Project 3

Characterization of tumor neoantigens in glioblastoma patients

Data overview

Glioblastoma (GBM) is a very aggressive brain tumor with no standard therapy after recurrence and median patients' survival shorter than 12 months. In a recent study, GBM tumors have been characterized using whole-exome (WES) and RNA sequencing (RNA-seq) [1]. These data have been used to predict computationally patient-specific neoantigens, namely short peptides generated from the expression of mutated genes that bind to the cancer cell Human Leukocyte Antigen (HLA) molecules and can be recognized by T cells. The authors used these predicted neoantigens to design personalized anticancer vaccines. In one patient, the vaccine elicited a $CD8^+$ T-cell response towards two tumor neoantigens generated from mutations in the SLX4 and ARHGAP35 genes.

In the Supplementary Material of this article, is available an Excel table containing the predicted neoantigens and their features: https://static-content.springer.com/esm/art%3A10.1038%2Fs41586-018-0792-9/MediaObjects/41586_2018_792_MOESM5_ESM.xlsx. The file contains info like the patients' identifiers, the name of the mutated gene, the HLA types, the sequence affinity in nM of the mutated and wild-type peptides, the sequence of the immunizing peptide (i.e. the peptide used for the vaccine), and the normalized expression of the mutated gene in transcripts per millions (TPM).

Analysis to be performed

Import in R the table with the features of the predicted neoantigens, paying attention to the formatting of the first rows and header: some lines should be skipped and some columns might need to be re-named after data loading in R.
Only for the responder patient (n. 7), extract or compute the following neoantigen features:

n	Feature	Value for peptides recognized by T cells
1.	Affinity (IC50 in nM) of the mutated peptide	Low (i.e. the mutated peptide binds strongly to the HLA)
2.	Log-fold-change of affinity the wild-type vs. mutated peptide (WT/MUT)	Higher than zero (i.e. the mutated peptide binds more strongly than the wild-type peptide to the HLA)

3.	Length of the immunizing peptide	-
4.	Gene expression in TPM	High (i.e. the mutated gene is highly expressed)

Not all peptides are recognized by T cells. The table above reports, in the last column, the features of the neoantigens that are recognized by T cells (e.g. they usually have a high expression of the mutated gene).

For each feature, plot the value distribution across all candidate neoantigens as histograms or density plots, and mark with vertical lines and text the x values corresponding to the two neoantigens recognized by $CD8^+$ T cells: MVNTVAGAMK (ARHGAP35 gene) and TTAATHREK (SLX4 gene).

Report

The analysis above should be described in a short report that will be evaluated and considered for the final grade. The report should:

- Contain the **code** implemented to run the analysis above, together with the **results** (as tables, plots, or just numbers reported within the text) and their **description/discussion**.
- Be at **maximum 6 pages** long.
- Be saved in a Word doc named **"Surname_Name_Project3.doc"**.
- Be sent by e-mail to Dr. Finotello not later than **June 03, 2019**, using **"RProject3_2019"** as e-mail object.

References

[1] Keskin DB, Anandappa AJ, Sun J, Tirosh I, Mathewson ND, Li S, Oliveira G, Giobbie-Hurder A, Felt K, Gjini E, Shukla SA, Hu Z, Li L, Le PM, Allesøe RL, Richman AR, Kowalczyk MS, Abdelrahman S, Geduldig JE, Charbonneau S, Pelton K, Iorgulescu JB, Elagina L, Zhang W, Olive O, McCluskey C, Olsen LR, Stevens J, Lane WJ, Salazar AM, Daley H, Wen PY, Chiocca EA, Harden M, Lennon NJ, Gabriel S, Getz G, Lander ES, Regev A, Ritz J, Neuberg D, Rodig SJ, Ligon KL, Suvà ML, Wucherpfennig KW, Hacohen N, Fritsch EF, Livak KJ, Ott PA, Wu CJ, Reardon DA. ***Neoantigen vaccine generates intratumoral T cell responses in phase Ib glioblastoma trial***. Nature. 2019 Jan;565(7738):234-239.