Gabriel A. Rabinovich

Profile

Dr. Gabriel Adrián Rabinovich obtained his BSc Biochemist degree in 1993 followed by his Ph.D. degree both from the School of Chemical Sciences of the National University of Córdoba. Curreently, he is a Principal Investigator of the Argentinean National Research Council (CONICET), Head of the Laboratory of Immunopathology and Vicedirector of the Institute of Biology and Experimental Medicine, and Professor of Immunology at the Faculty of Exact and Natural Sciences (University of Buenos Aires). Also Dr. Rabinovich is Visiting Professor at the University of Maryland, Dana Farber Cancer Institute in Harvard Medical School and University of Miami. He serves as Editor of several journals including Glycobiology, Cell Death and Differentiation, Oncoimmunology, Immunology and Cell Biology and Emerging Infectious Diseases. Using an interdisciplinary approach, **Dr. Rabinovich's lab aims to identify different therapeutic targets, based on protein-glycan interactions, to differentially modulate immune-mediated disorders including cancer, autoimmunity and chronic inflammation.** For his scientific and professional achievements Dr. Rabinovich was awarded with the John Simon Guggenheim fellowship (USA), Third World Academy of Sciences (TWAS) Award in Medical Research (Italy), Bunge Born Award (Argentina), Bernardo Houssay Award (Argentina), and Cancer Research Institute Investigator Award (USA). He has published 145 articles in international leading journals including *Cancer Cell, Nature Immunology, Nature Medicine, Immunity, Journal of Experimental Medicine, Nature Rev Immunol, PNAS, J Immunol and Annu Rev Immunol,* has written several chapters in books, and presented eight patents of his work.

Regulatory circuits mediated by lectins and glycans in immune tolerance and inflammation

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Homeostatic signals delivered in the form of immunosuppressive cytokines or inhibitory receptors are integrated into regulatory circuits that sustain peripheral tolerance mechanisms. These mechanisms serve to prevent collateral tissue damage resulting from over-exuberant immune responses to pathogens or seemingly-innocuous environmental stimuli [1]. Disruption of single pathways underlying these circuits leads to substantial inflammatory and autoimmune states. Conversely, their aberrant activation represents a significant hurdle for the development of anti-tumor immunity. Although under-appreciated for many years, exciting findings underscore the essential contribution of cell surface glycosylation and lectin-glycan signaling to these regulatory circuits operating in immune homeostasis. Indeed, endogenous glycan-binding proteins or lectins specifically decode glycan-containing information and convey this information into functional cellular responses [2].

Galectins are a family of soluble lectins characterized by a conserved carbohydrate recognition domain (CRD) that recognizes *N*- and O-glycans expressing the disaccharide N-acetyllactosamine (Galβ(1-4)-GlcNAc or LacNAc) [2]. Secreted galectins, in contrast to cytokines or chemokines, do not have specific receptors, but can mediated cellular communication through recognition of a preferred set of cell surface glycoconjugates [3]. **In our laboratory, we work at the interface of immunology and glycobiology using *in vitro* and *in vivo* approaches to understand the role of glycans and glycan-binding proteins in immune tolerance and inflammation.**

Research over the past decade revealed a prominent expression of galectin-1 in tumor cells and its association with malignant progression. These observations led us to investigate the role of galectin-1-glycan interactions in tumor biology. By a combination of *in vitro* and *in vivo* experiments we identified a crucial role for galectin-1 in tumor-immune escape [4]. We found that both human and murine melanoma cells secrete functional galectin-1, which substantially contributes to the immunosuppressive activity of these cells. Targeted inhibition of galectin-1 gene expression rendered mice resistant to tumor challenge and stimulated the generation of a tumor-specific Th1-type response [4]. Supporting these findings, we found that Hodgkin lymphoma cells selectively overexpress galectin-1, favoring the secretion of Th2-type cytokines and blunting specific T-cell immunity [5]. Notably, the observed role for galectin-1-glycan interactions in the establishment of immune privileged microenvironments was important not only in tumor settings but also at the fetomaternal interface [6]. In an established model of stress-induced failing pregnancy, galectin-1 had a critical role in preventing fetal loss and restoring tolerance *in vivo*. Galectin-1-deficient (*Lgals1*$^{-/-}$) female mice showed higher rates of fetal loss compared to their wild-type counterparts in allogeneic, but not in syngeneic matings. Investigation of the mechanisms underlying these regulatory effects revealed the ability of galectin-1 to restore the Th1/Th2 cytokine balance and promote the expansion of IL-10-producing T_{reg} cells [6]. These effects were recently confirmed in several autoimmune, inflammatory and tumor settings [7].

To understand the cellular mechanisms underlying these immunoregulatory effects, we performed *in vitro* and *in vivo* studies. We found a link between differential glycosylation of T helper cells, susceptibility to galectin-1-induced cell death and termination of the inflammatory response [8]. While Th1- and Th17-differentiated cells expressed the repertoire of cell surface glycans that are critical for galectin-1 binding and cell death, Th2 cells were protected from galectin-1 through differential α2,6 sialylation of cell surface glycoproteins [8]. More recently, we investigated the relevance of galectin-glycan lattices within the dendritic cell (DC) compartment. Notably, DCs differentiated in a galectin-1-enriched microenvironment acquired a distinctive 'regulatory signature' characterized by abundant secretion of IL-27 and IL-10 [9]. When transferred *in vivo*, these DCs promoted antigen-specific T-cell tolerance, blunted Th1 and Th17 responses and halted autoimmune neuroinflammation through mechanisms involving DC-derived IL-27 and T cell-derived IL-10. Thus, using IL-27 receptor-deficient (*Il27ra*$^{-/-}$) and IL-10-deficient (*Il10*$^{-/-}$) mice, we have identified an immunoregulatory circuit linking galectin-1 signaling, IL-27-producing tolerogenic DCs and IL-10 secreting T_{reg} cells. Remarkably, galectin-1 expression increased during the peak and recovery phases of experimental autoimmune encephalomyelitis (EAE), and animal model of multiple sclerosis (MS), and was dramatically up-regulated by tolerogenic stimuli. Moreover, galectin-1-sufficient but not galectin-1-deficient DCs were able to restore tolerance and contribute to EAE recovery [9], suggesting a crucial role of endogenous galectin-1 in 'fine-tuning' the immunogenic function of DCs. Furthermore, we recently identified an essential role of galectin-1-glycan interactions in tempering microglia activation, brain inflammation and neurodegeneration with critical therapeutic implications in MS [10]. We found that galectin-1 limits M1 microglia activation and neurodegeneration, by targeting the activation of p38MAPK- and CREB-dependent pathways and hierarchically controlling downstream pro-inflammatory mediators such as iNOS, TNF and CCL2. Mechanistically galectin-1 acted by specifically interacting on core 2 O-glycans on CD45 and retaining this glycoprotein on the surface of microglia cells, thus favoring its phosphatase activity and amplifying its inhibitory effect. Targeted deletion of galectin-1 resulted in pronounced inflammation-induced neurodegeneration in an animal model of multiple sclerosis. Moreover, adoptive transfer of astrocytes secreting galectin-1 or administration of recombinant galectin-1 rescued this phenotype through mechanisms involving microglia de-activation [10]. Thus, similar to the effects observed at the peripheral compartment, our results show that galectin-1-glycan interactions are key mediators of different cellular processes central to immune regulation in the central nervous system.

Taken together, our findings set the bases for the design of novel therapeutic strategies aimed at potentiating antitumor responses, preventing fetal loss and favoring the resolution of chronic inflammation and autoimmune disorders.

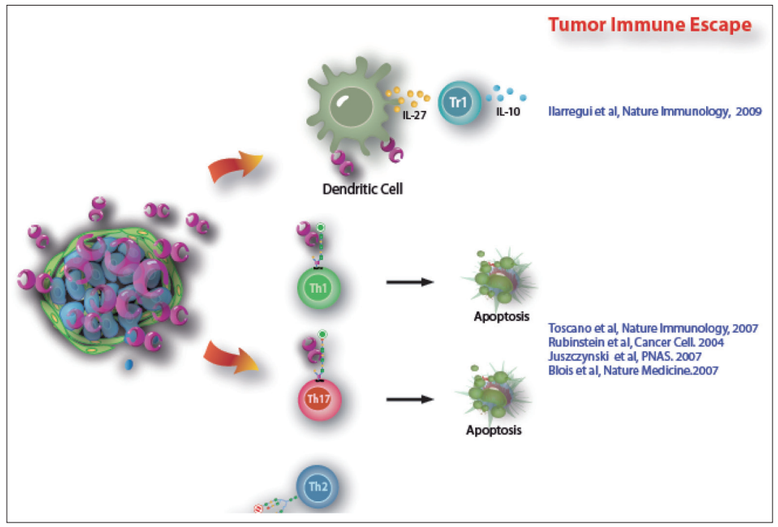

Figure 1. Tumour secreted galectin-1 promotes tumour immune escape through modulation of DCs differentiation and functionality and regulation of T cell homeostasis.
DCs differentiated in a galectin-1-enriched microenvironment acquire a tolerogenic phenotype characterized by abundant secretion of IL-27 and induction of IL-10 secreting T_{reg}. In addition, galectin-1 differentially regulates apoptosis of T cell populations. While Th1- and Th17-differentiated cells express the repertoire of cell surface glycans that are critical for galectin-1 binding and cell death, Th2 cells are protected from galectin-1 through differential α2,6 sialylation of cell surface glycoproteins .

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