Histological Mapping and Subtype-Specific Functions of Galectins in Health and Disease

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Abstract

Galectins, \( \beta \)-galactoside-binding lectins, consist of 15 members and are broadly distributed in the mammalian body in organ- and cell-specific manners. This minireview summarizes current knowledge on the cellular localization of galectin subtypes in various organs including the digestive tract, lymphatic system, respiratory system, urinary system, and reproductive system. We also summarize the specific localization of galectins in the epithelium with a focus on the characteristic morphologies of epithelia. In addition, we discuss the functions of galectins in the reproductive and endocrine systems, pathogenic angiogenesis, and the regulation of stem cells. The regulatory mechanism of galectin expression is also discussed based on findings obtained from luteal cells. Various glycoconjugate ligands for galectins have been identified, and notably the ligands for galectins differ in each galectin-expressing cell. The physiological and pathological states of cells affect the expression of galectin and glycoconjugate ligands, and the extracellular environment, such as the concentration of growth factors, nutrients, and oxygen also controls the expression levels. Future studies to identify the cellular and intracellular localization of galectins using histological analyses will provide a better understanding of the potential functions of galectins in healthy and disease states.

A. Introduction

Galectins are \( \beta \)-galactoside-binding animal lectins and consist of 15 members. They have been classified into three groups according to their structural features: proto (galectin-1, -2, -5, -7, -10, -11/15, -13, -14, and -16), chimera (galectin-3), and tandem repeat types (galectin-4, -6, -8, -9, and -12) (1). Most galectin subtypes are maintained beyond species, whereas some, including galectin-5, -6, -10, and -16, only exist in a few species (2–5). The 15 galectin members are broadly distributed in the mammalian body and exhibit organ- and cell-specific expression. We herein summarize current knowledge on the cellular localization of galectins in various organs, and discuss the potential functions of galectins in healthy and disease states. Most morphological findings have been obtained from rodents; however, some information from humans and other animals has also been included in this review.

B. Organ-Specific Expression of Galectins

Among the 15 galectin members, galectin-1 and -3 are ubiquitously expressed in the mammalian body. Galectin-1 is astromal type of galectin that is mainly expressed in fibroblasts in connective tissues. Muscles also contain abundant amounts of galectin-1. Although galectin-3 is an epithelial type of galectin, certain lineages of leukocytes, including monocytes, neutrophils, and macrophages, produce galectin-3 (6). Other subtypes exhibit organ-specific expression, and the digestive tract expresses the most galectin members (galectin-2, -3, -4, -6, -7, and -9) (7, 8) (Fig. 1A). Galectin-2, -4, and -6 are specific to the gastrointestinal tract, while galectin-2 is limited to the glandular stomach and small intestine. The lymphoid system, including the thymus, spleen, and lymph nodes, mainly expresses galectin-1, -3, and -9 (6, 9–11) (Fig. 1B). In the thymus, galectin-1 and -9 are abundantly expressed in the cortex and medulla (Fig. 1C). The liver contains several galectin subtypes, such as galectin-3, -8, and -9 (6, 10–12) (Fig. 1B). Galectin-3 is a major subtype in the respiratory system and localizes to the epithelium and alveolar macrophages (6) (Fig. 1D). Galectin-8 and -9 are expressed in the lung (10–12). Galectin-3 is a major subtype in the urinary system (13), while galectin-8 and -9 have also been detected in the kidney (10, 12) (Fig. 1E). The major galectin subtypes in the reproductive system are galectin-1 and -3 (Fig. 1F), and their expression changes during the estrous cycle in females (14, 15). Galectin-7 has been detected in the ovarian surface epithelium (14). The organ-specific localization of galectin subtypes appears to be established during the developmental stage because the distribution of major galectin subtypes in the fetus is found to be similar to that in matured mice (Fig. 1G).

C. Galectins in the Epithelium

The epithelium is histologically classified into a simple or stratified epithelium. The skin is covered by a stratified squamous epithelium, whereas the vascular endothelium and mesothelium consist of a simple squamous epithelium. The gastrointestinal tract is lined with a simple columnar epithelium; however, cell types
Fig. 1. Organ-specific localization of galectin subtypes in mice. The organ-specific expression of each galectin subtype is summarized in the digestive tract (A), lymphoid tissues and liver (B), respiratory system (D), urinary system (E), and reproductive system in females (F). The expression of major galectin subtypes is analyzed by in situ hybridization in the mouse fetus on embryonic day 15.5 (G). C is X-ray images of the thymus showing the expression of galectin mRNAs analyzed by in situ hybridization. G, galectin.
consisting of the epithelium differ depending on the region of the gastrointestinal tract. The transitional epithelium is unique to the urinary system, while the upper respiratory tract, including the nasal cavity and trachea, is covered by a ciliated pseudostratified columnar epithelium. The epithelium functions as a barrier to separate the internal environment from the external environment, and is particularly important for avoiding infection in the skin, digestive tract, respiratory system, and external genitals. As described above, galectin-3 is an epithelial type of galectin that is broadly expressed in various types of epithelia in the body. Galectin-7 is a specific subtype expressed in the stratified squamous epithelium such as that in the skin, lips, oral cavity, esophagus, forestomach, and anus in the digestive tract and the vagina in the female reproductive tract (7, 8) (Fig. 2A). Galectin-3 is also expressed in the stratified squamous epithelium; however, cells at the basal layer of this epithelium lack the galectin-3 expression (Fig. 2B). The unique transition of the major galectin subtype during epithelial differentiation is observed in the simple columnar epithelium of the

Fig. 2. Galectins in the epithelium. The stratified squamous epithelium in the perioral skin of the mouse contains abundant amounts of galectin-7 (A) and -3 (B). The basal layer of this epithelium does not express galectin-3 (B). C is a schema showing the transition of the galectin subtype expressed during epithelial differentiation in the small intestine. Goblet cells express galectin-2 throughout the villi (C). The transitional epithelium in the urinary bladder expresses galectin-3 (D). The ciliated pseudostratified columnar epithelium in the nasal cavity (E) and trachea (F) strongly expresses galectin-3. Chondrocytes in the tracheal cartilage are also positive for galectin-3 immunoreactivity (F). The olfactory epithelium lacks immunoreactivity for galectin-3 (G). Arrows in G show the border of the respiratory epithelium and olfactory epithelium.
gastrintestinal tract. In the glandular stomach and small intestine, a shift occurs in the galectin subtypes expressed in the epithelium from galectin-2, to galectin-4/6, and then galectin-3 in association with epithelial cell differentiation and maturation (7, 8). For example, immature epithelial cells in the upper crypts and bottom of the villi in the small intestine contain abundant amounts of galectin-2. Absorptive epithelial cells located in the middle of the villi contain galectin-4/6, whereas mature and aged epithelial cells at the tip of the villi express galectin-3 (Fig. 2C). The transitional epithelium in the renal pelvis, ureter, urinary bladder, and urethra strongly expresses galectin-3 (13) (Fig. 2D). The ciliated pseudostratified columnar epithelium in the nasal cavity and the trachea strongly expresses galectin-3 (Fig. 2E, F), whereas that in the lung does not. The olfactory epithelium in the superior nasal meatus lacks immunoreactivity for galectin-3 in adult mice (Fig. 2G), whereas galectin-1 and -3 are detected in the human olfactory epithelium, suggesting the differential expression of galectins in the olfactory epithelium among species (16). The simple squamous epithelium including vascular endothelium and mesothelium does not express any galectin in a healthy state, although that in the ascending thin limbs of Henle’s loop of the kidney expresses galectin-3 (13).

D. Galectins in the Reproductive and Endocrine Systems

Although the expression levels of galectins in the digestive tract, urinary system, and other organs remain consistent throughout life, those of galectin-1 and -3 in the female reproductive tract markedly change during the estrous cycle. We previously reported that the corpus luteum, which produces progesterone for the establishment and maintenance of pregnancy, stage-specifically produces galectin-1 and -3 in mice, cows, and women, suggesting their involvement in the regulation of luteal function (17). Changes in galectin expression during the estrous cycle are also observed in other parts of the female reproductive tract, including the oviduct, uterus, and vagina, indicating that ovarian steroids regulate galectin expression in these organs (6). The expression of galectin-1 and -3 in the implantation site in the mouse uterus and placenta was previously reported by Phillips et al. (18). Other galectins including galectin-9, -11/15, -13, -14, and -16 are known to be expressed in the placenta of women and domestic animals (5, 19–22), suggesting an important role for galectins in the establishment and maintenance of pregnancy.

We recently found that the pituitary gland contains galectin-3 and its expression changes during the estrous cycle in association with the function of the pituitary gland (our unpublished data). Although the role of galectin-3 in the pituitary gland in a healthy state currently remains unclear, previous studies demonstrated that galectin-3 is expressed in pituitary tumors including prolactinoma, corticotroph adenoma, and folliculostellate cell tumors (23, 24). The expression of galectin-1 and -3 in the adrenal gland and pineal gland in a healthy state has been reported in mice (6, 25). Galectin-3 is an established diagnostic marker for thyroid cancers, and galectin-1 is also involved in thyroid cancer progression (26, 27).

E. Pathological Angiogenesis and Galectins

Although endothelial cells in blood vessels and lymphatic vessels do not express galectins in a healthy state in mice, there is evidence to show the expression of several galectins in the endothelium in association with pathological angiogenesis. Galectin-1 and -3 were previously reported to be involved in the regulation of angiogenesis under ischemic conditions and in the tumors. Ischemic conditions induce the expression of galectin-3 as well as galectin-1 in the endothelium, thereby promoting the activation, proliferation, migration, tube formation, and sprouting of endothelial cells (28, 29). Galectin-8 and -9 in the endothelium are also involved in the regulation of angiogenesis in certain tumors (29–31). Galectin-1 and -3 bind to vascular endothelial growth factor receptor 2 (VEGFR2) to regulate angiogenesis (32, 33), and galectin-1 promotes VEGFR2 signaling independent of its ligand, VEGF-A (32). Dos Santos et al. (34) recently reported that galectin-3 regulates Notch signaling by binding to Jagged-1, a Notch ligand, in order to promote sprouting angiogenesis.

Ischemic conditions induce the expression of galectin-1 and -3 in endothelial cells and other cell types. In models of focal brain ischemia and stroke, galectin-1 and -3 were found to be up-regulated in astrocytes and microglial cells, respectively (35–38). Although the precise functions of galectins under ischemic conditions remain unclear, galectin-1 and -3 may improve the functional recovery of the damaged brain tissues (37, 38).

F. Stemness and Galectins

Convincing evidence has been obtained to support the role of galectins in the regulation of stem cells. Galectin-1 is involved in the differentiation and fusion of myoblasts during the development of muscular tissue (39, 40). In galectin-1 null mice, a sub-population of primary sensory olfactory axons failed to reach their targets in the olfactory bulb (41). Sakaguchi et al. (42) reported that galectin-1 in astrocytes promoted the proliferation of neural stem cells in the adult mouse brain. In addition, galectin-1-positive reticular cells were found to make close contact with pre BII cells in bone marrow, suggesting its involvement in hematopoiesis (43). Galectin-1, -3, and -9 are strongly expressed in mesenchymal stem cells derived from bone marrow and umbilical cord blood (44–47).
CD34-positive endothelial progenitor cells contain high levels of galectin-3 (48). In a disease state, hepatic progenitor cells in the injured livers of mice and humans contain galectin-3 (49), and cancer stem cells express galectin-3 in breast and ovarian cancers (50, 51). These findings suggest that galectins play important roles in the maintenance of stemness, differentiation and proliferation of particular cell lineages, and in the migration of stem cells.

G. What Regulates Galectin Expression?

It currently remains unclear why the organ- and cell-specific expression of galectins is established and maintained in mammalian bodies. In the ovary, we found that the molecules regulating luteal function, namely, prolactin (PRL), prostaglandin E₂ (PGE) and PGF₂α (PGF), luteinizing hormone (LH), and human chorionic gonadotrophin (hCG), affected the galectin expression in luteal cells (17). Galectin-1 expression in luteal cells is induced by luteotrophic LH, hCG, and PGE, while the mechanisms regulating galectin-3 expression in luteal cells are complex. The loss of luteotrophic signals results in an increase in galectin-3 in luteal cells, and luteolytic PGF only enhances galectin-3 expression when the corpus luteum cannot produce progesterone. Tumor necrosis factor α (TNF) enhances the expression of both galectin-1 and -3 in human luteal cells. We speculate that galectin expression is related to activated signaling pathways in cells (Fig. 3). PRL acts through the Janus kinase/Signal transducers and activator of transcription (Jak/Stat) pathway and inhibits the expression of galectin-1 in mouse luteal cells. LH/hCG/PGE activate the cAMP/Protein kinase A (PKA) pathway in order to stimulate galectin-1 expression as well as steroidogenesis in human luteal cells, whereas galectin-3 expression is inhibited by this pathway. The activation of protein kinase C (PKC) by PGF results in an increase of galectin-3 in mouse and bovine luteal cells; however, this increase is blocked by cAMP/PKA activation. An activator for PKC, Phorbol 12-myristate 13-acetate (PMA), is known to up-regulate galectin-3 in macrophages (52). TNF acts through the NF-κB signaling pathway, and enhances the expression of galectin-1 and -3 in luteal cells. Galectin-7 is also known to be induced by TNF through NF-κB in breast cancer cells (53). Furthermore, galectins regulate the expression and signaling pathway of the molecules involved in galectin expression. For example, galectin-1 supports hCG-mediated cAMP/PKA activation in human luteal cells (our unpublished data), while loss of galectin-3 results in a decrease of TNF synthesis in various disease (54, 55). The phosphatidylinositol 3 (PI3) kinase/Akt (Protein kinase B) pathway, which is activated by integrin, VEGF, and other growth factors are also involved in the regulation of galectin expression. In addition, the Transforming growth factor (TGF)/β/Smad, Wnt/β-catenin, and Notch signaling pathways control galectin expression in cancer or other cells, and extracellular or intracellular galectins may also regulate these pathways.

The cellular expression of galectins correlates with changes in the glycan structure. We previously reported that α2,6-si-

![Fig. 3. Signaling pathways involved in the regulation of galectin expression in luteal cells. G1, galectin-1; G3, galectin-3; hCG, human chorionic gonadotrophin; Jak, Janus kinase; LH, luteinizing hormone; PGE, prostaglandin E₂; PGF, prostaglandin F₂α; PKA, protein kinase A; PKC, protein kinase C; PMA, Phorbol 12-myristate 13-acetate; PRL, prolactin; Stat, Signal transducers and activator of transcription; TNF, tumor necrosis factor α.](image-url)
alylation on the terminal galactose on glycoconjugates, which inhibits galectin-1 binding, negatively correlated with the expression of galectin-1 in luteal cells (17). The differential expression of α2,6-linked sialic acid and galectin-1 has also been observed in cancer cells, and is related to sensitivity to anti-VEGF treatments to inhibit angiogenesis in tumors (33). Our preliminary study revealed that the expression of galectin-1 and -3 in human luteal cells was related to the ability to produce glycosphingolipids, particularly gangliosides, and glycosphingolipids synthesis appears to be regulated by sex steroids such as estrogen and progesterone secreted by luteal cells.

H. Closing Remarks

Galectins are involved in various physiological and pathological events, and many extracellular and intracellular ligands for galectins have been identified. For example, β1-integrin, laminin, VEGFR2, Jagged-1, CD45, CD90, T-cell immunoglobulin and mucin domain 3, ganglioside GM1, keratan sulfate, and chondroitin sulfate proteoglycan have been identified as ligands for galectin-1, -3, and other subtypes (32–34, 56–59). The ligands for galectins differ among each galectin-expressing cell, and the physiological and pathological states of cells also affect the expression of galectin and the glycans structures of their ligand glycoconjugates. The extracellular environment, such as the concentration of growth factors, nutrients, and oxygen, affects the expression of galectin as well as glycoconjugate structures, and the loss of trophic signals may appear to result in the accumulation of anti-apoptotic galectin-3 in the cytoplasm for survival under a severe condition. As reported previously by Prof. Kasai (60), “The ‘one galectin-one phenomenon’ relationship does not exist and the lack of specific and principal roles is the nature of the galectin family.” However, cell- and stage-specific expression of galectin subtypes in cells reminds us an existence of fundamental rules to regulate the expression of galectin and its ligand glycoconjugates. We believe that revealing these rules will help better understanding for the function of galectin and its ligand glycoconjugates in various physiological and pathological events.

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References

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