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Review

Role of galectin-3 in autoimmune and non-autoimmune nephropathies

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ABSTRACT

Galectins are evolutionary conserved β-galactoside binding proteins with a carbohydrate-recognition domain (CRD) of approximately 130 amino acids. In mammals, 15 members of the galectin family have been identified and classified into three subtypes according to CRD organization: prototype, tandem repeat-type and chimera-type galectins. Galectin-3 (gal-3) is the only chimera type galectin in vertebrates containing one CRD linked to an unusual long N-terminal domain which displays non-lectin dependent activities. Although recent studies revealed unique, pleiotropic and context-dependent functions of gal-3 in both extracellular and intracellular space, gal-3 specific pathways and its ligands have not been clearly defined yet. In the kidney gal-3 is involved in later stages of nephrogenesis as well as in renal cell cancer. However, gal-3 has recently been associated with lupus glomerulonephritis, with Familial Mediterranean Fever-induced proteinuria and renal amyloidosis. Gal-3 has been studied in experimental acute kidney damage and in the subsequent regeneration phase as well as in several models of chronic kidney disease, including nephropathies induced by aging, ischemia, hypertension, diabetes, hyperlipidemia, unilateral ureteral obstruction and chronic allograft injury. Because of the pivotal role of gal-3 in the modulation of immune system, wound repair, fibrosis and tumorigenesis, it is not surprising that gal-3 can be an intriguing prognostic biomarker as well as a promising therapeutic target in a great variety of diseases, including chronic kidney disease, chronic heart failure and cardio-renal syndrome. This review summarizes the functions of gal-3 in kidney pathophysiology focusing on the reported role of gal-3 in autoimmune diseases.

Contents

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1. Introduction

Considerable interest has recently arisen in the intriguing properties and biological functions of galectins as household master regulators of cell homeostasis throughout eukaryote taxa [1–3].

Galectins constitute a large family of β-galactoside binding lectins that are defined by a evolutionarily conserved primary structure, consisting of 135 amino-acid carbohydrate recognition domain (CRD) that binds different self and non-self glycoconjugates, including N- and O-linked glycoproteins and glycolipids, thereby affecting a wide variety of physiological and pathological processes [4,5].

Hirabayashi and Kasai classified galectins into three types based on their domain organization: prototype galectins, tandem-repeat galectins and chimera type galectin. The prototype galectins (galectin-1, -2, -5, -7, -10, -11, -13, -14, and -15) have a single CRD (~15 kDa) existing as a monomer or forming noncovalent linked homodimers. The tandem-repeat-type galectins (galectin-4, -6, -8, -9 and -12) are composed of two distinct but homologous CRDs, though a novel galectin with 4 CRDs has been recently identified [6,7]. Galectin-3 (gal-3) is the unique chimera-type galectin among vertebrates and is composed of a single CRD connected to a non lectin N-terminal domain through a collagen like internal R domain [8].

Galectins preferentially bind glycans that contains N-acetyllactosamine and polylactosamine chains, yet they can significantly differ in their binding specificity for more complex glycoconjugates, due to structural differences and a certain CRD plasticity [6,7]. Furthermore, in human, the overall inter-galectins homology is about 20% and a difference in galectin ligand specificity has been reported not only across different species, but also between different cell types [9].

Galectins affinity depends on ligand mode of presentation and is enhanced by more extended glycans through interactions with different subsites [6,7,10]. However, multivalent glycan recognition can complicate the thermodynamics of ligand-lectin interactions, suggesting also a role for the “bind and jump” mechanism [6,7,10].

Galectins stability and activity respectively depend on availability of high-affinity ligands and, in the absence of substrates, on reducing redox conditions [10]. Therefore, galectins properties can significantly change, also considering that after being secreted, galectins tend to lose their binding and oligomerization capacity [7]. In fact, in the extracellular space galectins are susceptible to proteolysis and/or to oxidation of the free cysteine residues on the CRD, which can be partially prevented by the immediate ligand binding [7].

Notably, galectins recognize only a limited number of the large amount of galactose-containing glycoproteins and glycosylation is not always necessary for galectin binding, suggesting a carbohydrate-independent function [11]. Therefore, for each of the 15 currently identified members of the mammalian galectin family the detailed binding specificity/affinity and the carbohydrate-independent activities have not been clearly defined, yet [10].

Unlike cytokines, galectins do not seem to have a specific individual receptor, and yet they can affect a great variety of events, either in an extracellular or intracellular fashion. Furthermore, not all galectin interactions do necessary result in a biological effect [2]. Despite considerable functional redundancy, galectin family members may play different and even opposite roles. Even galectins with very similar substrate backbones can differ in their functions from site to site [4], depending on tissue location/cell compartmentalization and stoichiometric regulation within the galectin participants [11]. Thus, the predominance of one galectin over the others defines the final effect, also at sites where the concentrations of galectins are equivalent.

Galectins display sulfhydryl dependency, calcium independency and the ability to agglutinate cells as well as cross-link and clusterize glycans on the surface of host/foreign cells [10]. Multivalent galectin-glycoprotein lattices or microdomains can modulate receptor functions, prolong glycoprotein residence time at cell surfaces opposing their endocytosis, enhance their activity or prevent protein–protein interactions in any given cell [2,3]. It has been reported that galectins can also modulate apical protein sorting and cell surface receptors trafficking [1,12]. Thus, galectins, thanks to their relatively broad ligand specificity, can modulate cellular responsiveness to extracellular signals acting as multivalent adaptive sensors.

Furthermore, cells show a surprising high variability in the susceptibility to each galectin, depending on their type/state. Since the glycosyltransferase enzymes profile progressively changes during the differentiation process, cells can show a wide range of different galectin ligands. In addition, cells display specific galectins isoforms or different post-translational modification in different conditions [4]. In view of the above regulatory mechanisms, it is conceivable that galectins may act as essential cell-cycle regulators [8,13]. Interestingly, galectins can also control the expression of several regulatory genes but most of their intracellular functions seem to be independent from their carbohydrate binding capability. Such a complexity in galectin properties suggest that galectins can modulate numerous biological processes not only through their ability to decipher glico-codes but also through glycan-independent activities.

2. Galectin-3 in kidney development and homeostasis

Among galectins, gal-3 has been extensively evaluated in several biological processes to define its role in balancing the inflammatory response [1,3,11]. Gal-3 promotes cell migration by modulating cell–cell adhesion and cell-matrix adhesion which are critical aspects for embryogenesis, inflammation as well as for cancer dissemination [12]. Gal-3 expression has been reported in several epithelia during embryogenesis as well as in adult tissue; however, gal-3 and its ligand expression patterns are tissue and time-dependent suggesting that their expression is strictly regulated [2,3]. Gal-3 knockout (KO) mice show architectural abnormalities in granulomas, tumor stroma and in intestinal epithelium [1,11,13] suggesting that gal-3 contribution to optimal cell polarization/migration and cell/matrix interactions plays a pivotal role in tissue organization. As one might expect, gal-3 plays a pivotal role in the kidney, an organ in which architecture and function are very complex and closely related.

In the urinary system of adult mice, gal-3 is the major galectin subtype and it is selectively expressed in epithelia of the uretic bud- and cloaca-derivatives [14]. Conserved differences have been reported in site/subtype expression of gal-3 as well as in gal-3 specific binding sites reflecting functional difference among various kidney regions [14,15]. As well, gal-3 is confined to the apical face of some distal tubules in human, rat, mouse and hamster mature kidney; by contrast, gal-3 is not at all or only weakly expressed at glomerular/mesangial level under normal conditions [16,17]. However, gal-3 can be found also in glomeruli and interstitium in several pathological conditions in human as well as in animal models [17,18]. In rats, gal-3 non-polarized neo-expression is observed in cytoplasm and on basal face of distal tubules, including macula during experimental glomerulonephritis (GN) [16]. Taken together, these findings suggest that gal-3 plays an active role in tubular cell homeostasis in normal tissue, yet it expression can be induced by various stimuli.

Non-polarized gal-3 expression has been reported in human tubular epithelia during normal kidney development and in kidney cystic disease suggesting its pivotal role in orchestrating duct morphogenesis [14]. Since gal-3 association with the centrosomes transiently occurs during the process of epithelial polarization, gal-3 deficiency leads to dramatic centrosomal abnormalities in the kidney both in vitro and in vivo [19]. Even if gal-3 is expressed in cyst epithelia, exogenous gal-3 reduced cyst formation in suspension culture of cystic kidneys suggesting a role in epithelial stabilization, organization and maturation through ciliary signaling modulation [19]. Thus, gal-3 upregulation in ureteric bud and derivate is critical to modulate ureteric bud branching limiting dilation/distortion of developing epithelia [14,19].