Data Driven Target Discovery in Lung Squamous Cell Carcinoma

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OBJECTIVE

Analyze data from 500 patients with lung squamous cell carcinoma to identify proteins that have a high change in expression between patient groups and could be good targets for drug discovery.

ABSTRACT

➢Lung squamous cell carcinoma (LSCC) accounts for 25-30% of all lung cancers; however, it has not been researched to the same extent as other types of non-small cell lung cancer.

➢*PI3K* was found to be the primary oncogene in nearly 6% of all LSCC patients with *p16* (a tumor suppressor) being rendered incapable of function.

➢A comparison between LSCC patients with '*PI3K* upregulated, *p16* knockout' and LSCC patients with other oncogenic drivers can yield the most specific target for this cancer subtype.

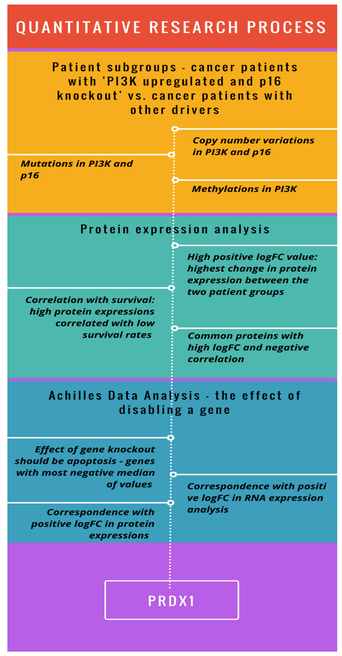
➢The Cancer Genome Atlas has data for 500 LSCC patients; it includes information such as gene expressions, copy number variations, and protein expressions.

➢ShRNA knockout gene data is available from the Achilles Data Portal. Gene knockout simulates the effect of halting gene function and highlights whether the inhibition of a gene causes cell death. Genes with evidence of high rates of cell death can be potential targets.

➢A mouse model has been developed that can simulate '*PI3K* upregulated, *p16* knockout' lung squamous cell carcinoma. Any gene discovered in this analysis can be tested using this model.

RESEARCH METHODOLOGIES

A. Computational Analysis



B. Literature Review

- Find evidence that the gene has been researched successfully in many types of cancer → probability of success in LSCC increases
- However, not excessive evidence for gene's significance → there is room for further research
- Ask "Is the gene a factor in a pathway leading to cell proliferation? Are there existing inhibitors for this gene so that it can be tested?"
- Analyze 50 genes and select a gene satisfying the criteria

RESULTS AND ANALYSIS

Statistical Significance of PRDX1 in Six Analyses

Legend:
● = PRDX1
○ = candidate genes

Although it seems that many genes are significant in these graphics, PRDX1 satisfied all the criteria in both quantitative analyses and literature reviews.

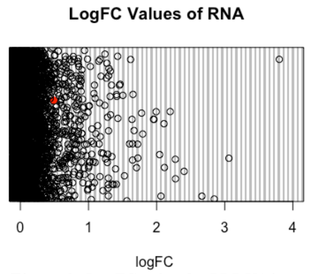


Figure 1. LogFC value for PRDX1 is higher than 94.122% of the RNA logFC values

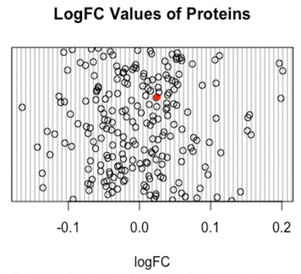


Figure 2. LogFC value for PRDX1 is higher than 66.368% of the protein logFC values

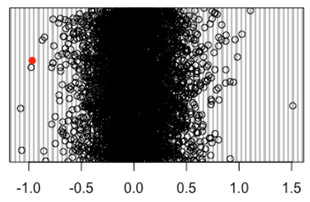


Figure 3. PRDX1 clearly stands out as having the effect of cell apoptosis when inhibited.

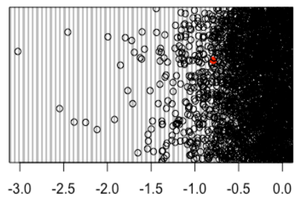


Figure 4. PRDX1 has a median value higher than 94.558% of the genes.

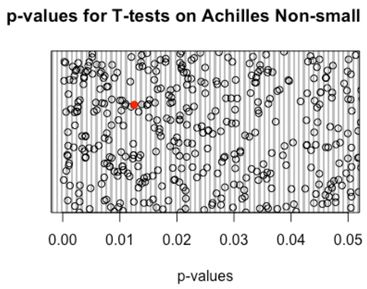


Figure 5. A section of the range of p-values. The P-value for PRDX1 supports the argument that there is reasonable evidence for PRDX1 playing a role in cell death.

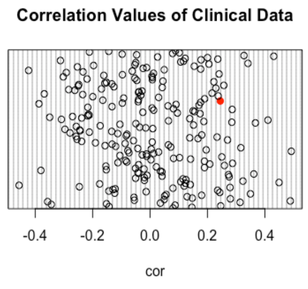
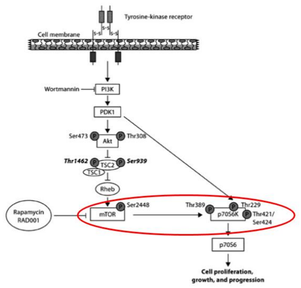


Figure 6. Although PRDX1 seems to correlate positively with patient survival, note that factors such as age were not accounted for.

In all the above six analyses, PRDX1 is shown to have a significant role in cell growth at a cellular level - it has a high change in protein and RNA expression between the patients, as well as a notable effect while inhibited. Although the patient survival data contradicts its role in proliferation, it is important to consider that other factors in patient records were not accounted for. The data at a cellular level strongly supports PRDX1 as a medium for cell growth.

Literature review yielded evidence of significance in hilar cholangiocarcinoma, liver cancer, esophageal squamous cell carcinoma and lung cancer and showed criticality for mitotic progression.

CONCLUSION



PI3K/AKT/mTOR pathway and highlighted mTOR/p70s6k pathway

Why is ***PRDX1*** a good target?

Compared to other genes in the database, PRDX1 had the highest change in expression between the patient groups ***and*** the greatest effect on cell growth when knocked out.

Evidence was found for PRDX1's presence in other cancers, even lung cancer, but little to no research has been done for lung squamous cell cancer.

The pathway shown above, that PRDX1 plays a key role in, is an extension of the ***PI3K pathway*** used in our patient group. Inhibiting PRDX1 would halt the pathway's functionality that leads to proliferation.

RELEVANT APPLICATIONS

- A PRDX1 inhibitor has not been a drug discovery target yet. Research so far has used a lentivirus to inhibit PRDX1; for humans, however, new drugs need to be developed to inhibit PRDX1.
- In conducting such comparisons between the subtype "PI3K upregulated, p16 knockout" and other LSCC subtypes, we can find specific targets that are driving these cancers.

As of now, lung squamous cell carcinoma patients are being treated with a nonspecific cocktail of drugs. Analysis of cancer subtypes can unearth targets that are strongly implicated in the subtype's development. Further investigation of PRDX1 will be a step forward towards ***personalized medicine.***

ACKNOWLEDGEMENTS / REFERENCES

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Works Cited:

1. "What Is Non-small Cell Lung Cancer?" *What Is Non-small Cell Lung Cancer?* N.p., n.d. Web. 07 Nov. 2016. <http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-what-is-non-small-cell-lung-cancer>.
2. Kim, Cheol Hyeon. "Druggable Targets of Squamous Cell Lung Cancer." *Tuberculosis and Respiratory Diseases*. The Korean Academy of Tuberculosis and Respiratory Diseases, Dec. 2013. Web. 07 Nov. 2016. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3884109/>.
3. Zhou, J. "Overexpression of Prdx1 in Hilar Cholangiocarcinoma: A Predictor for Recurrence and Prognosis." *International Journal of Clinical and Experimental Pathology*. U.S. National Library of Medicine, n.d. Web. 28 Feb. 2017.
4. Sun, YL. "Aberrant Expression of Peroxiredoxin 1 and Its Clinical Implications in Liver Cancer." *World Journal of Gastroenterology*. U.S. National Library of Medicine, n.d. Web. 28 Feb. 2017.
5. Lim, JM. "Control of the Pericentrosomal H2O2 Level by Peroxiredoxin I Is Critical for Mitotic Progression." *The Journal of Cell Biology*. U.S. National Library of Medicine, n.d. Web. 28 Feb. 2017.
6. Kim, JH. "Up-regulation of Peroxiredoxin 1 in Lung Cancer and Its Implication as a Prognostic and Therapeutic Target." *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*. U.S. National Library of Medicine, n.d. Web. 28 Feb. 2017.
7. Ren, Pengfei, Hua Ye, Liping Dai, Mei Lin, Xinxin Liu, Yurong Chai, Qing Shao, Yang Li, Ningjing Lei, Bo Peng, Wu Yao, and Jianying Zhang. "Peroxiredoxin 1 Is a Tumor-associated Antigen in Esophageal Squamous Cell Carcinoma." *Oncology Reports*. D.A. Spandidos, Nov. 2013. Web. 28 Feb. 2017.
8. Ding, Chenbo, Xiaobo Fan, and Guoqiu Wu. "Peroxiredoxin 1 – an Antioxidant Enzyme in Cancer." *Journal of Cellular and Molecular Medicine*. John Wiley and Sons Inc., 21 Sept. 2016. Web. 14 Mar. 2017.
9. Heist, Rebecca S., Lecia V. Sequist, and Jeffrey A. Engelman. "Genetic Changes in Squamous Cell Lung Cancer: *A Review*." *Journal of Thoracic Oncology*. U.S. National Library of Medicine, May 2012. Web. 14 Mar. 2017.