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REVIEW

Midkine as a regulator of B cell survival in health and disease

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In healthy individuals, the pool of peripheral lymphocytes is constant in size. The control of lymphoid homeostasis is the result of a very fine balance between lymphocyte production, survival and proliferation. Survival factors have been shown to play a critical role in maintaining the correct size of lymphocyte populations. Midkine, a heparin-binding cytokine was recently shown to be involved in cell proliferation, differentiation and apoptosis in various cell types including normal and malignant B cells. This review focuses on the role of midkine in the regulation of peripheral B cell survival in health and disease.

LINKED ARTICLES
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Abbreviations
ALL, acute lymphocytic leukaemia; TNFSF13B (BAFF), B cell activation factor of the TNF family; BCR, B cell receptor; BM, bone marrow; CLL, chronic lymphocytic leukaemia; FO B cell, follicular B cell; MHC, major histocompatibility complex; MIF, macrophage migration inhibitory factor; MK, midkine; NHL, non-Hodgkin lymphoma; PTPRZ1, protein tyrosine phosphatase ζ receptor

B cell differentiation

B lymphocytes arise from multipotent haematopoietic stem cells that first appear in the fetal liver. By the middle of the second trimester of pregnancy, they can be found in the bone marrow (BM), which, just before birth, becomes their exclusive home. BM B-lineage precursors proliferate and progress through differentiation steps that result in the production of immature, surface immunoglobulin (Ig)-expressing B-lymphocytes. After migrating from the bone marrow to the spleen, immature B cells pass through two transitional stages, which are known as transitional type I (T1; newly formed B cells) and transitional type II (T2), before differentiating into naive mature or marginal zone (MZ) B cells (Figure 1) (Loder *et al.*, 1999). Of the approximately 2×10^7 IgM+ B cells that are generated daily from the BM, 10% survive to enter the spleen, and only 1–3% enter the follicular B cell (FO B cell) pool (Melchers *et al.*, 1995; Su and Rawlings, 2002) (Figure 1). FO B cells (also called B-2 cells) represent the most mature B cells, developing throughout life from transitional B cells in the spleen (Casola, 2007). Mature B cells leave the spleen and recirculate throughout the periphery, remaining quiescent until they encounter their cognate antigen. FO B cells are capable of participating in both T-cell-dependent and -independent antibody responses and, in the former case, can further differentiate in germinal centres to give rise to high-affinity isotype-switched plasma and memory cells (Allman and Pillai, 2008) (Figure 1).

Regulation of mature B cell survival

The maintenance of peripheral B cell homeostasis relies on three key elements (Figure 2), (i) B cell receptor (BCR) tonic signals (e.g. Igα and Syk), (ii) the B cell activating factor, belonging to the TNF family (TNFSF13B; also known as BAFF, BlyS, TALL-1, THANK, zTNF4) (Mackay *et al.*, 2010), (iii) CD74 (invariant chain, Ii) and its ligand, macrophage migration inhibitory factor (MIF) and their downstream molecules hepatocyte growth factor (HGF) and midkine (MK). These pathways have complementary roles in B cell survival. Currently, there are indications of crosstalk between the downstream biochemical pathways of the BCR and the BAFF receptor (TNFRSF13C), such that BCR signals generate a limiting substrate for TNFRSF13C signal propagation (Cancro, 2009). The crosstalk with the MIF/CD74 induced cascade is still under investigation. Drug/molecular target nomenclature throughout this manuscript conforms to BJP's Concise Guide to PHARMACOLOGY (Alexander *et al.*, 2013).

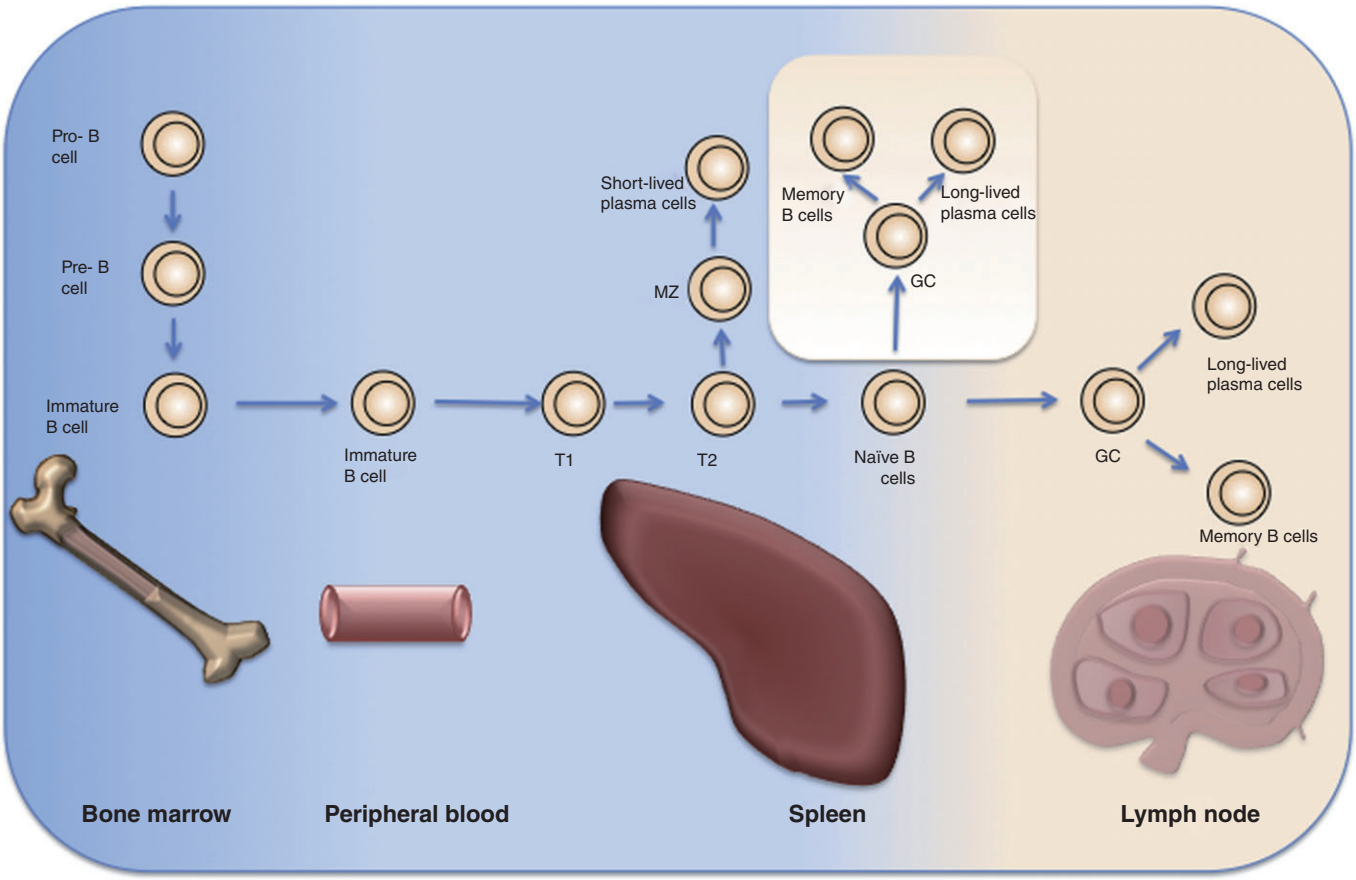

Figure 1

Multiple steps of antigen-independent (blue background) and dependent (cream background) differentiation events of B cells in the bone marrow (BM) and periphery. B cell differentiation is a multistep process. In the adult animal (similar pathways were demonstrated in the mouse and human), the early stages of B cell development occur in the BM, resulting in the formation of immature B cells. Immature B cells leave the BM and home to the spleen. These cells, now referred to as transitional 1 (T1) cells, differentiate into transitional 2 (T2) cells, which can complete their maturation to become naïve mature or marginal zone (MZ) B cells. Naïve B cells leave the spleen and recirculate *via* secondary lymphoid organs and the blood. Encounter with an antigen leads to activation of a naïve B cell and to the formation of the germinal centres (GC). Cells with a high affinity for antigens are incorporated into the long-lived peripheral lymphocyte pool and selected to differentiate into either memory B cells or long-lived plasma cells.

The BCR

Expression of a functional BCR is a key requirement for peripheral B cell survival. BCR signalling triggers maturation-state-specific signals, which can lead to differentiation, survival or apoptosis of developing B cells. The BCR-induced functional response depends on signal duration and strength, the involvement of co-receptors and the expression of intracellular signalling/adaptor proteins (Kurosaki, 2002; Bannish *et al.*, 2003; Dal Porto *et al.*, 2004). Deletion of the BCR heavy chain leads to a rapid loss of peripheral B cells (Lam *et al.*, 1997; Kraus *et al.*, 2004). Lam *et al.* (1997) demonstrated that the loss of BCR expression by conditional knockout prevents all further development from the transitional to mature B cell stages. In addition, disruption of any of the various components of the BCR signalling pathways including Bruton's tyrosine kinase, C-cell linker protein (BLANK), PI3K, PLCγ2, PKCβ or Vav leads to a loss of BCR-dependent NF-κB activation, a crucial pathway for mediating cell survival, and results in developmental arrest at the T2 to mature B cell transition (Rawlings *et al.*, 1993; Rawlings and Witte, 1994; Fruman *et al.*, 1999; Pappu *et al.*, 1999; Saijo *et al.*, 2002; Su and Rawlings, 2002; Suzuki *et al.*, 2003).

TNFSF13B (BAFF), a member of the TNF family

TNF is a prototypical member of a family of cytokines whose activity is largely determined by the cell type to which they bind, and the presence of additional protein regulators (Balkwill, 1989). Members of the TNF cytokine family fulfil crucial roles in the immune system, and are critically involved in the regulation of infection, inflammation, autoimmune disease and tissue homeostasis (Smith *et al.*, 1994). TNF family ligands are primarily expressed as trimeric type II transmembrane proteins and are often processed into soluble variants that maintain their trimeric structure. Thus, these ligands can act in an autocrine, paracrine or endocrine manner (Smith *et al.*, 1994; Walczak *et al.*, 1999). The TNF family member that has received particular attention, due to

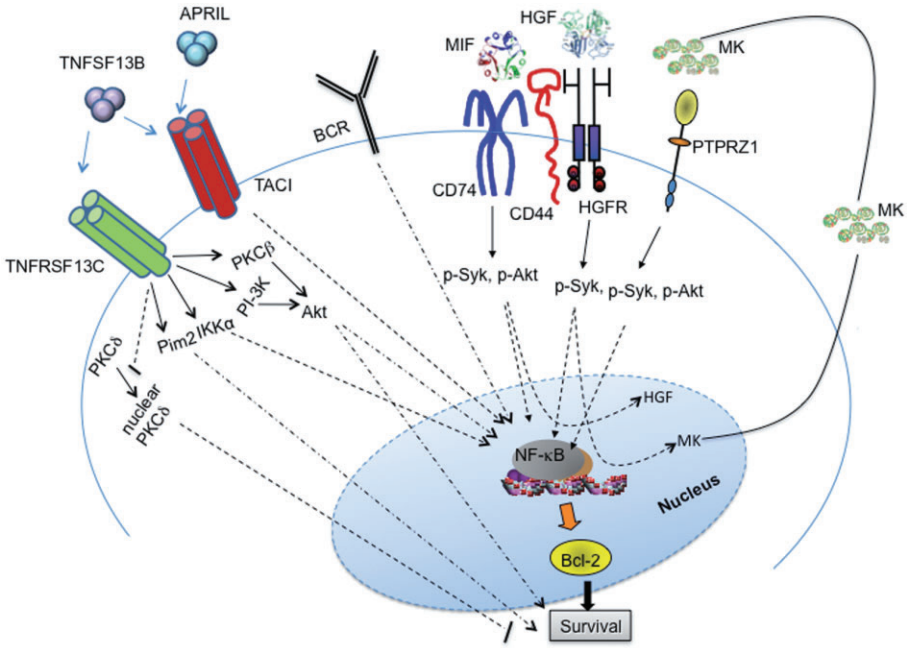

Figure 2

Schematic representation of cytokines and their receptors regulating peripheral B-cell survival. B-cell homeostasis relies on three cascades, BCR, TNFSF13B (BAFF)/TNFRSF13C (BAFFR) and MIF/CD74. The crosstalk between these cascades is shown. CD74 activation by MIF leads to the elevation of HGF and its receptor, HGFR (c-Met). HGFR engages with CD74 and CD44 on the cell membrane and, together with HGF, initiates an additional signalling pathway, leading to the up-regulation of MK. MK binding to its receptor, PTPRZ1 (RPTPζ), results in a survival pathway that involves the phosphorylation of Akt and Syk and elevation of Bcl2 levels.

its role in supporting peripheral B cell survival, is TNFSF13B, also known as BAFF, BlyS, TALL-1, zTNF4 or THANK (Schiemann *et al.*, 2001; Mackay and Browning, 2002).

TNFSF13B is a critical B cell survival and maturation factor and is expressed by multiple immune cell types and by non-lymphoid tissues (Hahne *et al.*, 1998; Nardelli *et al.*, 2001; Litinskiy *et al.*, 2002; Mackay and Browning, 2002; Mackay *et al.*, 2003; Ng *et al.*, 2005; Schneider, 2005; Mackay and Schneider, 2009; Moisini and Davidson, 2009). TNFSF13B-deficient mice lack most mature follicular and MZ B cells due to a block at the early T1 B cell stage, while B cell development in the BM is not affected (Gross *et al.*, 2001; Schiemann *et al.*, 2001). TNFSF13B-signalling induces the expression of anti-apoptotic molecules *in vivo* and *in vitro*, confirming the significant role TNFSF13B plays in promoting B cell survival (Mackay *et al.*, 1999; Do *et al.*, 2000; Hsu *et al.*, 2002).

Three types of receptors are known for TNFSF13B: B-cell maturation antigen (also known as TNFRSF17), transmembrane activator and calcium-modulator and cytophilin ligand interactor (also known as TNFRSF13B) and TNFRSF13C (also known as BR3 or BAFF-R) (reviewed in Mackay *et al.*, 2003). TNFSF13B binds with high affinity and is the sole ligand for TNFSFR13C, which accounts for most of the survival outcome of B cells (Mackay and Schneider, 2008).

TNFSF13B-mediated B-cell survival is regulated by at least five pathways that result in attenuation of apoptosis: (i) activation of classical and alternative NF-κB; (ii) activation of the anti-apoptotic proteins, Mcl-1 and Pim2; (iii) down-regulation of the pro-apoptotic protein, Bim; (iv) nuclear exclusion of PKCδ; and (v) PKCβ-dependent activation of Akt (Claudio *et al.*, 2002; Woodland *et al.*, 2008; Hildebrand *et al.*, 2010; Khan *et al.*, 2010).

The MIF/CD74 pathway

CD74 (Invariant chain; Ii) is a type II integral membrane protein that is expressed on antigen-presenting cells, and was initially thought to function mainly as a major histocompatibility complex (MHC) class II chaperone (Stumptner-Cuvelette and Benaroch, 2002). A small proportion of CD74 is modified by the addition of chondroitin sulfate, and this form of CD74 is expressed on the cell surface. The cell surface CD74 molecule serves as a receptor in many types of cells and can initiate various signalling cascades (Naujokas *et al.*, 1993; Maharshak *et al.*, 2010). The cytokine, MIF, was found to be the natural ligand of CD74. MIF binds to the extracellular domain of CD74 with high affinity ($K_D = 1.40 \times 10^{-9}$ M) and initiates a signalling cascade (Leng *et al.*, 2003). CD74 forms a complex with CD44, which is essential for the MIF-induced signalling cascade (Shi *et al.*, 2006; Gore *et al.*, 2008).

In murine B cells, CD74 expression is directly involved in shaping the B cell repertoire by regulating mature B cell survival (Shachar and Flavell, 1996; Matza *et al.*, 2002; Matza *et al.*, 2003). MIF binding to CD74 induces a signalling pathway that involves the Syk tyrosine kinase and the PI3K/Akt pathway, induction of CD74 intramembrane cleavage and the release of the CD74 intracellular domain (CD74-ICD). CD74-ICD translocates to the nucleus where it induces

activation of transcription mediated by the NF-κB p65/RelA homodimer and its co-activator, TAFII105, resulting in the regulation of transcription of genes that control B cell proliferation and survival (Matza *et al.*, 2001; Starlets *et al.*, 2006; Gore *et al.*, 2008). MIF was found to regulate cell entry into the S-phase in a CD74- and CD44–dependent fashion, by elevating cyclin E levels, resulting in cell proliferation. In addition, this cascade augments Bcl-2 expression, further supporting cell survival (Starlets *et al.*, 2006; Gore *et al.*, 2008). Thus, the MIF binding to CD74/CD44 complex initiates a survival pathway, resulting in proliferation of the mature B cell population and prevention of their death.

Activation of the CD74/CD44 complex on B cells augments the cell surface expression of the tyrosine kinase receptor hepatocyte growth factor receptor (HGFR) (c-Met) and secretion of its ligand HGF (Gordin *et al.*, 2010). Following MIF stimulation, HGF engages with CD74 and CD44 on the cell membrane and, together with HGF, triggers a signalling cascade, which is necessary to initiate the MIF-induced survival cascade (Gordin *et al.*, 2010).

MK as a regulator of mature B cell survival. The MIF/CD74/HGFR-induced cascade was recently shown to control expression of MK, a heparin-binding cytokine, *in vitro* and *in vivo* (Cohen *et al.*, 2012). Stimulation of cultured splenic B cells with MIF up-regulates MK mRNA and protein levels. Moreover, following MIF injection to C57BL/6 mice, a significant elevation in MK protein was detected, demonstrating the modulation of MK expression by MIF. This activation is CD74-specific, since no change in MK levels was observed following stimulation of CD74 deficient B cells with MIF. Thus, MIF binding to its receptor, CD74, regulates MK expression in B cells (Cohen *et al.*, 2012).

MIF and CD74 regulate the expression of the tyrosine kinase receptor, HGFR, and its ligand, HGF, which are essential for the CD74-induced survival cascade (Gordin *et al.*, 2010). Interestingly, stimulation of HGFR with HGF elevates MK mRNA and protein levels in both wild-type and CD74-deficient B cells. Moreover, blocking c-Met activity using the c-Met inhibitor PHA-665752, a selective small molecule, active-site inhibitor of the catalytic activity of HGFR kinase (K_i 4 nM), which competes with its ATP binding (Ma *et al.*, 2003), or with anti-HGF blocking antibody (Gordin *et al.*, 2010), decreases intracellular protein levels of MK. Together, these results suggest that stimulation of CD74 with MIF leads to an up-regulation in the expression of HGF and HGFR. The binding of HGF to HGFR in turn promotes the expression of MK in mouse splenic B cells ultimately leading to cell survival (Cohen *et al.*, 2012).

MK was previously shown to act as an anti-apoptotic factor in the human haepatoma cell line, HepG2, by down-regulating the activity of caspase-3 (Ohuchida *et al.*, 2004). MK stimulation of cultured splenic B cells triggers the Syk and Akt signalling cascade (Cohen *et al.*, 2012), which elevates the expression of the anti-apoptotic gene, Bcl-2, and inhibits the activity of caspases 3 and 7, leading to mature B cell survival and an elevation in the percentage and number of mature B cells. The MK-induced survival cascade can partially bypass the lack of survival signals transmitted in CD74-deficient B cells. MK is also able to induce survival in cells in which HGFR activity is perturbed, indicating that MK activation is a downstream event to the MIF/CD74 and HGF/HGFR induced survival cascade (Cohen *et al.*, 2012).

Several cell-surface receptors were found to recognize MK, including members of the syndecan family, namely syndecan-1, -3 and -4 (Nakanishi *et al.*, 1997), protein tyrosine phosphatase ζ (PTPRZ1 also known as RPTPζ) (Maeda *et al.*, 1999), transmembrane protein low-density lipoprotein receptor-related protein (Muramatsu *et al.*, 2000), the anaplastic lymphoma kinase (ALK) (Stoica *et al.*, 2002), and the integrins α4β1 and α6β1 (Muramatsu *et al.*, 2004). PTPRZ1 is expressed in normal B cells and was shown to be the most important MK receptor for regulating B cell survival (Cohen *et al.*, 2012). Characterization of the peripheral B cell repertoire of PTPRZ1-deficient mice revealed a significant decrease in the proportion of mature B cells. These results demonstrate the essential role of PTPRZ1 in controlling and shaping the B cell repertoire. Moreover, in the absence of PTPRZ1, neither both MK, MIF nor HGF were able to enhance cell survival, demonstrating that PTPRZ1 is essential for the survival cascade induced by MIF/CD74 and HGF/HGFR (Cohen *et al.*, 2012) (Figure 2).

MK and B cell malignancies

Dysregulation of gene expression is a key factor in the pathogenesis of B cell malignancies. Numerous studies have demonstrated that MK has a role in tumour development and progression. Furthermore, MK serum levels were shown to be increased in blood derived from patients with various types of cancer (Ikematsu *et al.*, 2000; Shimada *et al.*, 2003; Obata *et al.*, 2005) including B cell malignancies.

MK expression has been detected in Hodgkin's lymphoma (HD) (Kato *et al.*, 2000), B cell chronic lymphocytic leukaemia (CLL) (Cohen *et al.*, 2012) and B-precursor acute lymphoblastic leukaemia (ALL) (Hidaka *et al.*, 2007; Wang *et al.*, 2008; Hu *et al.*, 2010). Among the known MK receptors, ALK and PTPRZ1 were found to be expressed in a subtype of large B cell lymphoma and in CLL cells respectively (Wan *et al.*, 2006; Cohen *et al.*, 2012).

Hodgkin's and non-Hodgkin's lymphoma

Lymphomas are solid tumours of the immune system. Hodgkin's lymphoma (HD) accounts for about 10% of all lymphomas, and the remaining 90% are referred to as non-Hodgkin lymphoma (NHL) (Shankland *et al.*, 2012).

HD is a unique neoplasm of B lymphocytes, characterized by a small number of putative malignant Hodgkin Reed-Sternberg (R-S) cells. R-S cells are often multinucleated and are usually very rare in the tissue. Although R-S cells are derived from B lymphocytes, they have largely lost their B cell phenotype and show a very unusual co-expression of markers of various haematopoietic cell types (Poppema, 1996; Ohno *et al.*, 1997; Küppers and Rajewsky, 1998; Vockerodt *et al.*, 1998). NHL is a heterogeneous group of malignancies, 85–90% of which arise from B lymphocytes, while the remainder derive from T lymphocytes or NK cells. NHL usually develops in the lymph nodes, but can occur in almost any tissue, and ranges from the more indolent follicular lymphoma, to the more aggressive diffuse large B cell and Burkitt's lymphomas (Shankland *et al.*, 2012).

MK gene expression is universally detected in lymphomas (of both HD and NHL types). However, analysis of protein expression using immunostaining revealed that R-S cells of HD express MK, while MK protein was detected in only about 5% of NHL (B cell type) (Kato *et al.*, 2000).

CLL

CLL is the most common leukaemia in the Western world. It is characterized by the progressive accumulation of CD5+ B lymphocytes in peripheral blood, lymphoid organs and BM (Caligaris-Cappio and Hamblin, 1999). CLL cells are small, mature lymphocytes that are significantly hampered in their ability to undergo further maturation into immunoglobulin secreting cells. These cells express MHC II molecules but are very poor antigen presenting cells (Stevenson and Caligaris-Cappio, 2004). CLL might result from a multistep process, beginning with antigen-driven polyclonal expansion of CD5+ B lymphocytes that, under the influence of mutational agents, is eventually transformed into monoclonal proliferation. Neoplastic CD5+ B lymphocytes are constantly overexpressing Bcl-2, thereby leading to inhibition of apoptosis and to the prolonged survival of CLL cells (Hanada *et al.*, 1993; Gale *et al.*, 1994). The median age at diagnosis is 65 years, with only 10 to 15% of patients under 50 years of age. The course of the disease is variable. Whereas some patients with CLL have a normal life span, others die within 5 years after diagnosis (Dohner *et al.*, 2000). Although infiltration of the marrow is evident from the very early stages of the disease, it is much more pronounced in advanced stages, and disease progression is uniformly manifested by clinically evident cytopenia, immune dysfunction and eventually death (Caligaris-Cappio, 2003).

Both MIF and CD74 have been associated with tumour progression. In CLL, CD74 and its ligand, MIF, play a pivotal role in the regulation of cell survival (Binsky *et al.*, 2007). CLL cells exhibit markedly up-regulated expression of both cell surface CD74 and MIF. Stimulation of CD74 with the MIF ligand (as well as with an activating antibody) initiates a signalling cascade leading to IL-8 transcription and secretion in all CLL cells, regardless of the clinical status of the patients. Secreted IL-8 induces the transcription and translation of the anti-apoptotic protein, Bcl-2, and thus activates an anti-apoptotic pathway, although no effect on proliferation is observed. Blocking of CD74 [using a humanized anti-CD74 mAb (milatuzumab; hLL1)], MIF [using ISO-1, a non-toxic inhibitor of MIF (Dios *et al.*, 2002)] or IL-8 results in dramatic down-regulation of Bcl-2 expression and augmentation of apoptosis.

MK, as a target gene of CD74, was recently shown to regulate CLL survival (Figure 2). Stimulation with MIF induces the expression and secretion of MK in CLL cells (Cohen *et al.*, 2012). As in normal B cells, MK stimulation suppresses CLL apoptosis by elevating the expression of Bcl-2 and inhibiting caspase-3 and -7 activity. Moreover, incubation of CLL cells with a blocking antibody that recognizes the extracellular domain of PTPRZ1 results in cell death, and inhibition of the MIF/CD74-induced survival cascade, thereby demonstrating the major role of the MK/ PTPRZ1 pathways in the MIF/CD74 survival cascade in CLL (Cohen *et al.*, 2012). Furthermore, elevated levels of MK were detected in sera derived from both early and advanced CLL patients, suggesting that MK can serve as a prognostic marker even at early stages of the disease. Thus, MK and PTPRZ1 together play an important role in the MIF/CD74 induced survival cascade in CLL cells (Cohen *et al.*, 2012).

B-precursor ALL

B-precursor ALL is the most common childhood tumour and the leading cause of cancer-related death in children and young adults. Despite impressive advances in the outcome of therapy with cure rates now exceeding 80%, ALL remains a leading cause of cancer-related death in children and young adults (Pui *et al.*, 2009a,b; Mullighan, 2012).

ALL arises from a single lymphopoietic progenitor cell that has sustained specific genetic damage leading to malignant transformation and proliferation. The initiation and progression of ALL is driven by successive mutations that vary, depending on the developmental stages of the affected blast cells. Thus, ALL can involve either B-cell or T-cell lines and can occur in cells at any stage of haematopoiesis. The genetic mutations identified in ALL not only cause uncontrollable cellular proliferation, but also prevent cells from undergoing normal differentiation. The patient is therefore overwhelmed by many immature blast cells that ravage the marrow and compete with healthy tissues (Redaelli *et al.*, 2005). Moreover, increasing evidence indicates the prevalence of functional defects in both soluble and cellular components of the ALL microenvironment; thus, changes in both cell composition and function of the haematopoietic microenvironment may govern stem cell activity and lead to disease (Renström *et al.*, 2010; Purizaca *et al.*, 2012). In recent years, studies have yielded important advances in the investigation of genetic, molecular, karyotypic and phenotypic abnormalities prevalent in this malignant disorder. However, the understanding of the mechanisms that damage the earliest programme of lymphoid development remains incomplete (Inaba *et al.*, 2013).

Analysis of BM MK mRNA levels revealed a significant increase in MK expression in ALL patients compared to normal controls (including pro-B-ALL, common-B-ALL and pre-B-ALL) as well as in adult and childhood B-ALL patients. This suggests that MK can serve as a prognostic marker and a marker for B-ALL patients (Hidaka *et al.*, 2007). In addition, it was found that MK gene expression correlates with the multidrug resistance of leukaemia cells (Hu *et al.*, 2010).

In order to investigate the role of MK in the pathogenesis of B-ALL, Wang *et al.* transfected MK cDNA into IL-3-dependent pro-B cell line, Ba/F3. They showed that MK potentiates proliferation by promoting cell cycle progression and proliferation, and partially inhibits apoptosis in these cells. In addition, exogenous MK could induce the phosphorylation of Raf-1, and inhibit the expression of Bax in the MK transfected BA/F3 cells. These results indicate that MK might be involved in the pathogenesis of leukaemia, and could be taken as an ideal diagnostic marker and molecular target for the treatment of ALL (Wang *et al.*, 2009).

Conclusion

Our knowledge regarding the role of MK in regulating B cell survival has been expanding rapidly. In addition to its role in

survival, MK can also serve as a prognostic marker at early stages of B cell malignancy. Thus, the development of novel therapeutic strategies aimed at interrupting the MK survival pathway may offer a new strategy for targeting B cell malignancies.

Conflict of interest

The authors have no financial conflicts.

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