IgM-Rheumatoid Factor as a novel biomarker for a reduced survival in anti-PD-1 treated NSCLC patients through the decrease of CD137+ T-cells.

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ABSTRACT

BACKGROUND. Despite anti-PD-1 targeting with Immune-Checkpoint Inhibitors (ICIs) has markedly improved the survival of Non-Small Cells Lung Cancer (NSCLC) patients, the onset of both primary and secondary resistances still occur in the majority of patients. The association between autoimmunity and cancer is an area of particular interest being the latter, as in the case of autoantibodies, an indication of a dysfunctional immune system.

METHODS. We enrolled 42 patients with metastatic NSCLC before and during anti-PD-1 treatment, evaluating circulating levels of different autoantibodies and Peripheral Blood Mononuclear Cells (PBMCs) populations. RESULTS. The presence of IgM-Rheumatoid Factor (IgM-RF) in patients sera was strongly associated (OR, 7.66; 95% CI, 1.62 to 36.18; p=0.005) with the development of early progression. IgM-RF positivity resulted also as an important prognostic factor for a worse outcome in terms of both PFS (p=0.035) and OS (p=0.034), with a more marked reduction of PFS rate (p=0.002) identified when patients were further stratified on IgM-RF titers. IgM-RF+ patients showed a significant reduction (p=0.02) of the circulating tumor-specific CD137+ T-cell population. To confirm the importance of this T-cell population in driving patients response, an higher percentage of CD137+ T-cells at baseline correlated with a better outcome in terms of both PFS (p=0.006) and OS (p=0.002). Mechanistic experiments demonstrate that IgM-RF preferentially bound to naive and central memory T-cells (p<0.0001) and a robust impairment (p=0.0001) of their migratory ability in response to CCL-19 was observed when exposed to IgM-RF. CONCLUSIONS. IgM-RF can be ascribed as a novel biomarker that is able to predict the development of early progression and, in addition, as a prognostic factor for a reduced PFS and OS in NSCLC patients in treatment with anti-PD-1 ICIs. The reduction of anti-tumor CD137+ T-cells that was observed in IgM-RF+ patients could make account for the reduced survival of the patients, since the frequency of this population in the blood of NSCLC patients resulted as an independent prognostic factor for a better outcome.

SUMMARY

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**Fig. 1. IgM-RF and NSCLC patients outcome.**

Left. Percentage of early progressions in NSCLC patients divided in RF+ vs RF- subgroups. Right. Odds ratios for development of early progression in pre-assigned clinical subgroups. **p<0.01.

**Fig. 2. CD137+ T-cells and NSCLC patients outcome.**

Kaplan-Meier representation of PFS (left and middle) and OS (right) after the anti-PD-1 treatment among the NSCLC patients divided into RF+ vs RF- (left and right) and RF+ vs RF- subgroups (middle); ms = median survival.

**Fig. 3. IgM-RF impairs naïve and CMem T-cells migration.**

a. Percentage of IgM+ T-cells at baseline in NSCLC patients divided in RF+ vs RF- subgroups. b. Percentage of IgM-positive T-cells after the T-cells and anti-IgM staining on PBMCs isolated from NSCLC patients at baseline, divided into RF+ and RF- groups. c. Percentage of IgM-positive T-cells in vitro. d. Fold change compared to the experiment control (untreated sample) of the percentages of proliferated (left), CCRT positive (middle) and migrated (right) T-cells of untreated, control IgM or IgM-RF treated T-cells. *p=0.05; **p<0.01; ***p<0.001; ****p<0.0001.

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