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Inhibition of Ras-Mediated Signaling Pathways in CML Stem Cells

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Abbreviations

PI3K: Phosphoinositide 3-Kinase; sFRP: Secreted Frizzled-Related Protein; Fz: Frizzled; LPR5/6: Low-density Lipoprotein Receptor-Related Protein 5/6; Dvl: Disheveled, GSK3β; Glycogen Synthase Kinase 3 β, APC: Adenomatous Polyposis Coli; CK1α: Protein Casein Kinase 1 α; SHP-1: SH2-Domain-Containing Protein Tyrosine Phosphatase-1; PP2A: Protein Phosphatase 2A; AHI1: Abelson Helper Integration Site 1;JAK2: Janus Kinase 2, STATs: Signal Transducer and Activator of Transcription; SOCS: Suppressor of Cytokine Signalling; Cby: Chibby, LEF: Lymphoid Enhancer-Binding Factor; TCF: T Cell Factor

Introduction

Chronic myeloid leukemia (CML) is one of the most controversial issues in the field of myeloproliferative neoplasms (MPNs) that is known as the Philadelphia chromosome, resulting from translocation occurs between Abelson (ABL1) gene on chromosome 9 and breakpoint cluster region (BCR) gene on chromosome 22 [1].

Aberrant activation of this protein tyrosine kinase in cells with pluripotent hematopoietic stem cells (HSCs) origin give rise to various clinical and biological findings in each of the stages as the disease progression. Despite significant efforts to increase the effectiveness of tyrosine kinase inhibitors (TKIs) through the recovery process, the occurrence of second mutations in the BCR-ABL1 kinase domain, as well as the persistence of quiescent leukemic stem cells (LSCs) ultimately may lead to relapse. Thus, finding progression-related risk factors, especially toward an acute leukemia would be beneficial for better understanding of CML pathogenesis and development of targeted therapies, in the following [2].

CML stem cell transformation is a multi-step process that involves multiple molecular changes and dysregulation of signaling pathways, controlling cellular activities during their evolution [3]. As soon as it became clear that BCR-ABL1 transcripts could be detected in HSCs, the existence of a pre-CML state before the chronic phase was firmly proved over the recent years. Oncofusion gene is expressed at low levels in pre-LSCs, which is increased in parallel with CML development, so that the progress of the phase transformation is vital for LSC formation [4]. By considering this issue, identification of CML using detection techniques for BCR-ABL1 chimaera seems to be impossible in the initial stages of disease. Designation causes of BCR-ABL1 burden upregulation is a serious matter for early diagnosis of CML patients, as the levels of BCR-ABL1 tyrosine kinase is not being irrelevant with the achievement of best molecular and cytogenetic responses in such cases.

It seems that only the acquisition of BCR-ABL1 is not enough for the oncogenic features of CML stem cells and additional changes are required for the maintenance of such malignant cells in the bone marrow niche. In addition to genetic changes involved in the CML development, epigenetic modifications play a significant role in the molecular events of CML stem cells. DNA methylation as a part of epigenetic programming is a transcriptional regulator through the cellular pathways controlling the proliferation, self-renewal and differentiation, as well as survival of myeloid progenitors [5]. Therefore, it should come as no surprise that defects in such signaling pathways resulted in leukemogenesis. DNA methylation of HSCs ensures lifelong regulation of oncogenes and tumor suppressor genes expression, as well as genomic imprinting and X-chromosome inactivation. However, it seems to be the epigenomic instability contributes to aberrant DNA methylation patterns define the phenotypic and functional characterization of CML stem cells in the early events of differentiation and cell fate decisions [6]. Despite intensive studies of any epigenetic modification occurring through the CML development, the exact nature of this cooperation remains unknown.

It is obvious that uncontrolled expansion and persistence of myeloid progenitors, is the leading cause of CML stem cell clones' predominance over normal HSCs in bone marrow niche [7]. Nevertheless, the acquisition of BCR-ABL1 is not the mere cause of self-renewing and massive proliferation of malignant cells, hence additional methylation changes of key factors through the signaling cascades are expected to have synergetic behavior with BCR-ABL1 oncoprotein and even contribute to increase the fusion gene expression during the course of CML (Figure 1). Therefore, the molecular analysis of patients with CML is essential in order to identify the multiple BCR-ABL kinase-independent pathways over the early stages of the disease. On the other hand, molecular events underlying TKI-resistance, as well as its recurrence suggests that tyrosine kinase activity is not the only cause of increased proliferation and self-renewal of malignant cells and multiple signaling pathways remain permanently active by unknown reasons [8].

Nowadays, considering the significance of SOCS proteins in JAK-STAT pathway, the hypermethylation status of this negative regulator gene has been the topic of various studies, as a new approach has been established explaining the causes of proliferation and the development of resistant cells in CML patients [9,10]. Wnt/β-catenin pathway inhibitors, one of the most important signaling pathways involved in self-renewal of CML stem cells, are not unaffected of epigenetic alterations particularly DNA methylation. Secreted Frizzled-Related Protein 1 (SFRP1) and Chibby1 (Cby1), antagonists of Wnt andβ-catenin proteins, undergo hypermethylation in CML, as somehow the stemness regulatory pathway remains to be active in LSCs [11,12]. Since the inhibition of Wnt/β-catenin can also affect the survival of HSCs, there is a lot of concern about the therapy methods and inhibition of pathway components, specifically β-catenin. The hypermethylation of tumor suppressor SH2-domain-containing

protein tyrosine phosphatase-1 (SHP-1) gene, as an inhibitor of β-catenin protein, is another evidence of continuous activation of Wnt/β-catenin signaling pathway [13,14]. This phosphatase also has an inhibitory effect on BCR-ABL1 oncoprotein and somehow it can be claimed for its influence on the function of activated CML signaling pathways.

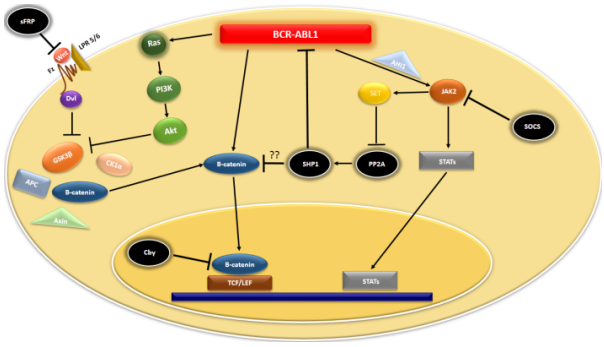

Figure 1: Proposed association between gene methylation and permanent activation of signaling pathways in CML stem cells. Hypermethylated components are shown in black.

The sequence of molecular events that have ever been known to control the CML stem cell activity share common characteristics with those in HSCs, therefore finding a completely distinct mechanism for identification of new diagnostic and therapeutic targets, as well as differentiation of recurrent can be feasible only by understanding the biology of CML and its activated signaling pathways. Finally, an investigation into the DNA methylation patterns of proteins involved in CML signaling pathways suggested new mechanisms of such dysregulations and thus guide to treatment targets through the different stages of disease.

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