A NEW BIOINFORMATIC TOOL IN THE PRECISION MEDICINE PERSPECTIVE: PRELIMINARY EVIDENCE OF ITS PROGNOSTIC AND PREDICTIVE VALUE

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Introduction: The level of T-cell infiltration (Tci) is considered to be essential for the diagnosis and prognosis of many solid tumors. Indeed, it is known that one of the independent factors for assessing the prognosis of neuroblastoma is the level of Tci of the tumor, as evaluated by immunohistochemistry. Moreover, the level of Tci of cancers may be one of the parameters useful to predict the outcome of treatment with immune checkpoint inhibitors in the precision medicine perspective. In fact, the kind of cancers that are more responsive to immune checkpoint inhibitors show heavy infiltration by T cells.
T-cell signatures try to guess the number of T cells that infiltrate a tissue by evaluating the mRNA levels of specific genes as detected by mRNA arrays or high throughput RNA sequencing. We recently set-up a new T-cell signature (signature-H) that might have a higher sensitivity than the published T-cell signatures. Aim of the study was to test the diagnostic and predictive value of our signature.

Materials and methods: The signature-H was developed using GeneVestigator software, by which we tested 1507genes included in previously reported T cell signatures, and we selected genes that were expressed at a considerably higher level by T cells than by non-lymphoid cells/tissue through six rounds of filtering. To evaluate the prognostic value of signature-H, we analyzed 709neuroblastoma specimens downloaded from the ArrayExpress database. Tci of the specimens according to signature-H was correlated with survival time of the patients, and to classification/stage according to the Children's Oncology Group (COG), and the International Neuroblastoma Staging System (INSS) using one-way ANOVA. For the comparison of Kaplan-Meier curves of patients with different levels of Tci, the log-rank Mantel-Cox test was used. To evaluate the capacity of the signature-H to predict the response to nivolumab treatment, we analyzed 26melanoma specimens downloaded from Gene Expression Omnibus. Results were analyzed by using the contingency chi-square test and the Pearson correlation coefficients. For the comparison of Kaplan-Meier curves, the log-rank Mantel-Cox test was used.

Results:
1. Prognostic value of the signature-H. Tci of neuroblastoma specimens evaluated by signature-H correlates with patients survival, as demonstrated by immunohistochemistry. In particular, Tci values increase until patient survival is equal to 4-7years, after which it remains at the same level. Moreover, Tci correlates significantly with COG risk groups the and tumor stage according to the INSS. Consequently, the Tci levels evaluated by signature-H have prognostic value, as demonstrated by the Kaplan-Meier curves of the patients classified according to Tci. The patients with the lowest Tci (<0.125) had a death hazard ratio (HR) of 6.2as compared to patients with the highest Tci (>2).
2. Predictive value of the signature-H. We set up and tested a multiparametric tool, that includes Tci based on signature-H, to predict the response of melanoma to the anti-PD-1antibody nivolumab; patients who satisfied all the parameters were included in the good signature-3group, and the other patients were included in the bad signature-3group. Results show that the overall response rate of the patients belonging to the good and bad signature-3groups was 90% and 31%, respectively. Of note, the survival time of the good and bad signature-3groups was much different ($p=0.0011$) with an HR equal to 7.3.

Conclusion: We demonstrate that signature-H works as well as immunohistochemistry methods to assess the prognosis of neuroblastoma and that it is able to predict the response of melanoma to the anti-PD-1antibody nivolumab. These preliminary findings suggest that the new T-cell signature can be used as a prognostic tool and in tailoring treatment, in the precision medicine perspective.