Analysis of RNA binding proteins on the regulation of tumor suppressor gene PTEN

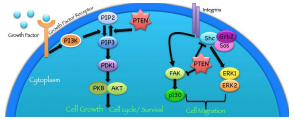
Thamanna Muhammed Hashir Advisor: Ihab Younis
Biological Sciences Program, Carnegie Mellon University Qatar

Abstract

PTEN a tumor suppressor gene has low expression in 80% breast cancer. (ZHANG, 2013). One reason for this low expression might be alternative splicing of PTEN. Alternative splicing is method by which the increases the coding capacity of the eukaryotic genome. Previous research has shown that RBPs play a role in splicing, we want to know if they have a role in the alternative splicing of PTEN, which leads to intron 1 of PTEN not being spliced out properly. This will help us in the diagnosis of the type of breast cancer and target the RBPs for breast cancer treatment to improve prognosis.

Introduction

- PTEN is a tumor suppressor gene located at the 10q23 region of chromosome 10.
- PTEN is part of the PI3K/AKT/PTEN pathway, which is responsible for the maintenance of functions relevant to cancer, such as apoptosis, metabolism, cell proliferation, and cell growth.



The PTEN protein works in different ways to suppress the formation and spread of tumors.
Credit: Front Oncol Feb 2015. doi: 10.3389/fonc.2015.00024. CC BY 4.0.

- In 80% of breast cancer, there is a low expression PTEN gene which results in tumor progression and poor prognosis, however, the amount of somatic mutation in the PTEN gene is less than 5% (ZHANG, 2013).

This suggests that there are other mechanisms that account for PTEN's low expression, one possibility is due to the alternative splicing of the gene, which leads to the expression of non-functional PTEN. Thus, in this project we will be studying the Role of RNA-binding protein as a potential splicing regulator of the Alternative splicing of PTEN.

Methods

Information was obtained using these public databases

- USCS browser
- AmiGO
- POSTAR
- NCBI
- PubMed

Results

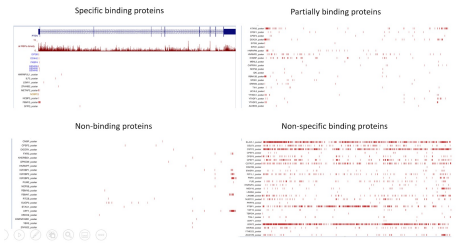


Figure 1: Binding sites of the POSTAR RBPs in the USCS genome web browser.

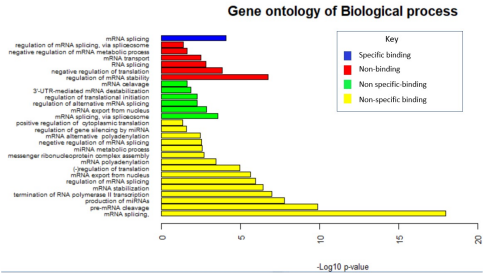


Figure 2: Gene ontology of the biological functions enriched in each of the 4 types of RBPs

RBP	Binding site	Splicing function	Relation to cancer	Pearson's rho	P-value	Significance of correlation	Total
RBM15	10	10	8	-0.1121	0.00008815	3	31
DDX4	7	10	10	0.05445	0.05749	1	28
METAP2	10	3	10	0.1592	2.33E-08	5	28
FKBP2	9	3	7	-0.3135	3.54E-29	8	27
EI3B	6	2	6	-0.3932	2.56E-46	8	22
GEMIN5	8	8	0	0.1879	3.84E-11	5	21
NCBP2	6	4	6	-0.1222	1.91E-05	3	19
NCBP3	8	4	6	-	-	-	18

Table 1: Specific binding RBPs sorted from most likely to least likely to regulate splicing of PTEN.

Discussion and Conclusion

- We classified them into 4 categories based on their specificity and where they bind.
- We found 16 RBPs, which were specifically only bound to the intron 1 or exon 1. There were more RBPs in other categories, with 23 partially binding RBPs, 20 non-binding RBPs, and 46 Non-specific binding RBPs.
- To understand which functions are elevated we performed gene ontology studies and looked at the biological processes which were enriched in these 4 categories of RBPs.
- Splicing via spliceosome, was a function that was enriched in the specific binding RBPs. It was the only function that was enriched for the specific RBPs, with 6 of the 16 RBPs showing this function. This was a significant discovery as when we look at the other categories, many other functions are enriched along with the splicing function.
- The Specific binding proteins were sorted based on the known information about them in PubMed. This sorting was done to determine which RBP is most likely responsible for the splicing. RMB15 was the top contender with a score of 31 points.

In conclusion, RBM15 is the most probable RBP which could regulate alternative splicing of PTEN

Acknowledgments

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