Abstract 30

ANALYSIS OF ANTITUMOR IMMUNE RESPONSES INDUCED BY SIMVASTATIN PLUS ANTI-PD1 IN MICE AND HUMAN MELANOMAS

Oral

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Retrospective clinical data on melanoma and non-small cell lung cancers have shown that patients taking statins before the onset of checkpoint inhibitors (CPI), have a better progression free survival (PFS) and overall survival (OS). Starting from this evidence, we investigated the efficacy and the biologic mechanisms of simvastatin plus anti-PD1 in melanoma patients and melanoma-baring mice.
We analyzed PFS and OS from our cohort of metastatic melanoma patients and performed in vivo experiments to compare the effect of simvastatin, anti-PD1 or the combination of simvastatin plus anti-PD1 in C57BL/6 mice bearing the B16F1 melanoma. We measured tumor growth and weights and analyzed by flow-cytometry (FACS) the tumor-infiltrating immune cells. As we observed an effect on dendritic cells (DCs), we performed in vitro experiments on simvastatin-treated bone-marrow derived DCs (BMDCs).
In our melanoma cohort, 2-years PFS was 50% vs. 10% (p=0.01), 2-years OS 75% vs. 50% (p=0.03) and the median-OS was 24 months vs. not reached in favor of statin-treated patients. Pre-clinical experiments in mice showed that the combinatorial treatment (simvastatin plus anti-PD1 mAb) was capable of slowing down tumor growth. Importantly, this synergistic effect was seen only in mice pretreated with simvastatin before tumor challenge, but not in those treated with statins and CPI concomitantly. FACS analysis of tumor-infiltrating immune cells revealed that intratumoral dendritic cells (DCs) from simvastatin-treated mice displayed higher surface levels of MHC-II and CD40 molecules. In vitro, in simvastatin-treated BMDCs, we confirmed the upregulation of CD40 molecules, and detected an increase of phospho-p38 mitogen-activated protein kinase as well as the increased expression of the inflammatory cytokines IFNγ, IFNβ, TNF and of the inflammasome components NLRP3 and Caspase 1.
We have recently performed high-dimensional flow cytometry to analyze basal and post-treatment PBMCs of our cohorts of CPI-treated melanoma patients (taking or not taking statins) to identify immune cell subsets correlating with the positive clinical outcome induced by statins plus CPI.
We have observed an increased PFS and OS in metastatic melanoma patients taking statins and treated with CPI. We replicated this effect on melanoma-baring mice, in which we also observed intratumoral DCs expressing higher levels of activation markers. In vitro, we observed the upregulation of activation markers as well as increased p38 phosphorylation and pro-inflammatory cytokine expression in simvastatin-treated DCs. These data might explain the improved efficacy of immunotherapy in melanoma patients taking statins. A better definition of the signaling pathway is under way.