ImmunoTools *special* Award 2016

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Heterotypic cell interactions in Cancer: role of mast cells in melanoma

Mast cells are derived from hematopoietic precursors in the bone marrow and migrate still undifferentiated to tissues where they will differentiate and reside following microenvironmental cues. Two main types of mast cells result from differentiation in tissues: mucosal mast cells and connective tissue mast cells.

IL-3 is the main stimulus for mucosal mast cells to differentiate in cells smaller in size and histamine content. The main proteoglycan stored in their granules is chondroitin sulphate. Connective tissue mast cells, such as those found in skin, are larger cells with large amounts of histamine and heparin stored in their granules. The main stimulus for differentiation and survival of connective tissue mast cells is SCF. Mast cells also respond with degranulation and inflammatory mediator release upon stimulation of the tyrosine kinase receptor c-kit by SCF, including the release of proteases, lipid mediators, cytokines and growth factors.

Mast cells-derived mediators play a central role in the establishment of an immunosuppressant environment in the skin after UV irradiation thus may contribute to the early steps of melanoma. Mast cells are usually found in the periphery of melanoma and their presence directly correlates with the degree of malignancy. This location suggests a role also in the production of pro-angiogenic factors and in remodelling of extracellular matrix, thus regulating invasiveness and metastasis. However, the stimuli responsible for the accumulation and activation of mast cells in melanoma periphery is not known.

Melanocytes produce and respond to several cytokines and growth factors such as IL-3, IL-6, TNF, SCF, TGFb, GF, MSH. Since cancer cells may become self-sufficient for growth signalling through increased production of autocrine signals,

many of these cytokines and growth may be overproduced by melanoma. Mast cells also respond to many of these signals and they may contribute to increased recruitment of precursors from the blood stream or local proliferation, and subsequent local differentiation. However, it is not known how peripheral mast cells differentiate in response to these melanoma-derived mediators: is the impact limited to increased density or mast cell function is also modified?

Mast cells are the main source of VEGF in invasive melanoma lesions and may contribute with several other mediators that may enhance the malignant phenotype of melanomas. Mast cells may also directly influence the behaviour of melanoma through the production of inflammatory mediators. Thus, elucidation of the crosstalk between mast cells and melanoma may provide new insights in the biology of this particular cancer. New avenues of treatment are also sorely needed as metastatic melanoma has proved resistant to classic chemotherapy and even targeted therapy has produced small improvements in prognosis for most of the patients.

ImmunoTools reagents will be used for culture, differentiation, and activation of mast cells derived from bone marrow of mice and to identify how culture conditions that mimic the microenvironment surrounding melanoma lesions may interfere with the differentiation and activation of mast cells (through cell surface marker staining and flow cytometry analysis). The relevance of cytokines and growth factors combinations similar to what is produced by melanomas that significantly upregulate that ability of mast cells to produce VEGF and/or matrix metalloproteinases (MMPs) will be tested in *in vivo* model of mast dependent metastatic melanoma.

ImmunoTools *special* AWARD for **Bruno L. Diaz** includes 25 reagents

PE - conjugated anti-mouse CD117, isotype control IgG2b

recombinant mouse cytokines: rm EGF, rm Eotaxin / CCL11, rm FGF-a / FGF-1, rm Flt3L / CD135, rm G-CSF, rm GM-CSF, rm IGF-I, rm IL-1alpha, rm IL-1beta, rm IL-3, rm IL-4, rm IL-5, rm IL-6, rm IL-9, rm IL-13, rm IL-17E / IL-25, rm IL-33, rm NGF-beta, rm SCF, rm sRANKL, rm TNFa, rm VEGF DETAILS more AWARDS