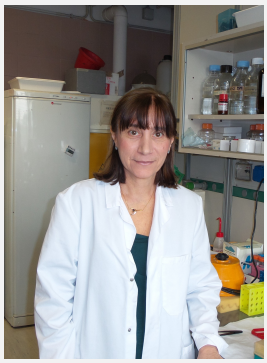
ImmunoTools *special* Award 2019



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Targeting the tumor microenvironment to enhance the efficacy of immune checkpoint inhibitors for malignant melanoma treatment

Background

Despite progress in the therapy of metastatic melanoma, patients diagnosed at advanced stages have low survival rates. Immune checkpoint inhibitors (ICIs) [anti-CTLA-4 and anti-PD-1 monoclonal antibodies (mAbs)] have shown efficacy, but many patients fail to respond or undergo recurrence. Recently, special attention has been given to the role of the tumor microenvironment (TME) on resistance to ICI.

Aim of this study is to investigate whether targeting of the TME by inhibition of the vascular endothelial growth factor receptor-1 (VEGFR-1) might represent a suitable strategy for improving ICI efficacy. The VEGFR-1 is a tyrosine kinase receptor for the angiogenic factors VEGF-A and placental growth factor (PlGF), expressed in endothelial cells during vessel formation and remodeling, macrophages and myoepithelial cells, favoring cell migration and survival. It is also involved in the mobilization of myeloid bone marrow-derived progenitors that generate tumor-associated macrophages (TAM), which, upon M2 polarization, contribute to tumor progression and spreading. Thus, we hypothesize that VEGFR-1 blockade may enhance the ICI efficacy by increasing T cell recruitment to the tumor, as a result of vessel normalization, and by decreasing protumoral M2. In addition, VEGFR-1 does not play a relevant role in physiological angiogenesis in the adult, while it is important in tumor angiogenesis. Thus, its blockade is expected to produce less adverse effects.

VEGFR-1 blockade will be obtained by using D16F7, a mAb generated in our laboratories that inhibits melanoma growth by inhibition of: a) tumor-associated angiogenesis; b) myeloid progenitor mobilization and tumor infiltration by M2; c) chemotaxis and vasculogenic mimicry of melanoma cells.

Project tasks

Based on D16F7 effects on TME and on the role of M2 cells in regulating immune responses and tumor susceptibility to ICIs, project tasks will include: a) evaluation of D16F7 effect on M2 polarization/activity, b) analysis of D16F7 and ICIs combination on tumor leukocyte infiltration. We expect to define VEGFR-1 role in the protumoral activity of melanoma-infiltrating M2 and to identify TME biomarkers as druggable targets (i.e., VEGFR-1 and molecules regulated by the receptor) to improve ICIs efficacy in malignant melanoma.