

Role of galectins in lung cancer (Review)

WEI-AN CHANG^{1,2}, MING-JU TSAI^{2,3}, PO-LIN KUO¹ and JEN-YU HUNG^{2,3}

¹Graduate Institute of Clinical Medicine, College of Medicine, Kaohsiung Medical University; ²Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital; ³Department of Internal Medicine, School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung 807, Taiwan, R.O.C.

Received August 17, 2016; Accepted July 7, 2017

DOI: 10.3892/ol.2017.6882

Abstract. Lung cancer is the leading cause of cancer-associated mortality worldwide and is also associated with a poor prognosis. As in numerous other types of cancer, galectins have been demonstrated to be involved in the progression of lung cancer. Galectins belong to a superfamily of lectins, which are carbohydrate-binding proteins. There are at least 15 members in the galectin family, however, only galectin-1, -2, -3, -4, -7, -8, -9, -10, -12, and -13 are found in humans. Galectins are able to mediate interactions between cells, including homotypic and heterotypic interactions; they also facilitate the bindings between cells and extracellular matrix components. These cell-cell and cell-matrix interactions, as well as the galectin signaling on the cell surface, are able to modulate signaling pathways and thereby influence cellular functions and behaviors. Galectin-1, -3, -4, -7, -8 and -9 are associated with lung cancer. These galectins are associated with tumor invasion, migration, metastasis and progression, and may serve important roles in the tumor microenvironment of lung cancer. The majority of galectins are associated with the progression of lung cancer, with the exception of galectin-9, which is associated with enhanced anticancer immunity. Therefore, galectins may be potential targets for developing novel lung cancer therapies.

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Correspondence to: Dr Jen-Yu Hung, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital, 16ES, 100 Tz-You 1st Road, Kaohsiung 807, Taiwan, R.O.C.
E-mail: jenyuhung@gmail.com

Key words: lung cancer, galectin, tumor microenvironment, malignancy

1. Introduction

Galectins, whose name was proposed in 1994 from their description as β -galactoside-binding lectins, are a family of animal carbohydrate-binding proteins that agglutinate cells (1-3). Since their initial isolation from animals, including electric eels, chicks and calves in the 1970s, at least 15 members of this family have been identified. Galectins were systematically renamed in 1994, primarily based on the order in which they were identified (4).

Galectins perform their biological functions principally through interactions with specific glycoconjugates. Galectins possess high affinity for N-acetylglucosamine sequences through their highly conserved carbohydrate recognition domains (CRDs) (5). All galectins possess at least one CRD.

Galectins are classified by the number and structure of CRDs into three major groups: Prototypical galectins, tandem-repeat galectins and chimeric galectins (Fig. 1) (1,4,6,7). The prototypical galectins, including galectins-1, -2, -5, -7, -10, -11, -13, -14 and -15, contain two identical CRDs to form homodimers and are therefore occasionally known as dimeric galectins. Tandem-repeat galectins, including galectins-4, -6, -8, -9 and -12, are characterized by containing at least two distinct CRDs, connected by linker domains, within a single polypeptide. Galectin-3 is the only chimeric galectin identified in vertebrates; it contains a single CRD and a large amino-terminal domain, which contributes to self-aggregation, resulting in its common appearance of multiple identical subunits (6).

Not all galectins are present in humans: Only galectin-1, -2, -3, -4, -7, -8, -9, -10, -12, and -13 (6). Galectin-5 and galectin-6 are present in rodents, and galectin-11, -14, and -15 are observed in sheep and goats (4,6). Notably, a number of galectin transcripts may be differentially spliced in certain types of tissue to generate a variety of isoforms. For example, at least seven different mRNAs encoding human galectin-8 have been identified, some in prototypical isoforms and others in tandem-repeat isoforms; these isoforms may be expressed differentially in various tissues (4). Three isoforms of galectin-9 with variations in their linker domain length have been identified (4).

2. Functions of galectins

Galectins are able to mediate certain interactions between cells, including homotypic and heterotypic interactions; they

also facilitate the bindings between cells and extracellular matrix components. These cell-cell and cell-matrix interactions, as well as galectin signaling on the cell surface, are able to modulate signaling pathways and thereby influence cellular functions and behaviors (Fig. 2) (7-9).

Roles of galectins in apoptosis. Galectin-1, -2, -3, -7, -8, -9, and -12 are able to induce apoptosis in certain types of blood cells (10). Galectin-1-induced apoptosis involves interactions between T cells and surface glycoproteins, associated with cluster of differentiation (CD)7, CD29 and CD43. The apoptosis induced by galectin-3 is associated with CD71 and CD45 (11), and the overexpression of intracellular galectin-3 may exhibit anti-apoptotic activity (12).

Roles of galectins in development. Galectins have also been demonstrated to be involved in animal development. For example, galectin-3 ablation in mice is associated with decreased mast cell function, as well as fatty liver disease, liver fibrosis, age-dependent glomerular lesions and lung fibrosis (13). Galectin-1 is involved in pathfinding and axon regeneration, and its ablation in mice is associated with a decreased sensitivity response to noxious thermal stimuli. As such, galectin-1 may be associated with anatomical and functional deficits in the development of neurons (14). Additionally, galectins are also involved in post-developmental processes, including immune regulation (10).

Roles of galectins in inflammation and immune responses. The regulation of inflammatory and immune responses is a major function of galectins. Numerous types of blood cells express galectins, including activated T and B cells, regulatory T cells, dendritic cells, mast cells, monocytes/macrophages, eosinophils and neutrophils. Depending on various inflammatory stimuli, the microenvironment and the target cells, galectins are associated with pro- or anti-inflammatory responses (10). In a study of autoimmune retinal disease, galectin-1 was demonstrated to be able to induce anti-inflammatory cytokines, including interleukin (IL)-5 and IL-10, and to suppress the expression of interferon γ , ultimately suppressing the inflammatory response (15). Additionally, galectin-3 serves an important role in the activation of T cells, potentially associated with its interaction with poly-N-acetyllactosamine-containing N-glycans on T-cell receptors (16). In certain immune cells, particularly eosinophils, the addition of galectin-3 leads to the suppressed production of IL-5 by downregulation of the expression of the IL-5 gene (17). Other blood cells, including mast cells, neutrophils, lymphocytes and monocytes, are activated by galectin-3 (18). In the function of mast cells, endogenous galectin-3 is involved in the phagocytosis of macrophages and the promotion of inflammation in the airway (19).

3. Roles of galectins in cancer

Galectins contribute to carcinogenesis and cancer progression. Protein-glycan interactions are important in the progression of cancer, including being involved in carcinogenesis, proliferation, metastasis, angiogenesis and the immune response (20). Galectins are modulated during the differentiation of cells and the development of organs; errors in this modulation occur in

a number of physiological and pathological conditions (21). Additionally, galectins serve a role in tumor transformation and survival, having been demonstrated to be involved in tumorigenesis, the regulation of apoptosis, tumor invasion and angiogenesis, the adhesion of cells during metastasis and the tumor immune response (21). Each galectin exhibits distinct effects in different cancer types. Previous studies have demonstrated that galectin-1 and -3 promote pro-tumorigenic activity by binding to the ligands of cancer cells (22), potentially promoting the progression of distinct types of cancer (6). These pro-tumorigenic activities may include affecting tumor growth, metastasis and angiogenesis, and the promotion of radio- and chemo-resistance, while galectin-1 and -3 also suppress T cell function to affect the tumor microenvironment (6). Other galectins also contribute to the progression of various types of cancer, for example galectin-7 promotes metastatic potential and apoptosis-resistance in breast cancer (23), and is overexpressed in esophageal squamous cell carcinoma (24). Notably, increased galectin-7 expression is associated with improved outcome following radiotherapy for cervical cancer (25) and serves a tumor-suppressive role in gastric cancer (26). In addition, galectin-4 is important in the metastatic potential of lung adenocarcinoma (27) and may also prevent detachment of pancreatic cancer cells through its adhesion molecule-like function (11). Galectin-9 is a good prognostic factor in breast cancer due to its anti-metastatic potential (12). Galectin-2, -4 and -8 may increase adhesion of colon cancer cells to endothelial cells, enhancing the metastasis of colon cancer (28).

Galectin expression in cancerous tissues. Expression of galectins is observed in numerous types of cancer tissue, including cancer of the digestive, reproductive, respiratory, neural, urinary and hematological systems (7). The galectins most extensively studied in oncology are galectin-1, -3, -4, -7, -8 and -9, with numerous studies comparing the expression levels of galectins between normal and malignant tissues. Notably, each galectin may exhibit increased expression in distinct types of cancer, but decreased expression in others; similarly, a specific cancer may have increased expression levels of certain galectins, but decreased expression levels of others (7). For example, galectin-1 expression is increased in the majority of cancer types (7,29), although certain studies have revealed decreased galectin-1 expression in malignant tissues of bladder cancer (30), uterine cancer (31) and head and neck squamous cell carcinoma (13), whereas other studies have observed increased galectin-1 expression in these same types of cancer (14-16). The expression of galectin-3 is also heterogeneous, with increased expression levels identified in thyroid cancer, lung cancer, and the majority of digestive tract and urinary system tumors, whereas decreased expression levels have been observed in reproductive system tumors (7). Studying the expression of galectin-8 and -9 in cancer is complicated due to extensive splicing of their mRNA transcripts, generating various isoforms (7). As a result, they may exhibit decreased mRNA levels (17), but increased protein levels (18).

Galectin expression and cancer prognosis. Much effort has been made to determine the association between galectin

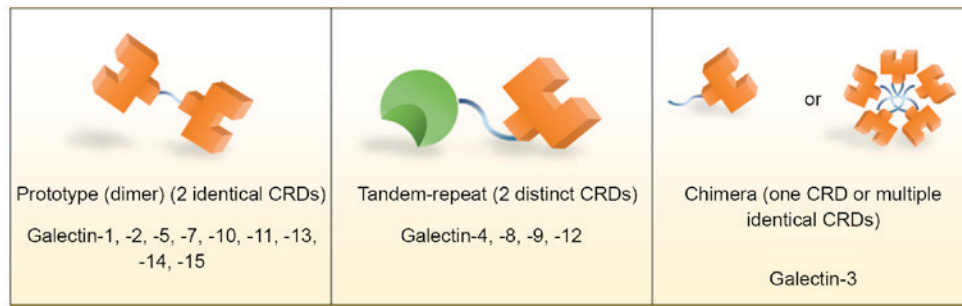


Figure 1. Classification of galectins into prototypical (dimeric), tandem-repeat and chimeric galectins. Prototypical (dimeric) galectins possess two identical CRDs. Tandem-repeat galectins possess two distinct CRDs. Chimeric galectins possess a single CRD, and may aggregate to form its common appearance with multiple identical CRDs. CRD, carbohydrate-recognition domains.

expression level and cancer prognosis. Irrespective of the cancer type, increased expression of galectin-1 is generally associated with poor overall and disease-free survival rates (7). By contrast, studies of galectin-3 for the prediction of cancer prognosis revealed various results, mostly depending on the cancer types. Increased expression of galectin-3 in brain cancer (32), acute myeloid leukemia (33) and colorectal cancer (34) is associated with poorer overall survival times and rates, while increased expression of galectin-3 is associated with improved survival rate in gastric cancer (19). In addition to predicting cancer prognosis, the levels of galectins are also associated with the stages and grades in different cancer types. A positive correlation between the expression level of galectin-1 and cancer stage has been observed in gastric cancer (35), ovarian cancer (36) and chronic lymphocytic leukemia (37). In colon cancer, the expression of galectin-3 has proven to be correlated with the stage of colon cancer (38). A positive correlation between the expression of galectin-3 and tumor grade has also been reported (39).

Galectins as diagnostic biomarkers. As aforementioned, cancer typically exhibits altered galectin expression. Since galectins are secreted, their circulating levels may be taken as useful biomarkers to predict the presence of malignancies. For example, a previous study revealed that serum galectin-1 levels were increased in patients with lung cancer compared with healthy subjects, as well as increased mRNA expression levels of galectin-1 in tumor sections compared with non-tumor sections (40). The circulating levels and tissue levels of galectin-1 and -3 are increased in thyroid cancer patients (41), with similar results observed in clinical cases such as that for galectin-3 expression in melanoma (42) and galectin-8 expression in breast cancer (28). However, a study of thyroid tumors has demonstrated a dissociation between circulating galectin levels and tissue galectin levels (43). These observed discrepancies in the literature may be due to a number of reasons, including the non-classical secretion pathways of galectins and the abnormal activity of cellular signaling pathways in tumor cells (7).

Galectins as biomarkers for prognosis and treatment response. Circulating galectins may also be useful biomarkers for predicting cancer prognosis and treatment response. For example, in Hodgkin's lymphoma, the circulating galectin-1 expression level is well correlated with tumor burden, clinical

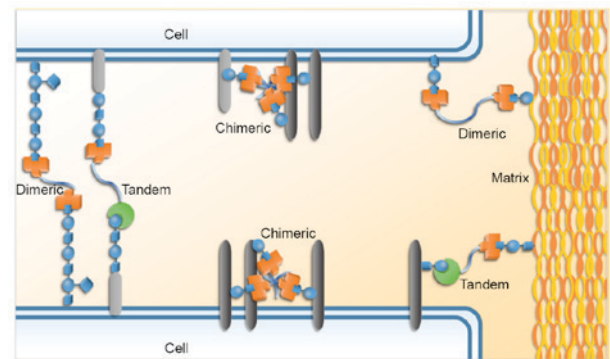


Figure 2. Galectins are able to mediate cell-cell and cell-matrix interactions, and thereby modulate signaling pathways and influence cellular behavior.

staging and other prognostic markers (44). Similarly, circulating galectin-3 expression level is a valuable prognostic marker in patients with advanced melanoma (45). In breast and gastrointestinal cancer, serum galectin-3 expression level is significantly different between patients with metastatic and non-metastatic diseases (46). In colon cancer, serum galectin-3 and galectin-4 expression levels are distinct between patients with metastatic and non-metastatic disease (47).

Serum galectins are also useful for monitoring therapeutic response in patients with cancer. In a previous study, serum galectin-3 expression level decreased significantly following surgery in patients with pancreatic cancer (48). Serum levels of galectin-1, -3 and -4 were increased in patients with colorectal cancer, and their serum levels of galectin-1 and -4 decreased significantly following curative surgery (49). In head and neck squamous cell carcinoma, galectin-1 and galectin-3 also decreased following surgical and chemotherapeutic treatments (50).

Taken together, circulating galectin levels may be potential biomarkers for detecting cancer, and for predicting disease prognosis and therapeutic efficacy (7).

4. Roles of galectins in lung cancer

Overview. Lung cancer is one of the most common types of cancer, as well as being the leading cause of cancer-associated mortality worldwide (51,52). Lung cancer is classified as either non-small cell lung cancer (NSCLC) or SCLC. NSCLC is traditionally classified into squamous cell carcinoma, large

Table I. Effects of each galectin identified to affect lung cancer progression.

Galectin	Type	Effects in lung cancer (Reference)
Galectin-1	Dimeric	Galectin-1/interleukin-10 functional axis may be an important regulator in lung cancer-mediated immune suppression (40). Upregulates and promotes migration and invasion (54). Lymph node metastasis of lung cancer (54). Mediates tumor progression and chemoresistance of non-small cell lung cancer (55).
Galectin-3	Chimeric	Enhances lung cancer adhesion to extracellular matrix components, cell motility and <i>in vitro</i> invasiveness (56). Promotes cancer stem cell formation, chemoresistance, tumorigenicity, tumor initiation and sphere-forming capacity (57). Promotes epidermal growth factor receptor activation and enhances lung cancer stemness through the EGFR/c-Myc/Sox2 axis (58).
Galectin-4	Tandem	Expressed in the cytoplasm, nucleus and membrane of lung adenocarcinomas (27). May be an independent predictor for lymph node metastasis (27).
Galectin-7	Dimeric	May be associated with the metastasis of other types of cancer to the lung (59).
Galectin-8	Tandem	Associated with metastatic progression of lung cancer (60).
Galectin-9	Tandem	Suppresses pulmonary metastasis by tumor cell, tumor attachment and tumor invasion (61). Promotes activation of natural killer cells (62).

cell carcinoma, adenocarcinoma and other less frequently observed cell types (53). Although NSCLC is often attributed to cigarette smoking, adenocarcinoma is often observed in individuals who have never smoked. Numerous compounds and molecular mechanisms are involved in the formation and progression of lung cancer; as for other cancer types, galectins serve important roles in these processes (6). Previous studies have demonstrated that galectin-1, -3, -4, -7, -8 and -9 are associated with lung cancer (Table I) (27,40,54-62), whereas the roles of galectin-2, 5, -6, -10, -11, -12, -13, -14 and -15 in lung cancer are, to the best of our knowledge, yet to be investigated.

Galectin-1. Galectin-1 was the first identified galectin and it is overexpressed in numerous types of cancer, including lymphoma, astrocytoma and melanoma, as well as oral, colon, liver, pancreatic, bladder and ovarian cancers (63). A previous study demonstrated that the galectin-1/IL-10 functional axis may be an important regulator in lung cancer-mediated immune suppression (40). Galectin-1 is an immune modulator of the development of monocytes, which is controlled via IL-10 and granulocyte-colony stimulating factor (64). Galectin-1 is overexpressed in highly-invasive lung cancer cell lines and is important in promoting lung cancer cell invasion and migration (5). Galectin-1 derived from lung cancer modifies dendritic cells to produce mitogenic and pro-invasive factors, which subsequently promote tumorigenic potentiation of dendritic cells by expressing heparin-binding epidermal growth factor (EGF)-like growth factor (65). Galectin-1 also possesses the potential to be a prognostic marker in early-stage NSCLC (66). Patients with tumors exhibiting increased galectin-1 expression experience poorer clinical outcomes (67). Galectin-1 is upregulated in CD133⁺ lung adenocarcinoma cells, occasionally designated as cancer stem cells, which promotes the growth of CD133⁺ lung

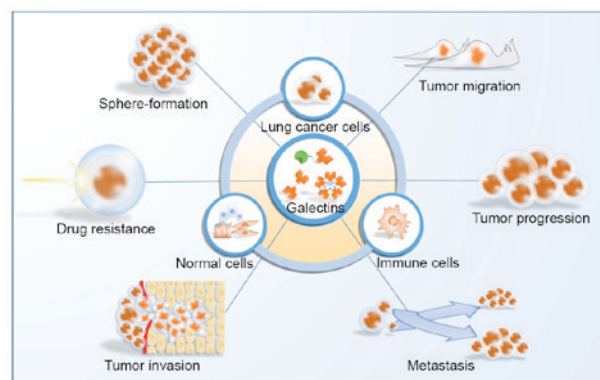


Figure 3. Roles of galectins in lung cancer. Galectins affect the progression of lung cancer in multiple aspects, including tumor migration, tumor progression, metastasis, tumor invasion, drug resistance, sphere-formation and the interactions between cells in the tumor microenvironment.

adenocarcinoma (54). Serum galectin-1 level is positively correlated to the stage and prognosis of patients with lung adenocarcinoma (54), and has also been revealed to mediate the tumor progression and chemo-resistance of NSCLCs by activation of p38 mitogen-activated protein kinase, extracellular signal-regulated kinase and prostaglandin-endoperoxidase synthase 2 (55). In NSCLC, tumor-associated galectin-1 secretion mediates radiotherapy-associated systemic lymphopenia and may affect tumor progression (68).

Galectin-3. The role of galectin-3 in lung cancer has also been extensively studied. Expression of galectin-3 has been observed extensively in normal lung cells, including bronchial epithelial cells, chondrocytes of the bronchial cartilage, pneumocytes of the alveolar wall, alveolar macrophages and interstitial fibroblasts (69). NSCLC generally possesses

significantly increased galectin-3 expression compared with SCLC (3). Galectin-3 was found in extracellular and intracellular compartments of NSCLC; in squamous cell carcinoma, galectin-3 was primarily identified in the cytoplasm, whereas it was observed in the cytoplasm and nucleus in adenocarcinoma (3). Overexpression of galectin-3 in DLKP lung cancer cells enhances their adhesion to extracellular matrix components, increasing cell motility and invasiveness (56). Overexpression of galectin-3 in A549 cells promotes their sphere-forming capacity (a character of cancer stem cells), and suppression of galectin-3 in H1299 cells *in vitro* decreases the expression of stemness-associated genes, their sphere-forming capacity, tumorigenicity, chemo-resistance; *in vivo*, suppression of galectin-3 in H1299 cells also decreases tumor-initiating capacity in NOD/SCID mice (57). In Lewis lung carcinoma-bearing mice, increased expression of galectin-3 may promote the migration of myeloid-derived suppressor cells to the tumor microenvironment following exposure to cisplatin, contributing to the immuno-suppressive status of the tumor microenvironment (70). Galectin-3 may also be used as a prognostic marker; nuclear galectin-3 expression has been revealed as an independent predictive factor for the recurrence of NSCLC (55). Detection of galectin-3 and CD82 may be associated with the initiation, development and metastasis of NSCLC (71). Galectin-3 has also been demonstrated to promote EGF receptor activation in lung cancer, leading to the upregulation of sex determining region Y-box 2 expression and sphere formation (58).

Galectin-4. In contrast to its almost exclusive distribution in the cytoplasm of breast cancer and colon cancer cells, galectin-4 is extensively detected in the cytoplasm, nucleus and membranes of lung adenocarcinoma (72). In lung adenocarcinoma, the expression of galectin-4 is associated with clinicopathological variables of disease progression, including tumor size, nodal status, pleural or venous invasion, and tumor-node-metastasis staging, and may be an independent predictor for lymph node metastasis of intermediate power (27). Unlike gastric carcinoid tumors, which exhibited increased galectin-4 expression, a limited number of pulmonary carcinoids possessed decreased galectin-4 expression (73).

Galectin-7. With regard to cancer progression, galectin-7 has distinct functions in various types of cancer. Galectin-7 has been revealed to be associated with the sensitivity of human cervical carcinoma cells to chemotherapy-induced apoptosis (74). In melanoma, galectin-7 has been found in the primary site and the lung metastasis site (75). Although no convincing evidence has demonstrated that galectin-7 is directly associated with lung cancer, it may be associated with cancer metastasis to the lung; for example, it has been demonstrated to promote the bone and lung metastasis of breast cancer (59).

Galectin-8. Human galectin-8, encoded from the lectin galactoside-binding soluble 8 gene, has a variety of isoforms as a result of alternative splicing. Galectin-8 was initially isolated from the prostate [prostate carcinoma tumor antigen (PCTA)-1] and lung [Po66 carbohydrate-binding protein (Po66-CBP)] (76-78). PCTA-1 and Po66-CBP share 98.7%

of their amino acid sequence (79). Galectin-8 is widely expressed in normal tissue, as well as in tumor tissue (79); however, it is overexpressed in squamous cell carcinoma, with its expression level associated with the degree of tumor differentiation (76,80). Using cell-extracellular matrix microarrays, galectin-8, in combination with fibronectin, has been demonstrated to be associated with the metastatic progression of lung adenocarcinoma (60). The marked difference in galectin-8 expression levels between lung cancer cells and normal lung tissues may provide the opportunity to use monoclonal antibodies for preventing and treating lung cancer (79,81).

Galectin-9. A limited number of studies have investigated the role of galectin-9 in lung cancer, however, it has been widely studied in the field of immunity and inflammation. Increased cytoplasmic galectin-9 expression in tumor cells may suppress pulmonary metastasis and recurrence of malignant melanoma and breast cancer, which may be associated with the suppressive effect of galectin-9 on the attachment and invasion of tumor cells (61). Galectin-9 is also important in anticancer immunity. For example, galectin-9 has been revealed to increase T-cell immunoglobulin and mucin-domain containing (TIM)-3⁺ dendritic cells and CD8⁺ cytotoxic T cells, and to enhance anticancer immunity through its interaction with TIM-3 in MethA cell-bearing mice (82). In a study using Lewis lung carcinoma cell-bearing mice, galectin-9 was demonstrated to induce macrophage differentiation into plasmacytoid dendritic cell-like macrophages, which may augment the activation of NK cells that prolong the survival of tumor-bearing mice (62).

5. Conclusions and future perspectives

Each galectin possesses specific functions and is observed at distinct locations. Galectins serve important roles in cell survival, cellular proliferation, adhesion and migration (83), and they also participate in cell-cell and cell-matrix interactions (84). These characteristics may suggest that galectins may be an important component of the tumor microenvironment. The tumor microenvironment has been recognized as an important contributor to cancer progression, chemo-resistance (85), invasion and metastasis (86). The majority of galectins have been revealed to be associated with lung cancer, including galectin-1, -3, -4, -7 and -8, which are associated with the progression of lung cancer, while galectin-9 may decrease metastasis and enhance anticancer immunity. However, with the exception of galectin-1 and -3, the roles of galectins in lung cancer are not fully understood and require further investigation. The roles of galectins in lung cancer are much more complicated than suggested thus far, since numerous types of cell, particularly immune cells, in the tumor microenvironment may participate in their interactions (Fig. 3). Future studies to improve our understanding of the roles of galectins in the carcinogenesis, progression, invasion, metastasis and chemo-resistance of lung cancer are required in order to identify potential therapeutic targets for novel anti-cancer treatments.

Acknowledgements

The present study was supported by the Ministry of Science and Technology (grant no. MOST 104-2320-B-037-014-MY3) and the Kaohsiung Medical University 'Aim for the Top Journals Grant' (grant no. KMU-DT106005).

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