International Journal of Scientific Research in Engineering and Management (IJSREM)
Volume: 07 Issue: 06 | June - 2023 SJIF Rating: 8.176 ISSN: 2582-3930

The Role of BCR-ABL Gene on Chronic Myeloid Leukemia: An Overview

Vaishnavi Nagaraja

Keywords: BCR-ABL, Breakpoint Cluster Region, Chronic Myeloid Leukemia, Philadelphia Chromosome, Imatinib, Dasatinib.

Abbreviations: BCR, Breakpoint Cluster Region; CML, Chronic Myeloid Leukemia; ALL, Acute Lymphoblastic Leukemia; AML, Acute Myeloid Leukemia; STAT, Signal Transducer and Activator of Transcription; OD, Oligomerization Domain; GRB2, Growth Receptor Bound protein 2; SOS, Son of Sevenless; GAB2, GRB2 Associated Binding protein 2; SNIPER, Specific and Non-genetic inhibitor of apoptosis protein (IAP)-dependent Protein Erasers; PROTAC, Proteolysis Targeting Chimeras; UPS, Ubquitin Proteasome System;

Introduction:

The Breakpoint Cluster Region is a protein encoded by the BCR gene with its partially discovered function to generate instructions for producing a protein and also to encode serine/threonine kinase protein. There are three Breakpoint cluster regions; major (M-bcr) which is high in CML patients, minor (m-bcr) with a 1-2% contribution in the CML, and micro (μ-bcr) which is very rare in the case of CML. The ABL1 encodes for the ABL1 protein which can function as a tyrosine kinase. The translocation of the ABL gene on chromosome 9 at the band 34 to the BCR gene on chromosome 22 at band 11 leads to the fusion of the BCR-ABL gene which is responsible for Chronic Myeloid Leukemia (CML), Acute Myeloid Leukemia (AML), and Acute Lymphoblastic Leukemia (ALL). Chromosome 22 with this hybrid gene called a Philadelphia chromosome codes for a BCR-ABL protein that enhances the activity of tyrosine kinase thereby activating numerous signaling pathways. If there is a translocation of BCR to chromosome 9, which will cause the emergence of the ABL-BCR gene (9q+). [1][4][5][6] The role of the BCR-ABL gene in CML is to increase the growth and proliferation of myeloid cells, avoid apoptosis, increase c-independent growth, induce aberrations in the cytoskeletons, etc. [3]

The three variants of the BCR-ABL gene; p190, p210, and p230 are the isoforms of tyrosine kinase oncogene with their protein molecular mass 190kD, 210kD, and 230kD respectively. Diagnosis of p190 which is coded by e1a2 transcripts (exon 1 of BCR + exon 2 of ABL) indicates majorly ALL, whereas the p210, coded by the transcripts b2a2 (exon 13 of BCR + exon 2 of ABL) or b3a2 (exon 14 of BCR + exon 2 of ABL) specifies CML in most of the cases. The p230, coded by e19a2 transcript (exon 19 of BCR + exon 2 of ABL) has the least tyrosine kinase activity when compared to p190 and p210 and this can be seen in the patients with Chronic Neutrophilic Leukemia (CNL). [1][2]

Activated molecular mechanisms by BCR-ABL proteins

Due to the hybridization of BCR and ABL genes, many pathways that take part in regular cellular processes like STAT, RAS, PI3K, ROS, etc get altered significantly. The main function of the BCR gene is to produce a serine/threonine kinase domain which is made of three major domains; Oligomerization domain (OD), Diffuse B-cell Lymphoma (DBL) homology domain, and Guanosine tri-phosphatase (GTPase) Activating Protein (GAP) homology domain. However, OD of BCR-ABL protein plays a major role which activates ABL kinase via oligomerization reaction. This, in turn, activates Growth Receptor Bound protein 2 (GRB2) which consecutively generates two proteins; SOS protein that disturbs the RAS pathway leading to increased cell growth and proliferation, and GRB2 Associated Binding protein 2 (GAB2) that significantly transmits numerous signals via cytokines and growth factor receptors to accelerate the PI-3 kinase activity thereby reducing the apoptosis. Correspondingly, a mutation in the Y^{177} or Tyr^{177} site of the BCR gene autophosphorylates the tyrosine kinase of the ABL domain resulting in various genomic instabilities. Additionally, this autophosphorylation increases the f-actins which are essential proteins in cell migration leading to focal adhesion and ending up with Cytoskeleton abnormalities as shown in the figure-1. All these aberrations and uncontrolled mechanisms cause oncogenesis in the myeloid cells developing into CML. [4][5]

BCR-ABL gene Inhibitors

Since tyrosine kinase activity is the key factor in adverse functioning of BCR-ABL, an inhibitor against the kinase could be a fruitful solution for CML; the efficient inhibitor is Imatinib. These molecules bind to the BCR-ABL domain in order to avoid the phosphorylation of the protein and further decreases the CML aggression as shown in the figure-2. [7][8]

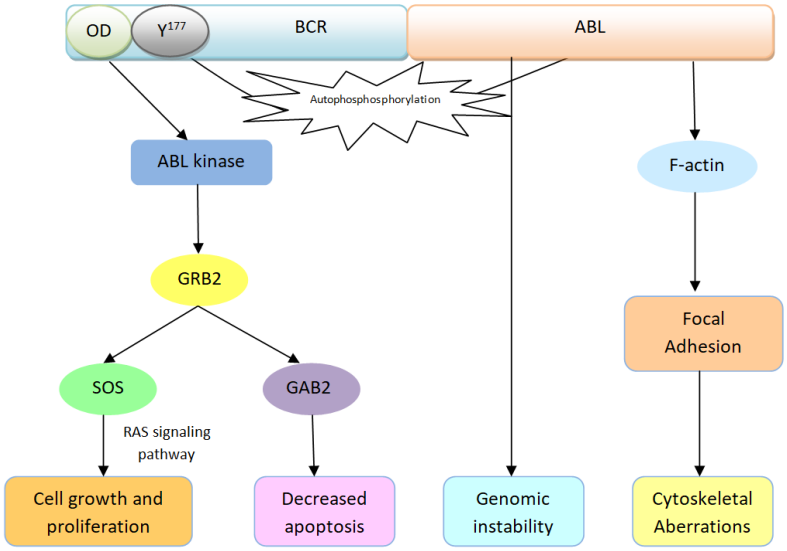

Figure 1: Schematic structure of the molecular mechanism of causing cell aberrations by the OD of BCR like uncontrolled growth and proliferation by SOS protein via the RAS pathway, reduced cell death. The autophosphorylation in the Y177 activates the ABL kinase, in turn leading to genomic stability as well as abnormalities in the cytoskeletons.

The additional efficient inhibitor is dasatinib. The crucial role of this tyrosine kinase inhibitor is to shut down the activity of T-cells which are involved in cancer cell growth and proliferation, cytokine production, etc. On the other hand, dasatinib also activates the innate immune system via Lysosomal acidification which is involved in the apoptosis of a cancer cell. In addition, a modern system that knockdowns the protein called SNIPER have also been an effective way to prevent CML proliferation. This technology directly targets the adverse BCR-ABL protein with the help of SNIPERs and PROTACs; the two different ligands attached by a linker. One ligand binds to the BCR-ABL and the other to the E3 ubiquitin ligase breaking down the ATP molecule and transferring the Ubiquitin to form an E2 Ligase. This E2 ligase further activates the Ubiquitin Proteasome System and successfully degrades the target protein. [7]

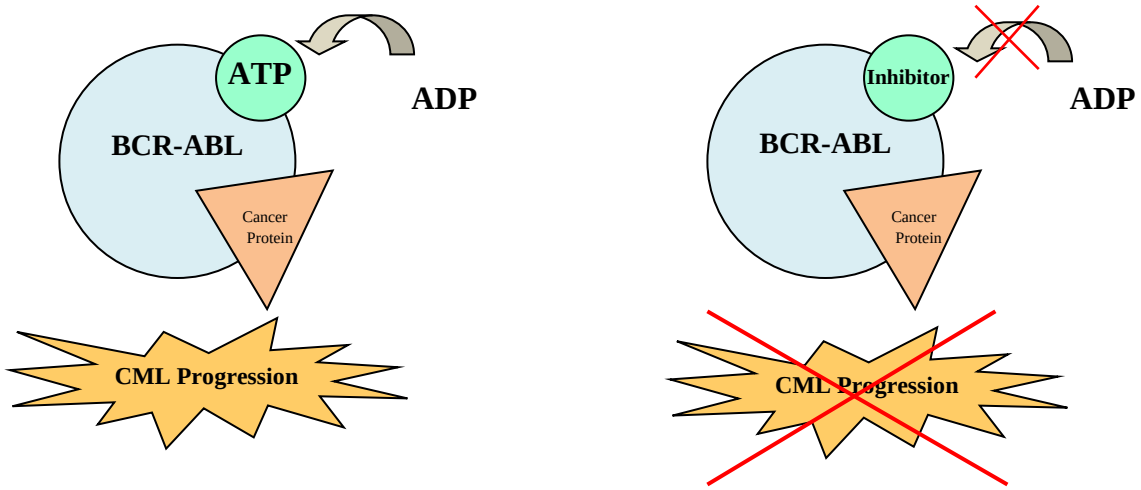

Figure 2: The basic mechanism behind the inhibition of BCR-ABL protein phosphorylation by Imatinib

References:

1. Melo, J. V. (1997). 2 BCR-ABL gene variants. *Baillière's clinical haematology*, *10*(2), 203-222.
2. Li, S., Ilaria Jr, R. L., Million, R. P., Daley, G. Q., & Van Etten, R. A. (1999). The P190, P210, and P230 forms of the BCR/ABL oncogene induce a similar chronic myeloid leukemia–like syndrome in mice but have different lymphoid leukemogenic activity. *The Journal of experimental medicine*, *189*(9), 1399-1412.
3. Advani, A. S., & Pendergast, A. M. (2002). Bcr–Abl variants: biological and clinical aspects. *Leukemia research*, *26*(8), 713-720.
4. Sattlermc, M., & Griffin, J. D. (2003, April). Molecular mechanisms of transformation by the BCR-ABL oncogene. In *Seminars in hematology* (Vol. 40, pp. 4-10). WB Saunders.
5. Kashiwagi, S., Fujioka, Y., Kondo, T., Satoh, A. O., Yoshida, A., Fujioka, M., ... & Ohba, Y. (2019). Localization of BCR-ABL to stress granules contributes to its oncogenic function. *Cell structure and function*, *44*(2), 195-204.
6. Goldman, J. M., & Melo, J. V. (2008). BCR-ABL in chronic myelogenous leukemia–how does it work?. *Acta haematologica*, *119*(4), 212-217.
7. Shibata, N., Ohoka, N., Hattori, T., & Naito, M. (2019). Development of a potent protein degrader against oncogenic BCR-ABL protein. *Chemical and Pharmaceutical Bulletin*, *67*(3), 165-172.
8. Burchert, A. (2014). Maintaining low BCR-ABL signaling output to restrict CML progression and enable persistence. *Current hematologic malignancy reports*, *9*, 9-16.