Journal of Oncology Translational Research

Methodology for In Silico Modeling of p210BCR-ABL Oncoprotein Isoforms found in Chronic Myelogenous Leukemia

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Abstract

Chronic Myelogenous Leukemia (CML) affects the hematopoietic stem cells of the bone marrow. It develops as a chromosomal abnormality due to the presence of the Philadelphia chromosome carrying the BCR-ABL oncogene. This gene expresses two oncoprotein isoforms, b2a2 and b3a2, produced by the head-to-tail fusion of p160BCR and p145ABL proteins. The two oncoproteins differ in amino sequence by a 25 residue insertion and a Glu903Asp substitution. In silico modeling, using the PSIPRED server has provided the secondary structural elements of the two oncoprotein isoforms. This program normalizes the amino acid sequences generated by PSIBLAST and then uses a neural network to produce the secondary structure. Chronic Myelogenous Leukemia (CML) develops when a single, hematopoietic stem cell acquires a Philadelphia (Ph) chromosome carrying the BCR-ABL fusion oncogene which gives its progeny an advantage for proliferation over normal RBCs and allows the Ph-positive clone gradually to displace normal RBCs during hematopoiesis. The abnormal Ph chromosome is produced by the translocation between chromosomes. The major consequences of Philadelphia translocation is the fusion of the ABL gene on chromosome 9 with the BCR gene on chromosome 22. The BCR-ABL fusion oncogene encodes new fusion proteins of 190, 210 and 230 kDa molecular weight. The p210BCR-ABL isoforms have an increased level of tyrosine kinase activity, which is important for the development of the disease. The production of fusion proteins increases the diversity of proteinprotein binding domains associated with tyrosine kinase activity.

19th Global Summit on Breast Cancer
October 30, 2020

Citation: Nadeem Kizilbash, Methodology for In Silico Modeling of p210BCR-ABL Oncoprotein Isoforms found in Chronic Myelogenous Leukemia, Breast Cancer Meet 2020, 19th Global Summit on Breast Cancer, October 30, 2020, Page No-04