Drug resistance in the cancer kinase BCR-ABL regarding Chronic Myeloid Leukemia

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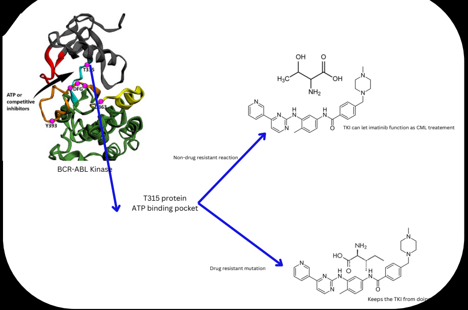
Background

- CML is a blood cancer with uncontrolled white blood cell growth.
- TKIs like imatinib target BCR-ABL, revolutionizing CML treatment.
- BCR-ABL, from the Philadelphia chromosome, drives cell overgrowth.
- TKIs bind to BCR-ABL's ATP pocket, halting cell growth.
- Drug resistance reduces TKIs' effectiveness in controlling BCR-ABL.
- Mutations in the ATP pocket cause resistance by changing its structure.
- Understanding these changes is vital for overcoming TKI resistance in CML.

Abstract



Methodology

- Utilized tools like PyMOL for structural analysis of protein mutations.
- Collected data from protein databases to identify mutations associated with drug resistance.
- Analyzed IC50 values from previous studies to determine the effectiveness of drugs against specific mutations.
- Graphed distances using Prism software to visualize structural changes.
- Examined the mean difference in distances between mutations and drugs to identify mutations with the greatest impact on drug resistance.

Measurements made in PyMOL

Data collected and analyzed in Prism

Researchable Question

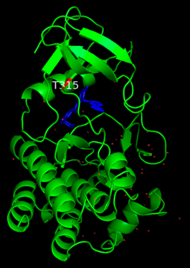
What is the influence of specific mutations in the BCR-ABL kinase on drug resistance in chronic myeloid leukemia (CML)?

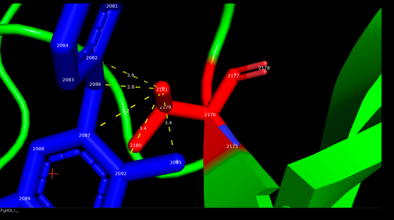
Hypothesis

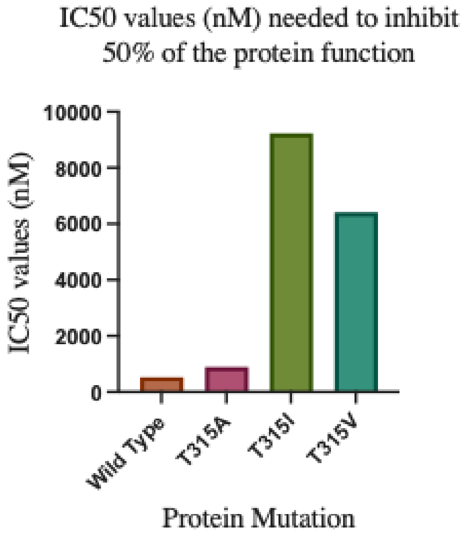
Mutations in the Thr315 residue of the BCR-ABL kinase are pivotal contributors to drug resistance in chronic myeloid leukemia (CML).

Main Takeaway

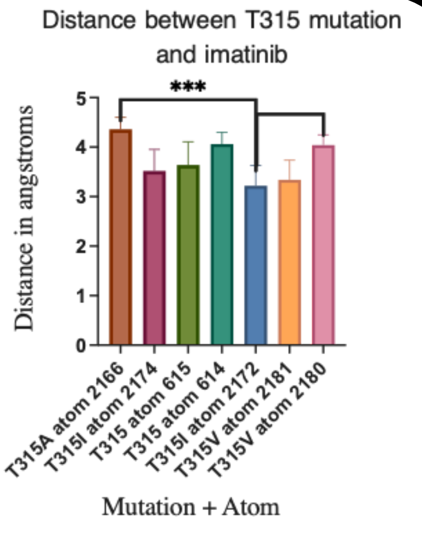
Mutations within the BCR-ABL kinase domain, particularly the T315I mutation, exhibit a significant impact on drug resistance in chronic myeloid leukemia (CML) by altering the spatial relationship between the protein and the drug.







nM of IC50 required in order to inhibit 50% of the protein's function as calculated through Redaelli et al.



The distances between the BCR-ABL mutation atom and the drug imatinib measured through PyMOL in angstroms

Analysis

- Utilized statistical analysis, including a one-way ANOVA test, to compare the distances between mutations and the drug imatinib.
- The one-way ANOVA test yielded a statistically significant result, with a P-value of .0001, indicating a strong correlation between mutations and drug resistance.
- Specifically, the mean difference in distance for the T315I mutation was calculated to be 3.22 angstroms, highlighting the substantial structural alterations associated with drug resistance.
- This observation suggests that the T315I mutation has the largest effect on drug resistance in CML with the BCR-ABL kinase.

ANOVA summary	
F	6.992
P value	0.0001
P value summary	***
Significant diff. among means (P < 0.05)?	Yes
R squared	0.5997

Conclusion

- This study gives insight into why drugs stop working in CML.
- Used different methods to understand how mutations affect treatment outcomes.
- Found mutations like T315I make drugs less effective by being very close to the drug's target.
- Urges the need for new treatments targeting these mutations.
- Shows potential for developing better drugs to target resistant mutations.
- Leads to further research into understanding how mutations cause drug resistance in CML.
- Aim to find new ways to treat CML patients better in the future.

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