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Review

Galectin expression in cancer diagnosis and prognosis: A systematic review ☆

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ABSTRACT

Galectins are a family of proteins that bind to specific glycans thereby deciphering the information captured within the glycome. In the last two decades, several galectin family members have emerged as versatile modulators of tumor progression. This has initiated the development and preclinical assessment of galectin-targeting compounds. With the first compounds now entering clinical trials it is pivotal to gain insight in the diagnostic and prognostic value of galectins in cancer as this will allow a more rational selection of the patients that might benefit most from galectin-targeted therapies. Here, we present a systematic review of galectin expression in human cancer patients. Malignant transformation is frequently associated with altered galectin expression, most notably of galectin-1 and galectin-3. In most cancers, increased galectin-1 expression is associated with poor prognosis while elevated galectin-9 expression is emerging as a marker of favorable disease outcome. The prognostic value of galectin-3 appears to be tumor type dependent and the other galectins require further investigation. Regarding the latter, additional studies using larger patient cohorts are essential to fully unravel the diagnostic and prognostic value of galectin expression. Furthermore, to better compare different findings, consensus should be reached on how to assess galectin expression, not only with regard to localization within the tissue and within cellular compartments but also regarding alternative splicing and genomic variations. Finally, linking galectin expression and function to aberrant glycosylation in cancer cells will improve our understanding of how these versatile proteins can be exploited for diagnostic, prognostic and even therapeutic purposes in cancer patients.

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1. Introduction

Galectins are part of the lectin superfamily and they exert their main biological functions by interacting with specific glycoconjugates, i.e. carbohydrate structures linked to proteins, peptides and lipids. This way, galectins decipher the information encoded by the glycosylation machinery and translate this information into cellular functions. The interactions between galectins and glycoconjugates are mediated via a conserved carbohydrate recognition domain (CRD) of approximately 14 kD which shows binding affinity – albeit not exclusively – for β-galactosides [1,2]. Based on structural features, galectins can be classified into three subgroups, i.e. prototype galectins, tandem repeat galectins and chimeric galectins [3](Fig. 1A). An important feature of galectins is their ability to homodimerize and oligomerize which increases the glycan binding valency and allows galectins to simultaneously interact with multiple glycoconjugates [4,5]. As a result, galectins can mediate homo- and heterotypic interactions between cells, facilitate the binding of cells to extracellular matrix components and modulate signaling pathways and cellular behavior by e.g. receptor clustering [6,7](Fig. 1B).

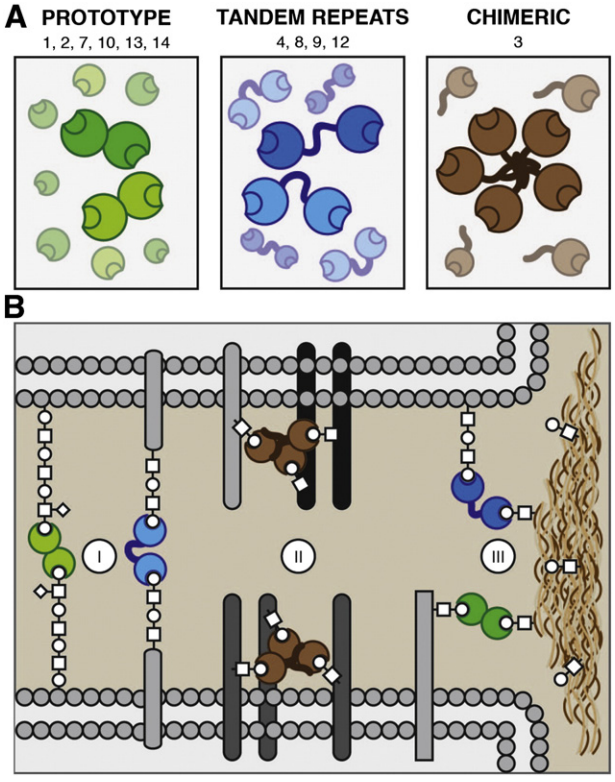

Fig. 1. The human galectin family and galectin function. A) The human galectin family consists of 11 members that are characterized by the presence of a conserved carbohydrate recognition domain. Based on the structural organization of these domain the galectins are divided of three subgroups. Prototype galectins consist of a single domain which can homodimerize. Tandem repeat galectins have two domains which are connected by a flexible linker, the length of which can vary due to alternative splicing. Chimeric galectins consist of a single domain fused to a N-terminal 'tail' of short stretches of proline, tyrosine and glycine-rich tandem repeats. B) Schematic overview of the most common extracellular functions of galectins. Dimerization and multimerization allows galectins to simultaneously bind multiple glycoconjugates. This way galectins can (I) mediate homo- and heterotypic cell-cell interactions, (II) stimulate or prolong signaling by clustering of cell-surface receptors, and (III) mediate cell-extracellular matrix interactions.

Galectins also engage in direct protein-protein interactions, thereby influencing cell signaling, cell-cycle progression, apoptosis and even pre-mRNA splicing [8,9]. In line with this functional diversity, galectin dysfunction or altered expression has frequently been associated with disease, including cancer [10–12]. In the last two decades it has been shown that galectins contribute to many hallmarks of cancer [13], including sustained proliferative signaling, resistance to cell death signals, evasion of immune surveillance, induction of angiogenesis, and activation of the metastatic potential [2,9,14–16]. Consequently, efforts are being made to develop galectin-targeting compounds, ranging from competing carbohydrate ligands to small non-carbohydrate binding molecules and blocking antibodies [2,17]. Several of these compounds have been shown to possess anti-tumor activity *in vitro* as well as to hamper tumor progression in pre-clinical cancer models *in vivo* [18–23]. Currently, several clinical trials with different galectin-targeting agents are ongoing (Table 1). This marks the coming of age of galectin-based cancer therapies which is further exemplified by different patent applications for galectin inhibitors [24]. However, to successfully implement such inhibitors in future therapies it is pivotal to identify the patients that are likely to benefit most from these agents, i.e. patients in which galectins are associated with disease outcome. To facilitate this, we performed a systematic review of studies that reported on galectin expression in human cancer patients. We evaluated the diagnostic and prognostic value of galectin expression in tumor tissues as well as of circulating galectins. This not only resulted in a timely overview of the current knowledge but also identified the areas that require further investigation. This will help ongoing efforts that aim to implement galectin-targeted therapies in the clinic for the treatment of cancer patients.

2. Galectin expression in cancerous vs. normal tissues

Over 200 original studies were identified that reported on galectin expression in cancer patients, covering most tissues and cancer types (Fig. 2A). The median number of patients was 73 (range 4–2978) and 83 studies included 100 or more patients. The majority of the studies, i.e. >70%, focused on galectin-1 and galectin-3 while tumors of the digestive tract and the reproductive system were the best studied cancer types, accounting for a little over 50% (Fig. 2B + C). To get more insight in the involvement of galectins in cancer biology we first evaluated the studies that compared the expression of galectins in healthy and malignant tissues. Out of the 144 studies in which this comparison was performed, no change in galectin expression was reported only 23 times. In the majority of studies, alterations in expression were reported as discussed in the following paragraphs (Table 2).

2.1. Galectin-1

Galectin-1 expression is frequently reported to be increased in tumor tissues as compared to normal or benign tissues. Especially in tumors of the reproductive system there is ample evidence that malignant transformation is accompanied by elevated galectin-1 levels. Interestingly, the increase is often observed in the tumor stroma [25–28] a feature which is also reported in tumors of the digestive tract, including colon [29], liver [30] and pancreas [31–34] as well as in several lymphoid malignancies [35,36]. Apart from the reproductive system,