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Bone marrow sinusoidal endothelium as a facilitator/regulator of cell egress from the bone marrow

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ABSTRACT

Despite more attention to cell migration from circulation into the bone marrow (BM), particularly homing of haematopoietic stem/progenitor cells, the process and mechanisms of cell mobilisation from the BM into the circulation remain largely underexplored. The process of cell mobilisation or transcellular cell migration from BM into the circulation (cell egress) is a crucial biological process in mammals as it is important to maintain homeostasis of various physiological functions including, but not limited to, the immune system, erythropoiesis, platelet release, and stem cell migration. The BM microvascular system composes of a monolayer of specialized endothelial cells, called sinusoidal endothelial cells (SECs). While it is very well evident that the process of cell egress occurs exclusively through BM SECs, there is a lack of systematic analyses addressing the extent of contribution of BM SECs to the process of cell egress from the BM. Therefore, this review aims to address the potential ability of BM SECs in regulating and/or facilitating the process of cell egress from BM. In this review, we address, firstly, the unique ultra-/structural and molecular features of BM SECs and discuss the possible biological interactions between BM SECs and various egressing cells in physiological conditions. Secondly, we propose the potential role of BM SECs in egress of leukemic cells from BM into the circulation. Finally, we discuss the potential role of BM SECs in homing of haematopoietic stem cells. Collectively, the current review suggests that the BM SECs may not be merely a neutral gatekeeper for cell intravasation and extravasation, but rather is a dynamic trafficking surveillance system, thereby the process of BM cell egress/mobilisation can be regulated.

1. Background

In mammals, bone marrow (BM) microvascular system possesses specific features which distinguish it from microvasculature in other organs/tissues. The BM microvascular system composes of a monolayer of specialized endothelial cells, called sinusoidal endothelial cells (SECs) (Kopp et al., 2005). SECs are also found in other tissues such as liver (Samson, 2013) and spleen (Huang et al., 2014). By delivering oxygen, nutrients, cells, and growth factors, the BM microvascular system plays a substantial role in orchestrating diverse physiological functions including haematopoiesis, bone formation and bone remodelling (Hassanshahi et al., 2018, 2019). Moreover, the BM microvascular system possesses a strong regeneration-enabling potency, for example for BM haematopoiesis by providing tissue/organ-specific "angiocrine factors" (Rafii et al., 2016). Furthermore, as illustrated in mice recently by Itkin et al, cell trafficking between BM and circulation occurs exclusively through BM sinusoidal endothelium (BMSE) (Itkin et al., 2016). However, although the trafficking or egress of mature, stem, and leukemic cells from BM has been a subject of interest for many years, less attention has been paid to the role of BMSE in modulating the process of cell egress from BM. Although several factors including alterations in cell motility and cell deformation that occur in egressing cells which may facilitate their egress from BM (Lichtman et al., 1989), specific features of BMSE by which the process of cell egress could be inhibited/facilitated have not been sufficiently addressed.

Herein, we attempt to address the questions to what extent BMSE can affect the process of cell egress in physiological and pathophysiological circumstances, whether BMSE is just a neutral gatekeeper for cell intravasation and extravasation, or whether it is actually a dynamic trafficking surveillance system. As discussed later, BMSE interacts with the egressing cells (including involvement of chemotactic factor

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receptors and/or adhesion molecules) in order to facilitate their egress into the circulation. However, such interactions/contributions might be specific for particular cells spatially and temporally. In addition, as it is also important to address how transplanted haematopoietic stem cells (HSCs)/progenitor cells (HSPCs) find their way home into the BM, this review will also summarise specific characteristics of BMSE by which transplanted HSPCs recognize their home. Furthermore, this review will discuss roles of BMSE involved in transferring signals and information between circulation and BM cavity to maintain the homeostasis of cell trafficking and other physiological functions within the bone and BM.

Addressing the above questions has become more important. Since the BM SECs are the last cells with which egressing cells are directly and/or indirectly in contact before egressing into the circulation, any alterations or damage to the BMSE influence the process of cell mobilization from BM into the circulation. Shedding new lights/insights on those questions will improve our understanding of the important roles and involved mechanisms of BM SECs in regulating cell trafficking and can open new avenues for employing better approaches to deal with mobilization of cells from BM into circulation, thereby providing improved and better treatments.

2. Bone marrow sinusoidal endothelium features for cell egress

2.1. Ultra-/structure of bone marrow sinusoidal endothelium

The BMSE possesses an incomplete basement membrane and has been known to be devoid of supporting cells such as pericytes (Kopp et al., 2005). However, recent studies in mice showed that BM capillaries (type H capillaries) are surrounded with mesenchymal cells expressing two markers of pericytes, namely platelet-derived growth factor (PDGF) receptor β2 and neural/glial antigen 2 (known as NG2) in the metaphysis (a region of long bone with more trabecular bone and more active bone remodelling), but not those (type L capillaries) in the diaphysis (a region with less trabecular bone and less active remodelling) (Itkin et al., 2016). While it has been stated that adventitial cells reside in the proximity of SECs and cover about 60% of BMSE (Petrides and Dittmann, 1990), electron microscopy studies by Muto illustrated that cell egress occurs from those sites in SECs where adventitial cells are absent (Muto, 1976). Similarly, it was also reported that BM cell mobilization into the peripheral blood (PB) takes place in regions of micro-vessels where the adventitial cells are absent and blood-barrier is solely composed of BMSE (Furze and Rankin, 2008). With this regard, early studies have shown that adventitial cells are retracted when egressing cells move towards the BMSE (Becker and De Bruyn, 1976). In addition, it was suggested that BMSE in mice lacks tight junctions which govern SECs to interdigitate and slide over each other, which leads to changes in sinusoidal calibre and thus can facilitate the egress of cells into the circulation (Tavassoli and Shaklai, 1979). Considering the fixed volume of marrow in the rigid frame of bone, even rhythmic calibre changes of BMSE affects the cell egress from BM, and as a result, cells can be displaced into the lumen of BM sinusoids and subsequently egress from the BM (Chamberlain and Lichtman, 1978).

Early studies by Chamberlain et al revealed that the process of cell egress is transcellular and does not occur in random loci, but occurs in parajunctional zones where the cytoplasm of SECs is attenuated and thinned (Chamberlain and Lichtman, 1978). Consistently, it was observed that cell egress occurs in regions known as diaphragmatic fenestrae, where the endothelial luminal and abluminal cell membranes are fused (Campbell, 1972; Levesque et al., 2002). Interestingly, it was observed that even though SECs are fenestrated, formation of fenestrae (small pores which are smaller than the sizes of egressing cells) is transitory and they form at the time of cell egress (Chamberlain and Lichtman, 1978). Consistent with the report that the sinusoidal wall in the BM is discontinuous (Inoue and Osmond, 2001), the process of cell egress from BM appears to occur in BM micro vessels whose basement membrane is absent and also through the fenestrae which are formed at the time of cell egress. However, as fenestrae are not pre-existing in BM SECs, it is worthwhile to investigate whether formation of fenestrae in BM SECs is a process independent of BM SECs (i.e. merely relying on the ability of egressing cells to penetrate the BM SEC cytoplasm) or whether BM SECs also contribute in this process. Although early studies showed that BM SECs facilitate the egress of cells into the circulation by discharging the contents of lysosomal vesicles in their own cytoplasm, leading to segmental destabilization and also autolysis of endothelium, and thus creating a suitable area of cytoplasm for cell egress (Aoki and Tavassoli, 1981), further mechanistic studies are required to explore the process of fenestra formation by BM SECs.

2.2. Similarities between bone marrow and hepatic sinusoidal endothelial cells

In an elegant study by Nolan et al, tissue-specific molecular signatures of various microvascular endothelial cells were investigated (Nolan et al., 2013). Transcriptional profiling of microvascular endothelial cells revealed that BM SECs have strong similarities with hepatic SECs. Another similarity of the liver with BM could be the fact that liver is also a location of haematopoiesis in certain circumstances (Kim, 2010), in where the homing, differentiation and trafficking of HSPCs are supported by hepatic SECs (Cardier and BarberaGuillem, 1997). Therefore, for haematopoiesis and egress of haematopoietic cells (HCs), BM and hepatic SECs have close similarities in terms of expression of extracellular matrix (ECM) components, chemokines and their receptors, adhesion molecules, and other factors which are required for aforementioned purposes. In addition to the similarities of their molecular signatures, BM SECs (Qian et al., 2009) and liver SECs are both potent scavenger cells and belong to the family of scavenging endothelial cells (Milo et al., 2013; Sorensen et al., 2012). This scavenging property has been used by McCourt et al as a means to in vivo label and thereby prospectively isolate functional BM SECs (McCourt et al., 2015). In addition, similar to BMSE, sinusoids in the liver are also fenestrated, suggesting that the mechanism(s) of fenestra formation in liver and BM have considerable similarities.

Taken together, considering similarities in physiological, structural and molecular features of SECs in the liver and in the BM, and the difficulties of isolating and studying BM SECs (Hooper et al., 2009), for the sake of mechanistic exploration of cell egress from BM, investigations on hepatic SECs may unravel important insights into the potential roles of BM SECs in egress of cells from BM.

2.3. Molecular features of bone marrow sinusoidal endothelium and cell egress

2.3.1. Expression of adhesion molecules and chemokines

BM SECs plays a crucial role in maintenance of cell trafficking homeostasis by providing specific adhesion molecules, chemoattractants, and others to the mobilizing cells (Table 1). BM SECs possess a unique feature of constitutive expression of adhesion molecules such as E-selectin, P-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) (Furze and Rankin, 2008) (Table 1). Previous studies showed that constitutively expression of P- selectin, E-selectin, and VCAM-1 by BM SECs are essential for rolling of HSPCs in BMSE (Mazo et al., 1998). It has been proposed that some of these adhesion molecules are important for a particular subtype of cells. For instance, normal HCs bind to VCAM-1; and CD34+ cells bind to ICAM-1, ICAM-2, and ICAM-3 adhesion molecules expressed in the microenvironment, mostly by endothelial cells (Bradstock and Gottlieb, 1995).

Additionally, BM SECs have been reported to express some chemoattractants which are important for cell egress. BM SECs express C-X-C motif chemokine ligand 12 (CXCL12) (Burger and Sipkins, 2012), as a well-known chemoattractant factor, which may affect the process of cell egress for most HCs (Table 1). Furthermore, mobilization of HSCs into

Table 1
Bone marrow sinusoid endothelial cell (BM SEC)-derived factors which may influence the egress process of normal and/or leukemic cells from the bone marrow. *Intercellular adhesion molecule (ICAM); vascular cell adhesion molecule (VCAM); C-X-C motif chemokine ligand (CXCL); von Willebrand Factor (vWF); Roundabout homolog 4 (ROBO4).*

Potential factors expressed/provided by BM SECs	BM egressing cells affected	detected in BM SECs and references:
Adhesion molecules	• Basophils, haematopoietic stem/progenitor cells, leukemic cells, acute myeloblastic leukaemia	• (Furze and Rankin, 2008)
• E-selectin	• Mast precursor cells, basophils	• (Furze and Rankin, 2008)
• P-selectin	• Haematopoietic stem/progenitor cells, mast precursor cells	• (Furze and Rankin, 2008)
• ICAM-1	• Haematopoietic stem/progenitor cells	• (Bradstock and Gottlieb, 1995)
• ICAM-2	• Haematopoietic stem/progenitor cells	• (Bradstock and Gottlieb, 1995)
• ICAM-3	• Neutrophils, eosinophils, basophils, mast precursor cells, B lymphocytes, platelets, leukemic cells, acute myeloblastic leukaemia	• (Furze and Rankin, 2008)
• VCAM-1		
ECM components	• Platelets, leukemic cells, chronic myeloblastic leukaemia	• (Nilsson et al., 1998)
• Collagen type IV	• Mast precursor cells, platelets, leukemic cells, acute myeloblastic leukaemia, chronic myeloblastic leukaemia	• (Gu et al., 1999)
• Laminin	• Eosinophils, basophils, mast precursor cells, platelets, leukemic cells, acute myeloblastic leukaemia, acute lymphoblastic leukaemia	• (Zuckerman and Wicha, 1983)
• Fibronectin	• Eosinophils, basophils, mast precursor cells	• (Soda and Tavassoli, 1984)
• Sialic acid	• Haematopoietic cells	• (Nakamura-Ishizu et al., 2012)
• Tenascin-C	• Haematopoietic cells	• (Rafii et al., 1994)
• Thrombospondin	• Neutrophils, eosinophils, basophils	• (Bradstock and Gottlieb, 1995)
• Hemonectin	• Leukemic cells	• (Avigdor et al., 2004)
• Hyaluronic acid		
Chemokines	• Neutrophils, basophils, B lymphocytes, platelets, haematopoietic stem/progenitor cells, leukemic cells, acute myeloblastic leukaemia, acute lymphoblastic leukaemia	• (Burger and Sipkins, 2012)
• CXCL12	• Neutrophils	• (Dimasi et al., 2013)
• CXCL1	• Neutrophils	• (Dimasi et al., 2013)
• CXCL2	• Haematopoietic stem/progenitor cells, B lymphocytes	• (He et al., 2014)
• c-kit ligand		
Glycoproteins	• Platelets	• (Pusztaszeri et al., 2006)
• vWF		
Other factors	• Haematopoietic stem/progenitor cells, haematopoietic cells	• (Bixel et al., 2017)
• Low flow velocity	• Haematopoietic stem/progenitor cells, haematopoietic cells	• (Bixel et al., 2017)
• Low shear stress	• Haematopoietic stem/progenitor cells	• (Smith-Berdan et al., 2015)
• ROBO4		

the circulation requires cooperation of the signaling of c-kit ligand (eg stem cell factor or SCF)/c-kit receptor (CD117) (Wozniak and Kopec-Szlezak, 2004). Interestingly, the expression of c-kit ligand by BM endothelial cells was detected and reported to be important for HSCs maintenance and expansion (Ding et al., 2012).

Furthermore, it has been also reported that the process of detachment involved in cell egress is mediated by a proteolytic microenvironment which is induced by proteolytic enzymes produced by monocytes and granulocytes, as well as administration of granulocyte-colony stimulating factor (G-CSF) (Levesque et al., 2010) (see below). Matrix metalloproteinase-9 (MMP-9), for example, has been proposed to play a key role to regulate normal HC egression from BM (Lane et al., 2000). While production of MMP-9 by hepatic SECs has been reported (Yu et al., 2013), further studies will reveal whether BM SECs also produce MMP-9 and hence have any roles in egress of cells from BM. Taken together, BM SECs appear to be involved in regulation of cell egress from BM by providing adhesion molecules, chemokines, and possibly MMP-9 to the egressing cells.

2.3.2. Extracellular matrix components and other factors

BM SECs also produce important ECM proteins such as collagen type IV and laminin (Gu et al., 1999; Nilsson et al., 1998; Zuckerman and Wicha, 1983) by which attachment and detachment of egressing cells can be modulated (Table 1). In mouse BM, it was found that laminin-10 ($\alpha5\beta1\gamma1$) was the only expressed isoform of laminin which was expressed by BM SECs, and it was shown that this isoform is potentially involved in adhesion to BM cells during trafficking of the mature blood cells (Gu et al., 1999). Tenascin-C is another ECM component produced by BM SECs (Nakamura-Ishizu et al., 2012), which promotes HSC proliferation (Mendelson and Frenette, 2014). Tenascin-C seems to possess anti-adhesive features for some cell types, but acts as an adhesive molecule for others such as fibroblasts. However, in the haematopoietic system, it was indicated that various human myeloid cell lines adhered to tenascin-C (Klein et al., 1993), and it was suggested that tenascin-C influences both proliferation and adhesion of developing HCs (Klein, 1995).

Thrombospondin, another ECM protein in BM microenvironment, is also produced by BM SECs (Rafii et al., 1994), and can act as an adhesion molecule for developing HCs (Klein, 1995). However, when HCs become mature, their expression of receptors for thrombospondin is downregulated (Long and Dixit, 1990). In haematopoietic progenitor cells, thrombospondin together with c-kit ligand and cytokines have synergistic adhesion functions (Long et al., 1992). Hemonectin, which is a BM-specific adhesion protein (Anklesaria et al., 1991), has been also reported to be expressed by BM endothelial cells (Bradstock and Gottlieb, 1995), and is found in BM stem cell niche (Campbell et al., 1987). It was shown that the loss of binding to hemonectin may lead to egress of mature granulocytes from BM (Campbell et al., 1987). In the latter study, hemonectin was found to be a lineage-specific adhesion molecule for granulocyte lineage cells. In a similar study, Anklesaria et al found that the adhesion of haematopoietic progenitor cells to the stromal cells was mediated and inhibited by hemonectin and anti-hemonectin, respectively (Anklesaria et al., 1991).

Fibronectin is another ECM protein which is expressed by BM adherent cells including endothelial cells (Zuckerman and Wicha, 1983). Expression of fibronectin has been also detected in human umbilical vein endothelial cells (HUVECs) (Midulla et al., 2000) and hepatic SECs (Rieder et al., 1987). HCs also interact with fibronectin in the BM microenvironment via very late antigen-4 (VLA-4) and VLA-5 on HCs. Adhesion of fibronectin to VLA-5 has been suggested to negatively affect the haematopoiesis (Klein, 1995).

Within the BM, anti-adhesiveness proteoglycans such as heparan sulfate proteoglycan perlecan also modulate development of HSPCs (Klein, 1995). It has been reported that heparan sulfate proteoglycans are produced by BM stromal cells which are involved in differentiation and proliferation of HCs, and maturation of myelomonocytic cell line

HL60 (Klein, 1995). In the liver, hepatic SECs produce perlecan alongside with collagen IV and laminin, which induces interaction with integrins of hepatocytes (Rescan et al., 1993). Nevertheless, whether perlecan is produced by BM SECs and also has any roles in egress of HCs requires further studies.

Taken together, BMSE provides facilitator molecules (including adhesion molecules, ECM components, chemokines, glycoproteins and others) to the egressing cells, thereby allowing the egressing cells to directly and/or indirectly interact with BMSE and thus egress from BM. However, it remains to be further explored whether BMSE can govern expression of cell/lineage specific molecules spatially and temporally and thus selectively affect the process of egress of specific cells from BM. In the following sections we will address how BMSE might influence the egress of specific HCs from BM.

3. Interactions between bone marrow sinusoidal endothelium and egressing cells in physiological conditions

In early studies, Aoki and Tavassoli proposed that the process of cell egress from BM depends on the interaction between BM endothelium and migrating cells (Aoki and Tavassoli, 1981). It has been also stated that all cells which are produced in BM are thought to enter the circulation through sinusoids (Pereira et al., 2009). Although the main steps of cell egress from BM are detachment of egressing cells from the haematopoietic microenvironment, followed by contact and recognition by BM SECs (Berger et al., 1994), BM SECs, as discussed above, regulates the egress of HCs from BM by providing required adhesion molecules, chemokines, and ECM proteins to the egressing cells. In this section, the potential role of BMSE in facilitating/regulating the egress of BM HCs from BM in physiological conditions is discussed (Fig. 1).

3.1. Egress of granulocytes from bone marrow

About 10^{11} neutrophils are mobilized into the PB per day without affecting the integrity of BMSE (Furze and Rankin, 2008). It has been stated that the egress of neutrophils from BM is mediated via CXCL12/C-X-C motif chemokine receptor 4 (CXCR4) axis (Christopher and Link, 2007). Modulation of CXCL12/CXCR4 axis has been proposed to be potentially used to control neutrophil mobilization (Fig. 1). In addition, expression of CXCR2 on mature neutrophils was also proposed to facilitate their egress into the circulation upon binding to CXCL1 and CXCL2, both expressed by BM endothelial cells (Eash et al., 2010; Martin et al., 2003) (Fig. 1). CXCR2 and CXCR4 have been demonstrated to antagonistically regulate neutrophil release from the bone marrow (Eash et al., 2010). Roles of CXCL12/CXCR4 axis and CXCR2 signalling have also been demonstrated to be important for the function of G-CSF, which is a very well-known mobilizing factor and used clinically for mobilizing cells from BM (see below). In a study by Boettcher et al, it was demonstrated that BM endothelial cells (as the primary source of G-CSF) translate pathogen signals into G-CSF–driven emergency granulopoiesis and can facilitate the migration of neutrophils from BM (Boettcher et al., 2014). The direct infusion of G-CSF into the BM vasculature triggered the mobilization of neutrophils selectively (Devi et al., 2013; Wengner et al., 2008) by reducing the expression of CXCL12 in the BM (Semerad et al., 2005) and CXCR4 on neutrophils (Sierra et al., 2007), indicating that disruption of CXCL12/CXCR4 signalling is an important key in G-CSF-induced egress of neutrophils from BM (Christopher and Link, 2007). G-CSF promotes expression of CXCL1 and CXCL2 in BM SECs, and supresses the expression of CXCR4 and CXCL12 in the BM (Dimasi et al., 2013) by which egress of neutrophils can be triggered. In mice, the sole receptor for CXCL1 and CXCL2 is CXCR2 (expressed on neutrophils), and signalling via CXCR2 markedly directs release of neutrophils from BM (Day and Link, 2012). Similarly, administration of exogenous CXCL1 and CXCL2 led to egress of neutrophils from BM in mice (Delano et al., 2011). In addition, a crosstalk between CXCR2 and CXCR4 signalling has been also reported and a substantial role has been suggested from both the CXCR2 and CXCR4 signalling pathways in egress of neutrophils from BM (Day and Link, 2012). Therefore, G-CSF induces the egress of neutrophils from BM via affecting CXCL12/CXCR4 signalling and probably promoting expression of CXCL1 and CXCL2 by BM endothelial cells

Another signalling pathway involved in regulating the egress of neutrophils from BM seems to be via the VLA-4/VCAM-1 axis (Fig. 1). It was revealed that VLA-4, which is expressed by neutrophils and is required for egress of neutrophils from BM (Christopher and Link, 2007), binds to VCAM-1 (an adhesion molecule expressed by BM SECs) (Issekutz et al., 1996), and that this binding facilitates the egress of neutrophils into the circulation from BM (Furze and Rankin, 2008). Conversely, egress of neutrophils was significantly reduced following blockade of VLA-4 (Christopher and Link, 2007). Interestingly, it was reported that the CXCL12/CXCR4 axis modulates VLA-4/VCAM-1 signalling pathway and thus regulates retention and egress of neutrophils from BM (Petty et al., 2009). Collectively, BM SECs appear to play a crucial role in egress of neutrophils by producing chemokines such as CXCL12 and CXCL1 and adhesion molecules such as VCAM-1.

BM SECs facilitates the egress of mast cell precursors, basophils, and eosinophils via providing adhesion molecules, ECM proteins, and chemokines. It has now been clear that human eosinophils, basophils, and mast cells share a number of chemotactic factor receptors and adhesion molecules (Bochner and Schleimer, 2001). VLA-4, for instance, is expressed by those three cell types and thus can bind to VCAM-1 and fibronectin that are expressed by BM SECs (Bochner and Schleimer, 2001), and thus their egress can be facilitated (Fig. 1). Another adhesion structure which eosinophils, basophils, and mast cells have in common is sialoadhesin family member 2 (known as siglec-8) which binds to sialic acids (Kikly et al., 2000) and is expressed by BM SECs (Soda and Tavassoli, 1984). However, how mast cell precursors egress from BM is still unclear, although it has been reported that rolling on P-selectin is an important factor for their release (Sriramarao et al., 1996). In addition, mast cells have been shown to have receptors for ligands such as fibronectin, laminin, VCAM-1, ICAM-1 (Bochner and Schleimer, 2001) which are expressed by BM SECs. However, it is yet to be investigated whether and how mast cell precursors exploit these ECM proteins and adhesion molecules for their mobilization from BM.

Regarding the egress of basophils from BM, it has been reported that basophils express CXCR4, C-C chemokine receptor 2 (CCR2), P-selectin glycoprotein ligand (PSGL-1), sialyl Lewis x (CD15 s), and sialyl-dimeric Lex. These molecules bind to CXCL12, C-C chemokine ligand 2 (CCL2), P-selectin, E- and P- selectins, and E-selectins, respectively, thereby through which basophil egress can be regulated (Fig. 1).

Freshly isolated eosinophils were shown to have a significant preference for binding to VCAM-1 (Matsumoto et al., 1997). Interestingly, it was found that eosinophil adhesion and their transendothelial migration were enhanced following exposure to GM-CSF (Tomioka et al., 1993) which has been also reported to be produced by hepatic SECs (Connolly et al., 2010). BM SECs hence might play a crucial role in egress of eosinophils from BM as they provide various adhesion molecules and chemokines.

Similar to the necessity of sphingosine-1-phosphate (S1P)/S1P receptor (S1PR) signalling in the egress of T lymphocytes from lymphoid organs (Cyster and Schwab, 2012), S1P/S1PR signalling also facilitate the egress of eosinophils from BM, as eosinophils express S1PR on their surface (Blaho and Hla, 2014). SEW2871 and FTY720, as antagonists of S1P and S1PR, were shown to inhibit the migration of S1PR1 + eosinophils towards S1P and thus inhibited the migration of eosinophils from BM to the circulation (Sugita et al., 2010). Furthermore, previous studies reported the expression of S1P in HUVECs (Ancellin et al., 2002), lymphatic endothelial cells (Pham et al., 2010), endothelial cells during organogenesis (Ramasamy et al., 2015) and its receptors in vascular endothelial cells (Xiong and Hla, 2014). However, investigations are required to address whether S1P and its receptors are

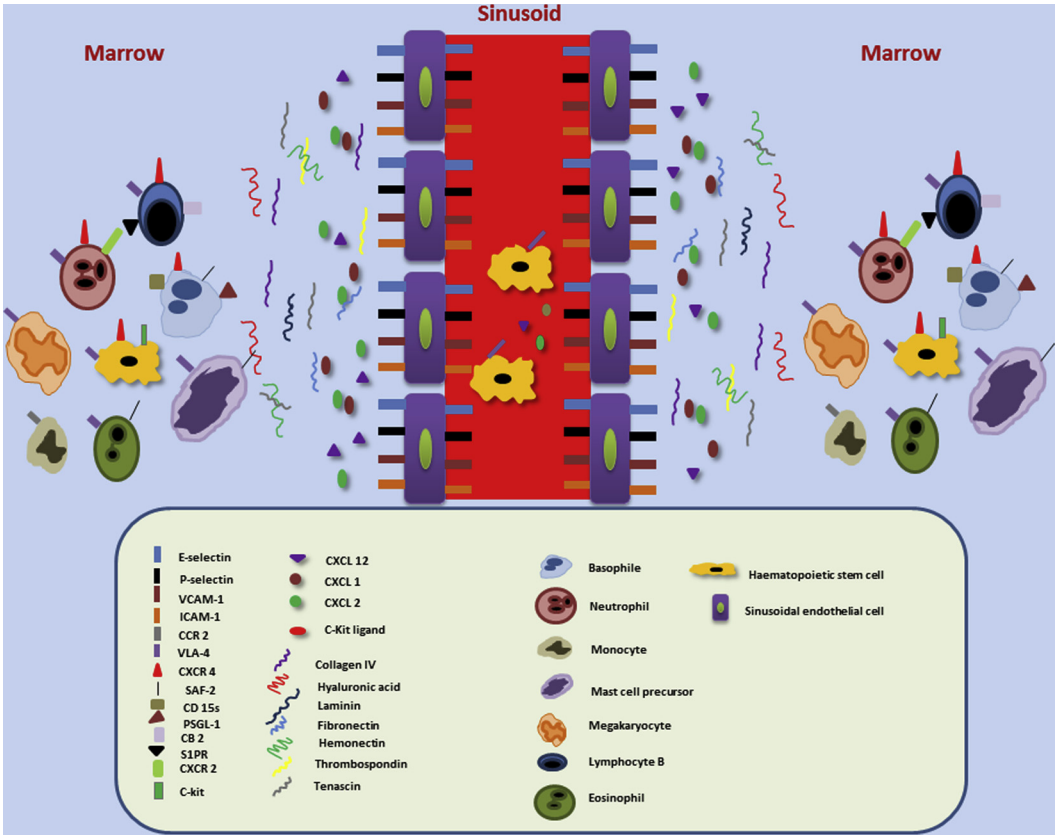

Fig. 1. Potential regulatory roles of BM SECs in egress of cells from BM into the circulation. BM SECs constitutively provide adhesion molecules such as E-selectin, P-selectin, ICAM-1, and VCAM-1 to the cells within the BM which have corresponding ligands by which the egress of cells from BM into the circulation might be facilitated/regulated. Apart from expressing adhesion molecules, BM SECs regulate egress of BM residing cells by providing chemokines including CXCL1, CXCL2, and CXCL12, and also by providing ECM proteins including collagen IV, laminin, fibronectin, hemonectin, hyaluronic acid, thrombospondin, and tenascin to the egressing cells. *Intercellular adhesion molecule (ICAM); vascular cell adhesion molecule (VCAM); C-X-C motif chemokine ligand (CXCL); C-C chemokine ligand (CCL); C-C chemokine receptor (CCR); C-X-C motif chemokine receptor (CXCR4); very late antigen-4 (VLA-4); cannabinoid receptor 2 (CB2); Sialoadhesin family member 2 (SAF-2); P-selectin glycoprotein ligand (PSGL-1); Sphingosine-1-phosphate receptor (S1PR); tyrosine-protein kinase kit (c-kit).*

expressed by BM SECs, and more importantly whether they affect the process of cell egress from BM.

Collectively, even though the molecular mechanisms of the above described molecular interactions between BMSE and egressing cells are still unclear, it seems that it is through these molecular interactions between the BMSE and the basophils, eosinophils and mast cell precursors, that the egress of these cells from BM can be regulated.

3.2. Egress of monocytes from bone marrow

BM SECs might affect the process of monocyte egress from BM by providing chemokines such as CCL2 and CCL7 (Fig. 1). Monocytes express high levels of CCR2 whose activation is required for the egress of monocytes from BM (Jung et al., 2015; Serbina and Pamer, 2006). Binding of CCL2 (also known as monocyte chemoattractant protein-1 (MCP-1)) to CCR2 is involved in the release of monocytes from BM to PB (Jung et al., 2015; Serbina and Pamer, 2006). Interestingly, the production of CCL2 in the proximity of BM vascular sinusoids attracts monocytes and thus egress of monocytes occurs from BM (Shi and Pamer, 2011). Interestingly, in a study by Shi et al it was demonstrated that the lack of CCL2 production by BM endothelial cells significantly reduced monocyte egress from BM into the circulation (Shi et al., 2011). Furthermore, it was reported that CXCL12/CXCR4 signalling can upregulate CCL2 in the BM niche and thus CCR2-positive monocytes would egress from BM via CCL2/CCR2 signalling (Jung et al., 2015).CCL7 (or MCP-3) is another ligand for CCR2 which was stated to have a key role for efficient egress of monocytes from BM (Tsou et al., 2007). However, more investigations are required to address whether and to what extents BM SECs affect the egress of monocytes from BM.

3.3. Egress of B-lymphocytes from bone marrow

Despite the diversity of BM cell populations, lymphocytes are enriched within sinusoids, suggesting that there might be lymphocyte loading of sinusoids (Pereira et al., 2009). One of the signalling pathways which has been debated regarding its role in governing the egress of B cells from BM is the S1P/S1P receptor signalling pathway. It has been reported that S1P/S1P receptor signalling is involved in regulating egress of immature B cells (Pereira et al., 2010). With this regard it was demonstrated that S1P receptor deletion in mice led to egress of immature B cells from BM (Cinamon et al., 2004). Furthermore, S1P expressed by platelets, vascular endothelial cells, and erythrocytes attract B cells from where the S1P concentration is low (Pieper et al., 2013). Thus, these studies propose that S1P signalling has a role in regulating B cell egress from BM. However, further studies are required to investigate whether BM SECs express S1P and whether BMSE-derived S1P affects the egress of immature B cells from BM.

It has been demonstrated that B cells require CXCR4 and VLA4 for retention in BM parenchyma. However, while VLA4 is indispensable for B cell retention in the sinusoids, CXCR4 is dispensable (Cyster and Schwab, 2012). Studies by Beck et al demonstrated that CXCR4 controls B lineage cell motility in BM, while developing B cell migration is strictly dependent on VLA-4/VCAM-1 signalling (Beck et al., 2014). Furthermore, adhesion of pre- and pro- B cells to $CXCL12^{+}$ cells was

reported to be mediated via VLA-4/VCAM-1 signalling (Tokoyoda et al., 2004). *In vitro* studies showed the migration of $CXCR4^+$ pre- and pro- B cells towards CXCL12 and it was found that CXCL12 promoted the proliferation and survival of $CXCR4^+$ pre- and pro- B cells by acting synergistically with c-kit ligand (Tokoyoda et al., 2004). However, a recent study by Fistonich et al described molecular mechanisms governing proB, preB cell adhesion to CXCL12-expressing cells and retention in BM (Fistonich et al., 2018). This study demonstrated that proB and IL-7+ cells create a cell circuit regulated by IL-7R signaling, which regulates CXCR4 and focal adhesion kinase (FAK) expression and controls proB cell movement owing to enhanced adhesion to $IL\text{-}7^+CXCL12^{hi}$ cells. In pre B cells, however, this circuit system is disrupted, leading to increased CXCR4 and reduced FAK/α4β1 expression by preB cells, establishing a fast-moving and lower-adhesion state for preB cells. Therefore, these studies suggest the important roles of CXCL12/CXCR4 signalling and VLA-4/VCAM-1 signalling in regulating B cell development and homeostasis within BM and B cell egress from BM.

Apart from the potential role of CXCL12/CXCR4 signaling pathway, cannabinoid receptor 2 (CB2), expressed by B cells (Fig. 1), was proposed to promote VLA-4/VCAM-1-mediated adhesion of B cells to BM SECs (Pereira et al., 2009). Interestingly, 2-arachydonoyl glycerol (known as 2-AG), the ligand of CB2 receptor, was reported to be produced by mouse hepatic SECs (Wojtalla et al., 2011) and human endothelial cells (Sugiura et al., 1998).

Taken together, it seems that CXCL12/CXCR4 and VLA-4/VCAM-1 are two important signalling pathways which may independently or together impact the egress of immature B cells from BM.

3.4. Contribution of bone marrow sinusoidal endothelial cells to the release of platelets from megakaryocytes in the bone marrow

Megakaryocytes (MKs) are BM specialised cells that produce platelets (Psaila et al., 2012). Kopp et al showed the positive correlation between MK numbers and BM sinusoidal microvascular density (Kopp et al., 2006). This study also stated the dependence of MK development on properly functional BMSE, since the disruption of vascular remodelling resulted in selective loss of MKs. Early studies by Tavassoli and Aoki showed that MKs are directly in contact with BM sinusoids (Tavassoli and Aoki, 1981). Mature MKs are located at a close proximity of abluminal surface of sinusoids where they extend transendothelial pseudopods to produce platelets.

Furthermore, MKs have been shown to be attracted to the BMSE in response to fibroblast growth factor 4 (FGF-4) and CXCL12 (Avecilla et al., 2004). FGF-4 promotes adhesion of MKs to VCAM-1 (expressed on BM SECs), via upregulation of VLA-4 on the surface of MKs (Johns and Christopher, 2012) (Fig. 1). Chemoattractant CXCL12, also produced abundantly by BM SECs, is known to attract MKs.

Moreover, compared to other endothelial cells such as HUVECs, BM SECs are more specialised in regard to supporting MK differentiation (Rafii et al., 1995). BM SECs supports MK differentiation possibly via secretion of the thrombopoietic cytokines interleukin-6 (IL-6) and c-kit ligand (Rafii et al., 1997). Direct contact of $CD34^+$ cells and endothelium showed greater numbers of $CD34^+$ cells differentiating into MK progenitors (Rafii et al., 1995).

BM SECs affects the fate of MKs and their release of platelets by regulating the production of ECM proteins for MKs. While some early studies observed that the distribution of collagen type IV and laminin, two ECM proteins produced by SECs, is absent at the MK/SEC interface (Hamada et al., 1998), some other studies showed that collagen type IV, which is produced by SECs (Table 1), supports proplatelet formation (Nilsson et al., 1998; Pallotta et al., 2009). Glycoprotein Ib (GpIb), which is deficient in patients with Bernard-Soulier syndrome, contains binding sites for adhesion for plasma glycoprotein von Willebrand Factor. Since von Willebrand Factor is expressed on endothelial cells, GpIb presence is crucial for adhesion of platelets to the endothelium (Geddis and Kaushansky, 2004), proposing its importance in supporting platelet formation. Consistently, *in vitro* studies showed that antibodies against GPIb significantly inhibited the formation of proplatelets (Balduini et al., 2011; Takahashi et al., 1999).

Furthermore, fibronectins, which are abundant in BM vascular niche and also expressed by SECs, have a potential role in platelet release. Studies showed that VLA-4 and VLA-5, activated by fibronectins, contribute to the formation of proplatelets via increased activation of extracellular signal–regulated kinase 1/2 (Erk1/2) (Matsunaga et al., 2012). In addition, other necessary factors for platelet release could also include mechanical forces and blood flow-induced hydrodynamic stress which shear off fragments of megakaryocyte protrusions, resulting in platelet release into the circulation (Kacena et al., 2006; Wang et al., 1998). Consistently, fluid shear forces in sinusoids were demonstrated to support the intravascular release of fragments protruding from MKs (Dunois-Larde et al., 2009; Junt et al., 2007).

Collectively, based on the stronger preference of MKs to interact with BM SECs than other types of endothelial cells, and also considering the involvement of BMSE in the MK development by providing chemoattractants, adhesion molecules, and ECM proteins to MKs, BMSE plays a key role in release of platelets from BM.

3.5. Egress of reticulocytes from bone marrow

Reticulocytes are immature red blood cells which are developed within the BM and then egress into the circulation to eventually give rise to mature red blood cells (Ah-Moye et al., 2014). In order to proliferate and differentiate within the BM, erythroblasts are located within erythroblastic islands which are composed of erythropoietic progenitor cells attached to a central macrophage (Wang et al., 2013). Previous studies have demonstrated that the erythroblastic islands adjacent to the BM sinusoids contain mature erythroblasts, while immature erythroblasts are populated away from the BM sinusoids in the erythroblastic islands (Yokoyama et al., 2003). In order to egress into the circulation, mature reticulocytes require to detach from the central macrophages and migrate into the circulation through BMSE (Manwani and Bieker, 2008). In addition, early studies showed that reticulocytes undergo significant deformation to pass through the BM sinusoidal pores which are made at the time of cell egress (Lichtman and Santillo, 1986).

Several studies showed that BMSE can contribute significantly in proper egress of reticulocytes from BM. It has been shown that the attenuation of BM SECs cytoplasm occurs at the site of cell egress, facilitating the egress of reticulocytes from BM (Lichtman and Santillo, 1986). Furthermore, the egress of reticulocytes through the BM sinusoidal endothelial pores needs higher pressure in the direction of the sinusoids (Yokoyama et al., 2003), and pre-existing pressure across the sinusoidal membrane drives the reticulocytes to egress through the sinusoidal pores (Lichtman and Santillo, 1986). Pioneering studies on the process of reticulocytes egress from BM revealed that BMSE undergo several alterations by which the egress of reticulocytes are facilitated/regulated (Chamberlain and Lichtman, 1978). Of such, at the time of red cell egress through BM SECs, BM SECs slide over each other in response to the luminal pressure, and subsequently sinusoids become dilated, leading to increase of the BM sinusoidal surface area and thinning the BM SECs, which facilitate the egress of mature reticulocytes into the circulation. In addition, the presence of vesicles containing a flocculant substance in the BMSE at the time of reticulocyte egress suggested that these vesicles are lysosomes and create areas of cytoplasm suitable for cell migration by i) autolysis of the endothelium, and ii) discharging their contents into the cytoplasm and causing segmental destabilization in BM SECs (Chamberlain and Lichtman, 1978). Another mechanism by which BM SECs can affect the mobilisation of reticulocytes from BM is the ability of BMSE to regulate their cell surface positive/negative charge. It has been demonstrated that BMSE reduce the expression of cell surface sialic acids by which the

negative charge of BM SEC cell surface is reduced (Soda and Tavassoli, 1984). This phenomenon leads to the attraction and mobilisation of mature reticulocytes which have negative cell surface charge toward the BMSE and permits cell-cell interaction between reticulocytes and BM SECs and eventually egress of reticulocytes from BM (Soda and Tavassoli, 1984). Therefore, by undergoing significant physical alterations/adaptation, BMSE can regulate/facilitate the egress of reticulocytes from BM.

The molecular interactions between mature reticulocytes and BM SECs have not been sufficiently explored. However, it has been widely reported that reticulocytes express a wide range of adhesion molecules including α4β1 and ICAM-4, which interact with corresponding receptors of VCAM-1 and αv, respectively, expressed by central macrophages within the erythroblastic islands near the BM sinusoids (Manwani and Bieker, 2008). It is known that VCAM-1 and αv receptors are expressed by endothelial cells and thus it may be speculated that reticulocytes can communicate with BM SECs via their surface adhesion molecules. It should be noted that αv heterodimerizes with β3 to form αvβ3 integrin which has been detected in BM endothelial cells (Vandoorne et al., 2018). Moreover, BMSE-derived ECM proteins can regulate the migration of mature reticulocytes from BM. It has been stated that the affinity of maturing reticulocytes (via α4β1 and α5β1) for fibronectin reduces with maturation (Telen, 2000), which can lead to their passing through the matrix around the sinusoids and egress (Chasis and Mohandas, 2008). However, unlike fibronectin, the presence of laminin, particularly laminin 10/11, which are present in the subendothelial basement membrane of bone marrow sinusoids (Gu et al., 1999), can function to localize reticulocytes to the BM sinusoids (which is considered as an initial step of reticulocytes egress into the peripheral circulation) (Chasis and Mohandas, 2008). Therefore, the BMSE can regulate/facilitate the egress of reticulocytes into the circulation by providing an appropriate physical transendothelial route and by providing an appropriate extracellular matrix environment to the reticulocytes.

3.6. Bone marrow sinusoidal endothelium and egress of haematopoietic stem/ progenitor cells from bone marrow

Apart from the potential roles of BMSE in controlling egress of mature and also more specialised cells from BM, BMSE also potentially contributes/regulates the egress of HSPCs from BM. Hypothetically, the mechanism of egress of HSCs or HSPCs from BM might be somewhat similar to the process of their homing into the BM (discussed later). In this section we aim to address the potency of BMSE-derived chemoattractants, adhesion molecules and other potential factors which might directly and/or indirectly influence migration of HSPCs from BM (Fig. 1).

3.6.1. CXCL12/CXCR4 and VLA-4/VCAM-1

BM endothelial cells have been reported to facilitate the diapedeses of stem cells more than endothelial cells of other organs (Imai et al., 1999). HSPCs are anchored to their niche in the BM due to interactions of CXCL12 and VCAM-1, provided by niche, with their corresponding receptors CXCR4 and VLA-4 expressed on HSPCs (Levesque et al., 2010) (Fig. 1). Treatment with AMD3100 (an antagonist for CXCR4 and a rapid stem cell mobilizer) was demonstrated to induce cytokine c-kit ligand abundance preferentially on BM SECs, and cause rapid HSPC mobilization from BM via shedding and releasing of CXCL12 and c-kit ligand from BM (Itkin et al., 2016). In the steady state in mice, CXCL12-derived from BM stromal cells was shown to be a pivotal factor for the egress of haematopoietic progenitor cells from BM, but not for egress of mature leukocytes (Dar et al., 2011). It should be noted that the extent, temporal and spatial patterns and mechanisms for the activation of the CXCL12/CXCR4 signalling pathway may vary in different HCs for mobilisation into the circulation. For instance, Petit et al. demonstrated that administration of G-CSF (a widely used BM cell mobiliser that interferes with CXCL12/CXCR4 axis) led to gradual reduction of CXCL12 levels but an increase in CXCR4 expression within the human and murine BM, which resulted in egress of HSCs from BM (Petit et al., 2002). Similarly, in a study by Katayama et al, decreased CXCL12 expression was demonstrated in bone following G-CSF therapy in mice, which negatively affected the egress of haematopoietic stem cells from BM (Katayama et al., 2006). In contrast, exogenously elevation of CXCL12 resulted in increases in numbers of HCs with repopulating capacity, progenitor cells, and precursor cells (Hattori et al., 2001). Taken together, the temporal and spatial changes in CXCL12 and/or CXCR4 expression determine the role and the extent of importance of the CXCL12/CXCR4 signalling for haematopoietic (stem-) cell egress from BM.

CXCL12 can also trigger activation of CD44 (receptor for hyaluronic acid) on HSCs which binds to hyaluronic acid (expressed by BM endothelium (Avigdor et al., 2004)) and functions as a ligand for E-selectin, and L-selectin (Schroeder and DiPersio, 2012). Exposure of $CD34^+$ cells to CXCL12 has been reported to increase the affinity of VLA-4 to VCAM-1 (Sison and Brown, 2011). Interestingly, the homing of HSCs in adult spleen and BM was prevented by inhibition of VCAM-1, CD44, and VLA-4 (Papayannopoulou et al., 1995; Vermeulen et al., 1998; Williams et al., 1991). In humans, mobilization of HSCs following disruption of VLA-4/VCAM-1 axis has been evident (Zohren et al., 2008). In the BM niche, SECs also express E-selectin (Yin and Li, 2006) and soluble factors like c-kit ligand which binds to c-kit (expressed on HSCs) and promotes HSC growth and proliferation (Brandt et al., 1992), suggesting a key role of BM SECs in haematopoiesis and possibly for HSPC migration from BM.

3.6.2. Adhesion molecules

Adhesion molecules such as ICAM-1, ICAM-2, VCAM-1, L-selectin, and E-selectin have been suggested to be involved in egress of stem cells from BM. The loss of CAMs and acquisition of membrane structure facilitate normal egress of cells from BM (Cavenagh et al., 1994). In addition, it was reported that the egress of CD34+ progenitor cells from BM was due to selectin-mediated adhesive interactions with BM endothelium (Cavenagh et al., 1994). However, further studies are required to elaborate the role of such adhesion molecules and their involvement in egress of HSCs from BM to PB.

3.6.3. G-CSF- and chemotherapy- induced HSC egress and vascular integrity

The exact mechanisms by which HSCs egress from BM following G-SCF therapy or in combination with chemotherapy are still unclear (Szmigielska-Kaplon et al., 2014). It should be taken into consideration that chemotherapy agents and/or G-CSF influences the physiology of BM sinusoids (Hassanshahi et al., 2017), resulting in the egress of HSCs from BM. For example, in mice, it was observed that mobilization of HSCs from BM following G-SCF administration was associated with reduced expression of VCAM-1 in BM endothelial cells (Salvucci et al., 2012). Apart from the role of G-CSF in egress of HSCs from BM, chemotherapy can also affect the process of HSC egress from BM. It was reported that the high dose chemotherapy in animal models and patients induced BM niche damage, leading to failure of stem cell mobilization to BM, following transplantation (Bendall and Bradstock, 2014). In another similar study, the high-dose chemotherapy damaged the sinusoidal endothelium of BM and thus altered the interaction between BM SECs and CD34+ cells and their ability to mobilize these cells into the circulation (Liesveld et al., 1994). It was also shown that reducing the loss of endothelial cells in the BM niche following neurotoxic chemotherapy would significantly overcome failure of the autologous donor mobilization and thus enhance regeneration of the haematopoiesis (Lucas et al., 2013). Therefore, it seems that alteration of the physiology/function of BMSE could be one of the mechanisms involved in G-CSF and chemotherapy-induced HSC egress from BM.

Collectively, as revealed from investigations into the mechanism

how BM retains HSPCs and how chemotherapeutic- and mobilising agents induces the egress of HSPCs from BM, the egress of HSPCs from BM might be obtained through perturbing VLA-4/VCAM-1 and CXCL-12/CXCR4 signalling axes within the BM.

4. The role of bone marrow sinusoidal endothelium in egress of leukemic cells

Some early studies had investigated whether BMSE impacts egress of cells in pathological conditions, with some reporting that BMSE may not impact the egress of cells in a pathological conditions (Bruyn et al., 1977), and others stating that the egress of cells in a pathological state might be due to breakdown or alterations in marrow-blood barrier (Chen et al., 1972). Despite these early controversial reports, more recent studies, as discussed below, have shown that BMSE does affect cell egress in pathological conditions through its altered physiology. It was reported that patients with acute leukaemia and preleukemia diseases, such as myeloproliferative neoplasms, myelodysplastic syndromes, had higher levels of angiogenesis and vascularization in BM (Ayala et al., 2009). In addition, enhanced angiogenesis as induced by leukemic cells increase survival of leukaemia cells in the BM (Mirshahi et al., 2009; Perez-Atayde et al., 1997) and potentially can affect the egress of leukemic cells from BM. Moreover, while under normal conditions the passage of myeloid blood cells from BM into the circulation is restricted to mature forms of the cells, in the abnormal conditions such as in AML, the selectivity in the egress of myeloid cells into the PB is disturbed, and thus many immature cells appear in the circulation (Bruyn et al., 1977). Since one of the major obstacles in leukaemia treatment now is excessive egress of leukemic cells from BM and invasion into the various tissues/organs, studying the potential role of BMSE in egress of leukemic cells is important.

4.1. Altered ECM components of bone marrow sinusoidal endothelial cells by leukemic cells

In an early study, Berger et al examined interactions between leukaemia blast cells with ECM proteins such as laminin, collagen type IV, and fibronectin which are produced by BM SECs, and observed an inverse correlation between binding of blasts cells to ECM (Berger et al., 1994). This study concluded that the ability of cells to egress into the PB depends on the degree of cell binding to the ECM of haematopoietic microenvironment (Berger et al., 1994). It has been also stated that malignant B cells interact with the fibronectin and HA of ECM of BM niche via VLA-4 and CD44, respectively (Burger and Sipkins, 2012). In both acute myeloblastic leukaemia (AML) and acute lymphoblastic leukaemia (ALL) cells, β1 and to the lesser extent β2 integrins were shown to be important for interactions with cellular and extracellular microenvironment in BM (Bendall et al., 1993). Studies have proposed that such interactions between the leukemic cells and ECM components are important for acute leukemic cell behaviour and remission following chemotherapy (Bradstock and Gottlieb, 1995). BM endothelial cells produce a wide range of matrix components such as hemonectin, sialoadhesion, thrombospondin, and tenascin, which are likely to be involved in adhesion of both normal haematopoietic and leukemic cells (Bradstock and Gottlieb, 1995). In leukaemia, it has been stated that the BM stem cell niche, where the endothelial cells are in close proximity with stem/progenitor cells, is hijacked by leukaemia cells (Schroeder and DiPersio, 2012). In addition, it was observed that the adherence of CD34+ leukemic cells to the HUVECs was due to an increase in expression of E-selectin, but not VCAM-1, in HUVECs (Liesveld et al., 1994). Therefore, while further studies are required to confirm this, it might be speculated that the expression of ECM components by BM SECs can be modulated by leukaemia cells as they need to migrate from BM.

AML blasts, similar to normal HSCs, express a variety of adhesion molecules such as CD44, VLA-4, CD117, and receptors such as CXCR-4, which mediate the interactions of AML blasts with BM stromal cells, promote survival and proliferation of both cell types (Nervi et al., 2009). Alterations in molecular expression and thus adhesive phenotypes of AML cells facilitates their egress from BM to the circulation, as well as governing proliferative advantages in the BM (Cavenagh et al., 1994). Consistently, early studies showed that AML blast cells adhere to human ECs via selectin- and VCAM-1-mediated adhesive interactions (Cavenagh et al., 1994). Among AML cells, some adhere to fibronectin and laminin in their microenvironments via β-integrin VLA-4, VLA-5, and VLA-6 (Kortlepel et al., 1993). In addition, CD31 (also known as PECAM-1) was expressed in all cases of AML cells, which could bind to the BM endothelium (Bradstock and Gottlieb, 1995). AML cells can also bind to the endothelium by interactions of VLA-4 and sialylated Lewis X on AML cells with VCAM-1 and E-selectin of endothelium, respectively (Cavenagh et al., 1993).

In the case of CML, CML progenitors do not adhere to fibronectin nor BM stroma; but they adhere to collagen IV and laminin, whereas normal progenitors do not (Verfaillie et al., 1992). Consistently, it was suggested that one of the potential reasons of early egress of morphologically mature CML granulocytes from BM is due to lowered adhesion of fibronectin in those cells (Vijayan et al., 1994). Similarly, CML granulocytes showed a considerably decreased binding to P-selectin, when compared to normal cells, which might implicate the early egress of those cells from BM (Vijayan et al., 1997).

Since such interactions confers cell adhesion-mediated drug resistance by which the malignant cells become resistant to chemotherapy (Nervi et al., 2009), understanding the interactions between leukemic cells with their niche, particularly with BM SECs, may provide better treatments for those diseases. It might be worthwhile to speculate that AML/CML cells manipulate the proper function of BM SECs in order to provide ECM proteins to the cancer cells by which their egress can be facilitated.

4.2. Altered expression of proteolytic enzymes and leukemic cell egress

Another feature of leukemic cells by which their egress could be facilitated is their ability to produce gelatinase that degrades collagen type IV, which is the major component of basement membrane produced by BM SECs (Van Agtmael and Bruckner-Tuderman, 2010). In addition, elastase, which is normally produced by neutrophils (Yang et al., 2016), was illustrated to increase expression of E-selectin on endothelial cells, and thus facilitating the motility and dissemination of cancer cells (Nozawa et al., 2000). It was also found that elastase degrades VCAM-1, ICAM-1, P-selectin, CXCL12, and c-kit ligand (Lapidot and Petit, 2002) and facilitates the process of transendothelial migration (Ginzberg et al., 2001).

In AML cells, the expression of elastase was found to be regulated by CXCL12, and inhibition of elastase activities impaired homing of human AML cells in the BM (Tavor et al., 2005). Interestingly, the proliferation of human AML cells was also shown to be elastase-dependant (Tavor et al., 2005). The latter study showed that the inhibition of elastase reduced the adhesion of AML cells to the BM endothelial cells, and concluded that proliferation and egress of AML cells from BM are regulated by cell surface elastase which is CXCL12-dependant. Moreover, elastase, like other proteolytic enzymes such as MMPs, is involved in the process of G-CSF-induced mobilization of stem/progenitor and mature cells (Tavor et al., 2005). As mentioned above, neutrophils and monocytes pave the way for egress of other cells from BM; and therefore, it might be postulated that neutrophils can also pave the way for egress of leukemic cells from BM by (over) expression of elastase, thereby expression of BM SEC-derived adhesion molecules and chemokines required for leukemic cell egress can be regulated.

A study by Song et al found that the increased invasiveness and the acquired drug resistance feature of human AML cells were obtained via upregulation of MMP-2 (Song et al., 2009). Consistently, MMPs, particularly MMP-2 and MMP-9 were reported to be important for migration

of human AML cells (Hatfield et al., 2010). While CXCL12 signalling can be altered by MMPs, CXCL12 induces secretion of MMP-9 and MMP-2 in $CD34^+$ cells (McQuibban et al., 2001). As Hartfield states, CXCL12, along with MMP-2 and MMP-9, might function as a regulator for AML cell egress (Hatfield et al., 2010). Therefore, BMSE-derived CXCL12 might contribute to the egress of AML cells via promotion of MMPs in the egressing cells.

Collectively, the cellular behaviour/functions of BMSE can be altered during pathological circumstances such as haematological malignancies. The BMSE manipulated by leukaemia cells thus provides factors required for their egress from BM. Therefore, it makes BMSE a good target for further investigations into the strategies to inhibit migration of leukaemia cells from BM.

4.3. Potential roles of CXCL12/CXCR4 and VLA-4/VCAM-1 signalling pathways in egress of leukaemia cells from bone marrow

Moreover, production of CXCL12 and IGF-1 (also expressed by hepatic ECs (Zimmermann et al., 2000)) by BM stromal cells was shown to increase in patients with acute leukaemia (Mirshahi et al., 2009), and CXCR4 has been found to be commonly expressed by a variety of leukaemia cells (both myeloid and lymphoid) (Mohle et al., 2000). In addition, CXCL12/CXCR4 signalling pathway has been found to increase the affinity of VLA-4 to VCAM-1 (Burger and Sipkins, 2012). Thus, CXCL12 has been implicated to be a very important element in promoting adhesion of malignant cells to the blood vessels in the BM (Sipkins et al., 2005), and CXCL12/CXCR4 axis has been shown to have a substantial role in egress of leukemic cells from BM. Furthermore, as CXCL12, provided in BM niche, would confer proliferation and survival of leukemic cells, targeting CXCL12/CXCR4 axis might overcome the resistance of leukemic cells to chemotherapy (Sison and Brown, 2011). Interestingly, targeting CXCL12/CXCR4 axis has been reported both preclinically and clinically to be an effective approach to treat AML, ALL, chronic myeloblastic leukaemia (CML), and chronic lymphoblastic leukaemia (CLL) diseases (Sison and Brown, 2011).

VLA-4 integrins also cooperate with the chemokine receptors of malignant B cells, including multiple myeloma, CLL, and mantle cell lymphoma to adhere to the BM stromal cells (Burger and Sipkins, 2012). Leukaemia cell lines and primary AML blasts were shown to express VLA-4 consistently (Sison and Brown, 2011), and it has been suggested that VLA-4 is a prognostic indicator of paediatric AML (Walter et al., 2010) and CLL (Burger and Sipkins, 2012). Consistently, it was also revealed that adhesion of leukaemia cells to stromal cells was interrupted by targeting either VCAM-1 or VLA-4 (Liesveld et al., 1993). Similarly, Spiegel et al showed that treatment of precursor-B ALL cells with VLA-4 antibodies resulted in considerably less homing of the cells in the BM (Spiegel et al., 2004). It should be noted that VLA-4/VCAM-1 adhesion pathway may be similarly important as the CXCL12/CXCR4 axis pathway, as both are important for egress of haematopoietic (stem-) cells and leukemic cells. However, while this VLA4/VCAM1 adhesion pathway is involved in the regulation of mobilisation of haematopoietic (stem-) cells in a physiological condition, it is dysregulated in a pathological condition such as leukemia (probably by leukemic cells).

In T-cell acute lymphoblastic leukaemia (T-ALL), leukaemia initiating cells, which are believed to be responsible for relapse following chemotherapy, reside within BM niches, which are composed of CXCL12-produing SECs and perivascular cells (Sugiyama and Nagasawa, 2015). Pitt et al demonstrated that T-ALL cells are directly in contact with CXCL12-producing BM stroma. This study further showed that BMSE-derived CXCL12 impeded tumor growth, while the adventitial cells-derived CXCL12 was dispensable (Pitt et al., 2015), which may imply the importance of BMSE-derived factor for survival and proliferation of leukemic cells. This study suggests that targeting CXCL12/CXCR4 signalling could be a robust therapeutic approach for this devastating cancer (Pitt et al., 2015). BMSE might also have a role in development of B-ALL as adhesion of pre-B lymphoid cells to their microenvironments is facilitated by their binding to fibronectin via VLA-4 and VLA-5 expressed by ALL cells (Makrynikola and Bradstock, 1993). Thus, potential interactions between BMSE (by providing required chemoattractants and ECM proteins) and ALL cells might be necessary for ALL cells to egress from BM. However, whether BM SECs are influenced by ALL cells to provide necessary egressing factors remains a mystery and thus warrants further studies.

Therefore, similar to the potential of CXCL12/CXCR4 and VLA-4/VCAM-1 signalling pathways for egress of mature and HSPCs from BM, aforementioned signalling pathways can also be important for migration of leukaemia cells from BM, and targeting the VLA-4/VCAM-1 axis, alone or in combination with targeting CXCL12/CXCR4 signalling pathway, may provide better approaches to manage the egress of leukemic cells into the circulation.

5. The role of bone marrow sinusoidal endothelium in haematopoietic stem cell homing and engraftment

Apart from the roles of BMSE in retaining and regulating proliferation, differentiation, and egress of HSCs, BMSE can also be involved in facilitating homing of HSCs (Asri et al., 2016). Due to the importance of the biological process and the significance of BM/HSC transplantation in clinical practice, it is crucial to investigate the cellular and molecular mechanisms underlying the homing of the circulating HSCs into the BM. With this regard, pioneering studies demonstrated the importance of BM microvascular system (by providing required adhesion molecules and chemokines) in homing of HSPCs into the BM (Frenette et al., 1998; Hidalgo et al., 2002; Mazo et al., 2002; Mazo and von Andrian, 1999). It could be hypothesized that the process of HSCs homing into the BM is somewhat similar to the process of HSC egress from BM into the circulation via coordination between chemokines, selectins, and integrins which has been reported to be necessary for homing of HSCs into the BM (Asri et al., 2016). Hypothetically, it might be even very similar to the process of transendothelial migration of inflammatory cells into the injury sites, in which a complex but regulated interaction between circulating inflammatory cells and endothelial cells exist. Therefore, considering the unique molecular features of BMSE, herein we address the potential role of BMSE in facilitating the homing of HSCs into the BM and also in the success of BM transplantation.

5.1. The role of bone marrow sinusoidal endothelium in homing of HSCs into the bone marrow

BMSE plays a crucial role in facilitating the initial steps of HSC homing (Perlin et al., 2017b). BMSE not only directs HSCs to the BM, but also functions as a molecular brake and affects the process of migration of HSCs into the BM by slowing the process of cell homing under hemodynamic shear stress (Sackstein, 2016).

The homing of HSCs occurs via rolling and firm adhesion of HSCs to the BMSE and transendothelial migration of HSCs across the endothelium/ECM barrier and subsequent anchoring of HSCs to their niche (Mosaad, 2014). The coordinative interactions between molecules expressed by BMSE including E- and P-selectin, VCAM-1, ICAM-1, ICAM-2, ICAM-3, and CXCL12 with corresponding molecules of HSCs results in homing of HSCs into the BM (Mosaad, 2014) (Fig. 1). PSGL-1, CXCR4, and type 1 receptor for S1P are the most important receptors involved in HSPC homing into the BM (Xia et al., 2004) (Fig. 1). Constitutively expression of P-selectin by BM SECs can interact with mucin, known as PSGL-1, expressed on HSPCs, resulting in homing of HSPCs (Xia et al., 2004). Loss of function studies demonstrated that the homing of HSCs was significantly impaired due to E- and P-selectin deficiency (Frenette et al., 1996; Mazo and von Andrian, 1999; Schweitzer et al., 1996). In addition, studies by Adamiak et al revealed that expression of S1P within the BM plays a substantial role in homing

of HSPCs, and also suggested the potential role of HA and CD44 interactions for HSPC homing (Adamiak et al., 2015). Moreover, the rolling of HSCs to the BMSE has been reported to be mediated via expression of E- and P- selectins on BM SECs. Following rolling, expression of ICAM-1 and VCAM-1 adhesion molecules by BM SECs then is promoted, by which further firm attachment of HSCs to the endothelial cells is in turn granted (Suarez-Alvarez et al., 2012). Interestingly, HSCs express corresponding molecules to ICAM-1 and VCAM-1, called function-associated antigen 1 (LFA-1) and VLA-4, respectively. Therefore, by providing adhesion molecules to the HSPCs, BM SECs can interact with HSPCs and facilitate/regulate their homing into the BM.

Recent studies in zebrafish revealed that niche-derived CXCL8/CXCR1 signaling increases HSPC niche colonization via remodelling the vascular caudal haematopoietic tissue niche (Blaser et al., 2017). CXCR 1 and its ligand CXCL8 are expressed in endothelial cells in caudal haematopoietic tissue of zebrafish, and this CXCL8/CXCR1 axis modulates the HSPC retaining and the number of cell divisions in the vascular niche in the BM (Perlin et al., 2017a). Interestingly, enhanced expression of CXCL12 leads to the increased volume of the vascular niche, and through this mechanism CXCR1 increases the HSPC niche engraftment (Blaser et al., 2017). Moreover, expression of CXCL12 can enhance attachment of LFA-1 and VLA-4 to their corresponding endothelial ligands (Suarez-Alvarez et al., 2012). After rolling and attachment, degradation of basement membrane is then facilitated by expression of MMPs; and following extravasation, retention of HSCs is provided by expression of CXCL12 in the niche (Suarez-Alvarez et al., 2012). Similar to its role in retaining and in enabling rapid mobilization of HSCs into the circulation, the importance of CXCL12/CXCR4 axis in homing of HSCs into the BM has been reviewed previously (Georgiou et al., 2010) (Fig. 1).

Modifying the levels of expression and functions of molecules involved in BM homing has been reported to increase the rate of HSCs homing. This strategy can enhance the expression of cell surface receptors and/or increasing the biological adhesiveness function of HSCs (Ratajczak and Suszynska, 2016). Apart from the role of adhesion molecules in homing of HSCs, reduced BM sinusoidal flow velocities and low shear stress were also found two key elements of BMSE that facilitate homing of HSPCs into the BM (Bixel et al., 2017). Also, in an elegant study by Smith-burden it was demonstrated that Roundabout homolog 4 (known as ROBO4) protein, expressed by BM SECs, is necessary for homing of HSCs, but is dispensable for egress of HSCs from. In all steps mentioned above, BMSE potentially can play a crucial role in regulating/facilitating the homing of HSCs into the BM. Therefore, BMSE seems to be an important part for the homing and also engraftment of HSPCs by providing ROBO4, CXCL12, HA, S1P, adhesion molecules, fine-tuned flow velocities, and sheer stress.

5.2. *Bone marrow sinusoidal endothelium and the success of haematopoietic cell transplantation*

As a potentially curative therapeutic approach, haematopoietic cell transplantation (HCT) is conducted for treatment of various non-malignant and malignant haematopoietic diseases. The success of HCT mainly depends on the engraftment of HSCs and reconstitution of haematopoiesis. The conditioning regimen, i.e. chemo-radiotherapy, is an essential component of autologous and allogenic HCT and is usually conducted in order to reduce the tumour burden, and provide adequate immunoablation to prevent graft rejection (Gyurkocza and Sandmaier, 2014). Since chemo-radiotherapy can damage BMSE which could affect the process of HSPC homing and engraftment, it is very important to consider or anticipate the chemo-radiotherapy-induced BMSE damage (Hassanshahi et al., 2017). As many studies revealed, radiotherapy (Hooper et al., 2009; Slayton et al., 2007) and chemotherapy caused BMSE damage (Hassanshahi et al., 2017, 2019; Kopp et al., 2005) and as a consequence, reconstitution of haematopoiesis can be affected. Chemotherapy and irradiation can also alter the fine-tuned level of BM oxygenation, resulting in negative effects on the process of cell trafficking (Spencer et al., 2014). Apart from delivery of oxygen by BMSE into the BM, BMSE provides paracrine growth factors, called “angiocrine factors” (Rafii et al., 2016), by which regeneration and replenishment of HSPC population are supported following myeloablation (Kobayashi et al., 2010). Interestingly, as a novel therapeutic approach, *ex vivo* co-culture of HSCs and endothelial cells not only showed improved expansion of mouse and human HSPCs *ex vivo*, but also increased long-term multi-lineage engraftment and re-constitution of HSPCs *in vivo* (Butler et al., 2012, 2010; Gori et al., 2017; Hadland et al., 2015; Kobayashi et al., 2010; Poulos et al., 2015). Taken together, BMSE not only influences the HSPC retention, proliferation, differentiation and mobilization, but also maintains the homeostasis of haematopoiesis by facilitating the homing and engraftment of HSCs. Conversely, any damages to BMSE leads to imbalance of various physiological processes including cell trafficking and haematopoiesis.

6. Conclusions

BMSE is biologically very well structured and suited for rapid cell trafficking within the BM. It is now clear that BMSE has an important role in regulating cell egress from, and homing into, the BM in physiological and pathophysiological conditions. BMSE provides a wide variety of factors/molecules such as cytokines (including chemokines), adhesion molecules, and ECM proteins, which facilitate/regulate the cell egress or homing temporally and spatially. BMSE also plays a crucial role in homing and engraftment of transplanted HSPCs within the BM. In addition, it seems that the egress of leukemic cells from BM is facilitated due to remarkably altered ECM components of BM SECs by leukemic cells and interaction of BMSE with leukemic cells via CXCL12/CXCR4 and VLA-4/VCAM-1 signalling pathways. Therefore, the current review suggests that the BMSE is not merely a neutral gatekeeper for cell intravasation and extravasation, but rather is a dynamic trafficking surveillance system, thereby the process of BM cell egress can be regulated/facilitated. However, more investigations are required to elaborate the regulatory role of BMSE in the process of cell trafficking in physiological and pathological conditions.

Conflict of interest

The authors declare that they have no conflict of interest.

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