The role of galectins-1, 3, 7, 8 and 9 as potential diagnostic and therapeutic markers in ovarian cancer (Review)

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Abstract. The incidence of ovarian cancer is increasing, particularly throughout the highly developed countries, while this cancer type remains a major diagnostic and therapeutic challenge. The currently poorly recognized lectins called galectins have various roles in interactions occurring in the tumor microenvironment. Galectins are involved in tumor-associated processes, including the promotion of growth, adhesion, angiogenesis and survival of tumor cells. Results of research studies performed so far point to a complex role of galectins-1, 3, -7, -8 and -9 in carcinogenesis of ovarian cancer and elucidation of the mechanisms may contribute to novel forms of therapies targeting the proteins. In particular, it appears important to recognize the reasons for changes in expression of galectins. Galectins also appear to be a useful diagnostic and prognostic tool to evaluate tumor progression or the efficacy of therapies in patients with ovarian cancer, which requires further study.

Contents

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1. Introduction

Ovarian cancer has been the greatest challenge in gynecological oncology, constituting a group of heterogeneous and rapidly progressing neoplasm with high mortality, the pathogenesis of which has remained to be fully elucidated (1,2). The major subtypes of ovarian cancer are high-grade serous carcinoma, endometrioid carcinoma, clear cell carcinoma, low-grade serous carcinoma and mucoid carcinoma.

Immunological response disorders have an important role in the course of such malignancies, involving the so far poorly recognized lectins called galectins (3,4). Galectins have been the focus of multiple studies, basically due to their substantial role in numerous physiological processes as well as pathologies, e.g. apoptosis, angiogenesis, adhesion, immunological and inflammatory response, as well as the formation and progression of certain neoplastic lesions (5,6). Various studies also indicated that certain galectins may potentially serve as diagnostic and prognostic markers, rendering them targets of anticancer therapies (7-10). Therefore, the major objective of the present review was to discuss the role of selected galectins and their possible clinical applications in ovarian cancer.

The following galectins have been observed to take a significant role in the formation and progression of ovarian cancer: Galectin-1, 3, 7, 8 and 9.

2. Galectin-1

Galectin-1, encoded by the LGALS1 gene located on chromosome 22q12, is a 14 kDa monomer or a non-covalent homodimer with one conserved carbohydrate-recognition-binding domain (CRD) per subunit. The presence of more than one CRD in the homodimer makes it suitable for mediation of cell adhesion, triggering the intracellular signaling and forming multivalent lattices with the cell surface glycoconjugates. In the extracellular matrix (ECM), homodimers are able to link several membrane receptors, therefore facilitating cell signaling and cell-cell interactions, which allows for homotypic and heterotypic aggregation (11).

Galectin-1 takes a substantial part in both physiological and pathological processes. Expression of galectin takes place in multiple tissues, usually in the skeletal muscle cells, the

thymus gland, lymph nodes, neurons, the kidneys, the skin and the placenta, where it is present both intracellularly and extracellularly in the stroma of such organs. The extracellular effect of that protein is closely associated with the CRD activity through their effect on neutrophil surface receptors, as well as components of the extracellular matter, such as integrin, laminin, cancer fetal antigen, fibropontin, osteopontin, thrombospondin and vitronectin (12-14). Extracellular galectin-1 has a molecular weight (~15 kDa) that is slightly higher than the 14 kDa form found in cell lysates, suggesting that the secreted galectin-1 undergoes further post-transitional modifications prior to or after secretion (15). It was demonstrated that extracellular 15 kDa galectin-1 was able to bind cell surfaces at specific locations. Since galectin-1 lacks the required signaling peptide for secretion, it was suggested that post-translational modifications, resulting in a high molecular mass of galectin-1, were required for galectin-1 to be exported to the extracellular compartment (15). The intra cellular protein is found in the nucleus, cytoplasm and the inner leaflet of the cytoplasmic membrane and, similar to other members of this family, secreted into the extracellular space despite the lack of the signaling sequences required for secretion via the standard endoplasmic reticulum/Golgi pathway (16).

Galectin-1 is an anti-inflammatory protein, inhibiting the synthesis of pro-inflammatory cytokines, affecting migration and function of neutrophils, eosinophils, macrophages and dendritic cells as well as inhibiting the degranulation of mast cells. Likewise, the lectin controls T-cell and B-cell compartments by modulation of the receptor clustering and signaling, therefore taking the role of a negative-regulatory checkpoint to reprogram the cellular activation, differentiation and survival (17). Under physiological conditions, that protein promotes apoptosis of the activated, yet not resting immune cells (18,19), with a notable exception of resting T cells, which are sensitized to CD95/Fas-mediated cell death (20). Galectin-1 also induces phosphatidyl-serine externalization with no associated apoptosis (21,22). Furthermore, galectins may cross-link glycosylated proteins, leading to signal transduction and direct cell death or activation of other signals regulating cell fate (13,23). Apoptosis of activated (antigen-primed) T-cells is induced by galectin-1 in a CD45-dependent manner, while T-cell homeostasis may be regulated by galectin-1 through inhibition of clonal expansion and induction of apoptosis. Activated T-cell apoptosis induced by galectin-1 is caspase-8- and -9-dependent (24). Of note, the activated T-cells alone may produce galectin-1 through the MEK1/ERK, p38 MAP kinase and p70S6 kinase signaling pathways, suggesting an autocrine suicide mechanism used to terminate the effector immune response (25). This glycan-binding protein inhibits the immune effector functions by shifting the balance towards a type 2 T-helper (Th2) cytokine profile (26,27), through selective deletion of Th1 and Th17 cells (28) and by promotion of differentiation of tolerogenic dendritic cells (29-31). Furthermore, the protein facilitates the expansion of IL-10-producing T regulatory type-1 cells (32) and contributes to immunosuppressive activity of $CD4^+CD25^+FoxP3^+$ T regulatory (Treg) cells (33,34). Galectin-1 also affects the humoral response, promoting maturation and differentiation of B lymphocytes in the bone marrow and stimulating the secretion of antibodies (13). In such cases, galectin-1 secreted by the bone marrow stromal cells, supports B-cell differentiation through pre-B cell receptor (BCR) activation and signaling (35,36). Furthermore, using an *in vitro* model of lipopolysaccharide-activated B cells, Tsai *et al* (37) determined that splenic plasma blasts expressed galectin-1 in a Blimp-1 dependent manner. They also indicated that ectopic expression of galectin-1 in mature B cells increased the immunoglobulin transcripts and secretion (Fig. 1).

Role of galectin-1 in ovarian cancer. Chen *et al* (38) indicated a relation between the increased expression of galectin-1 and elevated migration of cancer cells and tumor invasiveness in epithelial ovarian cancer (EOC). High expression of that protein correlated positively with the Internal Federation of Gynecology and Obstetrics (FIGO) staging and more frequent relapse of the disease. Galectin-1 expression is associated with activation of transcription factor NF-κBp65, resulting in poor prognosis in ovarian cancer. Activation of the NF-κBp65 signaling pathway results in elevated expression of matrix metalloproteinases (MMPs), MMP-9 and MMP-2 in particular. The activity of such ECM-degrading MMPs enhances malignant metastasis. However, the migratory and invasive abilities were significantly reduced after galectin-1 knockdown in the human EOC cell line HO8910, which was accompanied by suppressed NF-κB pathway activation and downregulation of MMP-2 and MMP-9 (38). This suggests that lower expression of galectin-1 inhibits activation of the NF-κBp65 signaling pathway, reduces the expression of MMPs and also restricts the metastatic capacity of the cancer cells (38).

Zhang *et al* (39) also evaluated the expression of galectin-1 in EOC. They indicated that elevated expression of this protein correlated positively with the cancer stage, which may promote growth, migration and invasion of the ovarian cancer cells, as well as their resistance to cisplatin. Galectin-1 was able to upregulate c-Jun, MMP-9, Bcl-2 and p21 expression, possibly through activation of H-Ras/Raf/ERK pathway. That protein also may be considered a potential therapeutic target to delay EOC progression and to increase sensitivity to cisplatin.

A study was performed by Kim *et al* (40), who evaluated the effect of galectin-1 expression and its functional role in cell proliferation and invasion in EOC. They observed that no expression of galectin-1 was present in normal ovarian tissues, while the protein was expressed in EOC tissues. Furthermore, the study revealed that galectin-1enhanced the proliferation and invasion of cancer cells. It was also demonstrated that treatment of EOC cells with galectin-1 short interfering (si)RNA and anginex inhibited cell proliferation and invasion *in vitro*. These results suggest that high galectin-1 expression may be a prognostic marker of EOC and that galectin-1 may be a potential therapeutic target to decrease tumor aggressiveness.

Furthermore, Schulz *et al* (41) analyzed galectin-1 expression in females with ovarian cancer. The patients with overexpression of galectin-1 in the cytoplasm and extracellularly had shorter overall survival, while higher expression of galectin-1 in the cytoplasm only was associated with higher metastatic potential of the cancer cells. Elevated expression of galectin-1 was present in both, the cell nucleus and cytoplasm of the ovarian cancer cells, as well as within the tumor stroma. The clinical significance of serum galectin-1 expression in patients

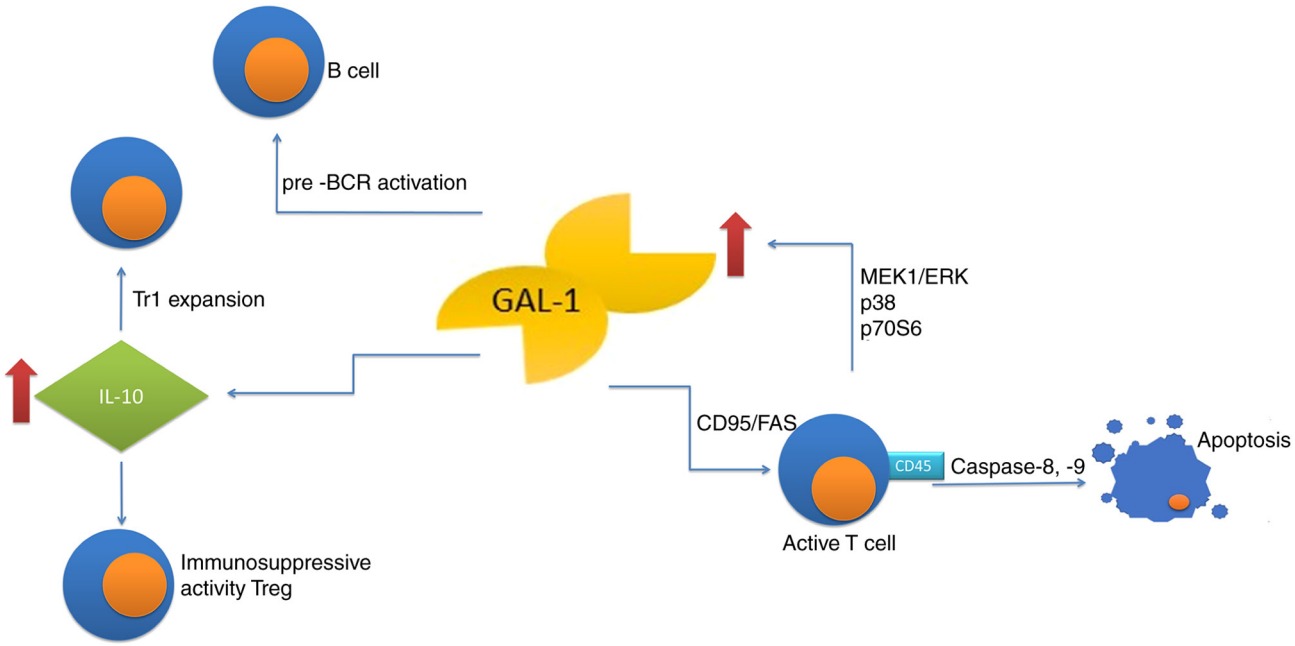

Figure 1. Role of galectin-1 in the inflammatory response. Based on (20,26,36,37). GAL-1, galectin-1.

with the EOC was evaluated by Chen *et al* (42). The authors reported increased galectin-1 expression in EOC, emphasizing the clinical significance of galectin-1 expression in sera and cancer-associated stroma, which may contribute to cancer progression.

Galectin-1 may be a key factor in the interaction of the tumor stroma with EOC where detection of increased serum galectin-1 in certain patients with cancer may reflect various aspects of the biological behavior of the tumor associated with a metastatic phenotype. Further studies are required to determine the clinical value of circulating galectin-1 in patients with early-stage cancer to be used as a predictor of tumor invasion and metastasis. The results of the previous studies suggested the role of galectin-1 as a novel prognostic and progressive biomarker in patients with EOC. Of note, Abdelwahab *et al* (43) evaluated the serum concentration of galectin-1 and its expression in patients with different stages of serous type ovarian cancer (SOC) in an attempt to define its value as a diagnostic and prognostic marker. The results indicated that the serum levels of galectin-1 were significantly associated with the FIGO stage of SOC ($P<0.001$) and were higher in stage III/IV as compared to stage I. Immunohistochemical staining indicated that high expression of galectin-1 was more frequent in patients with advanced stage as compared to the early stages, as it was present in 37.5, 50, 68.8 and 83.3% of cases in stage I, II, III and IV, respectively. These results support the usefulness of galectin-1 immunohistochemical expression in peri-tumoral cells as a prognostic biomarker of successful treatment or possible chemotherapeutic resistance. The results may suggest that galectin-1 is overexpressed in serum and tumor tissues of patients with SOC upon progression of the disease; this may support its usefulness as a non-invasive biomarker for diagnosis and prognosis of such patients (43).

Galectin-1 expression may be a potential prognostic marker, the value of which may depend on cell localization. Furthermore, evaluation of serum concentrations of this protein may serve as a novel, non-invasive biomarker in the diagnosis and prognosis of the therapeutic outcome.

3. Galectin-3

Galectin-3 is among the best recognized lectins with a chimeric structure. The coding gene LGALS3 is localized on chromosomes 1p13 and 14q21-22 (44,45) and the mass of this protein is 29-35 kDa. A characteristic feature is the presence of C-terminal domain recognizing carbohydrates (CRD), composed of ~130 amino acids and an N-terminal domain. The C-terminal domain frequently has the following sequence: Asparagine, tryptophan, glycine, arginine (NWGR). This chain is responsible for the anti-apoptotic activity of galectin-3, where the structural changes prevent the binding of galectin by the CRD domain (46). The CRD domain has a β-sandwich structure composed of 11 β strands: β1-β11 positioned antiparallel to each other. The β1, β3-6 and β10 strands form a sugar binding surface, the S-face, while the remaining five, namely β2, β7-9 and β11, form an antiparallel surface, the F-face (7). CRD contains the death domain (anti-death motif, NWGR), conditioning the anti-apoptotic functions of galectin-3 and BCL-2 and the effect of the protein with BCL-2 proteins. NGWR, i.e. the sequence aspartate-tryptophan-glycine-arginine, is highly conserved, while substitution of glycin with alanine reduces the anti-apoptotic effect of galectin-3 (47,48). The N-terminal domain (NTD) contains a region composed of multiple repetitions of glycine, proline, tyrosine and alanins referred to as a collan-like sequence, as well as a short NH_2-terminal region composed of 12 amino acids, which is the site of phosphorylation. NTD contains sites sensitive to the effects of MMP-2 and MMP-9, for which it is an endogenic substrate. Structural changes in the NTD inhibit the expression of galectin-3 and the anti-apoptotic effect of the protein. The NTD structure makes it possible for galectin-3 to form pentamers thanks to which galectin forms networks with glycoproteins and glycolipids (48-50).

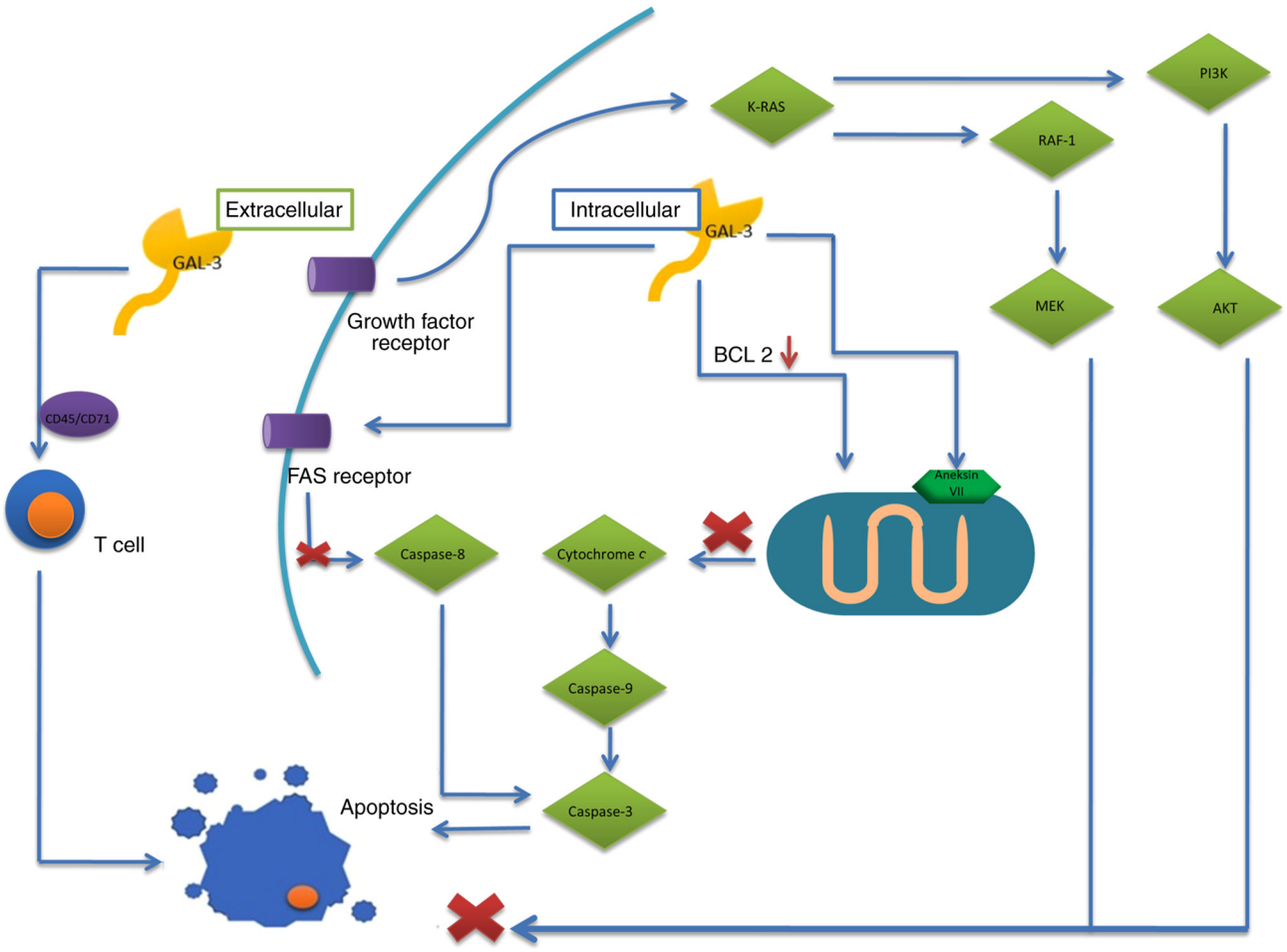

Figure 2. Role of galectin-3 in the inflammatory response. Based on (48,49,57,58). GAL-3, galectin-3.

The expression of this protein was proven in monocytes, macrophages, neutrophils, fibroblasts, activated T lymphocytes, eosinophils, basophils, mast cells, epithelial cells of the respiratory system, the kidneys, the alimentary tract as well as cancer cells, where the level of expression of this protein was associated with progression, invasion and the metastatic ability of the cells (51,52). The presence of galectin-3 is both intracellular-in the cytoplasm, mitochondria, the cell membrane and nucleus, as well as extracellular, which depends on its biological function (53). Acting together with its ligands, galectin-3 has different biological roles, such as cell growth regulation, pre-mRNA folding, effect on differentiation, transformation and cell motility, transduction of the cell signal, inhibition or induction of apoptosis, as well as modulation of the body's immunological response (41,54). It has a role in the formation of tumors and metastasis through upregulation of proliferation, cell migration, angiogenesis, apoptosis and adhesion (49,53). Galectin-3 has diverse effects on apoptosis, depending on the localization of this protein: In the cytoplasm the effect is anti-apoptotic, while if located extracellularly, it exerts apro-apoptotic effect. The anti-apoptotic effect of this galectin results, among others, from phosphorylation and dephosphorylation at theSer^6 position and the presence of NWGR (7,47). The galectin directly affects the anti-apoptotic proteins, members of the BCL-2 family, the activation of which prevents the expression of cytochrome *c* and leads to inhibition of apoptosis. It has also been observed that reduced cell expression of galectin-3 resulted in lower concentrations of BCL-2, therefore increasing the pro-apoptotic potential (48,55). In addition, the effect of galectin-3 on annexin VII, a protein reversibly binding calcium ions and phospholipids, leads to inhibition of the release of cytochrome *c* from the mitochondrion due to the transport of nuclear galectin-3 into the region of perinuclear mitochondria (7). Another mechanism to inhibit apoptosis is the binding of cytoplasmic galectin-3 with CD95/Fas receptor, leading to inhibition of caspase-8 activity and the pro-apoptotic cascade. That protein also binds to activated K-RAS, enabling activation of the anti-apoptotic survival pathways K-RAS/PI3K/Akt and K-RAS/Raf-1/MEK (47,55). On the other hand, the pro-apoptotic effect of galectin-3 includes, among others, the influence on T lymphocytes. Extracellular galectin-3 affects receptors CD45 and CD71, inducing apoptosis in human T lymphocytes. When present within T lymphocytes, that protein has an anti-apoptotic effect, promoting cell growth and enhancing TCR signaling (56). Galectin-3 influences cell adhesion through binding of glycoproteins occurring on the cell surface, e.g. integrins and cadherins. Initiation of a signaling pathway enables adhesion of cancer cells to the stroma (Fig. 2) (48). Galectin-3 also facilitates neo-angiogenesis, primarily through VEGF and basic fibroblast growth factor, as well as modified N-glycans

on integrin αvβ3. By activating the signaling pathways dependent on cytoplasmic tyrosine kinase, focal adhesion kinase, it modulates the migration of the endothelial cells (55).

Role of galectin-3 in ovarian cancer. The results obtained so far when evaluating the expression of galectin-3 in ovarian cancer are contradictory, indicating both elevated or reduced expression of the protein, as compared to its expression in normal ovarian tissue. Lee *et al* (57) evaluated the expression of galectin-3 in ovarian cancer. Their results indicated that the expression of galectin-3 was higher in clear cell carcinoma as well as serous and mucous tumors than in endometrial and transient ones. However, no differences in galectin-3 expression among benign, borderline, malignant mucous and serous tumors were obtained. Various noteworthy observations were also made by Kim *et al* (58), who evaluated the clinical role of galectin-3 expression in patients with EOC and its functional role in the proliferation of an ovarian cancer cell line. The results pointed to an increased expression of galectin-3 in the EOC with the absence of expression of this protein in normal ovarian tissues. Furthermore, elevated expression of galectin-3 was associated with shorter progression-free survival (PFS). The studies suggested that galectin-3 expression maybe a prognostic factor for PFS and may be involved in the regulation of the response to paclitaxel (PTX)-based chemotherapy in the treatment of EOC. Similarly, Brustman (59) analyzed the expression of the epidermal growth factor receptor (EGFR), galectin-3 and cyclin D1 in a cohort of patients with ovarian serous carcinomas with regard to outcome and clinicopathological parameters. Evaluation of EGFR and cytoplasmic galectin-3 immunohistochemically indicated that testing for multiple markers maybe an adjunct in the identification of high-risk ovarian serous cancers.

A study by Lu *et al* (60) revealed that inhibitors of the NF-κB pathway did not affect galectin-3 expression levels in ovarian cancer cells. That protein was able to regulate the migratory and invasive capabilities of cancer cells, as well as chemosensitivity to carboplatin in EOC. The results indicated that galectin-3 may be a potential novel therapeutic target in different types of ovarian cancer and may have a role in chemosensitivity to common chemotherapeutic drugs.

Kang *et al* (61) reported that overexpression of the gene LGALS3 increased the ovarian cancer cell invasion, migration and proliferation, while silencing of that protein with specific siRNA reversed these biological effects. The Notch signaling pathway was strongly activated by galectin-3 overexpression in A2780 cells. Silencing of galectin-3 reduced the levels of cleaved NICD1 and expression of the Notch target genes, Hes1 and Hey1. Thus, galectin-3 may be a potent target for regulating Notch1 signaling as a therapeutic strategy for ovarian cancer. In an endeavor to develop innovative and efficient therapies, Mirandola *et al* (62) generated a truncated, dominant-negative form of galectin-3, namely galectin-3C and applied it to ovarian cancer cell lines; furthermore, primary cells were established from patients with ovarian cancer. The results indicated that galectin-3C significantly reduced the growth, motility, invasion and the angiogenic potential of the cultured ovarian cancer cell lines and primary cells established from patients with ovarian cancer. Eliaz (63) presented a case of stage IV ovarian cancer for whom underlying pro-inflammatory comorbidities and the concentration of galectin-3 were monitored throughout the therapy. Initially, the patient's inflammatory condition was treated with an intensive integrative anti-inflammatory protocol using a combination of oral and intravenous nutrients and botanicals, along with pharmaceutical intervention. This was followed by a standard course of chemotherapy supported by an individualized integrative protocol. Galectin-3 levels as well as other inflammatory and tumor markers were monitored throughout the course of treatment. This case report was the first to demonstrate the clinical use of galectin-3 and its potential ability to reflect changes in both the cancer status and the inflammatory state of the patient. For the first time, galectin-3 was used to assess and monitor the patient's progress. However, the literature available fails to provide any explicit evidence of the role of galectin-3 as a marker and promotor of an inflammatory condition or cancer progression. The author emphasized the requirement of further studies, which should encourage clinicians to include the evaluation of the galectin-3 concentration in their therapy monitoring schemes. This may provide a valuable marker with significant prognostic potential that may be used to monitor the inflammatory condition, the tumor progression and response to treatment.

Hossein *et al* (64) sought to determine the role of galectin-3 in the chemo-resistance of the human ovarian cancer cell line SKOV-3 to PTX, where recombinant human (rh)galectin-3 and PectaSol-C modified citrus pectin (Pect-MCP) as a specific competitive inhibitor of galectin-3. The results indicated a 41% increase in cell proliferation, a 36% decrease in caspase-3 activity and a 33.6% increase in substrate-dependent adhesion in the presence of rhgalectin-3, as compared to the control case ($P<0.001$). The treatment of cells with a non-effective dose of PTX (100 nM) and 0.1% Pect-MCP in combination revealed a synergistic cytotoxic effect with cell viability reduced by 75% and a subsequent 3.9-fold increase in caspase-3 activity. Thus, inhibition of galectin-3 appears to be a useful therapeutic tool for combined therapy of ovarian cancer. In their subsequent study, Hossein *et al* (65) attempted to determine the relationship between STAT3 activity and galectin-3 and investigated the cytotoxic effect of Pect-MCP as a specific competitive inhibitor of galectin-3 in combination with PTX to kill SKOV-3 ovarian cancer cell multicellular tumor spheroids (MCTS). That study was the first to demonstrate enhanced STAT3 phosphorylation upon addition of exogenous galectin-3 to ovarian cancer cells. Furthermore, the study revealed that both the increased level of galectin-3 expression and STAT3 phosphorylation were associated with MCTS size. The authors also proved that galectin-3-mediated STAT3 phosphorylation was abrogated or reduced in the presence of PTX + Pect-MCP in an MCTS size-dependent manner. Higher expression of galectin-3 in MCTS maybe related to PTX resistance through the increased phosphorylated (p-)STAT3 levels and hypoxia-inducible factor-1α may further increase galectin-3 expression levels. For the first time, it was demonstrated that Pect-MCP may be considered as a potential drug to enhance the effect of PTX on ovarian cancer cell MCTS through inhibition of STAT3 activity. Cai *et al* (66) investigated the effect of galectin-3 on Toll-like receptor 4 (TLR4) signaling and thus PTX resistance and identified associations between serum galectin-3 levels or TLR4 expression and a PTX resistance phenotype. *In vitro* treatment with exogenous

galectin-3 restored cell survival and migration of SKOV-3 and ES-2 cells, which was decreased by galectin-3 silencing and PTX treatment. Furthermore, the protein suppressed the interaction between TLR4 and caveolin-1 (Cav-1) in SKOV-3 and ES-2 cells. In addition, overexpression of Cav-1 dampened the expression of MyD88 and p-p65 stimulated by galectin-3 and enhanced apoptosis in SKOV-3 cells under PTX exposure. The results indicated that exogenous galectin-3 may induce PTX resistance through TLR4 signaling activation by inhibiting the TLR4-Cav-1 interaction (66). Wang *et al* (67) related the mitochondrial function in galectin-3-mediated regulation to cisplatin resistance in ovarian cancer OVCAR-3 cells. The study indicated that cisplatin-promoted cytochrome *c* release from mitochondria, mitochondrial reactive oxygen species and superoxide were markedly inhibited by galectin-3 overexpression, while they were aggravated by galectin-3 knockdown. The cisplatin-downregulated MMP was also blocked by galectin-3 overexpression, while it was deteriorated by galectin-3 knockdown. It was suggested that galectin-3 inhibits the sensitivity of human EOC OVCAR-3 cells to cisplatin via inhibition of cisplatin-mediated growth reduction, induction of apoptosis and dysfunction of the mitochondria. This implies that galectin-3 maybe an effective target to sensitize ovarian cancer cells to chemotherapy.

Various noteworthy observations were made by Bieg *et al* (68) who assessed whether morin, a natural flavonoid, and a recognized NF-κB inhibitor are able to sensitize ovarian cancer cells to cisplatin through suppressed expression of galectin-3. They indicated that morin exhibited antineoplastic activity towards the ovarian cancer cell lines TOV-21G and SKOV-3 in terms of reduced cell viability and proliferation, as well as increased induction of apoptosis. Morin sensitized ovarian cancer cells TOV-21G and SKOV-3 to cisplatin, which was associated with lower expression of galectin-3. Of note, combined treatment with selected concentrations of morin and cisplatin had a synergic effect; morin sensitized the cells to cisplatin, which may be used to reduce the required therapeutic dosage in the future.

Another study by Bieg *et al* (69) reported that miR-424-3p suppressed galectin-3 expression and sensitized ovarian cancer cells to cisplatin. They indicated that miR-424-3p mimics sensitized the ovarian cancer cell lines TOV-21G and SKOV-3 to cisplatin through decreased expression of galectin-3. The authors suggested miR-424-3p as a useful candidate for combined treatment with cisplatin.

The role of galectin-3 expression in different malignancies remains controversial. However, it appears that galectin-3 maybe a promising target to develop novel diagnostic and therapeutic strategies in oncology.

4. Galectin-7

Galectin-7 is a protein with a molecular weight of 15 kDa; it is a member of the prototype galectin subgroup, encoded by the LGALS7 gene localized on chromosome 19q13.2 (70,71). It occurs as a monomer or a symmetric homodimer, the structure of which is stabilized by electrostatic activity between two monomers (7). As a monomer, galectin contains one conserved CRD and the homodimer contains two identical CRDs (72). Contrary to galectin-1 and galectin-3, galectin-7 has high tissue specificity. The expression is manifested in the heart muscle cells, epithelium of the alimentary system, fetal tissues, skin keratinocytes and other epithelial tissues (70,73). Similar to other galectins, galectin-7 has a role in the proliferation, adhesion, migration, apoptosis and modulation of the immunological system response. Galectin-7 has an oncogenic effect; however, in certain tumor types, it may also have an anti-carcinogenic role. It is suggested that increased expression of galectin-7 in cancer is induced by a muted form of p53 suppressor protein, which is present in certain types of tumor (41,74). Higher expression of galectin-7 might be involved in the regulation of carcinogenesis, contributing to the induction of apoptosis in tumor infiltrating T cells, both $DC4^+$ and $CD8^+$ as well as in regulation associated with macrophages, NK cells and dendritic cells (74,75).

Galectin-7 also contributes to increased migration of cancer cells, which is associated with reduced cell adhesion, through enhancing the activity of MMP-2 and MMP-9; this contributes to tumor progression and distant metastasis. Recent studies highlight the importance of the relationship between galectin-7 and p53 (76). The signaling pathways affected by galectin-7 to enhance proliferation, migration and invasiveness of cancer cells, are associated with kinases activated by mitogens through increasing the phosphorylation of ERK1/2 and JNK1/2 (77). The greater capacity of cancer cells to migrate is associated withgalectin-7-induced expression of the COL4α1 gene encoding chain α of type IV collagen and intracellular adhesion molecule 1 (71). It also activates the signaling pathway associated with serine-threonine kinase Akt and its effector, PI3K. The PI3K/Akt pathway has a particular role in neoplastic diseases, enhancing the viability and proliferation of cancer cells (Fig. 3) (70,78).

Role of galectin-7 in ovarian cancers. The studies performed so far focused primarily on the role of galectin-1 and -3 in ovarian cancer, while investigations regarding the role of galectin-7 in such malignancies have been scarce. The first to come was a study by Kim *et al* (79) who evaluated the prognostic significance of galectin-7 in patients with EOC and its functional role in cell proliferation in an ovarian cancer cell line. The results pointed to upregulated galectin-7 expression as compared to normal ovarian tissues, as well as an association of high galectin-7 expression with older age, high mortality and poor overall survival outcome. Furthermore, the residual tumor volume was larger in the high-expression group as compared to the low expression group. As indicated by *in vitro* results, knockdown of galectin-7 expression by using its siRNA inhibited proliferation of the tumor cells. High galectin-7 expression was suggested to be related to poor prognosis in EOC and that protein may have a possible functional role in cell proliferation. Future studies should address the potential use of galectin-7 as a useful therapeutic target in the treatment of EOC. Labrie *et al* (74) evaluated the expression of galectin-7 in EOC cells. Immunochemical analysis of galectin-7 expression in a tissue microarray suggested no presence of that protein in normal ovarian tissues; however, galectin-7 was present in the epithelial cells of all histological EOC subtypes, where expression in malignant tumors was significantly higher. The results indicated that elevated expression of galectin-7 was associated with tumor progression through increased invasiveness

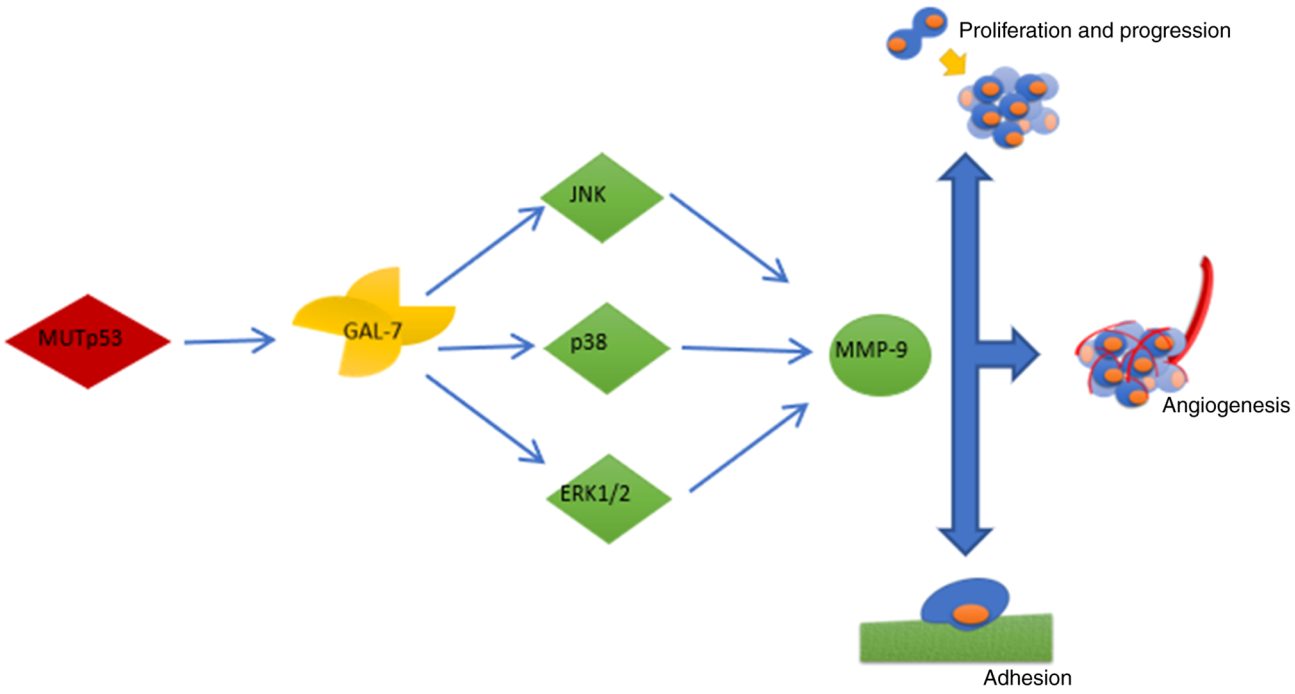

Figure 3. Role of galectin-7 in the inflammatory response. Based on (78,79). GAL-7, galectin-7.

of the cancer cells and a pro-apoptotic effect on cells of the immunological system. The authors pointed to the clinical significance of galectin-7 overexpression in ovarian cancer and provided a rationale for targeting galectin-7 to improve the clinical outcome (74). Furthermore, Bibens-Laulan and St-Pierre (80) evaluated the expression of that protein in ovarian and breast cancer. Their results suggested that targeting extracellular galectin-7 with either CRD-specific inhibitors or dimer-disrupting peptides may be more efficient for targeting intracellular galectin-7-mediated interactions than previously expected. The study indicated that extracellular galectin-7 controlled the intracellular pool of galectin-7. It does so via two distinct, yet complementary mechanisms: First, by increasing the transcriptional activation of LGALS7 gene transcription, and furthermore, via re-entry into the cells. Schulz *et al* (41) confirmed cytoplasmic galectin-7 expression as a negative prognostic factor for ovarian cancer. Galectin-7 may thus be a novel, promising and specific therapeutic target for EOC.

5. Galectin-8

Galectin-8 is a 'tandem-repeat'-type galectin, which contains two carbohydrate recognition domains connected by a linker peptide. The complexity of galectin-8 is related to the alternative splicing of its mRNA precursor, known to generate isoforms. Regarding its carbohydrate-binding specificity, galectin-8 has a unique feature among the galectins: Its C-terminal domain has a higher affinity for N-glycan-type branched oligosaccharides, while the N-terminal domain has a strong affinity for α2-3-sialylated or 3'-sulfated β-galactosides (81). The LGALS8 gene covers 33 kbp of the genomic DNA. It is localized on chromosome 1 (1q42.11) and contains 11 exons. Through alternative splicing, the gene produces 14 different transcripts, altogether encoding 6 proteins (82). That protein is expressed both in the cytoplasm and the nuclei of the vascular endothelial cells of normal and tumor-associated blood vessels, as well as in lymphatic endothelial cells (83). This galectin has both pro- and anti-adhesive functions, depending on its subcellular localization (84-86). Galectin-8 acts as an ECM protein, positively or negatively regulating cell adhesion, depending on the extracellular context, as well as on the cell surface counter-receptors, such as the integrins (82,84,85).

The impact of galectin-8 on the inflammatory system is highly complex. Under inflammatory stimulation, galectin-8 is secreted by the endothelium and exposed on its surface. Galectin-8 itself may activate endothelial cells by increasing their permeability, releasing inflammatory molecules and inducing adhesion of resting platelets. The interaction of galectin-8 with integrin αIIbβ3 and glycoprotein Ib (GPIb) at the platelet surface triggers adhesion, spreading, aggregation, release of granules content and P-selectin exposure. Furthermore, galectin-8 interacts with integrin αMβ2/Mac1in order to induce firm adhesion of neutrophils and the subsequent transendothelial migration and to trigger the production of superoxide. Another source of galectin-8 may be activated dendritic cells and B cells, which are able to be stimulated by lectin to produce proinflammatory cytokines. However, promotes antigen-independent proliferation of $CD4^+$ T cells, as well as their adhesion to the endothelium (Fig. 4) (87).

Galectin-8 has a role in autoimmune diseases, such as rheumatoid arthritis or lupus erythematosus, and modulates tumor progression (86).

It has been indicated that following secretion, galectin-8 acts as a matrix protein, equipotent to fibronectin in the promotion of cell adhesion, by ligating and inducing clustering of cell surface receptors. Immobilized galectin-8 dose-dependently enhanced cell adhesion of different cancer cell types, such

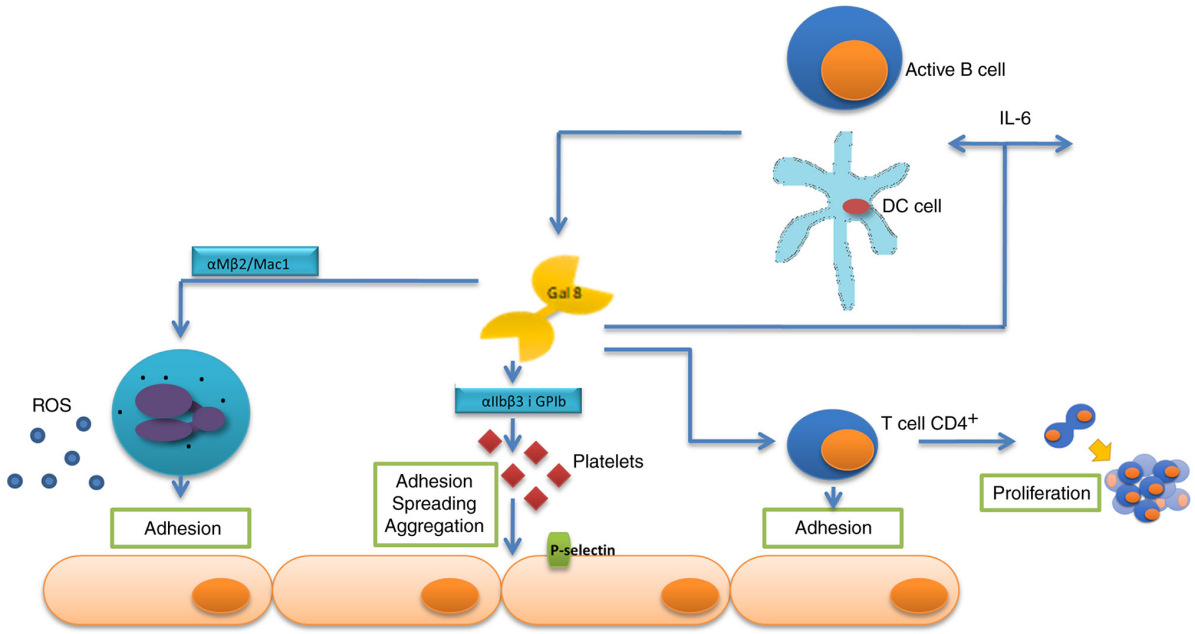

Figure 4. Role of galectin-8 in the inflammatory response. Based on (90). GAL-8, galectin-8.

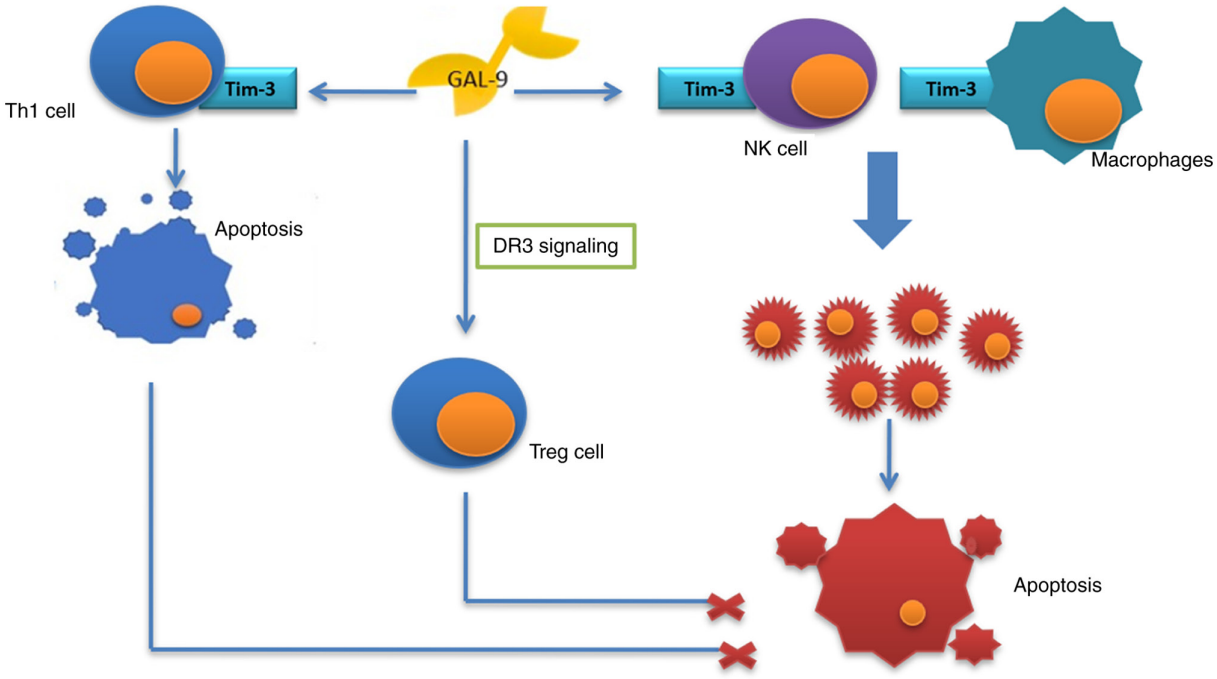

Figure 5. Role of galectin-9 in the inflammatory response. Based on (94,95). GAL-9, galectin-9.

as H1299 human non-small cell lung carcinoma cells, and promoted U373 glioblastoma cell migration. Furthermore, soluble galectin-8 induces migration of U87 glioblastoma cells (88).

6. Galectin-9

Galectin-9 is a protein with a 36 kDa molecular weight, a member of the tandem-repeat galectins and encoded by the gene LGAL9, localized on chromosome 17p11.2. Its structure contains two different CRD groups linked by a peptide with a sequence of ~70 amino acids. The protein may occur as a monomer but also a dimer or a multimer (7,53,89). Galectin-9 has high tissue specificity. Its expression is present mostly in the epithelial cells of the skin and the digestive system (53).

The role of galectin-9 in cancer progression has remained largely elusive; however, the effect of galectin-9 upon adhesion, migration and the immunological system suggests its significant role in tumor development. The protein was indicated to impair the anti-tumor response of the immunological system and also to stimulate the process (54). A growing body of evidence proves the anti-tumor function of

galectin-9. Enhancing adhesion of the tumor cells, it prevents their migration and infiltration of the tissues. It also has a role to increase apoptosis and suppress proliferation of cancer cells and supports the cytostatic function of the natural killer cells, acting together with Tim-3 receptor and stimulating the macrophages (90,91). The protein may, however, have a contrary effect, through activation of death receptor 3 (DR3) signaling, promoting activity of Treg lymphocytes and also, together with Tim-3 receptor, inducing apoptosis of Th1 lymphocytes (Fig. 5) (90).

Galectin-8 and -9 in ovarian cancer. Studies evaluating the role of galectin-8 and -9 in ovarian cancer are scarce. The original study to assess the expression of these proteins in cancer was performed by Lahm *et al* (92). The authors assessed the expression of the genes of all the currently known human galectins in tumor cell lines of different histogenetic origin (galectinomics). The presence of human galectin-1-4 and -7-9 mRNA was monitored by reverse transcription PCR analyses in a panel of 61 human tumor cell lines derived from a variety of cancer types, not only ovarian but also breast, colon, lung, brain, skin, kidney, urogenital system and hematopoietic system cancers. The results indicated that the most abundantly expressed member of this lectin family was galectin-8, with 59 positive cell lines. Signals for galectin-9 appeared in colorectal carcinoma cell lines with a frequency similar to that of galectin-4 but with certain inter-cell line differences. Its expression was restricted to cell lines of this tumor type-the tested ovarian carcinoma and hematopoietic malignancies (92).

The expression of galectin-8 and -9 in ovarian cancer was also evaluated by Schulz *et al* (41) using immunohistochemistry and the association of these results with clinical patient characteristics were determined. The impact of the levels of different types of galectin on disease-free survival and the overall survival was also assessed. Galectin-8 and -9 staining was detected in the cytoplasm of the ovarian cancer cells. The predominant staining intensity (0= negative, 1= low, 2= moderate and 3= strong) and percentage of the stained cells (0=0%, 1=1-10, 2=11-50. 3=51-80 and 4= 81-100% of the stained cells) were evaluated and scores were multiplied to obtain the Remmele immunoreactive score (IRS). In the survival analysis for galectin-8, patients were classified into low-expression IRS ≤1 and high-expression (IRS>1) groups. In terms of galectin-9, patients were divided into negative expression (IRS=0), moderate expression (1≥ IRS ≥6) and high-expression groups. The results indicated that galectin-8 expression was a positive prognostic factor for overall and disease-free survival of patients with ovarian cancer, while galectin-9 expression influenced overall and disease-free survival in two different ways: Moderate galectin-9 expression correlated with reduced survival as compared to galectin-9-negative cases, while patients with high galectin-9 expression had the best outcome (41).

7. Conclusions

The results of the studies performed so far point to complex roles of galectins-1, -3 and -7-9 in the carcinogenesis of ovarian cancer. Elucidation of the phenomenon may contribute to the development of novel therapies targeting these proteins. In particular, it appears important to recognize the reasons for changes in the expression of these galectins. Galectins may also become a useful diagnostic and prognostic tool to evaluate tumor progression or the clinical outcome in patients with ovarian cancer; this, however, requires further study.

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Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Authors' contributions

Conceptualization was by AMP; investigation by AMP and DW. Literature search and selection was by AMP and MSK. Original draft preparation was by AMP, AJ, PKD and MSK and reviewing and editing by AMP, AE and ZKA. Project administration was by AMP and DW. All authors have read and agreed to the published version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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