How the A119P Mutation Affects the Structure and Function of P53

Zachariah Zawahry
Florida State University Panama City

Abstract

My research study's goal is to understand how both the structure and function of the p53 protein are affected by the mutation of alanine on the 119th nucleotide to proline. P53 is considered the human body's last natural line of defense against cancer, but it can't correctly fulfill its duty when mutated, so understanding this mutation will possibly allow us to understand how to prevent or fix this mutation, which would be a major step in cancer research. Our research showed that the A119P mutation destroys the beta sheet in the DNA binding domain of p53 by distorting the protein's backbone and increasing misfolding in the area; this results in the loss of the protein's high affinity for DNA binding, causing its ability to trigger apoptosis, cell cycle arrest, and DNA repair to be impeded.

Introduction

One of the most important tumor suppressors in the body, so much so that it's often referred to as "the Guardian of the Genome". It functions as a transcription factor in the body that binds to DNA and triggers apoptosis, cell cycle arrest, and DNA repair. Most cancer related p53 mutations occur within p53's DNA binding domain. This domain has a verry precise structural integrity which needs to be upheld for it to correctly carry out its function. Residue alanine 119 is located within p53's DNA binding structure and helps keep the structure of the beta sheet in this domain stable. The mutation of this alanine to proline causes the flexible backbone of the beta sheet to become rigid, which disrupts hydrogen bonding and protein folding. Because p53 functionality is directly dependent on its extremely precise structure, even small single missense mutations like A119P can cause big damage to its functionality

Hypotheses

- • I hypothesize that this mutation will disrupt the beta sheet in p53's DNA binding domain.
- • I hypothesize that the A119P mutation will result in the protein's transcriptional and DNA binding activity drastically decreasing.
- • I hypothesize that the A119P mutation will cause p53 to lose its tumor suppressant capabilities

Methods

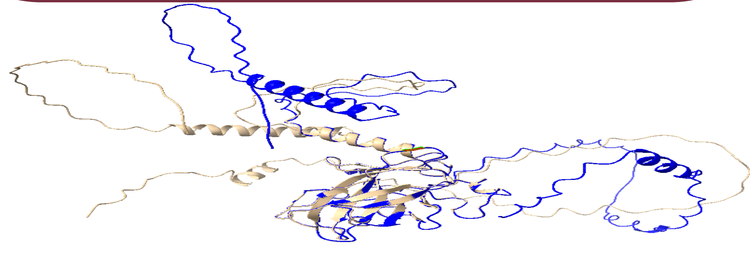
I plan to analyze the structure of p53 using published crystal structures. Use AlphaFold to predict how p53 would look with this mutation. Compare the DNA binding domains of the two models. Research how the changes in structure would affect this protein's ability to carry out its function, and back this up by researching published literature that discusses the mutations' effects in clinical trials.

- 1. Analyze p53's structure using published models
- 2. Create an AlphaFold model of p53 with the A119P mutation
- 3. Compare the models' structures, flexibility, and secondary structures' stability.
- 4. Use my findings along with published research on the mutation effects in clinical settings to conclude how the mutation affects its function

Results

Comparing the AlphaFold structure with the published models of the p53 protein resulted in the backbone of the beta sheet becoming rigid, which ruined that structure and introduced problems with the protein's folding. The comparison also revealed a major loss in hydrogen bonding capacity, which ruined many secondary structures near the 119th residue. Combining my findings with clinical research showed that these mutations caused a drastic reduction in its ability to activate target genes such as p21 and BAX, which are responsible for cell cycle arrest and apoptosis, respectively.

- • The mutation introduced rigidity to the backbone bone disrupting the beta sheet in the DNA binding domain
- • The mutation resulted in a major loss of hydrogen bonding capacity, disrupting secondary structures near A119
- • The mutation resulted in the loss of its ability to trigger cell cycle arrest and apoptosis



Discussion

The A119P mutation shows how a single missense mutation can have a major effect on both the structure and the function of a protein. In p53, the substitution of the flexible alanine with the rigid proline disrupts the structure of the backbone in the protein. This leads to the loss of hydrogen bonding capabilities within the structure, which therefore disrupts the folding of many of the secondary structures within the protein. The structure and function of a protein are directly related and intertwined with each other. So when you change the structure of p53, you also change how it functions. The A119P mutation results in two of p53's major functions being impaired. These are its ability to trigger apoptosis and cell cycle arrest. When applying this to the real world, the A119P mutation in the p53 protein results in its inability to correctly fulfill its duty as a tumor suppressant. This is significant as it will result in

Conclusions

- In conclusion, the A119P mutation caused the ruin of the structure of the beta sheet in the DNA binding domain of p53, as well as many other secondary structures around A119
- I also concluded that the A119P mutation caused a loss of p53's apoptosis and cell cycle arrest functions
- Lastly, I concluded that A119P caused p53 to lose some of its tumor suppressant abilities

References

• Stevens, M. (2020). p53 Structure, Function and Role in Disease. In Ebsco.com (1st ed., Vol. Nova science publishers. https://research.ebsco.com/c/oavkja/ebookviewer/pdf/jx772yqihr/page/pp_iii?location=https%25253A%25252F%25252Fresearch.ebsco.com%25252Fc%25252Foavkja%25252Fsearch%25252Fdetails%2525 2Fjx772yqihr%25253Fdb%25253De000xna
• Joerger, Andreas C, and Alan R Fersht. "Structural Biology of the Tumor Suppressor P53." Annual Review of Biochemistry, vol. 77, no. 77, 2008, pp. 557– 82, www.ncbi.nlm.nih.gov/pubmed/18410249, https://doi.org/10.1146/annurev.biochem.77.060806.091238. • AlphaFold Server. (2024). Alphafoldserver.com. https://alphafoldserver.com/welcome
• UCSF ChimeraX Home Page. (n.d.). Www.cgl.ucsf.edu. https://www.cgl.ucsf.edu/chimerax/