Characterization of GRB2 Binding Site Mutation in Oncogenic Fusion Protein BCR-FGFR1

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Introduction
Receptor Tyrosine Kinases (RTKs) are surface cell receptors which control signaling pathways and regulate various cell processes such as cell proliferation. The breakpoint cluster region-fibroblast growth factor receptor (BCR-FGFR1) fusion results from a chromosomal translocation, leading to unregulated and uncontrolled cell proliferation. This causes the development of cancer, such as leukemia. The adapter protein growth factor receptor bound protein 2 (Grb2) creates a multimeric signaling complex by joining a variety of signaling molecules. The goal of this study was to determine if mutating the protein 2 (Grb2) creates a multimeric signaling complex by joining a variety of cancer, such as leukemia. The adapter protein growth factor receptor bound protein 2 (Grb2) creates a multimeric signaling complex by joining a variety of cancer, such as leukemia.

Methods

Results

Discussion/Conclusion

According to the National Cancer Institute, cancer affects about 38.4% of men and women. This research will enable more people who are diagnosed with cancer to receive better treatment. This study, focused on the BCR-FGFR1 fusion which is found in some leukemias. Specifically, the Y177F mutation was investigated in order to abolish the Grb2 binding site in BCR.

This study used NIH3T3 (mouse) cells and HEK293T (human) cells. Western Blotting was done on the BCR-FGFR1 fusion protein in 293T cells. FGFR1 was present in the cells meaning we were able to successfully place the plasmid in cells. First, BCR-FGFR1 expression was confirmed through western blot. Then pSTAT3 activation was confirmed through western blot. The third test confirmed total STAT3 in the mock and BCR-FGFR1 cell lysates. The amino acid tyrosine can be phosphorylated however, phenylalanine is not able to be phosphorylated. The BCR(Y177F)-FGFR1 mutant was able to signal for cell proliferation, reduced the number of foci on the petri dish (Figure 3c) compared with the BCR-FGFR1 plate (Figure 3b).

It is crucial to identify and treat cancer in patients quickly and effectively. This research will someday help patients receive lifesaving treatment for leukemia. This study shows that mutating the BCR fusion protein does lower its signaling ability; the BCR(Y177F)-FGFR1 mutated fusion protein showed a decrease in signaling ability. Patients positive for BCR-FGFR1 fusion protein may benefit from drugs that target Grb2 signaling pathways.

Future

While there some mutations that are well studied, there are also many that are not well studied. In the future I would like to look at additional mutations in the BCR-FGFR1 gene.

References


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