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The roles of Galectin-3 in autoimmunity and tumor progression

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Abstract Galectin-3, a unique chimera-type member of the β-galactoside-binding soluble lectin family, is widely expressed in numerous cells. Here, we discuss the role of Galectin-3 in T-cell-mediated inflammatory (auto) immunity and tumor rejection by using Galectin-3-deficient mice and four disease models of human pathology: experimental autoimmune encephalomyelitis (EAE), Con-A-induced hepatitis, multiple low-dose streptozotocin-induced diabetes (MLD-STZ diabetes) and metastatic melanoma. We present evidence which suggest that Galectin-3 plays an important pro-inflammatory role in Con-A-induced hepatitis by promoting the activation of T lymphocytes, NKT cells and DCs, cytokine secretion, prevention of M2 macrophage polarization and apoptosis of mononuclear cells, and it leads to severe liver injury. In addition, experiments in Galectin-3-"knock-out" mice indicate that Galectin-3 is also involved in immune-mediated β-cell damage and is required for diabetogenesis in MLD-STZ model by promoting the expression of IFN-gamma, TNF-alpha, IL-17 and iNOS in immune and accessory effector cells. Next, our data demonstrated that Galectin-3 plays an important disease-exacerbating role in EAE through its multifunctional roles in preventing cell apoptosis and increasing IL-17 and IFN-gamma synthesis, but decreasing IL-10 production. Finally, based on our findings, we postulated that expression of Galectin-3 in the host may also facilitate melanoma metastasis by affecting tumor cell adhesion and modulating anti-melanoma immune response, in particular innate antitumor immunity. Taken together, we discuss the evidence of pro-inflammatory and antitumor activities of Galectin-3 and suggest that Galectin-3 may be an important therapeutic target.

Keywords Galectin-3 · Con-A-induced hepatitis · Multiple low-dose streptozotocin-induced diabetes · Experimental autoimmune encephalomyelitis · Melanoma metastasis

Introduction

The galectins are evolutionarily conserved carbohydrate-binding proteins that have received attention in immunopathology due to their modulating activities on both pro- and anti-inflammatory immune responses [1, 2]. All galectins contain conserved carbohydrate-recognition domains (CRDs) of about 130 amino acids with affinity for β-galactosides [3]. To date, 15 mammalian galectins have been identified and classified into three groups: proto-type galectins (Galectins-1, -2, -5, -7, -10, -13, -14 and -15), which contain one CRD; tandem-repeat galectins (Galectins-4, -6, -8, -9 and -12), which have two different CRDs joined by a linker peptide of variable length; and the unique "chimera-type" Galectin-3, which contains a single CRD fused to non-lectin amino-terminal region [3–5].

Many galectins are either bivalent or multivalent with regard to their carbohydrate-binding activities. These molecules do not have specific individual receptors, but

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