Delineating the “galectin signature” of the tumor microenvironment

Daniel Compagno,1,* Diego J. Laderach,1,* Lucas Gentilini,1 Felipe M. Jaworski1 and Gabriel A. Rabinovich1,2,*

1Laboratorio de Glicómica Estructural y Funcional; IQUIBICEN-CONICET; Departamento de Química Biológica; Facultad de Ciencias Exactas y Naturales; Universidad de Buenos Aires; Buenos Aires, Argentina; 2Laboratorio de Inmunopatología; Instituto de Biología y Medicina Experimental (IBYME-CONICET); Buenos Aires, Argentina

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Galectins, a family of glycan-binding proteins, can control tumor progression by promoting transformation, angiogenesis and immune escape. We identified a dynamically regulated ‘galectin signature’, which delineates the progression of prostate cancer, highlighting galectin-1 as an attractive target for anti-angiogenic therapy in advanced stages of the disease.

Galectins, a family of evolutionarily-conserved glycan-binding proteins, can influence tumor progression by mediating communication among tumor, stromal, endothelial and immune cells. These lectins are defined by a consensus sequence of approximately 130 amino acids within the carbohydrate-recognition domain (CRD), which mediates their specific interaction with N-acetyllactosamine [Galβ(1→4)-GlcNAc]-enriched glycoconjugates.1 Within the intracellular compartment, galectins can modulate a variety of signaling processes.1 However, these endogenous lectins can also be secreted in the extracellular milieu through a non-classical pathway, where they cross-link specific glycoconjugates and modulate a variety of cellular processes including proliferation, differentiation and apoptosis.1 A number of studies in preclinical models and cancer patients have documented a significant association between the expression of galectins and the aggressiveness of multiple tumor types. In most settings, galectin expression is associated with poor clinical outcome.1 Of note, whereas 15 galectins have been identified so far in a diversity of tissues and species, most studies have focused on galectin-1 and galectin-3.1

We and others have identified a critical role for galectin-1 in the evasion of tumor cells from immune responses in different types of cancer, including melanoma, Hodgkin’s lymphoma, lung carcinoma and neuroblastoma.1–5 The analysis of the mechanisms underlying these effects revealed the ability of galectin-1 to modulate T-cell survival, dendritic-cell immunogenicity and regulatory T-cell function.1–5 In addition, galectin-1 is strongly upregulated by hypoxia and has been shown to promote angiogenesis in different tumor types, including melanoma and Kaposi’s sarcoma.6–8 However, despite considerable progress in the understanding of the roles of individual galectins in tumor biology, an integrated view of the galectin network in the tumor microenvironment, including their regulation and coordinated function is still lacking. In an attempt to fill this gap, we conducted a study to delineate the ‘galectin signature’ of the human prostate cancer (PCa) microenvironment with the overarching goal of selecting novel molecular targets for prognostic and therapeutic purposes.9

The analysis of the galectin profile in prostatectomies from a cohort of therapy-naïve patients demonstrated that galectin-1 is the most abundantly expressed galectin in this setting and is the only member of the family that is substantially upregulated during PCa progression. A similar profile was observed in representative PCa cell lines, at both the mRNA and protein levels. All other galectin family members are expressed at comparatively lower levels. While galectin-3, -4, -9 and -12 are downregulated in the course of the disease, the expression of galectin-8 does remain unaltered during disease progression. The selective upregulation of galectin-1 prompted us to investigate the function of this lectin in the PCa microenvironment. As galectin-1-N-glycan interactions can link tumor hypoxia to angiogenesis in Kaposi’s sarcoma,6 we examined whether this lectin plays any role in PCa angiogenesis. In tissue arrays from PCa patients, elevated expression levels of galectin-1 correlated with increased number of blood vessels. This positive correlation was even more pronounced during advanced stages of the disease. However, no significant correlation was found in human breast cancer tissue arrays, suggesting a tissue-specific pro-angiogenic effect of this lectin.9

Given the promising therapeutic value of anti-angiogenic regimens for advanced castration-resistant PCa,10 we examined the effects of targeting galectin-1 during PCa angiogenesis. In vitro, the blockade of galectin-1 using a newly-developed neutralizing monoclonal antibody prevented the morphogenesis of endothelial cells as induced by human PCa cell
cancers are refractory to conventional chemotherapeutic, anti-angiogenic and immunotherapeutic agents, our results suggest an alternative strategy to suppress tumor growth and prevent tumor metastasis. Importantly, the blockade of galectin-1 may serve not only to prevent tumor angiogenesis, but also to stimulate T cell-mediated immunity and abrogate tumor-cell invasiveness and migration, as previously demonstrated in other tumor types\(^2\) (Fig. 1).

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.
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