβ2	S1P
CLL	+/+++	+/+++	+++	-/++	-	+/+++	NT
HCL	-/+	+++	-/+	++	-	-/+	NT
DLBCL	NT	Y	Y	-/+++	ND	-/+	$S1P_2$
FL	Y/N[a]	Y	Y	-/+++	NT	NT	NT
MZL	NT	-/+	-/+	-/+	-	NT	NT
MALT	NT	NT	NT	-/+	+	NT	NT
MCL	Y	Y	Y	Y	+[b]	Y	NT
BL	+++	NT	Y	Y	NT	+	NT
HL							
Classical	+++	+++	-/+	NT	NT	Y	NT
Nodular	-	Y	-/+				

-, No expression; +, low expression; ++, intermediate expression; +++, high expression. NT, no reports in the literature; Y, yes, but levels not reported. [a]Conflicting reports in the literature. [b]Tumours with GI involvement only.

5. Diffuse large B-cell lymphoma

Despite being the most common type of NHL, very little is known regarding the factors involved in the migration and trafficking of the malignant cells in this disease (Table II) (48,49). This is surprising given the effacement of LN architecture and frequent dissemination both within and outside of the lymphoreticular system (Fig. 2A and B). Diffuse large B-cell lymphoma (DLBCL) cells have been shown to express the chemokine receptors CXCR4 and CXCR5 (48). Primary CNS lymphomas, a rare subtype of DLBCL express these chemokines together with CCR7 (50); however, the expression of the receptor is confined to the cytoplasm. Whether or not the expression on other DLBCLs is on the surface, or in the cytoplasm has not been explored. With regard to integrins, a proportion of cases express α4β1 and αLβ2 (49), with high expression of α4β1 being associated with advanced stage disease (49).

With regard to S1P receptors, DLBCL cells preferentially express S1PR2, and mutations which inactivate the receptor were found in 27% of cases (51). S1PR2 inactivation is thought to play a critical role in the development of DLBCL as following the conditional knockout of S1PR2 in B cells 50% of mice developed the disease (51). S1PR2 differs from S1PR1 and S1PR3 in that it is coupled to $G_{12/13}$ rather than G_i. Hence, whereas S1PR1 and S1PR3 signal through Rac and promote motility, S1PR2 activates Rho and thereby inhibits motility (52).

6. Follicular lymphoma

Most patients with follicular lymphoma (FL) present with advanced-stage disease involving multiple LNs and BM (53). However, very little is known about how the malignant lymphocytes become disseminated (Table II). As would be predicted for lymphocytes that home to the lymphoid follicles, FL cells express CXCR5 (48,54). They also produce CXCL13 (the ligand for CXCR5), which may therefore play a role in attracting additional FL cells to existing sites of involvement (48). FL cells also express CXCR4 (29,48,54), which likely explains the high frequency of BM involvement. Although one might expect the surface expression of CXCR5 and CXCR4 to be downregulated in the LN and BM, respectively, due to ligand-induced receptor internalisation, expression of these two receptors is similar in different tissue compartments (29). There are conflicting reports concerning whether or not follicular lymphoma cells express CCR7 (29,54). With regard to adhesion molecules, the expression of α4β1 on FL cells varies not only in the number of positive cells but also in the intensity of expression on the positive cells (49). However, it is unclear whether α4β1 expression is associated with stage or prognosis. It is clear that the susceptibility of FL cells to anti-lymphoma therapy is strongly influenced by interaction with non-malignant cells in the tumour microenvironment (55) (Fig. 2C and D). In addition, it has been recently shown that there is bidirectional migration of lymphoma cells from the LN to the BM, and the cells that reside in the BM are responsible for relapse following chemotherapy (56).

7. Marginal zone lymphoma

Marginal zone lymphomas (MZL) are classified according to their tissue localisation into extranodal MZL of MALT, nodal MZL and splenic MZL. Extranodal MALT lymphomas comprises 50-70% of MZL and occur at mucosal sites including stomach, salivary glands, lacrimal glands, parotid glands, as well as skin, thyroid, lung and other organs. These lymphomas typically present as an isolated lesion, and the disease follows an indolent clinical course. More than 80% of MZLs arising in the stomach achieve 10-year survival when the *Helicobacter pylori* infection which drives the disease is

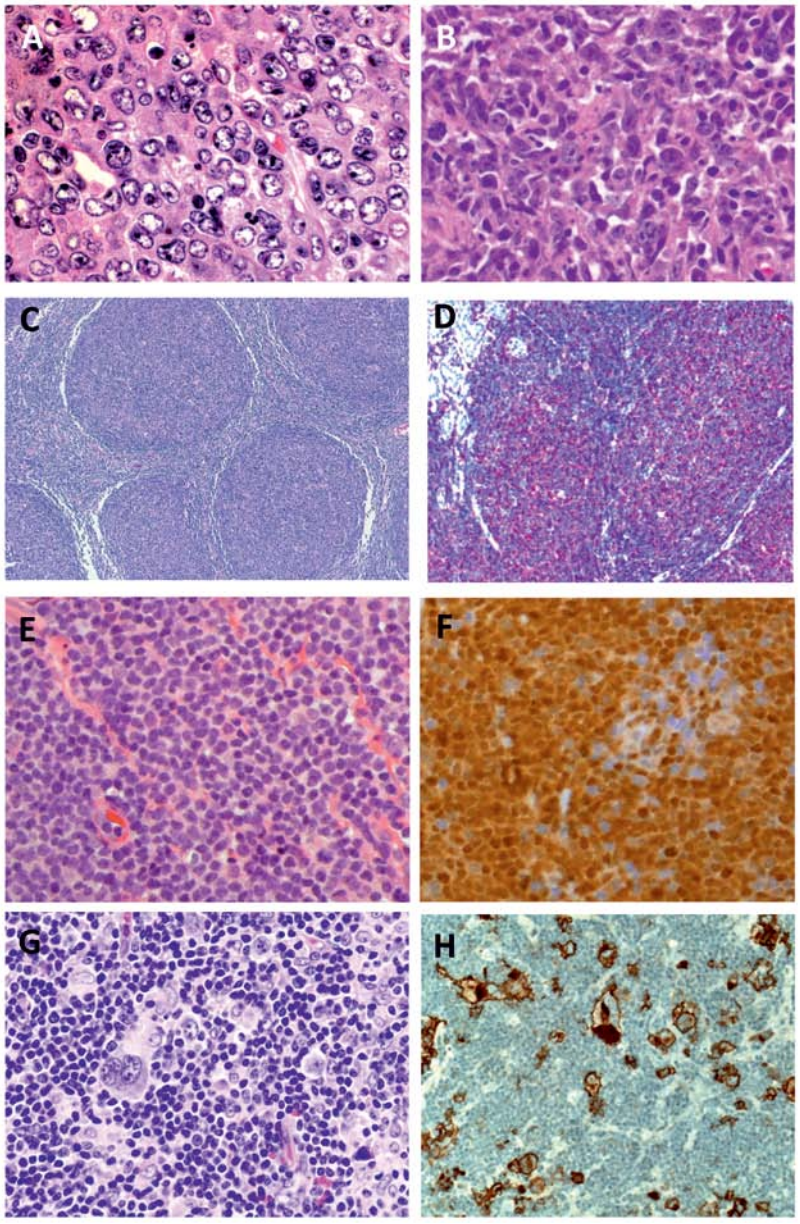

Figure 2. Microenvironments of B-NHL. (A and B) Diffuse large B cell lymphoma. (C and D) Follicular lymphoma; malignant lymphocytes in C are stained with Bcl-2. (E and F) Mantle cell lymphoma. Malignant lymphocytes in F are stained for cyclin D1; negative non-tumour accessory cells can clearly be seen. (G and H) Hodgkin's disease. Tumour cells stained with CD30 in (H) are clearly in the minority.

treated (57). In contrast, nodal MZL, which typically affects peripheral and intra-abdominal LNs and bone marrow, tends to be less responsive to treatment (58). Splenic MZL is a distinctive disease with splenic, BM and blood involvement (58). Given the unique tissue distribution of the different MZL subtypes, remarkably little is know about the factors that determine disease localisation (Table II). As might be predicted, MALT lymphomas express α4β7 (59), with some cases also expressing α4β1 (60). With regard to chemokines, MZL are reported to express low levels of CXCR4 and CXCR5 and migrate poorly in response to these chemokines (61). There is no information as to whether or not the expression of these chemokine receptors corresponds to infiltration at particular sites. Further investigation of the molecules involved in the tissue localisation of MZL is therefore needed with the potential to inform of novel therapeutic strategies to dislodge the lymphoma cells from their protective microenvironmental niches.

8. Mantle-cell lymphoma

Mantle-cell lymphoma (MCL) is a challenging disease to treat as it is neither low-grade nor curable with conventional therapy. In addition to LNs (Fig. 2E and F), the disease is usually present in the bone marrow and sometimes the blood. One very striking feature of MCL is its propensity to form colonic polyps which occur in a high proportion of patients (62). Although the treatment of MCL has improved in recent years owing to the use of high-dose cytarabine, stem-cell transplantation and rituximab (63,64), developing more effective therapy for this disease is a priority. MCL cells express high levels of all three chemokine receptors associated with lymphocyte homing,

namely CXCR4, CXCR5 and CCR7 (61) (Table II). They also express both αLβ2 and α4β1 (49) (Table II). Inhibition of the latter integrin on MCL cells has been shown to inhibit motility beneath (65), and adhesion to, marrow stromal cells *in vitro* (66). Furthermore, adhesion of MCL cells to a stromal cell line has been shown to protect them from drug-induced apoptosis *in vitro*. However, inhibition of α4β1-mediated adhesion with the monoclonal antibody natalizumab had a limited effect in overcoming protection in this system (66), suggesting that cytoprotection is likely mediated by soluble factors secreted by the stromal cells. In addition, it has been shown that expression of α4β7 by MCL cells in peripheral LNs was associated with gastrointestinal tract involvement in 5/7 cases studied; all cases were also positive for α4β1 (67). Whether or not MCL cells express $\alpha_E\beta7$ is unclear, one report suggests that mRNA levels were higher in non-nodal MCL (68), whereas another that the protein is not expressed (47). Further investigation of the factors involved in the spread of the tumour to different organs is clearly warranted.

Since BCR signalling is also thought to play a role in MCL, as with CLL, the BTK inhibitor ibrutinib has also been tested in the treatment of MCL where it also induces lymphocytosis and a decrease in LN size, suggesting that treatment displaces the MCL cells from their microenvironmental niches (69,70).

9. Burkitt's lymphoma

Burkitt's lymphoma (BL) is a highly aggressive disease that typically present with large abdominal masses plus bone marrow or CNS involvement in 70 and 40% of patients, respectively. A significant proportion of patients are not cured by intensive chemotherapy, and relapsed or refractory disease is associated a dismal outcome (71). Given that the CXCL13/CXCR5 axis was first identified in BL (72), and that CCR7 was identified as one of the most upregulated genes in BL (73) it is surprising that there have been no further studies regarding the role of chemokines and their receptors in primary BL cells (Table II). Aberrant expression of CXCL13 in the CNS has been associated with involvement of the brain as in DLBCL (74), and in the recruitment of B cells to the brain in paediatric Opsoclonus-myoclonus syndrome (75). It therefore seems likely that expression of CXCR5 by BL cells could control their homing to the CNS. With regard to integrins, BL cells express α4β1 and αLβ2 (76) (Table II). However, levels of αLβ2 are lower than in normal B cells owing to the overexpression of *c-myc* (77).

10. Hodgkin's lymphoma

Hodgkin's lymphoma (HL) is usually confined to the LNs. Lymphadenopathy is usually localised with involvement of contiguous nodes. Occasionally, the disease involves extranodal sites, the BM and lung being most commonly affected. The majority of patients with HL are curable. However, patients who fail frontline therapy have an uncertain prognosis (78). The expression of chemokine receptors by the malignant Reed-Sternberg (R-S) cells varies according to the subtype of HL (Table II). In classical HL, the R-S express high levels of CCR7 and CXCR4 and are located in the interfollicular areas. In contrast, in nodular lymphocyte predominant HL, the malignant cells expresses CXCR4, but not CCR7 (54). Expression of CXCR5 is typically low or absent and not linked to any particular subtype (54). The malignant R-S cells are surrounded by a dense infiltrate of non-malignant leukocytes which provide a protective and stimulatory microenvironment (Fig. 2G and H) (55,79,80). Consequently, in addition to the chemokines responsible for the localisation of R-S cells within the lymphoid tissues, it is also important to consider the chemokines responsible for attracting non-malignant cells to the R-S cells (80). In fact, R-S cells have been shown to produce CCL17, CCL22, CXCL9, CXCL10 and CX3CL1 which are thought to attract T cells and monocytes into the tumour (79,80). In contrast, little is known about which adhesion molecules are important in HL, although early reports indicate that R-S cells express αLβ2 and αXβ2 (81) (Table II). The importance of interaction between R-S cells and other leukocytes in HL offers the hope of a novel therapy that disrupts these interactions.

11. Conclusion

B-cell lymphomas are a diverse group of diseases that share many of the homing characteristics of normal B lymphocytes. The anatomical distribution of different B-cell malignancies can be partially explained by the profile of adhesion molecules, chemokine receptors and S1P receptors expressed, although there are still many unanswered questions. Drugs that target B-cell receptor signalling pathways clearly have an effect on cell trafficking, and it is intriguing to speculate that the therapeutic effects of these drugs might be mediated at least in part by dislodging malignant B cells from their protective microenvironment. Improving our understanding of the molecular mechanisms responsible for guiding malignant B cells to, and retaining them in, particular tissue sites is important as it provides an opportunity to develop new approaches to therapy based on the disruption of these processes.

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