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Role of macrophage inflammatory protein (MIP)-1α/CCL3 in leukemogenesis

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Abbreviations: AML, acute myeloid leukemia; BM, bone marrow; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HSC, hematopoietic stem cells; HSPC, hematopoietic stem/progenitor cells; LIC, leukemia initiating cells; LPS, lipopolysaccharide; MIP-1α, macrophage inflammatory protein-1α; SCI, stem cell inhibitor

The biologic function of the CC chemokine macrophage inflammatory protein-1α (MIP-1α/CCL3) has been extensively studied since its initial identification as a macrophage-derived inflammatory mediator. In addition to its proinflammatory activities, CCL3 negatively regulates the proliferation of hematopoietic stem/progenitor cells (HSPCs). On the basis of this unique function, CCL3 is alternatively referred to as a stem cell inhibitor. This property has prompted many researchers to investigate the effects of CCL3 on normal physiologic hematopoiesis and pathophysiologic processes of hematopoietic malignancies. Consequently, there is accumulating evidence supporting a crucial involvement of CCL3 in the pathophysiology of several types of leukemia arising from neoplastic transformation of HSPCs. In this review we discuss the roles of CCL3 in leukemogenesis and its potential value as a target in a novel therapeutic strategy for the treatment of leukemia.

Biologic Function of MIP-1α/CCL3 as a Stem Cell Inhibitor

Macrophage inflammatory protein-1α (MIP-1α, also known as CCL3) is a member of the CC chemokine family. *MIP-1α* cDNA was originally cloned from lipopolysaccharide (LPS)-activated RAW264.7 mouse macrophage cells as a gene encoding an endogenous inflammatory mediator.[1] CCL3 and related CC chemokines such as CCL4 and CCL5 are classified as inflammatory chemokines because of their ability to induce chemotactic mobilization of monocyte-lineage cells and lymphocytes into inflammatory tissues. CCL3 also regulates the proliferation of hematopoietic stem/progenitor cells (HSPCs) in the bone marrow (BM).[2] However, the contribution of endogenous CCL3 in the BM to normal physiologic hematopoiesis is poorly understood.

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Peripheral blood cells are continuously produced in adulthood by differentiation from a limited number of hematopoietic stem cells (HSCs) present in the BM. The HSC pool in BM is stably maintained by an intricate balance between differentiation, self-renewal, and reversible quiescent cell cycle arrest of HSCs. During the 1970s and 1980s, regulation of the steady-state quiescent status of HSCs was proposed to involve an unknown regulatory factor present in the BM microenvironment termed a stem cell inhibitor (SCI).[3,4] Immediately after the cloning of *CCL3* cDNA, Graham et al.[5] observed that culture supernatant of the J774.2 macrophage cell line contained a factor exhibiting SCI-like activity against colony formation of BM primitive cells. They further demonstrated that this factor was identical to CCL3. Subsequent studies revealed that CCL3 could reversibly inhibit colony formation and proliferation of HSPCs both in vitro and in vivo.[5-7] Intriguingly, CCL3 inhibits the proliferation of primitive progenitor cells but activates the proliferation of more mature progenitor cells.[7,8] Moreover, CCL3 can maintain a quiescent status in HSCs by blocking cell cycle entry,[9] thereby exhibiting a myeloprotective effect against cell cycle-specific anticancer drugs.[6,10] Furthermore, administration of a high dose of CCL3 rapidly induces mobilization of mouse[11] and human[12] HSPCs from BM to the peripheral blood. Thus, CCL3 potentially contributes to hematopoietic regulation in physiologic and pathologic conditions. However, the BM of CCL3-deficient mice does not exhibit any obvious hematopoietic abnormalities,[13] and a major cellular source of CCL3 in steady-state BM has not yet been identified. Thus, the precise regulatory functions of CCL3 in hematopoiesis under physiologic and various pathologic conditions remain elusive.

Chemokines execute their biologic activities through binding to their corresponding receptors, which are G-protein coupled receptors (GPCRs) with seven-span transmembrane (7-TM) portions. Human and mouse CCL3 bind to CCR1, CCR5, and D6 receptors, and mouse CCL3 can additionally bind to CCR3.[14] Among these receptors, CCR1 is responsible for CCL3-mediated mobilization of HSPCs, but not SCI activity.[15] Moreover, BM cells derived from *CCR1*$^{-/-}$, *CCR3*$^{-/-}$, *CCR5*$^{-/-}$, and *D6*$^{-/-}$ mice do not exhibit reduced SCI activity in vitro.[16] Further investigation of the molecular mechanisms underlying CCL3-mediated SCI

activity, in particular the identity of the receptor involved in this process, is required.

Leukemia is a hematopoietic neoplasm arising from neoplastic transformation of HSPCs and is assumed to involve oligoclonal or heteroclonal cells. Expansion of leukemia cells can arise from a small number of specialized leukemia cells called leukemia initiating cells (LICs).[17-24] Furthermore, LICs exhibit phenotypes similar to those of normal HSPCs, such as self-renewal and cellular quiescence. The control of LICs is therefore presumed to involve cellular and molecular mechanisms similar to those regulating normal HSPCs. Thus, CCL3, which has biologic activities in normal HSPC function, might also have a role in leukemogenesis. In this review article we focus on the roles of CCL3 in the multiple processes of leukemogenesis.

Pathologic Role of CCL3 in Chronic Myeloid Leukemia

More than 90% of cases of chronic myeloid leukemia (CML) are associated with the presence of the Philadelphia chromosome that arises from a reciprocal translocation between chromosomes 9 and 22. This chromosomal translocation results in the formation of a breakpoint cluster region and a constitutively activated tyrosine kinase, the BCR-ABL fusion protein.[25] BCR-ABL is a pathognomic protein for CML and its expression transforms HSCs into LICs whose maintenance in BM is indispensable for CML leukemogenesis.[26]

CML LICs share characteristic capabilities with normal HSCs, including self-renewal and cellular quiescence.[19,22] However, in contrast to normal HSCs, LICs are resistant to the SCI activity of CCL3 during in vitro proliferation.[27-30] Wark et al.[31] revealed that forced activation of the Abl tyrosine kinase in a multipotent stem cell line directly represses the CCL3-mediated increase in cytosolic Ca^+ concentration. In contrast, this treatment did not affect expression of the CCL3 receptor or its affinity for CCL3. Consistent with these findings, other independent groups have reported that CCL3 receptors are expressed at similar levels in normal and CML progenitor cells.[27,28] Based on this observation, it has been proposed that this Abl tyrosine kinase-mediated unresponsiveness to CCL3 contributes to the preferential expansion of CML LICs in the leukemic BM microenvironment. In contrast, we and other groups have observed decreased expression of CCL3 receptors, especially CCR5, in CML progenitor cells.[32,33] Thus, it remains controversial whether the unresponsiveness of LICs to CCL3 arises from decreased CCL3 receptor expression and/or functionality. Nevertheless, CCL3 exposure can preferentially induce quiescent cell cycle arrest in normal HSPCs but not in LICs. Moreover, pretreatment of normal HSPCs with CCL3 confers resistance to cell cycle-specific antileukemia drugs such as cytosine arabinoside (Ara-C), whereas cytotoxicity is preserved in LICs.[28,31] Thus, combined administration of CCL3 with antileukemia drugs was tested as an approach to selectively kill CML cells[28,31] before the advent of molecularly targeted drugs such as the tyrosine kinase inhibitor imatinib.[34-36]

In the early stages of CML a small number of LICs coexists with a large number of normal hematopoietic cells but over time the LICs gradually accumulate and eventually predominate in the limited space of the BM microenvironment. Several lines of evidence indicate a crucial role of CCL3 in the initiation and progression of CML. Zhang et al.[30] demonstrated that CML cells produce high levels of CCL3, which, in combination with other cytokines and chemokines, might confer a growth advantage to LICs over normal HSPCs. Schepers et al.[37] further demonstrated that CCL3 induces remodeling of the leukemia niche cell to effectively support LIC proliferation. We observed that $BCR\text{-}ABL^+lineage^-c\text{-}kit^-$ immature leukemia cells are a main source of CCL3.[32] Moreover, CCL3 can induce the mobilization of normal HSPCs from BM to peripheral blood and promotes the maintenance of LICs in BM of CML mice. Furthermore, CCL3-mediated maintenance of LICs was also observed in the setting of recurrence after cessation of imatinib treatment. Conversely, normal HSPCs can directly impede the maintenance of LICs in BM when the CML cells lack CCL3 or the normal HSPCs lack CCL3-binding receptors including CCR1 and CCR5.[32] Thus, CCL3 might act to expel normal CCR1- or CCR5-expressing HSPCs from the BM, making space available for LIC expansion.[32]

Pathologic Role of CCL3 in Acute Myeloid Leukemia

It was previously assumed that the outgrowth of acute myeloid leukemia (AML) cells is initiated and maintained from LICs with properties similar to those of normal HSCs,[22] as in CML. Based on detailed investigation of BM samples of human AML patients, Goardon et al.[18] recently demonstrated that a large number of patients with AML exhibit expansion of cells with LIC potential that are differentiated from HSCs and resemble lymphoid-primed multipotential progenitors or granulocyte-macrophage progenitors. Additionally, there is accumulating evidence that LICs are present among $CD34^+$ AML blast cells in human patients with AML.

$CD34^+$ AML cells are resistant to the SCI activity of CCL3 when cultured in the presence of CCL3, although the underlying molecular mechanism remains elusive.[38] Moreover, as in CML, CCL3 is produced abundantly in the BM of AML patients and contributes to remodeling of the microenvironment.[39] It has been proposed that leukemia cell-derived CCL3 inhibits osteoblastic cell functions, thus accelerating the disruption of normal BM microenvironment and hematopoiesis.[39] In the NUP98-HOXD13–mediated mouse AML model, the proto-oncogene *Meis1* accelerates AML development and induces CCL3 expression, which is at least partially responsible for the intra-BM survival of LICs by potentiating their repopulation capacity.[40] Moreover, binding of the homeodomain of MEIS1

to the regulatory sequence of the *CCL3* gene is required for CCL3 expression.[40] However, the detailed molecular and cellular mechanisms by which CCL3 contributes to AML pathophysiology remain unknown.

Pathologic Role of CCL3 in Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is a lymphoproliferative disorder in which neoplastic $CD5^+$ B cells clonally expand in the peripheral blood, secondary lymphoid tissues, and BM. Burger et al.[41] recently demonstrated that CLL B cells produce high levels of CCL3 and its related chemokine CCL4 in co-culture with $CD68^+$ nurse-like cells and after B-cell receptor stimulation. They further revealed that the plasma CCL3 level is a reliable prognostic marker in CLL patients.[42] Concomitantly, Zucchetto et al.[43] demonstrated that $CD38^+CD49d^+$ CLL cells selectively and aberrantly express CCL3 through interaction with CD38 and CD31 expressed on stromal cells in the BM microenvironment. CCL3 subsequently induces recruitment of macrophage-lineage cells into the leukemia niche. The recruited cells produce inflammatory factors including TNF-α that eventually activate stromal cells to express VCAM-1, a ligand for CD49d that delivers pro-survival signals to CLL cells through its interaction with CD49d. Thus, CCL3 can promote establishment of the leukemia niche, which is essential for CLL cell survival.

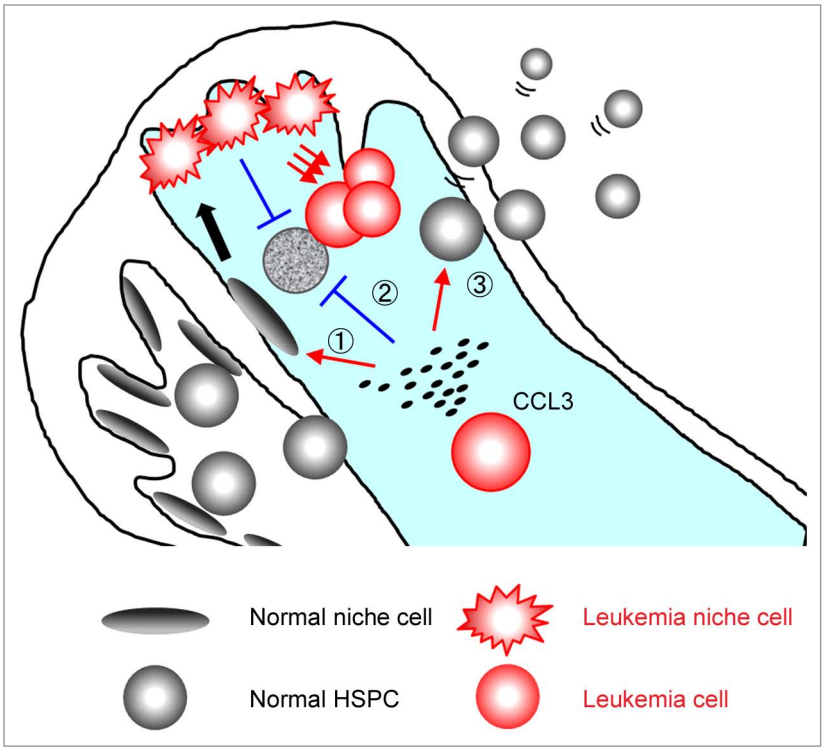

Figure 1. Function of CCL3 in the leukemic bone marrow microenvironment. In the leukemic BM microenvironment (blue shaded area), CCL3 can induce multiple processes that support the dominant proliferation of leukemia cells: (**1**) conversion of normal niche cells to leukemia-adapted cells; (**2**) selective inhibition of normal HSPCs; (**3**) mobilization of normal HSPCs from BM. Abbreviations: BM, bone marrow; HSPC, hematopoietic stem/progenitor cell

Perspective

The above experimental and clinical evidence indicates that CCL3 is crucially involved in multiple pathophysiologic processes of leukemogenesis in various types of leukemia. These processes include preferential proliferation of LICs, expulsion of normal HSPCs, and/or establishment of a leukemia-adapted niche in the BM (**Fig. 1**). Moreover, high levels of CCL3 expression are observed in other malignant hematopoietic neoplasms, such as adult T-cell leukemia[44] and multiple myeloma.[45] Myeloma cell-derived CCL3 can support the proliferation of myeloma cells directly[45] or indirectly through the accelerated formation of osteoclasts, which can provide a pro-myeloma niche within the BM.[46] Thus, CCL3 overexpression may have an important role in the progression of hematopoietic malignancies in general, although malignant transformation of each hematologic disease also involves individual and diverse intrinsic events. Given the crucial role of CCL3 in the leukemic BM microenvironment, we assume that therapeutic blockade of CCL3 activity in leukemia patients would correct the BM microenvironment and eventually inhibit the dominant proliferation of LICs through effects on normal BM cells, rather than through direct killing of LICs.

The development of antineoplastic drugs, including antileukemic drugs, requires identification of causative oncogenes and appropriate molecular targets. However, leukemia cells, especially LICs, crucially depend on the appropriate microenvironment for expansion in the BM, particularly during the initiation phase or chemotherapy-induced remission, when only a small number of LICs is present in the BM. Moreover, the creation of a favorable niche for normal HSPCs may create a disadvantage for growth of leukemia cells. Thus, in parallel with the pursuit of molecular targeted therapy, it is necessary to investigate the pathophysiologic roles of endogenous mediators such as CCL3 that can profoundly affect the proleukemic niche. This may lead to the development of novel antileukemic therapies that supplement molecular targeted therapy.

Conflict of interest

The authors do not have any potential conflicts of financial interest.

References

1. Davatelis G, Tekamp-Olson P, Wolpe SD, Hermsen K, Luedke C, Gallegos C, Coit D, Merryweather J, Cerami A. Cloning and characterization of a cDNA for murine macrophage inflammatory protein (MIP), a novel monokine with inflammatory and chemokinetic properties. J Exp Med 1988; 167:1939-44; PMID:3290382; http://dx.doi.org/10.1084/jem.167.6.1939
2. Cook DN. The role of MIP-1 alpha in inflammation and hematopoiesis. J Leukoc Biol 1996; 59:61-6; PMID:8558069
3. Toksöz D, Dexter TM, Lord BI, Wright EG, Lajtha LG. The regulation of hemopoiesis in long-term bone marrow cultures. II. Stimulation and inhibition of stem cell proliferation. Blood 1980; 55:931-6; PMID:7378583
4. Lord BI, Mori KJ, Wright EG, Lajtha LG. Inhibitor of stem cell proliferation in normal bone marrow. Br J Haematol 1976; 34:441-5; PMID:990183; http://dx.doi.org/10.1111/j.1365-2141.1976.tb03590.x
5. Graham GJ, Wright EG, Hewick R, Wolpe SD, Wilkie NM, Donaldson D, Lorimore S, Pragnell IB. Identification and characterization of an inhibitor of haemopoietic stem cell proliferation. Nature 1990; 344:442-4; PMID:2320111; http://dx.doi.org/10.1038/344442a0
6. Lord BI, Dexter TM, Clements JM, Hunter MA, Gearing AJ. Macrophage-inflammatory protein protects multipotent hematopoietic cells from the cytotoxic effects of hydroxyurea in vivo. Blood 1992; 79:2605-9; PMID:1586712
7. Broxmeyer HE, Sherry B, Lu L, Cooper S, Oh KO, Tekamp-Olson P, Kwon BS, Cerami A. Enhancing and suppressing effects of recombinant murine macrophage inflammatory proteins on colony formation in vitro by bone marrow myeloid progenitor cells. Blood 1990; 76:1110-6; PMID:2205307
8. Broxmeyer HE, Sherry B, Lu L, Cooper S, Carow C, Wolpe SD, Cerami A. Myelopoietic enhancing effects of murine macrophage inflammatory proteins 1 and 2 on colony formation in vitro by murine and human bone marrow granulocyte/macrophage progenitor cells. J Exp Med 1989; 170:1583-94; PMID:2478652; http://dx.doi.org/10.1084/jem.170.5.1583
9. Verfaillie CM, Catanzarro PM, Li WN. Macrophage inflammatory protein 1 alpha, interleukin 3 and diffusible marrow stromal factors maintain human hematopoietic stem cells for at least eight weeks in vitro. J Exp Med 1994; 179:643-9; PMID:8294873; http://dx.doi.org/10.1084/jem.179.2.643
10. Dunlop DJ, Wright EG, Lorimore S, Graham GJ, Holyoake T, Kerr DJ, Wolpe SD, Pragnell IB. Demonstration of stem cell inhibition and myeloprotective effects of SCI/rhMIP1 alpha in vivo. Blood 1992; 79:2221-5; PMID:1571537
11. Lord BI, Woolford LB, Wood LM, Czaplewski LG, McCourt M, Hunter MG, Edwards RM. Mobilization of early hematopoietic progenitor cells with BB-10010: a genetically engineered variant of human macrophage inflammatory protein-1 alpha. Blood 1995; 85:3412-5; PMID:7540061
12. Broxmeyer HE, Orazi A, Hague NL, Sledge GW Jr., Rasmussen H, Gordon MS. Myeloid progenitor cell proliferation and mobilization effects of BB10010, a genetically engineered variant of human macrophage inflammatory protein-1alpha, in a phase I clinical trial in patients with relapsed/refractory breast cancer. Blood Cells Mol Dis 1998; 24:14-30; PMID:9516378; http://dx.doi.org/10.1006/bcmd.1998.0167
13. Cook DN, Beck MA, Coffman TM, Kirby SL, Sheridan JF, Pragnell IB, Smithies O. Requirement of MIP-1 alpha for an inflammatory response to viral infection. Science 1995; 269:1583-5; PMID:7667639; http://dx.doi.org/10.1126/science.7667639
14. Nibbs RJ, Wylie SM, Yang J, Landau NR, Graham GJ. Cloning and characterization of a novel promiscuous human beta-chemokine receptor D6. J Biol Chem 1997; 272:32078-83; PMID:9405404; http://dx.doi.org/10.1074/jbc.272.51.32078
15. Broxmeyer HE, Cooper S, Hangoc G, Gao JL, Murphy PM. Dominant myelopoietic effector functions mediated by chemokine receptor CCR1. J Exp Med 1999; 189:1987-92; PMID:10377195; http://dx.doi.org/10.1084/jem.189.12.1987
16. Ottersbach K, Cook DN, Kuziel WA, Humbles A, Lu B, Gerard C, Proudfoot AE, Graham GJ. Macrophage inflammatory protein-1alpha uses a novel receptor for primitive hemopoietic cell inhibition. Blood 2001; 98:3476-8; PMID:11719391; http://dx.doi.org/10.1182/blood.V98.12.3476
17. Bonnet D, Dick JE. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat Med 1997; 3:730-7; PMID:9212098; http://dx.doi.org/10.1038/nm0797-730
18. Goardon N, Marchi E, Atzberger A, Quek L, Schuh A, Soneji S, Woll P, Mead A, Alford KA, Rout R, et al. Coexistence of LMPP-like and GMP-like leukemia stem cells in acute myeloid leukemia. Cancer Cell 2011; 19:138-52; PMID:21251617; http://dx.doi.org/10.1016/j.ccr.2010.12.012
19. Holtz M, Forman SJ, Bhatia R. Growth factor stimulation reduces residual quiescent chronic myelogenous leukemia progenitors remaining after imatinib treatment. Cancer Res 2007; 67:1113-20; PMID:17283145; http://dx.doi.org/10.1158/0008-5472.CAN-06-2014
20. Huntly BJ, Gilliland DG. Leukaemia stem cells and the evolution of cancer-stem-cell research. Nat Rev Cancer 2005; 5:311-21; PMID:15803157; http://dx.doi.org/10.1038/nrc1592
21. Ishikawa F, Yoshida S, Saito Y, Hijikata A, Kitamura H, Tanaka S, Nakamura R, Tanaka T, Tomiyama H, Saito N, et al. Chemotherapy-resistant human AML stem cells home to and engraft within the bone-marrow endosteal region. Nat Biotechnol 2007; 25:1315-21; PMID:17952057; http://dx.doi.org/10.1038/nbt1350
22. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. Nature 2001; 414:105-11; PMID:11689955; http://dx.doi.org/10.1038/35102167
23. Scadden DT. Cancer stem cells refined. Nat Immunol 2004; 5:701-3; PMID:15224098; http://dx.doi.org/10.1038/ni0704-701
24. Wang JC, Dick JE. Cancer stem cells: lessons from leukemia. Trends Cell Biol 2005; 15:494-501; PMID:16084092; http://dx.doi.org/10.1016/j.tcb.2005.07.004
25. Sawyers CL. Chronic myeloid leukemia. N Engl J Med 1999; 340:1330-40; PMID:10219069; http://dx.doi.org/10.1056/NEJM199904293401706
26. Koschmieder S, Göttgens B, Zhang P, Iwasaki-Arai J, Akashi K, Kutok JL, Dayaram T, Geary K, Green AR, Tenen DG, et al. Inducible chronic phase of myeloid leukemia with expansion of hematopoietic stem cells in a transgenic model of BCR-ABL leukemogenesis. Blood 2005; 105:324-34; PMID:15331442; http://dx.doi.org/10.1182/blood-2003-12-4369
27. Chasty RC, Lucas GS, Owen-Lynch PJ, Pierce A, Whetton AD. Macrophage inflammatory protein-1 alpha receptors are present on cells enriched for CD34 expression from patients with chronic myeloid leukemia. Blood 1995; 86:4270-7; PMID:7492787
28. Dürig J, Testa NG, Lord BI, Kasper C, Chang J, Telford N, Dexter TM, Heyworth CM. Characterisation of the differential response of normal and CML haemopoietic progenitor cells to macrophage inflammatory protein-1alpha. Leukemia 1999; 13:2012-22; PMID:10602423; http://dx.doi.org/10.1038/sj.leu.2401610
29. Eaves CJ, Cashman JD, Wolpe SD, Eaves AC. Unresponsiveness of primitive chronic myeloid leukemia cells to macrophage inflammatory protein 1 alpha, an inhibitor of primitive normal hematopoietic cells. Proc Natl Acad Sci U S A 1993; 90:12015-9; PMID:8265663; http://dx.doi.org/10.1073/pnas.90.24.12015
30. Zhang B, Ho YW, Huang Q, Maeda T, Lin A, Lee SU, Hair A, Holyoake TL, Huettner C, Bhatia R. Altered microenvironmental regulation of leukemic and normal stem cells in chronic myelogenous leukemia. Cancer Cell 2012; 21:577-92; PMID:22516264; http://dx.doi.org/10.1016/j.ccr.2012.02.018
31. Wark G, Heyworth CM, Spooncer E, Czaplewski L, Francis JM, Dexter TM, Whetton AD. Abl protein kinase abrogates the response of multipotent haemopoietic cells to the growth inhibitor macrophage inflammatory protein-1 alpha. Oncogene 1998; 16:1319-24; PMID:9546433; http://dx.doi.org/10.1038/sj.onc.1201914
32. Baba T, Naka K, Morishita S, Komatsu N, Hirao A, Mukaida N. MIP-1α/CCL3-mediated maintenance of leukemia-initiating cells in the initiation process of chronic myeloid leukemia. J Exp Med 2013; 210:2661-73; PMID:24166712; http://dx.doi.org/10.1084/jem.20130112
33. Nicholls SE, Lucas G, Graham GJ, Russell NH, Mottram R, Whetton AD, Buckle AM. Macrophage-inflammatory protein-1alpha receptor expression on normal and chronic myeloid leukemia CD34+ cells. J Immunol 1999; 162:6191-9; PMID:10229864
34. Buchdunger E, Zimmermann J, Mett H, Meyer T, Müller M, Druker BJ, Lydon NB. Inhibition of the Abl protein-tyrosine kinase in vitro and in vivo by a 2-phenylaminopyrimidine derivative. Cancer Res 1996; 56:100-4; PMID:8548747
35. Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, Zimmermann J, Lydon NB. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med 1996; 2:561-6; PMID:8616716; http://dx.doi.org/10.1038/nm0596-561
36. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, Lydon NB, Kantarjian H, Capdeville R, Ohno-Jones S, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 2001; 344:1031-7; PMID:11287972; http://dx.doi.org/10.1056/NEJM200104053441401
37. Schepers K, Pietras EM, Reynaud D, Flach J, Binnewies M, Garg T, Wagers AJ, Hsiao EC, Passegué E. Myeloproliferative neoplasia remodels the endosteal bone marrow niche into a self-reinforcing leukemic niche. Cell Stem Cell 2013; 13:285-99; PMID:23850243; http://dx.doi.org/10.1016/j.stem.2013.06.009
38. Owen-Lynch PJ, Adams JA, Brereton ML, Czaplewski LG, Whetton AD, Yin JA. The effect of the chemokine rhMIP-1 alpha, and a non-aggregating variant BB-10010, on blast cells from patients with acute myeloid leukaemia. Br J Haematol 1996; 95:77-84; PMID:8857942; http://dx.doi.org/10.1046/j.1365-2141.1996.7312349.x
39. Frisch BJ, Ashton JM, Xing L, Becker MW, Jordan CT, Calvi LM. Functional inhibition of osteoblastic cells in an in vivo mouse model of myeloid leukemia. Blood 2012; 119:540-50; PMID:21957195; http://dx.doi.org/10.1182/blood-2011-04-348151
40. Argiropoulos B, Palmqvist L, Yung E, Kuchenbauer F, Heuser M, Sly LM, Wan A, Krystal G, Humphries RK. Linkage of Meis1 leukemogenic activity to multiple downstream effectors including Trib2 and Ccl3. Exp Hematol 2008; 36:845-59; PMID:18375036; http://dx.doi.org/10.1016/j.exphem.2008.02.011

41. Burger JA, Quiroga MP, Hartmann E, Bürkle A, Wierda WG, Keating MJ, Rosenwald A. High-level expression of the T-cell chemokines CCL3 and CCL4 by chronic lymphocytic leukemia B cells in nurse-like cell cocultures and after BCR stimulation. Blood 2009; 113:3050-8; PMID:19074730; http://dx.doi.org/10.1182/blood-2008-07-170415
42. Sivina M, Hartmann E, Kipps TJ, Rassenti L, Krupnik D, Lerner S, LaPushin R, Xiao L, Huang X, Werner L, et al. CCL3 (MIP-1α) plasma levels and the risk for disease progression in chronic lymphocytic leukemia. Blood 2011; 117:1662-9; PMID:21115978; http://dx.doi.org/10.1182/blood-2010-09-307249
43. Zucchetto A, Benedetti D, Tripodo C, Bomben R, Dal Bo M, Marconi D, Bossi F, Lorenzon D, Degan M, Rossi FM, et al. CD38/CD31, the CCL3 and CCL4 chemokines, and CD49d/vascular cell adhesion molecule-1 are interchained by sequential events sustaining chronic lymphocytic leukemia cell survival. Cancer Res 2009; 69:4001-9; PMID:19383907; http://dx.doi.org/10.1158/0008-5472.CAN-08-4173
44. Matsumoto K, Murao K, Imachi H, Nishiuchi T, Cao W, Yu X, Li J, Ahmed RA, Iwama H, Kobayashi R, et al. The role of calcium/calmodulin-dependent protein kinase cascade on MIP-1alpha gene expression of ATL cells. Exp Hematol 2008; 36:390-400; PMID:18249060; http://dx.doi.org/10.1016/j.exphem.2007.11.013
45. Lentzsch S, Gries M, Janz M, Bargou R, Dörken B, Mapara MY. Macrophage inflammatory protein 1-alpha (MIP-1 alpha) triggers migration and signaling cascades mediating survival and proliferation in multiple myeloma (MM) cells. Blood 2003; 101:3568-73; PMID:12506012; http://dx.doi.org/10.1182/blood-2002-08-2383
46. Vallet S, Raje N, Ishitsuka K, Hideshima T, Podar K, Chhetri S, Pozzi S, Breitkreutz I, Kiziltepe T, Yasui H, et al. MLN3897, a novel CCR1 inhibitor, impairs osteoclastogenesis and inhibits the interaction of multiple myeloma cells and osteoclasts. Blood 2007; 110:3744-52; PMID:17715391; http://dx.doi.org/10.1182/blood-2007-05-093294