ImmunoTools *special* Award 2014

Margarita Martin
Associate Professor

Biochemistry and Molecular Biology Unit, Department of Physiological Sciences I, Faculty of Medicine, University of Barcelona, Casanova 143, Barcelona 08036

Modulation of the KIT receptor functions by CD150 family of receptors and related adapter molecules in health and pathology.

Our group is interested in the regulation of the immune system by receptors of the CD150 members and adapter molecules related to these families. In the last years we have focus mainly in the regulatory role of mast cells in innate and adaptative immunity.

Mast cells are currently recognized as effector cells in many settings other than mere allergic reactions, including innate immunity, autoimmunity, chronic inflammatory disorders and atherosclerosis. The classic and most studied activation pathway of these cells starts with the binding of IgE to the high-affinity Fc receptor for IgE (FcepsilonRI); and the release of histamine and other mediators after crosslinking of surface-bound IgE by allergen. Signaling pathways of mast cell responses have been explored in the past but these are still linked with single axes, such as the high affinity IgE receptor FcepsilonRI, presumably an exclusive determinant of the magnitude of the response to allergens. Appropriate activation and fine tunning of mast cell responses is mediated by a complex array of factors including IgE receptor, kinases/phosphatases, adaptor molecules, and various classes of co-stimulatory molecules that modulate their function. These molecules may therefore contribute to the outcome of mast cell-associated pathologies, and may constitute new therapeutic targets in such diseases.

In the last years our group has shown that CD84, a member of the CD150 family, negatively regulates IgE high affinity receptor signaling (Oliver-Vila I, et al. Mol. Immunol 2008; Álvarez-Errico D, et al, J. Immunol. 2011). Previously, our group reported that the adaptor molecule 3BP2 was biochemically and functionally linked to a pair of CD150 family receptors (Saborit-Villarroya I, et. al, J. Immunol 2005, Saborit-Villarroya I, et al, Mol. Immunol. 2008). Human 3BP2 is a 561-aa protein

containing an N-terminal pleckstrin homology (PH) domain, an SH3-binding proline-rich regions, and a C-terminal SH2 domain. 3BP2 is a cytoplasmic adaptor protein mainly expressed by haematopoietic cells that has been shown to play an important role in humoral responses and NK cell signal transduction. 3BP2 is an important regulator of cytotoxic granule release in NK cells. Mast cells similarly degranulate following antigen-dependent aggregation of the high affinity receptor for IgE (FcepsilonRI) on the cell surface. Recently, we have found that 3BP2 is required in optimal immediate and late mast cells responses such as degranulation and IL-8 or GM-CSF secretion. 3BP2 was determined to be necessary for optimal phosphorylation of Syk, LAT and PLC gamma-1, critical signals for calcium release (Ainsua-Enrich E, et al, J. immunol 2012). The KIT receptor, a member of growth factor tyrosine kinase receptor, whose ligand is the stem cell factor (SCF) is necessary for mast cell development, proliferation and survival as well as for optimal IgE dependent degranulation and cytokine production. Mutations in KIT are the responsible of diverse pathologies that range from inflammatory to cancer diseases such as mastocytosis, melanoma, and gastrointestinal stromal tumors… among others. In this project we approach the role of CD150 immunoreceptor family members and the associated adapter molecule 3BP2 in mast cell differentiation, survival and proliferation by focusing on KIT receptor functions in peripheral blood $CD34^+$ derived mast cells and patients derived-human cell lines. Primary mast cells will be generated from $CD34^+$ progenitors cultured to differentiate them using Immunotools' recombinant cytokines and growth factors and the phenotype and activation profile will be checked using Immunotools' antibodies. Lentivirus technology will be used to generate knock-down, knock-in and overexpressed cells.

ImmunoTools *special* AWARD for **Margarita Martin** includes 25 reagents

FITC - conjugated anti-human CD63, CD69, Control-IgG1, Annexin V,

PE - conjugated anti-human CD34, Control-IgG1, Annexin V,,

APC - conjugated anti-human CD25, CD63, CD69, Control-IgG1, Control-IgG2a, Control-IgG2b, Annexin V,

human IL-8 ELISA-set for 96 wells, (3 reagents),

recombinant human cytokines: rh IL-3, rh IL-6, rh SCF, rh PDGF-AA,

PE - conjugated anti-mouse CD34,

recombinant mouse cytokines: rm IL-3, rm IL-6, rm SCF

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