



Immature CML cells implement a BMP autocrine loop to escape TKI treatment

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Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder emanating from a reciprocal translocation between BCR on chromosome 22 and ABL kinase on chromosome 9, generally known as the Philadelphia chromosome. Although activity level of ABL kinase in the resting condition is preserved and regulated by a hydrophobic pocket, in CML, this pocket substitute with BCR that engenders in incessant activation of ABL and culminates in actuation of downstream signaling pathways (1,2). Introduction of tyrosine kinase inhibitors (TKIs), revolutionized the response criteria, progression free survival and overall survival in CML patients in contrast with the previous form of treatment comprise of interferon- α and cytarabine combination (3). Even though a sizable proportion of cells respond to TKIs in a highly efficient manner, a strong intimation of resistance has been received from a minority group called leukemic stem cells (LSCs), responsible for disease progression (4). Impervious to TKIs whether by the acquisition of some features such as domain mutations or inheritance hallmarks, come to pass in a spatial structure called bone marrow niche. So, acts as a shield in the way of targeting LSCs and plays an indispensable role in the development of leukemia (5).

Bone marrow niche

Generation of leukemic niche refers to this fact that normal hematopoietic stem cells (HSCs) microenvironment

become vanquished by the propensity of leukemic cells to evasion and persistence (6). In the leukemic condition, the interaction of CML stem cells with stromal cells mediated by CD44, selectins and their ligands and also mutual secretion of various soluble factors that propel CML cells into the quiescent state (7-10). It has been elucidated that expression of CXCR4 is downregulated in CML cells prior to treatment initiation. Instantly after applying tyrosine kinase inhibitors, CXCR4 is upregulated due to the direct correlation with BCR-ABL and cells migrate to the bone marrow milieu for the homing (11). This lodgment induces dormancy in CML cells and makes the bone marrow niche as a sanctuary for minimal residual disease (12). Various procedures have been taken into account in the bone marrow context to promote chemoresistance and one of the newly described one is attributed to bone morphogenic proteins (BMPs) family.

Bone morphogenic proteins

Bone morphogenic protein ligands as a member of transforming growth factor- β superfamily (TGF- β), have a crucial role in the bone formation, evolving of gastrointestinal tracts, heart, and also the genesis of primitive hematopoiesis in the embryo. Activation of BMP signaling pathway occurred in a Smad dependent and independent pathway. In the Smad dependent manner, as the primary mechanism, following attachment of BMPs to constantly active type 2 receptor (BMPIIR), it phosphorylates type 1 receptor

(BMPiR) and phosphorylation of the downstream Smads is conducted by BMPiR. Recruitment, formation and nucleus translocation of the transcriptional complex composed of Smad1, 5, 8 as R-Smads and Smad4 as co-Smad, regulates the gene expression process. These trends are governed and inhibited by Smad6 and 7 which suppress phosphorylation of the R-Smads (13). The contribution of BMP2, BMP4, BMP7 for the maintenance and self-renewal of HSCs is noteworthy, but perturbation of related signaling pathway in leukemia development is a formidable challenge (14). Align with these notions, a precious study about the role of BMP ligands has been carried out to shed light on the role of these double-edged proteins in induction of TKI resistance in primitive CML cells (15).

BMPs, guardian against tyrosine kinase inhibitors?

Grockowiak *et al.* measured the expression of BMPR1b transcript in 71 newly diagnosed CML patients. Elevated expression of BMPR1b in almost 40% of the cases referred to the importance of this element in CML pathogenesis. Following reaching complete cytogenetic response (CCyR), transcript level and also protein expression of BMPR1b in bone marrow CD34+ cells suppressed, but in contrary imatinib resistant population exerted a higher expression pattern. It became clear that imatinib has the ability to enhance the expression of BMPR1b in CD34+ CML cells invitro and indicated to new resistance mechanism in primitive cells. To find out whether this expression is concomitant with TKI resistance, LTC-IC and CFC assays was performed. Their results showed that cells expressing a higher level of BMPR1b were expanded and survived more in exposing to imatinib, INF- α and the combination than low expressing cells and this effect was intensified by the addition of BMP2 and BMP4 ligands. But how CML cells found the BMPs? Are there diverse resources for providing these proteins? Apart from mesenchymal stem cells (MSCs) in non-responder patients which secreted high amount of BMP4 in contrast with healthy one, a rise in transcript level of BMP2 and BMP4 in CD34+ CML cells of resistant patients was notable. However, patients follow up from diagnosis until reaching the CCyR or resistance state, declared a significant increase in BMP4 but not BMP2 in CML cells. This finding revealed that CML cells by production of BMP4 in an autocrine loop might tolerate TKI. Up-regulation of TWIST-1 as a modulator of tumor growth and drug resistance, was mediated by addition of

BMP ligands. Also, inhibition of this transcription factor by BMPR1b inhibitor posited the role of BMP4-BMPR1b-TWIST1 axis in resistance adoption.

Discussion

A reasonable percentage of CCyR (83%), event free survival (81%) and overall survival (85%) are achievable by considering imatinib as the first option for treatment of CML. But after a while emergence of resistance or tolerance attribute the liability to the bone marrow niche as the leading context where leukemic development is in progress (16,17). Secretion of G-CSF and IL-3 and also BMPs in an autocrine manner admitted this point that CML cells depend on the state of the disease are self-supporting (15,18). On the one hand, TWIST1 as a promoter of cell growth, survival and drug resistance has been reported to deregulated in CML patients. Imatinib suppresses the expression of this transcription factor but it remains high in the resistant clone which may refer to a decent prognostic factor for assessment of resistance in CML (19). On the other hand, adjustment of its expression by BMPs proved that an important target for breaking the wall of resistance came into existence (15). It has been elucidated that CML LSCs survive in a BCR-ABL independent fashion and in turn become contingent on Wnt- β Catenin, PI3K-AKT, Hedgehog and other signaling pathways (20). Mutual interaction of BMPs with these pathways (21) may bring new insight for further investigation in targeting CML LSCs. Meanwhile, one study stated that activation of BMP signaling leads to adherence of CML cells to stromal cells and this contact is an ample opportunity for leukemic cells to evade TKIs (22). Another finding demonstrated that treatment of bone marrow mesenchymal stem cells with imatinib increases the osteogenic markers such as BMP2, osteocalcin, and Runx2 and reflects the role of imatinib in niche modification (23). These concepts reiterated in acute promyelocyte leukemia which using ATRA downsized the expression of BMP expression in parallel with PML/RAR α fusion gene, however, in non-responder patients the expression pattern remained intact. They also posited the elevated expression of BMPs and related receptors in multiple myeloma and acute lymphoblastic leukemia reflect that BMPs family are a jack of all trades (24).

Conclusions

CML LSCs have shown to have an intrinsic resistance to

TKIs, and they persist even in patients with CCyR, and this frequently results in the relapse after discontinuation of the TKI therapy. Part of this immunity germane to the formation of BCR/ABL independent mechanisms. So, ascertaining the compensatory pathways such as BMP would be an intriguing solution to eliminate CML LSCs.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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