NETRAMARK NetraAI-driven discovery of novel biomarkers in MSI-high colon cancer for precision immunotherapy

#LB395

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INTRODUCTION

Colorectal cancer (CRC) ranks as the 3rd most prevalent cancer globally, accounting for ~10% of all cancer cases and standing as the 2nd leading cause of cancer-related deaths. Due to vague symptoms, CRC is often diagnosed at advanced stages, when treatment options are limited. Microsatellite instability-high (MSI-H) colon cancer, although representing a small fraction of only 5-20% of total colon cancer cases, stands out due to its distinct genetic profile. Defects in the DNA mismatch repair (MMR) system result in a high mutational burden, leading to significant molecular diversity within tumors and affecting patient responses to treatment.

MSI-H COLON CANCER CHALLENGES:

MSI-H tumors are characterized by an extensive mutational load, which fosters the production of neoantigens and amplifies immune visibility, making them prime candidates for immunotherapy. However, these same factors contribute to heterogeneity that further complicates the efficacy of targeted therapies.

The paradox of MSI-H colon cancer lies in its variable response: while some patients exhibit remarkable responses to immunotherapies, others experience resistance and poor outcomes, particularly when treated with anti-EGFR antibodies. The mechanisms underlying the diverse hypermethylation phenotypes and treatment resistance remain largely unknown.

OBJECTIVES:

Using NetraAI, a novel machine learning (ML) approach, we aim to dissect the complexity of MSI-H colon cancer by identifying novel molecular biomarkers which can be used to unlock personalized, precise immunotherapy strategies. With this approach, our goal is to transition beyond the one-size-fits-all treatment approach, paving a path toward improved clinical outcomes for patients.

METHODOLOGY

MACHINE LEARNING APPROACH:

NetraAI, powered by its unique Attractor AI algorithms is used to identify causal clusters of variables called *hypotheses* which attempt to explain specific subpopulations.

- NetraPerspectives are self-learned explainable populations that capture different aspects of complex diseases like colon cancer.
- NetraAI fractures the patient population into explainable and unexplainable subsets of patients according to a set of variables.

This approach provides a critical advantage over other traditional ML methods that reinforce what is already known about a disease, allowing us to overcome challenges associated with smaller datasets not reflecting the totality of the disease they represent.

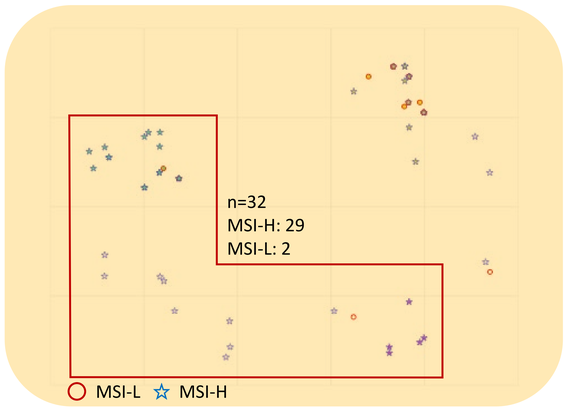
DATASET:

Using a dataset consisting of 390 samples of expression data from CRC patients (E-GEOD-41258), we compiled a smaller data set consisting of 141 RNA expression profiles, of which we used 21 MSI-low (MSI-L) and 44 MSI-H samples for our analysis.

RESULTS

NetraPerspective of a Subpopulation of MSI-H Colon Cancer Samples

In one NetraPerspective, there was a MSI-H subpopulation identified, consisting of 29 MSI-H and 2 MSI-L samples. This subpopulation is characterized by CATSPERB, MLPH, FUT8, DUSP4, and PLLP.



The dataset used consisted of a total of 22,283 variables.

- Multiple variables (gene probes) corresponding to the same genes were pulled out by NetraAI.
- These redundant variables validate the power of NetraAI to identify causal variables driving specific subpopulations.

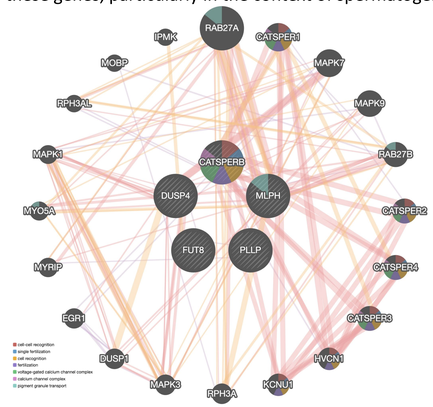
The NetraAI approach identified this subpopulation due to its ability to focus on a subpopulation that it deemed highly explainable.

Variable	Corresponding Gene	Significance (p-value)
B3KWW9 Q9H7T0	CATSPERB	$1.2x10^{-7}$
A0A024R492 Q9BV36 A0A024R4D3	MLPH (melanophilin)	$4.9x10^{-5}$
Q546E0 A8K8P8 Q9BYC5	FUT8 (alpha-(1,6)-fucosyltransferase	$8.6x10^{-5}$
Q13115	DUSP4 (dual specificity protein phosphatase 4)	$1.1x10^{-3}$
A0A024R6T3 Q9Y342	PLLP (plasmolipin)	0.01

Note: The p-values are obtained from comparing this MSI-H group to a mixed group containing 12 MSH-H and 17 MSI-L samples.

Protein-Protein Interaction Networks with Variables of Interest

The NetraAI-identified variables (CATSPERB, FUTB, PLLP, DUSP4, and MLPH) that may play significant roles in MSI-H colon cancer pathology. Constructing protein-protein interaction (PPI) networks revealed co-expression and interactivity that exist amongst these genes, suggesting a complex interplay among these genes, particularly in the context of spermatogenesis.



The relationship between spermatogenesis and MSI in colon cancer via CATSPERB gene overexpression presents an intriguing avenue for cancer research as both processes fundamentally rely on precise DNA MMR mechanisms.

- Spermatogenesis: the process of sperm production from male germ cells; ensures genetic integrity for reproduction.
- MSI: genetic hypermutability from impaired DNA mismatch repair; MMR system's failure leads to MSI-H colon cancer characterized by a high frequency of mutations in microsatellites.

CATSPERB, a protein primarily associated with calcium channels in sperm that is critical for spermatogenesis, overexpressed in a subset of MSI-H colon cancer patients, suggests a novel link between reproductive biology and cancer pathogenesis. This may be due to CATSPERB modulating calcium signaling pathways, which are known to be pivotal in several cellular processes that may favor cancer cell proliferation, survival, and metastasis.

The specificity of CATSPERB to an MSI-H colon cancer subgroup posits it as a potential biomarker for identifying patients who might benefit from tailored therapeutic approaches, contributing to the personalized medicine landscape.

CONCLUSIONS & SIGNIFICANCE

SUMMARY OF KEY FINDINGS:

- NetraAI identified a subpopulation of MSI-H colon cancer patient samples (n=32) characterized by CATSPERB, MLPH, FUT8, DUSP4, and PLLP.
- Constructed PPI network reveals a complex interplay via co-expression and co-localization between the 5 genes identified by NetraAI with functions related to cell-cell recognition, single fertilization, and fertilization.

SIGNIFICANCE OF FINDINGS:

- CATSPERB's specificity to MSI-H colon cancer suggests it could be a potential biomarker for identifying patients that may benefit from tailored therapeutic approaches.
- Investigating CATSPERB's overexpression and its functional implications in MSI-H colon cancer opens up new research avenues that could bridge gaps in our understanding of cancer biology, exploring the crossover of molecular mechanisms between reproductive processes and cancer biology.

FUTURE USE AND APPLICATIONS:

These results highlight the ability of NetraAI to contribute to the personalized medicine landscape through patient enrichment strategies, while also helping to lead to novel diagnostic and therapeutic avenues, enhancing patient care and outcomes in this complex disease landscape.

REFERENCES

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