Project 2

Estimation of T-cell receptor diversity after personalized vaccination of glioblastoma patients

Data overview

Glioblastoma (GBM) is a very aggressive brain tumor for with no standard therapy after recurrence and median survival shorter than 12 months. In a recent study, GBM patients have been treated with personalized cancer vaccines to stimulate the recognition of tumor cells by T cells [1]. T cells can eliminate cancer cells after interaction of the T-cell receptor (TCR) with tumor antigens bound to the Human Leukocyte Antigen (HLA) molecules of tumor cells. The TCR of most of T cells have consists of an alpha and a beta chain. In this study, blood samples collected from a responder patient before vaccination and after relapse were sequenced to reconstruct the TCR alpha and beta chains (only their complementarity-determining region 3, CDR3).

In the Supplementary Material of this article, is available a multi-sheet Excel file containing the estimated alpha or beta CDR3 sequences ("Alpha/Beta CDR3 amino acid seq" column) and their counts ("UMI_counts"), before treatment and after relapse: https://static-content.springer.com/esm/art%3A10.1038%2Fs41586-018-0792-9/MediaObjects/41586_2018_792_MOESM8_ESM.xlsx. The more abundant CDR3 sequences (i.e. with higher counts) reported on top, might represent clones of T cells with the same TCR that have expanded after recognition of a tumor antigens (e.g. after vaccination).

Analysis to be performed

Diversity indexes can be used to measure the compositional complexity of a set of TCR clones. *Diversity* increases when the number of different clones (called *richness*) and with the evenness of their relative abundances. For a given number of different clones, diversity is maximal when all clones are equally abundant.

Define two functions to compute the following indexes:

Richness ***R***: number of different CDR3 TCR clones.

Diversity ***D***, computed with the Inverse- Simpson index:

$$D = \frac{1}{\sum_{i=1}^{R} {p_i}^2}$$

Where i, …, R are the different CDR3 TCR clones and p_i are their relative counts, computed in R as:

```
pi <- UMI counts/sum(UMI counts)
```

Apply the functions to the four sets of alpha/beta TCR clones of the Excel table.

Separately for alpha and beta chains, show graphically the differences in richness and diversity of the samples before treatment and after relapse.

Separately for alpha and beta chains, calculate how many unqiue clones (with exactly the same sequence) are in common between the samples before treatment and after relapse.

Discuss the results considering the fact that vaccination might induce the expansion of antigen-reactive clones and/or appearance of new clones.

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.