Final Project Report

Project Title： Proteomic Analysis Identifies NDC80 as a Potential Biomarker for Radioresistance in Lung Cancer

Group Members and Their Contributions

Project Leader: Khuluod Alharbi (khuluodalharbi@gmail.com) - Conceptualization, methodology, data analysis, and manuscript preparation.

Group Member: Hugo Tavares - Collaborative contributions and guidance.

Project Mentor

Hugo Tavares, Department of Genetics, University of Cambridge

Project Objectives and Goals

The primary objective of this project was to identify and prioritize key regulatory proteins, specifically transcription factors (TFs), that contribute to radioresistance in a pan-cancer context. The goal was to uncover potential biomarkers and therapeutic targets that could be used to guide personalized cancer treatment.

Current Progress and Milestones Achieved

- Successfully reanalyzed proteomic data from radiation-exposed cells to identify protein changes linked to therapy response.
- Developed and applied a statistical prioritization pipeline to pinpoint master regulator transcription factors.
- Identified several highly significant regulators within the protein interaction networks.
- Performed functional enrichment analysis to confirm that the identified targets are involved in key cellular processes that mediate radiation response.
- Concluded that targeting these regulators could potentially disrupt the mechanisms of radioresistance, sensitizing cells to treatment across different cancer types.

Methodology and Approach

1. Calculating the ratio of a TF's significantly altered targets to its total predicted targets.
2. Applying a Fisher's exact test to assess the statistical enrichment of this proportion.
3. Correcting p-values for multiple comparisons using the Benjamini-Hochberg False Discovery Rate (FDR) method.

4. Ranking TFs by their FDR values to identify top-ranked hub regulators.
5. Performing functional enrichment analysis on the collective set of targets of these hub TFs to identify overrepresented biological processes and pathways.

Preliminary Results or Findings

The statistical analysis identified a set of central hub regulators. A protein interaction network analysis showed that these regulators control key targets involved in fundamental cellular pathways. Functional enrichment analysis of these target proteins confirmed their roles in critical cellular functions that are known to influence radioresistance, such as DNA repair and cell cycle regulation.

Challenges and Obstacles Encountered

The main challenge was the computational and statistical complexity of reanalyzing large-scale proteomic datasets and integrating network and enrichment analyses. Ensuring accurate mapping of protein identifiers across different databases required careful data cleaning and validation.

Next Steps and Future Work

Further work includes validating the regulatory links between the identified TFs and their targets through laboratory experiments. Additionally, analyzing clinical data to explore these TFs as potential prognostic biomarkers in a multi-cancer context is a crucial next step to guide personalized therapeutic strategies.

Resources and Tools Used

- Software and Languages: R, with libraries including STRINGdb, biomaRt, dplyr, igraph, ggraph, and limma.
- Databases: STRING protein interaction database, BioMart for gene annotations, and a custom transcription factor reference database.

References

1. J. A. Christopher, L. M. Breckels, O. M. Crook, M. Vazquez-Chantada, D. Barratt, and K. S. Lilley, “Global proteomics indicates subcellular-specific anti-ferroptotic responses to ionizing radiation,” Molecular & Cellular Proteomics, vol. 24, no. 1, p. 100888, Jan. 2025, doi: 10.1016/j.mcpro.2024.100888.

2. X. Xie et al., “Pan-cancer analysis of the tumorigenic role of Fanconi anemia complementation group D2 (FANCD2) in human tumors,” Genomics, vol. 115, p. 110762, Jan. 2024.

3. R. Wei et al., “Bioinformatic analysis revealing mitotic spindle assembly regulated NDC80 and MAD2L1 as prognostic biomarkers in non-small cell lung cancer development,” BMC Medical Genomics, vol. 13, Art. 112, Aug. 2020.

4. H. Liu et al., “NDC80 promotes lung adenocarcinoma progression and confers therapeutic resistance by regulating autophagy,” iScience, vol. 26, no. 8, 2023.