

## A Dual Origin for Bcr-Abl Gene Translocation/Fusion as Dynamics of Synergism of the Hematopoietic Stem Cell and Hemangioblast in Chronic Myeloid Leukemia

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Received date: December 14, 2015; Accepted date: December 29, 2015; Published date: December 30, 2015

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### Abstract

Contextual BCR-ABL tyrosine kinase over-activity determines in formulated fashion the emergence of proliferation and anti-apoptosis that arise largely as derived phenomena of otherwise homeostatic mechanisms of the c-ABL gene within hematopoietic stem cells and hemangioblasts in the bone marrow. The ability to suppress almost completely, both in terms of phenotype and cytogenetically, the myeloid cell line expansion by imatinib mesylate is indicative of a phenomenon that depends strictly on the transformed status of the cell of origin in the chronic myeloid leukemia process. It is with relevance to complex participation of the dynamics of the fused BCR-ABL protein product that contextual conditioning of the cells of origin of the gene translocation further motivates the dimensional expansion of the transformed myeloid cell clones to increasing proliferative rates, thus leading to blast crisis as eventual loss of differentiating potential.

**Keywords:** BCR-ABL; Hematopoietic stem cell; Hemangioblast; Leukemia

significant degree, prove to be elements of diversity in the dual process of transformation and of mitogenesis of the targeted cells.

### Introduction

The targeting of the hematopoietic stem cells bearing BCR-ABL translocation fusion gene is sufficient for phenotypic control of the proliferating myeloid cells in patients suffering from the chronic phase of chronic myeloid leukemia. Noncoding RNAs are involved in CML in particular, by regulating gene expression through binding to target mRNAs [1]. The dimensions of such suppression, however, allow for persistence of non-replicating hematopoietic stem cells in patients treated with imatinib mesylate. Imatinib has potent anti-cancer effect against leukemia associated with BCR-ABL and with solid tumors over-expressing c-kit and Platelet Derived Growth Factor Receptor [2]. Within such scenario, the question arises whether hemangioblasts are a real primary target for BCR-ABL fusion translocation; such possibility is significant in the possible realization of involvement of both hematopoietic stem cells and endothelial cells in malignant transformation, as has also been suggested in breast carcinoma and glioblastoma lesions.

### Primitive Cell of Origin

Such considerations indicate the directive involvement of a primitive cell line that is primarily non-differentiated but capable of significant divergent potential for differentiation as multi-potent cells of involvement in the transformation process. S-phase progression of the cell-cycle may be inhibited against lymphoid crisis in CML and Philadelphia chromosome-positive acute lymphoblastic leukemia [3].

The inclusive phenomenon of malignant transformation in the initial stages of chronic myeloid leukemia is derived from considerations also of the quiescent nature of such cells that, to a

### Chronic Phase

In line with the development of the chronic phase of chronic myeloid leukemia, there arises a complex derivation of the BCR-ABL fusion gene that is cytogenetically recognizable as the Philadelphia chromosome [Ph]. In 98% of CML patients with the Ph chromosome, there develops cleavage of the BCR gene within its major breakpoint region and breakage of the ABL within a 100-kbp region of exon 2a [4]. The intricate definition of the nature of the constitutive activation status of the tyrosine kinase domain of the ABL gene is linked to an overlapping break point of the BCR gene in the process of reciprocal translocation. Region choice for canonical siRNA design algorithms is restricted in a fusion junction site as BCR-ABL but potency may be enhanced by optimization outside of target sequence [5]. The mechanics of the translocation process itself between ABL and BCR appear obscure but might be implicated within the general presence of BCR-ABL fusion gene even in healthy individuals, albeit at low levels.

The discovery of oncogenic drives and development of targeted therapies such as imatinib has markedly improved outcome in CML patients [6]. Cancer cells efficiently utilize limited energy sources, and drugs that target cellular metabolism further improve the efficacy of imatinib therapy [7].

Such presence in patients, who do not in fact constitute early stages of chronic myeloid leukemia indicates a possible emergence of normal physiologic roles of ABL, within normal contextual conditioning of hematopoietic cells. In such manner, c-ABL is abundant especially within the cytosol and is present also combined with nuclear chromatin.

The BCR-ABL fusion protein product appears therefore to actively constitute an essentially over-amplified consequential process that is beyond simple considerations of parametric homeostatic control. Metastasis suppressor 1 is downregulated in hematopoietic stem and progenitor cells in patients with CML [8]. It is such quantitative over-expression of the tyrosine kinase activity that would promote a constitutive potentiality for expression of such tyrosine kinase. Also, variant complex translocations involving a third chromosome may be present in 5-8% of CML patients [9].

Significant is the emergence of the p120 BCR-ABL fusion protein as the common isoform in the development of growth-factor independence of the malignant myeloid cell proliferation in CML patients. By contrasting the conformational free energy landscape of mutants resistant to imatinib action with those of the wild-type tyrosine kinases it is possible to better understand the emergence of drug resistance [10].

## Phenotype

Consideration of the chronicity of the transformed myeloid cells is relative to advanced stages of the disease where blast crisis emerges in terms that phenotypically are expressed by both high proliferative rates and also as essential non-differentiation status; such blast cells are reflected in the generation of a large range of additional genetic lesions and also in the insensitivity of the tyrosine kinase activity to suppression by imatinib mesylate. Proteolysis Targeting Chimera technology utilizes small molecules that recruit target proteins such as BCR-ABL and c-ABL for the ubiquitination-proteasome for degradation [11].

It would appear that translocation in the generation of the BCR-ABL fusion gene occurs essentially within non-proliferative stem cells in a manner that is strictly cell-context dependent.

The realization of further expansion of the clonal proliferation of multi-potent cells is further indicative of possible primary targeting of the hemangioblast in a manner that bridges hemopoiesis and endothelial vascular genesis within the bone marrow, in early stages of transformation in CML patients. Mutations in chromatin regulators often result in more stem-like cells that seed a bulk leukemic population and therapeutic agents targeting these regulators are being developed [12].

## BCR-ABL Transformation

The derivative dimensions included within the establishment status of the BCR-ABL translocation allow for a permissive production of the corresponding fusion protein that may exceed the controllable limit of action of the highest tolerable levels achieved by imatinib mesylate therapy. Hyaluronan oligomers sensitize CML cells to the anti-proliferative effect of imatinib by increasing apoptosis and senescence [13].

The mechanism and natural history of CML is still unclear [14]. Hence, it is significant to view the c-ABL as potential overlap phenomenon with the BCR-ABL fusion gene in determining the nature of the malignant transformation process within hematopoietic stem cell and hemangioblast as a combined integral phenomenon of synergistic enhancement.

The further compounding effects of such synergism are reflected in a dual population of cell types that ensure the promoted transformation event as essential establishment and maintenance of

the tyrosine kinase over-activity in terms especially of constitutive activation. There is a significant association of defective apoptosis arising from promoter polymorphisms of Fas-FasL genes with the development of CML [15].

## Experimental Transfer

Biologic ineffectiveness in transfer of malignant transformation to many cell lines and to murine models indicates the failed susceptibility of a number of cell types to the establishment of early stages of oncogenesis in CML, in vitro and in vivo. The lack of a faithful model of the chronic phase of CML in the laboratory testifies to poorly understood dynamics of the translocation/fusion phenomenon in genesis of the BCR-ABL gene complex, and especially to the breakpoint dynamics of both BCR and ABL, but particularly within the breakage cluster regions of the BCR gene. In particular, the therapeutic resistance by the gatekeeper mutation T315I in BCR-ABL to imatinib is a significant problem clinically [16], but pyrazolopyrimidines may serve as lead compounds for development. MicroRNA employing non-viral vectors have been utilized to inhibit various cancer cells, and may prove useful in CML hematopoietic stem cells [17].

## Hemangioblast/Hematopoietic Stem Cell

ABL has been recognized as essential for the transformation process whereas the BCR appears to contribute to the maintenance of establishment and proliferation of the proliferating clone expansion in CML. Such considerations indicate the emergence of individual gene effects within complex realization of effects in oncogenesis. Modulation of aging-related inflammation within the bone marrow micro-environment may enhance the emergence of oncogenic events in stem cells [18]. Isohiocyanate treatment may correct inflammatory and defective DNA repair mechanisms in hematopoietic tissues [19]. The development of effective contextual requirement for the specific cellular micro-environment is dependent on the active genesis of the translocation event itself, but this also promotes the participation of the possible dual relevance of the hemangioblast and hematopoietic stem cell in malignant transformation.

Dysregulated cholesterol metabolism and/or accumulation occur in leukemia, and 2-hydroxypropyl-beta-cyclodextrin shows anti-CML effects by modifying cholesterol [20].

The pool of quiescent hematopoietic stem cells and the further possible forms of co-operability of hemangioblasts in malignant transformation indicate a basic dualism that is further defining dimension for contextual cellular requirements in the oncogenesis of CML. Dasatinib is a novel, multi-targeting kinase inhibitor of breakpoint cluster region Abelson [BCR-ABL] and Src family kinases, with a time-dependent anti-leukemic effect [21].

Parameters of multi-potentiality of these cells allow for a permissiveness of excessive proliferative cells that progress in terms of added realized constitutive activation of the tyrosine kinase of the fused ABL. The development of selective kinase inhibitors is challenging due to the large size of the kinome and the structural similarity between kinase active sites [22]. Multi-targeting of both BCR-ABL kinase and microtubules may be achieved with 2-acylaminothiophene-3-carboxamides [23].

## Genetic Instability

Dimensional correlation allows for the recognition of malignant permissiveness that correlates with possible generation of genetic instability, and thus to the generation of accumulated genetic defects within the neoplastic cells. Under-expression of miR-130a functions as tumor suppressor by inhibiting multiple anti-apoptosis proteins including BCL-2 [24]. Added to such phenomenon, however, is the significant phenotypic suppression of the malignant myeloid cells by primarily targeting the cells of origin of the chronic phase of CML. More inhibitors of the mutated ABL tyrosine kinase are absolutely required [25]. Inhibitors of BCR-ABL tyrosine kinase kill CML cells by stimulating pro-apoptotic BIM and inhibiting anti-apoptotic BCL2, BCLxL and MCL1 [26].

## Diversity in Transformation

Diversity of potential transformation is hence linked to the multi-potentiality of the cancer stem cell concept for oncogenesis but this is itself conditioned by dimensions found within the microenvironment of the bone marrow.

Such conditioning appears linked to the homeostatic functions of the c-ABL gene in enhancing intercellular adhesion and communication, on the one hand, and also of the determined cellular morphology of the targeted cells. Indicative parameters include integrin signaling and also a binding of the ABL to the actin within the cytosol of the cells concerned. A cytosol-nuclear transport also is relevant in that the BCR-ABL fusion protein loses nuclear target potential. Hence the relevance of strict dynamics of the BCR-ABL fusion protein is critical in the ongoing process in CML oncogenesis that is accompanied by a wide variety of down-stream signaling pathways such as Jun, STAT5, Ras pathway. Included also is the implied dysfunction of the 20S proteasome-ubiquitin mechanisms. Better understanding of CML hematopoietic stem cell biology is required to eradicate these cells responsible for disease recurrence and of residual disease [27].

## Alternative Pathways and Blast Crisis

CML therefore emerges as a series of alternative pathways of proliferation, on the one hand, and of differentiation pathways that are operative within the pool of differentiated malignant myeloid cells in patients who enter the chronic phase of the CML. Highly significant is the further advanced disease-state where differentiating potential is lost within contextual conditioning in establishment of higher proliferative rates of the malignant cells.

The BCR-ABL fusion gene doubles the expression level of genes involved in the regulation of the cell cycle, proliferation and apoptosis of CD34+ cells, with implications also of modified genes in PI3K/AKT and MAPK signaling in CML patients [28].

The blast crisis in CML patients indicates a dynamic process of evolving oncogenesis that is inclusive phenomenon for participation of the accumulating genetic lesions within the transformed myeloid cells. Linked to such phenomenon is the emergence in some patients of the p190 isoform of the BCR-ABL translocation fusion gene in patients with the acute ALL phenotype lacking an initial chronic phase.

Overall, there develops a progression of the disease state that closely correlates with dynamics of establishment of the malignant process that is maintained by a BCR-ABL fusion gene. The significant

suppression possible by specific imatinib-targeting of the cell of origin of the malignant transformation of CML indicates the highly constitutive nature of a malignant change that is ABL-tyrosine-kinase mediated.

## Concluding Remarks

Permutation of dynamics of the BCR-ABL fusion protein lies at the center of operative transfer of the constitutive activation of the tyrosine kinase domain of the ABL protein. Added formulation of breakage point involvement of the BCR and of significant participation in establishment of the malignant phenotype within the contextual cellular series of dual hematopoietic stem cell and of hemangioblast would lead to the recognition of a micro-environmental series of transforming changes inducing proliferation and anti-apoptosis leading to the eventual creation of blast cells that do not differentiate.

Further to the systematic parameters of proliferation is added an overall projected loss of potential differentiation that is maintained at the expense progressively increasing proliferative activity.

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