Cytokine & Growth Factor Reviews 24 (2013) 547–558

Contents lists available at ScienceDirect

Cytokine & Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Survey

# Vascular galectins: Regulators of tumor progression and targets for cancer therapy

Victor L. Thijssen [a,*], Gabriel A. Rabinovich [b,c], Arjan W. Griffioen [a]

[a] Angiogenesis Laboratory, Department of Medical Oncology, VU University Medical Center, Amsterdam, The Netherlands
[b] Laboratorio de Inmunopatología, Instituto de Biología y Medicina Experimental, Consejo Nacional de Investigaciones Científicas y Técnicas, 1428 Buenos Aires, Argentina
[c] Laboratorio de Glicómica Funcional, Departamento de Química Biológica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, 1428 Buenos Aires, Argentina

ARTICLE INFO

*Article history:*
Available online 12 August 2013

*Keywords:*
Endothelium
Endothelial cells
Metastasis
Immune response
Angiogenesis

ABSTRACT

Galectins are a family of carbohydrate binding proteins with a broad range of cytokine and growth factor-like functions in multiple steps of cancer progression. They contribute to tumor cell transformation, promote tumor angiogenesis, hamper the anti-tumor immune response, and facilitate tumor metastasis. Consequently, galectins are considered as multifunctional targets for cancer therapy. Interestingly, many of the functions related to tumor progression can be linked to galectins expressed by endothelial cells in the tumor vascular bed. Since the tumor vasculature is an easily accessible target for cancer therapy, understanding how galectins in the tumor endothelium influence cancer progression is important for the translational development of galectin-targeting therapies.



**Contents**



* Corresponding author at: Angiogenesis Laboratory, Department of Radiation Oncology, VU University Medical Center, De Boelelaan 1118, 1081 HV Amsterdam, The Netherlands. Tel.: +31 20 4442406; fax: +31 20 4443844.
*E-mail address:* v.thijssen@vumc.nl (V.L. Thijssen).

1359-6101/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.cytogfr.2013.07.003

## 1. The galectin family

The term galectins-previously referred to as β-galactoside-binding proteins – was coined in 1994 by Barondes et al. to define a family of lectins that share binding affinity for β-galactosides and that display significant sequence homology in their carbohydrate-binding domain [1,2]. In the following two decades, the protein family has expanded to 15 members that, with a few exceptions [3], meet the two galectin-defining requirements, i.e. beta-galactoside affinity and a conserved carbohydrate recognition domain (CRD). The CRD is the main functional domain of galectins. It is composed of approximately 130 amino acids forming two beta-sheets that fold in a beta-sandwich which is slightly bent. The outer or convex side of this sandwich is made out of 5 anti-parallel strands (F1–F5) while the inner or concave side contains 6 anti-parallel strands (S1–S6) (Fig. 1A). Carbohydrate binding occurs at the concave side in a groove formed by the curved shape of the sandwich. The core binding site for beta-galactoside containing disaccharides like lactose consists of conserved amino acids in strands S4–S6. However, the binding groove extends to strands S1–S3 which allows binding of more extended oligosaccharides with different affinities [4–6]. Such complex glycans are common and over the years several endogenous glycoproteins and glycopeptides have been identified as ligand for specific galectin CRDs, including extracellular matrix components, cell surface receptors, and adhesion molecules [7–11].

The increasing number of family members has allowed classification of galectins based on the number and organization of CRDs (Fig. 1B). At present, three subgroups are distinguished: (1) prototype galectins that consist of a single CRD which can dimerize, (2) tandem repeat galectins in which two CRDs are covalently bound by a linker peptide, and (3) chimeric galectins that contain an N-terminal tail of short amino acid repeats fused to the CRD [5,6]. Interestingly, several galectins can also assemble into non-covalently bound higher order oligomers [6,9,12–14]. This di- and multimerization is an important functional feature as it allows multivalent carbohydrate binding by which galectins can modulate the spatial organization and retention of glycoproteins at the cell surface [14–16]. In addition, it enables galectins to facilitate both intercellular interactions as well as interactions between cells and their environment. Galectins also engage in protein–protein interactions to mediate functions independent of carbohydrate binding. This type of binding mainly occurs intracellularly and further adds to the functional diversity of galectins [17,18].

## 2. Galectin expression in the endothelium

The expression of galectins has been frequently reported in endothelial cells of different sources and origin and appears to be confined to four family members, i.e. galectin-1, galectin-3, galectin-8, and galectin-9 [10,19–31]. Low mRNA levels of galectin-2, -4, and -12 have also been detected in cultured endothelial cells but expression at the protein level is still unresolved [32]. Endothelial galectins are found throughout the cell, i.e. in the nucleus, the cytoplasm and at the cell membrane [20,23,26,27,30,32–39] suggesting that they exert diverse functions in endothelial cell biology (Fig. 2A). This diversity is further increased by transcriptional and posttranslational modifications, including phosphorylation, proteolytic processing and mRNA splicing. For example, the two tandem-repeat galectins, i.e. galectin-8 and galectin-9, have been found to be subjective to extensive mRNA splicing [10,28–31,40]. At least two galectin-8 mRNA variants have been identified in cultured human endothelial cells [32]. Two bands reactive with anti-galectin-8 antibody have also been reported by Cueni et al. in lymphatic as well as in blood vessel derived human endothelial cells [10]. Delgado et al. reported the presence of 3 isoforms of galectin-8 in bovine aortic endothelial cells [30]. Regarding galectin-9 splicing, Spitzenberger et al. identified 3 mRNA transcripts which corroborates with other

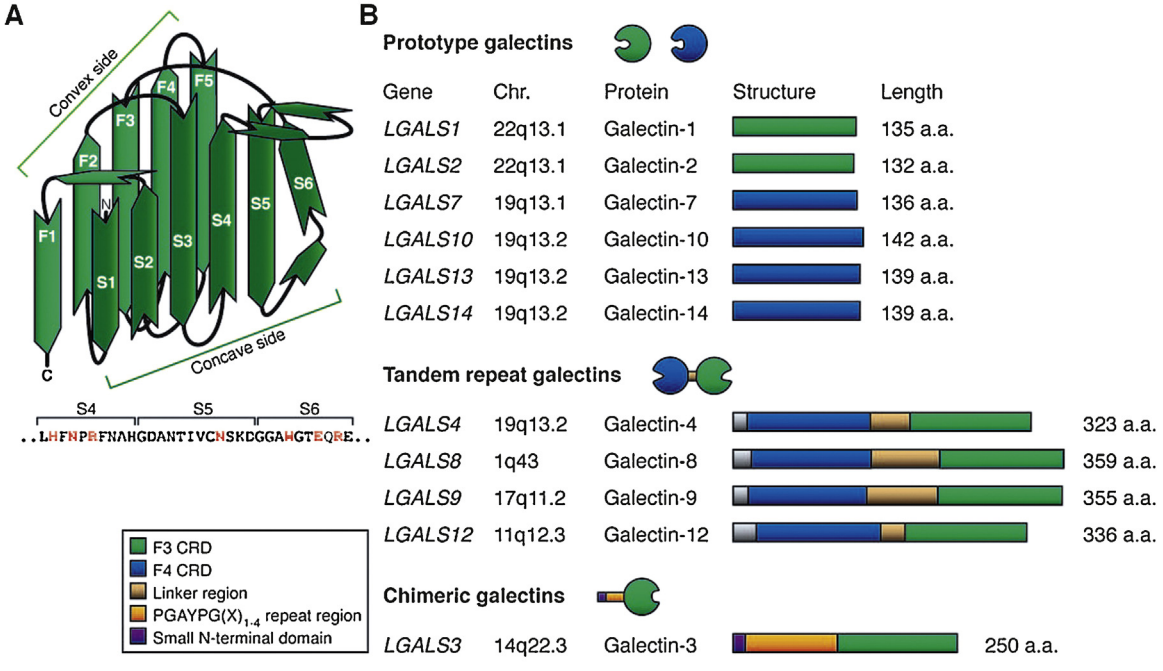


**Fig. 1.** The carbohydrate recognition domain and galectin classification. (A) Simplified cartoon of the conserved galectin carbohydrate recognition domain based on the crystal structure of galectin-1. The CRD is formed by two beta-sheets that are slightly bent resulting in a concave and convex side. The convex side consists of 5 anti-parallel strands (F1–F5) and the concave side of 6 anti-parallel strands (S1–S6). Carbohydrate binding occurs at the concave side and involves several conserved amino acids located in S4–S6 (shown for galectin-1 in the sequence below). (B) Classification of galectins in three subgroups, i.e. prototype, tandem repeat, and chimera, based on the protein structure and number of CRDs. For the tandem repeat galectins only the full length protein is shown. For several of these galectins alternative splicing has been reported which mainly affects the length of the linker region between the two CRDs.