REVIEWS

ROLE OF THE HYBRID Bcr/Abl KINASE IN THE PATHOGENESIS OF CHRONIC MYELOID LEUKEMIA LACKING C-Abl AND CXCR4 PROTEINS

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Philadelphia chromosome is a result of chromosomal rearrangement that leads to the appearing of the hybrid gene *bcr/abl*. A hybrid mRNA transcribes from bcr-promoter and many copies of hybrid molecules of Bcr/Abl protein are formed as a result of *bcr/abl* gene expression. It is supposed that a hybrid Abl molecule, replacing the normal one, in majority of cases functions abnormally or does not function at all. Also it is possible that Abl moiety of Bcr/Abl protein which is possibly recognized by some hypothetical cell control system interpreted by cell as an overproduction of *c-abl*. This, probably, leads to blocking the normal C-Abl molecules production from the normal *c-abl* gene transcribed from the second non-aberrant chromosome 9. Based on C-Abl physiological functions in conjunction with the most important proteins of which functions directly depend on its activity we tried to outline the research directions that might explain disruptions of the processes at chronic myeloleukosis such as cell migration due to CXCL12/CXCR4 axis activation, reparation, apoptosis, control for mitochondria state, and to propose new perspective therapeutic approaches based on all this knowledge.
Key Words: Bcr/Abl, CXCR4, C-Abl, chemokine, CXCL12.

C-Abl PROTEIN

140 kDa C-Abl protein is expressed in cells and localized in cell nucleus, on plasma membrane and cytoskeleton [1]. There are two different forms of C-Abl (types 1a and 1b), that result from alternative splicing of two small exons. Type 1a C-Abl contains C14 myristoyil fatty acid covalently bound to N-terminal region, and its expression level is higher than in 1b type. N-terminal region of C-Abl kinase is similar to those from Src family proteins and contains SH3 homology domain, SH2 domain and catalytic domain, but C-Abl differs from Src because of a bigger (60 kDa) C-terminal domain [1]. The mechanism of C-Abl catalytic activity regulation remains unknown [2].

PHYSIOLOGICAL ROLE OF C-Abl

C-Abl protein is widespread within cell; usually it is present at the tips of lamellipodia and filopodia [3, 4–8] and is localized in nucleus, cytoplasm, mitochondria and endoplasmic reticulum [9]. C-Abl is involved in a wide number of processes, such as regulation of cell growth and survival, oxidative stress reaction, response to DNA damage, also it plays some role in actin dynamics and cell migration [9]. While in nucleus C-Abl is connected to Rb protein and is not active during G0 and G1 phases of cell cycle. After starting of S phase Rb protein becomes phosphorylated that results in releasing C-Abl kinase from this complex [10]. In nucleus C-Abl kinase is used as apoptosis regulator and is also involved in the processes of reparation and recombination [11, 12]. It is known that ATM kinase, C-Abl and Rad51 are found as a complex after co-immunoprecipitation from plant extracts [13, 14]. C-Abl kinase activates p53 protein as well [13, 14].

C-Abl also has the ability to phosphorylate RAD52 [15] and RAD51 [16] proteins. After C-Abl phoshorylates Rad51, this protein forms a complex with RAD52 [15]. On obtaining signal from ATM kinase special protein instruments become active and perform reparation of DNA defects during G1 phase, and in case of irreparable damages induction of p53-mediated apoptosis takes place [17]. C-Abl binds to p53 and thus affects its activity. Also c-Abl contributes to p21 expression that confirms the participation of c-Abl in p53-dependent G1 phase control [17]. C-Abl also functions as proapoptotic JNK/SAPK and p38 MAPK pathways [17]. Moreover, ATM kinase also forms complex with C-Abl [13, 14]. ATM kinase together with NBS1 protein acts as primary detector of double-strand breaks of DNA in G1/S and G2/M checkpoints [18].

Cytoplasmic C-Abl also has important functions. It has been already mentioned that this protein is found in tips of lamellipodia and filopodia. C-Abl phosphorylates WAVE3 protein at four tyrosine residues, that presumably makes actin cytoskeleton dynamics possible, that is necessary for changing cell shape, adhesion property and migration [4–8]. Special Arg protein that is important in this process is also present here [19]. Cytoplasmic forms of C-Abl and Arg are activated after cell response to the oxidative stress [20–22]. GPx1 functions as a substrate for C-Abl-Arg-mediated phosphorylation at Tyr-96. C-Abl and Arg stimulate GPx activity and provide Gpx-mediated protection of cells from the oxidative stress [22]. Activation of C-Abl-Arg complex occurs after it contacts the mitochondria lacking transmembrane potential after cytochrome C release [21, 23]. H_2O_2-induced apoptosis mitigates in cells under lack of c-Abl or expression of kinase-inactive mutant Arg (K-R) [22]. Thus, c-Abl-Arg heterodimers are important for control of ROS rise and for apoptotic answer to the oxidative stress [22,

24]. This supports the hypothesis that in this case hyperexpressed Bcr/Abl doesn't perform the physiological function of normal c-Abl that either doesn't express or cannot compete with Bcr/Abl. So, the lack of this kinase activity might be the reason of the oxidative stress occurred. This assumption could also be extended to cell movement: Arg protein together with C-Abl also participates in lamellipodia and filopodia formation and activity [19]. In case of hyperexpression of Bcr/Abl some "paralysis" of lamellipodia and filopodia might occur. The same extrapolation to the role of Bcr/Abl in reparation is also possible: C-Abl exists normally in nucleus as a part of "reparation manipulator" — RAD52 complex that provides mechanical combination of broken DNA strands. In case of reparation inability the apoptosis is induced due to c-Abl and p53. If transcription of the normal *c-abl* gene is inhibited and C-Abl lack results in nucleus (because of the kinase-inactive Bcr/Abl presence in cytoplasm) the process of apoptosis initiation is blocked [17, 18].

One of the important physiological processes that is disrupted in chronic myelogenous leukemia (CML) and into which C-Abl is involved it is probably the motility of lamellipodia and filopodia during cell migration. As it has been discovered, migration of hematopoietic stem cell occurs under the constitutive CXCL12/CXCR4 axis activity [25]. This aspect is important for investigation of c-Abl influence on chemotaxis.

CHEMOTAXIS AND CXCL12/CXCR4 AXIS

Chemokines are the class of small (8–10 kDa) inflammatory or homeostatic cytokines which main biological activity is to control migration of different cell types. This includes lymphocytes, monocytes, neutrophils, endothelial cell, mesenchymal stem cells, malignant cells of epithelial nature, as it exactly occurs in early ontogenesis on different stages of embryonic metamorphosis. The same occurs in adult organism, where stem cells migration during differentiation and immune responses is necessary [26–28]. High affinity of chemokines to heparin prevents its distribution all over the space and forms local gradients [29, 30]. Chemokines consist of three conserved groups of elements: CXC, CC, C and also CX3C group depending on the quantity of N-terminal cysteine residues and gaps between them. CXC chemokines have a single non-conserved aminoacid residue (X) between first N-terminal residues (C). Chemokines CC have two adjacent cysteine residues. C chemokines have only one N-terminal cysteine while CX3C chemokines contain three non-conserved aminoacid residues separated by N-terminal cysteine pairs. After activation GPCR acts as guanidine-exchanging factor (GEF), promoting conformational change in Gα sub-unit and substituting the bound GDP into GTP. This exchange promotes subsequent conformational changes in Gα subunit and that allows trimer G-proteins releasing from the receptor and forming the GTP-bound Gα subunit and £B/G dimer. Both active components interact with different effector proteins and initiate unique intracellular signal cascades, for example, phosholipase C (PLC) activation, regulation of adenylatecyclase, including pathways of mitogen-activating protein kinase (MAPK) activation, c-Jun kinase (JNK), p38 and phosphoinositol-3-kinase (PI3K) [31–34].

Chemokine CXCL12 (SDF-1) and its cell surface receptor CXCR4 have been first identified as regulators of lymphocytes circulation in bone marrow [35]. Shortly after, it has been identified that CXCL12/CXCR4 axis is a regulator of breast cancer cells migration to loci of methastasis [29]. It has been recently found that CXCR4 plays a central role in cancer cells proliferation, invasion and spread of tumor cells in majority of malignant diseases [28].

CXCL12/CXCR4 axis is widespread in vertebrates and in human organism. Recent works have shown that CXCL12 also binds to one more chemokine receptor as CXCR7 is [35]. It has been given much attention to the study of CXCR4 because it works as a means of viruses (X4) penetration into T cells during HIV infection [36, 37]. Mouse and human chemokines CXCL12 are cross-reactive and differ by only one aminoacid. CXCL12 and CXCR4 play an important role in human stem cells migration and colonization in immune-deficient mice both NOD/SCID and B2mnull-NOD/SCID [38].

Studies of early human and other mammalian ontogenesis showed that CXCR4 has been identified more often than other chemokine receptors, especially in the process of gastrulation. During gastrulation CXCR4 expresses in tissues that later migrates through the primitive streak of ectoderm [26]. Primary blood cells in embryogenesis emerge at the early stage of the yolk sac. Analysis of 69 separate cell isolates has shown that most of them had CXCR4 receptor. Other strains instead had CCR4 chemokine receptor [29].

Using zebra fish model it has been shown that G-protein receptor CXCR4 and a chemokine CXCL12 as its ligand play an important role in migration of gonocytes to gonads [39]. Colonization of mouse embryonic gonads by gonocytes also occurs to ligand-receptor interaction between CXCL12 and CXCR4 [40]. Thus gonocytes express CXCR4 and cells of genital ridges of gonadal primordial express CXCL12 chemokine.

CXCL12 also concentrates at peripheral neuronal cranial tissue in pia mater. Expression of CXCL12 in pia mater occurs in close proximity of CXCR4-expressing neurons. Among many factors of CXCL12-CXCR4 axis action it is interesting that CXCR4 expresses at high levels in immune system cells — monocytes, lymphocytes, T-cells, and also in early hematopoietic progenitor cells in bone marrow [41].

Thus, CXCL12-CXCR4 axis in organisms of vertebrates is the main universal instrument of organization of directed stem cells migration to the places of their permanent living at all stages of ontogenesis.

It is known that hematopoietic stem cells have high hierarchy of differentiation [42]. Early cells-progenitors produce cell next generations with more advanced differentiation stage. They in turn produce cells of later

cytotype, and so on. It has been revealed that there are not only several consistent types of stem cells, but also special niches for their growth exist that are located at different places. For subsequent proliferation each stem cell has to migrate to a new region where chemokine secretion occurs [38].

ROLE OF CHEMOTAXIS IN CML

When gradient of chemokine which is available for cell receptors forms around the place of hematopoietic stem cells localization, cell polarizes [43]. A special "leg" with integrins for interaction with endothelial wall forms as well as a "nose" with chemokine receptors localized on it. Then cell defines the direction of high chemokine concentration (Fig. 1) and migrates through tissues to this direction [30, 39].
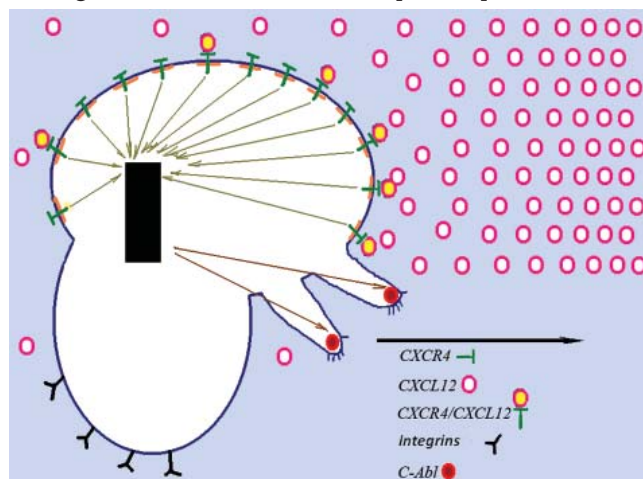

Fig. 1. Stem cell migrates to the higher concentration of the chemokine

It is known that after CXCL12 gradient forming and ligand-receptor interactions start a special mechanism of feedback begins to work. Proteosomal degradation of CXCR4-UB stops, previously ubiquitinated CXCR-UB is deubiquitinated by USP14 and forward to plasma membrane. In addition to this CXCR4 gene is induced for expression [25]. The duration of these reactions from the moment of changes in signalling is about 60 min long.

Currently it is considered that the cell movement is regulated in such a complex way as it is currently known for the process of gene transcription regulation [26]. We suppose that for cell movement to be regulated it is not the easiest task for the single cell. For the detecting of the right direction in the ligand concentration gradient formed the cell must evaluate simultaneously the state of its whole set of receptors, distinguish the difference in their state and appropriately response to this difference.

The difference between the movement potential of whole cell body and lamellipodia must be considered as well.

Lipid rafts system with receptors works as a special receptor field, and the phenomenon of positive feedback [39] acts very similar to the mammalian unconditioned reflex. Observation of several authors [26, 39] allows us suggesting that the main role of chemokine signaling is obtaining and transducing the information

to some hypothetical cell analyzer capable of coordinative reading of results arrived. This is required for their subsequent complex processing (pre-modeling) and preparing an answer in accordance to specific "instruction"-instincts algorithms [44]. Thus the cell behavior is probably determined not only by chemokine signaling influencing integrin activation and elimination as well as cell adhesion and proliferation status but also by the work of a putative analyser capable of considering both chemokine receptor status and different circumstances in cellular environment occurred [44].

There are evidences that in case of CML in the hybrid protein p210 Bcr/Abl hyperexpression certain threshold is reached and then the transcriptional silencing of CXCR4 expression is induced, that leads to chemotaxis disruption [45]. The other possible explanation of CXCR4 downregulation is the lack of the normal c-Abl molecule. The lack of c-Abl apparently emerges when *bcr/abl* gene that expresses from bcr promotor shows to a hypothetical cell control system the excess of c-Abl available in the cell, and initiation of transcription of the normal c-Abl from other, non-Philadelphia chromosome 9 does not occur (Fig. 2) [46].
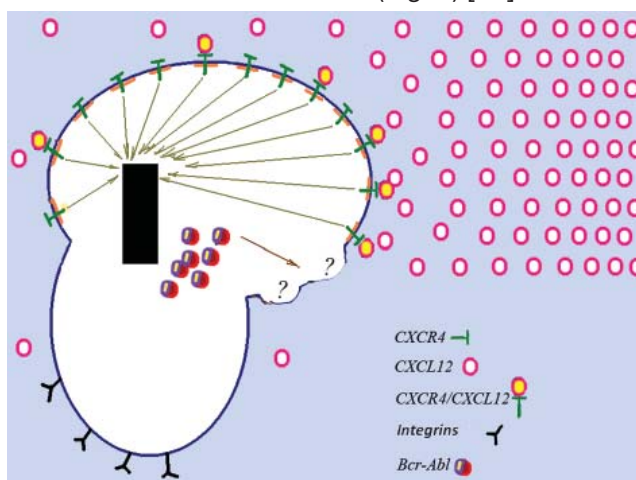

Fig. 2. Stem cell tends to migrate in direction of higher concentration of chemokine gradient. But, according to the hypothesis, no c-Abl is available at the tips of lamellipodia. This is because c-Abl expression is not initiated by some cell control system as a result of the hybrid protein Bcr/Abl molecules overproduction

Presumably, as a result of the hybrid protein the lack of normal C-Abl (which is normally found at tips of lamellipodia where it phosphorylates WAVE3 and controls actin cytoskeleton dynamics) emerges within cell. If the hypothesis about the C-Abl-free tips of lamellipodia in case of Philadelphia chromosome is correct, it is possible to suggest that cell might become "paralyzed". After CXCR4 interacts with CXCL12 cell "sees" chemokines gradient, tries to mobilize itself for migration but remains still. However, this hypothesis needs experimental verification. Absence of normal C-Abl within cell can also explain violation of reparation [10, 15, 17], apoptosis and oxidative burst phenomenon [21–23]. Accumulating in large quantity at the places of proliferation, paralyzed young stem cells can massively rush into blood stream changing blood formula and cell composition

of bone marrow. The main signs of CML might occur at this stage: lowering of alkaline phosphatase levels, oxidative burst and others.

We suppose that blocking of hybrid Bcr/Abl gene with Imatinib (Fig. 3) leads to recovering of normal C-Abl gene expression from chromosome 9, and after that cell "paralysis" disappears. Cell normalizes and likely migrates to its niche where its proliferation occurs. As soon as niches become occupied, cytokine stimulation of early progenitor cells stops as well as chemokine stimulation of their migration. Of course, this effect might be visible in case of discontinuous use of Imatinib only.
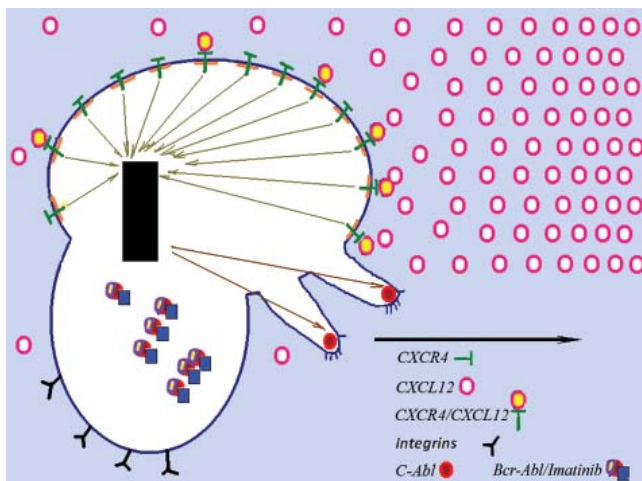

Fig. 3. Molecules of hybrid Bcr/Abl protein are hidden from cell system control by Imatinib molecules, due to this Abl moiety of the hybrid protein is not visible for hypothetical cell control system, and expression of c-Abl from normal chromosome is initiated. As a result, cell is normalized according to the hypothesis, cell migration and apoptosis are recovered, and oxidative burst disappears

MUTATION P190

In the light of our hypothesis disruption in reparation resulted from the lack of C-Abl in CML might enhance the changes of Imatinib delivery and changes in its intracellular concentration. This might lead to quick Bcr/Abl overproduction and to C-Abl deficit, and the subsequent reparation disruption, mutation frequency elevations and to increased probability of malignant transformation among cells bearing *bcr/abl* rearrangement. As a result of this the malignant leukemic clones could emerge with high frequency, and blast crisis might develop rapidly. Malignant transformation is usually related to the activation of other signaling pathways than those that operate in non-transformed cells. It is known that in case of p210 CML signaling goes through STAT1, STAT3 and STAT5 pathway in myeloid cells-progenitors, while in p190 Bcr/Abl CML signaling passes through IL-4, STAT6 pathway that are usually active not in myeloid, but in lymphoid cells [47]. This can also explain Bcr moiety shortening in p190 and p210 Bcr-Abl. The cause of this shortening is apparently that in lymphoid cells the shorter variant of Bcr/Abl is translated as a result of an alternative splicing. In conditions of active mutagenesis and cell population selection "truncated" versions of *bcr/abl* gene sufficient for transcription of Bcr moiety

in *p190 bcr-abl* remain in population. This indicates that *bcr* moiety is apparently important for realization of malignant phenotype. Proliferation of malignant cells with *bcr/abl p190* is likely possible to be in a niche of any stem cells of organism, that is why usage of Imatinib may contribute to generalization of proliferating sites of leukemic infiltration at blast crisis, restoring the ability of cells to migrate. To solve this problem AMD3100 (Plerixafor) which blocks CXCR4 receptors has been proposed. It has been shown that the use of AMD3100 considerably lowers the resistance of leukemic cells to the therapy [48]. Other researchers using AMD3100 have achieved a favorable therapeutic effect when mobilizing CD34 stem cells for autotransplantation of GSC to patients with multiple myeloma and non-Hodgkin lymphoma with just small side effects [49–52]. Using of AMD3100 leads to CXCR4 receptor inactivation that makes cell unable to sense chemokine gradient (Fig. 4). As a result, cell is inactive, fixes badly to intracellular matrix and, probably, because of this can easily penetrate into blood stream.
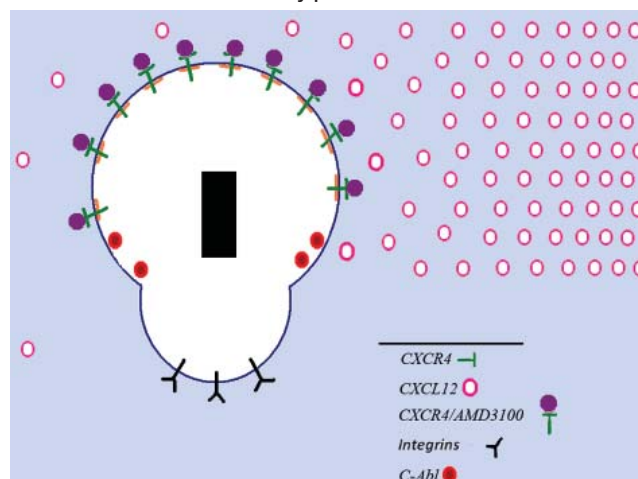

Fig. 4. Usage of AMD3100 leads to CXCR4 receptor inactivation that makes cell unable to recognize gradient of the chemokine

As a result of series of experiments using AMD3100 and G-CSF for mobilization of CD34+ cell populations it has been shown that AMD3100-mobilized CD34+ cells include more T- and B-cells progenitors, while cells mobilized with G-CSF have more granulocytes and mononuclear phagocytes progenitors [53]. These results lead to an interesting assumption. It is known that mature cells originate at the terminal differentiation of stem cells of appropriate type. Maybe "myeloid" cells during CML differentiate at proliferation of earlier lymphoid line cells-progenitors, that has undergone chromosomal aberration with formation of Philadelphia chromosome. Thus, "myeloid" phenotype forms because the formation of a lymphoid phenotype is possible only when terminally differentiated lymphoid cells-progenitors proliferate. In this case early lymphoid cells-progenitors [53] accumulating in a very large quantity have phenotype which is only similar to that of myeloid cells.

Thereby, the CML disease studying of currently identified molecular mechanisms of cell migration,

reparation and apoptosis has led to a significant progress in understanding CML nature. This allows us formulating a special hypothesis on the possible role of the hybrid Bcr-Abl molecule to deprive the cell of its ability to chemotaxis sensing the right direction of the ligand concentration gradient. We suppose that further researches in this field may lead to the improvement in treatment methods of this disease.

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