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Investigating if UCP2 expression in melanoma cells predicts therapeutic outcomes of checkpoint blockade

Summary

The development of cancer immunotherapies, including checkpoint blockade (e.g., anti-PD-1 and anti-CTLA-4 antibody treatment), yields extraordinary anti-tumor responses by rejuvenating antitumor immunity in melanoma as well as other tumor types. Nevertheless, it remains ineffective in a significant portion of patients treated with cancer immunotherapies. Moreover, it is unclear how to predict the therapeutic outcomes of patients receiving checkpoint blockade treatment. Thus, it is a critical clinical need to identify biomarkers for indicating therapeutic outcomes of cancer immunotherapy prior to treatments and assessing ongoing therapeutic responses in patients.

Recent findings suggest that the tumor microenvironment imposes environmental restrictions to prevent T cell infiltration, which has been referred to as “cold” tumor, and impair the anti-tumor effector functions of infiltrating T cells. The lack of T cell infiltration in tumors represents the major form of primary resistance to cancer immunotherapies. In support of this, it has been shown thatapproximately 40% of melanomas possess cold tumor phenotype and those melanomas are less responsive to anti-PD-1 and anti-CTLA-4 treatment. This cold tumor phenotype may be in part due to the disorganized tumor vasculature and an accumulation of immunosuppressive regulatory T cells, as well as anti-inflammatory and tolerogenic myeloid cells in tumors. Thus, greater investigation into the identification of immunostimulatory trigger(s) to “heat up” T cell infiltration in cold tumors is required to develop effective cancer immunotherapies. To address this critical but unsolved issues, we investigated whether there are any markers associated with stronger immune responses by mining melanoma patient samples in the The Cancer Genome Atlas (TCGA) database. We found that the mRNA expression levels of mitochondrial uncoupling protein 2 (UCP2) strongly associate with elevated anti-tumor immunity. By using doxycycline-inducible system and co-engraftment melanoma murine models, we uncovered that UCP2 induction in melanoma cells reprogram cytokine milieus in tumors, including CXCL9/10 and CCL5, and reduce tumor growth by promoting tumor infiltration of CD8+ T cells in a cDC1-dependent manner. In addition to engaging this cDC1-CD8+ T cell axis, UCP2 induction in melanoma cells promoted tumor vessel normalization featured by increased vessel thickness, expression of VCAM-1 on endothelial cells and pericyte coverage on tumor vessels. Most importantly, we demonstrated that inducing UCP2 expression with genetic and pharmacological approaches could sensitize PD-1 blockade-resistant tumors to PD-1 blockade treatment (published in Nature Immunology 2019).

Together, our results reveal that overexpression of UCP2 in melanoma cells effectively stimulate recruitment of CD8+ T cells and induce tumor regression in a CD8+ T cell-dependent manner in murine models, suggesting UCP2 expression in melanoma cells could determine the therapeutic responses to anti-PD-1 treatment. Moreover, our results reveal that elevated UCP2 expression associates with stronger T cell infiltration signature in the pan-tumor analysis, suggesting that UCP2-guided immunostimulatory properties in the tumor microenvironment might be a conserved phenotype in multiple types of tumors. Therefore, we hypothesize that UCP2 expression levels in melanoma cells could be a biomarker to indicate the immune state of the tumor microenvironment and therapeutic outcomes of checkpoint blockade therapies. The premise of the work proposed herein is to a better elucidate whether UCP2 expression in melanoma cells and its associated alterations in circulation could predict anti-tumor responses upon checkpoint blockade treatment in patients. This work could be pivotal in providing prognostic indicators for cancer immunotherapies.

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IMMUNOMICS: Co-evolutionary dynamics landscape of neoplastic cells and T-cells interactions during cancer immunotherapy

Summary

Checkpoint inhibitor therapies (CIT) have changed the treatment landscape in many cancer types and showed that CIT harbors the capacity to cure cancers even when presented in advanced, metastatic stages. Despite the unprecedented long-lasting results seen in a subset of patients, most of the patients will actually not benefit so predictive biomarkers of response are clearly needed. In the current project, we propose to develop a comprehensive genomics platform to portray the coevolutionary dynamics landscape of cancers cells and T-cells interactions of the patients enrolled in our Resistance to Immunoncology clinical platform of the Early Clinical Drug Development Unit at Vall d´Hebron hospital (360o RIO). With the development of such IMMUNOMICS platform, we aim to 1) to characterize genomic biomarkers of response and resistance to CIT, 2) to portray the genomic landscape of the co-evolutionary dynamics of cancer cells and TCR clonal repertoire during response, primary and acquired resistance to CIT and 3) to develop an innovative clonal evolution-based method for identification of clinically relevant neoepitopes to immunotherapy. For that, we will generate integrated genomic data of the patients and apply deconvolution analysis to determine tumor heterogeneity and clonal structure and correlate with clinical response and resistance to CIT. Common somatic events in cancer will be considered and clonal expansion will be hierarchically determined for the reconstruction of intra-tumor evolutionary trees. We will establish a bioinformatics database for efficient data analysis and aggregation with a structured clinical database with standardized clinical endpoints.
We envision that by expanding the current understanding of the genomic-driven evolutionary dynamics of cancer cells and the patient´s immune system occurring in the context of CIT, our study will identify predicting biomarkers as well as have direct implications in CIT drug development and on the design of novel clinical trials capable to explore such dynamics as an approach to elicit an immune response and increase response in a larger population of cancer patients treated with CIT.