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LECTINS AND PARTNER GLYCOCONJUGATES IN CURRENT ANTITUMOR TECHNOLOGIES. A REVIEW

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ABSTRACT

The analysis of the communication role of lectin and glycan receptors in the recognition and binding of patterns in human antitumor immunity is carried out. Anticancer current technologies involved lectins and their recognized glycoconjugates are systematized. Examples include realization of molecular, assembly, and intercellular connections based on lectin—glycan interactions in the study of the most known malignant tumors, including tumor cell lines. The most significant antitumor strategies for the combined use of lectins and glycans in relation to the functioning of the basic communication network of the body are indicated. Modulation of the expression of various lectins and their interactions with glycoconjugate patterns, as well as regulation of key combinations of lectins and CD antigens (including effector pairs in communication axes) between populations of protective cells (dendritic cells cDC, mDC, MoDC, pDC; macrophages M2 and M1, mucosal M cells, NK and CAT-T cells, CTL, other CD-antigen labeled types) have a place in the communication network. Such cell populations are involved in enhancing the responses of innate (basis) and related adaptive (superstructure) immunity. The effects of lectins and glycoconjugates are due to the targeted recognition of receptor glycoconjugates or lectin patterns by innate immune cells and the initiation of further intercellular communication cascades. Receptor and soluble lectins and glycoconjugates act as organized and directed synergists and antagonists. The most commonly used receptor lectins, their ligands and other communication axes effectors will be useful in the development of anticancer strategies, procedures and vaccines. In general,

lectins and their recognizable glycoconjugates have significant potential for combination therapy of tumors.

KEYWORDS: malignant tumors, lectins, glycoconjugates, targeting, CD, adjuvants, DC, macrophages M2, TAM, M cells, NK cells, CAR-T cells, CTL, TLR, innate immunity, protection cell populations, intercellular communications, TME, antitumor therapy, vaccines.

ABBREVIATIONS

APC antigen presenting cells

GC glycoconjugates

HCC hepatic cell carcinoma

PRR pattern recognizing receptors

RL receptor lectins

AMP associated molecular patterns

BDCA blood DC antigen

CAR chimeric antigen receptor

CARD9 caspase recruitment domain 9

CD cluster of differentiation, cluster designation

CLEC C-type lectin domain family

Clec9A NK-lectin group receptor-1, endocytic receptor; allows DC to be more capable of presenting antigens

CLL1 C-type lectin-like molecule-1

CTL cytotoxic lymphocytes

CTLD C-type lectin binding domain

DAMP danger-AMP

DC dendritic cells (cDC, mDC, moDC, pDC: conventional, myeloid, monocyte-derived, Plasmacytoid, Respectively)

DCIR DC immunoreceptor

DC-SIGN DC-specific ICAM3-grabbing non-integrin

Mincle macrophage-inducible C-type lectin

MMR macrophage MR

MR mannose receptor, phagocytic receptor

NK natural killer T cells

SAMP self-AMP

TAM tumor associated macrophages

TAMP tumor-AMP

TLR Toll-like receptors

TME tumor microenvironment

RL involved in human antitumor immunity (according to the present review)

*ASGPR1 AsialoGlycoproteinsReceptor-1 (HL-1; ASGPR; CLEC4H1)[9]

*CARD9 a molecule of the Dectin2 subgroup, neutrophils[26]

*CAR-T CAR-modified T-cells[9]

*BDCA Blood DC Antigen 1, 2, 3[66]

*CD69; hematopoietic stem cells, T cells, and many other cell types[48]

*CD163 haemoglobin scavenger receptor, macrophages M2[17,18,62]

*CD169/Siglec-1; human myeloid cells[4,63]

*CD206/MRC1 mannose receptor C type 1 (MRC1), macrophages M2[17,62]

*CD209/DC-SIGN; DC, human monocytes, U937 macrophages[13]

*CLEC4A2 C-type lectin domain family 4 member **A**, rat cells[73]

*CLEC6 C-type lectin domain family 6[77]

*CLEC9A C-type lectin domain family 9 member **A** (DNGR1, BCDA3, UNQ9341, CD370), DC, monocytes[59]

*CLEC10A C-type lectin domain family 10 member **A**)[47]

*CLEC13E C-type lectin domain family 13 member E) (Endo180, CD280, KIAA0709, MRC2, TEM9, uPARAP)[8]

*CLEC14A, CD93, CD248/endosialin, and thrombomodulin/CD141[75]

*CLEC2 C-type lectin domain family 2 (forms)[69]

*CLL1 C-type lectin-like molecule-1, myeloid cells[37,68]

*DC-ASGPR/CD301 asialoglycoprotein receptor on DC[77]

*DC-SIGN/CD209, cells CD8-T[77]

*DCIR2 dendritic cell immunoreceptor 2[77]

*DEC205/CD205 dendritic cell receptor for endocytosis[20,77]

*Dectin1/CLEC7A/CD369 NK-cell-receptor-like C-type lectin, beta-glucan receptor[15,77]

*E-selectin/CD62E, myeloma cells[52]

*Endo180/CD280/MRC2/uPARAP urokinase plasminogen activator receptor associated protein[8,64]

*KLRG1; T cells and CD56 NK cells[79]

*LOX1 the receptor for oxidized low-density lipoprotein (CD40), a Type II membrane protein with a typical C-type lectin structure at the extracellular C-terminus, endothelial cells.[6,8,51,77]

*Mincle/CLEC4E, macrophages[58]

*MRC1 mannose receptor C type 1 (CD 206), macrophages M2[17, 62]

*MR phagocytic receptor, MMR, MRC2, CLEC13D, CD206), macrophages[2,17,18]

*NKG2A (natural killer group 2A)/CD94, on pDC[12]

*NKG2D NK group 2D, KLRK1 (CD314), on pDC[12]

*Siglecs [29,50]

*Siglec-1/CD169 human myeloid cells[4,63]

*Siglec-7/CD328 eosinophils[72]

*Siglec-9 macrophages[15,72]

*Siglec-10 human CD4(+) T cells[4,29]

*Siglec-15 primarily expressed on a subset of myeloid cells[4,14,16]

*Siglec-G T-cells[76]

1. INTRODUCTION

Lectins and glycoconjugates (GC) are communicators in the body's defense network, promising biomarkers and bioeffectors of innate immunity, important components of the functioning of antigen-presenting cells (APC)[38] Researchers are paying increased attention to multifunctional receptor lectins (RL), which belong to one of the classes of pattern-recognizing receptors (PRR) capable of recognizing and binding disrupted 3D signaling patterns such as TAMP, DAMP and SAMP. Lectins perform a wide range of vital functions for the body. The properties of RL should be taken into account when developing vaccine glycoconjugate adjuvants,[19,22,26] antitumor dendritic cell vaccinesk,[59] anticancer T-cell and other preventive and therapeutic vaccine preparations[22,65,49,65,66,77] The aim is to evaluate the potential of the diverse participation of lectins in the intercellular communications of the body used in the development of anti-cancer strategies.

2. THE MAIN CONTENT

2.1. Anti-cancer strategies involving lectins

The selective effects of lectins on intercellular pathways reflect assembly processes, the participation of lectin(s)—GC complexes and supramolecular ensembles with a modulating pattern (mini- [pattern with minimal domain and carbohydrate binding site] and mega- [a

pattern depending on the assembly of molecules and 3D configurations of the supramolecular ensemble at the assembly junctions])-specificity to GC, the appearance of new ones, the disappearance of former target-oriented k specificities (by switching them, turning into latent/waiting/delayed or unmasked), or modification of the severity (amplitude) of former GC recognition activities-patterns.

The variety of specificity of lectins used in anti-cancer strategies is characteristic in terms of recognizing carbohydrate structures in GC (types of lectins are in brackets)

* alpha-2,3-Sia [Sialic glycans], alpha-2,6-Sia [Sialic glycans] (Siglecs)[50]
* Man-alpha-glycans of the oligomannoside type (soluble mannose receptor; RL LY75 [DEC205/CD205])[18,20]
* Fuc-alpha-1,6- in the bark of glycans (*Cephalosporium curvulum* lectin)[5]
* L-Rha-alpha-glycans (WCL lectin from white-spotted pike roe)[71]

The study of lectin communications should also take into account the deeper specificity of RL to whole GC molecules (glycoproteins, glycolipids, others), as well as the 3D configuration of glycans at the sites of supramolecular and intercellular contacts.

The dual, sometimes contradictory nature of RL functioning[7,17] reflects the ability of each lectin type to recognize sets of GC ranked by target specificity and accessibility of the targets themselves, which, in turn, indicates increased regulatory potential for RL and cells by external (exogenous) and internal (endogenous) GC-type ligands.

The latter determines the multifunctionality of lectins of innate immunity cells in relation to their participation in the communication intercellular network of the body, the ability of cells to select a pathway (several pathways) in the network, ultimately aimed at the selective antitumor effect of innate and adaptive immunity combinations.[7,17] From the point of view of symmetry, it is obvious that the final positive result can be obtained as a result of recognition and modulation of receptor GC by soluble (including recombinant) lectins as specific ligands.[36,74]

The combined participation of lectins, their recognized GC, and other key molecular effectors in the body's intercellular innate and adaptive communication network is diverse and may include lectin cascades (such as Galectin9—Dectin1)[15] functionally significant (key) pathways (such as CD24—Siglec10 with the synergy of both partners)[27] and directional

targeting axes (such as the PD axis [Programmed cell Death 1; CD279]-1/PD-L1 [Binding of PD-L1 to PD1 on T-lymphocytes] during targeting of Siglec15)[4] other combinations involving lectins (for example, combination of type adiponectin and intelligin1)[32]

Anticancer strategies are associated with the concepts of targeted (targeting) effects on cells with the participation of lectins (mainly receptor and less often – soluble, including recombinant and fused ones) and their GC ligands (agonists/antagonists, synergists, adjuvants), initiating (after cellular pattern recognition) further cascading events (intercellular and intracellular communications) and ultimately achieving antitumor responses of innate immunity (at the level of modulating the behavior of selective populations of defense cells) and antibodies-producing immunity with antitumor effects.

Widely used anticancer strategies include decoding ones that involve switching intercellular communication pathways in the directions of resulting antitumor protection of the body.[40,42]

Below are the applied antitumor combined strategies and procedures of a general and tactical plan using lectins (in most cases, RL as PRR as targets, Table. 1) and interacting GCS (receptor and soluble)[3,25,28,36,49,53,74]

2.2. Lectins, cells functioning through them, and other factors used in the current anticancer procedures and strategies

• Lectins as biomarkers of intercellular communications. In some cases, RL manifest themselves as obligate markers of tumor cells (Table. 1), for example, CLL1 on leukemic cells[68] tumor-associated Endo180[8] Clec9A on $CD141^{+}$ DC (dendritic cells)[59] Siglec-1/CD169 as a marker of prostate cancer[77] Biomarkers are favorable for a specific corrective effect on APC and protective cells in strategies for treating tumors and creating anti-cancer (nano)vaccines.[23,25,49,60]

• The RL markers of co-functioning cells ensures the convergence of protective communicators (cells, cell chains/ sequences, and metabolic cascade pathways) of immunity in RL-tropic tissues, which is widely used in anti-cancer strategies, including using T-cell purified populations, modified or chimeric T cells in anti-cancer vaccines.[9,22] Since cancer metastasis is stimulated by the tumor cell microenvironment (TME), a number of anti-cancer strategies aim to eliminate intercellular communication factors of tumor metastasis in TME[13,24,35,48,54]

• Population of macrophages CD169^{+} (CD169 as RL) in the sinuses of lymph nodes, it provides antitumor activity through the induction of antitumor cytotoxic T-lymphocytes (CTL).[63]

• DC management using lectin orthologs (for example, including mouse mSIGNR1, other homologues of DC-SIGN and human MGL) for cancer immunotherapy.

• Specific glycoliposomes, microparticles, and nanoparticles are used for phagocytic targeted delivery to cells via RL to enhance the resulting anti-cancer immunotherapy, including against the background of intracellular events at the organelle level (for example, the endoplasmic reticulum and mitochondria [10, 51]).

• Soluble lectins and soluble forms of RL (discarded cellular receptors from the cell surface) in the bloodstream, lymph, mucosa, extracellular matrix, and any biological fluids, serve not only as cancer biomarkers (for example, s[soluble]MR/CD206 and sCD163 in gastric cancer), but are also considered as ligand-target participants in intercellular communications.[2,18,49]

- Soluble lectins (including recombinant ones) in communications are involved in the selection and targeted delivery of GC, and complex systems acquire a wide regulated range of antitumor activities, expand the demand base of therapeutic lectin complexes by the body.

- Lectins are widely used against various tumors in targeted delivery procedures: phytolectins AAL (*Aleuria aurantia*), Con A (*Canavalia ensiformis*), BPL (algae *Bryopsis plumosa*) CSL (fungus *Cephalosporium curvulatum*), GS-I (*Griffonia simplicifolia*), MAL-II (*Maackia amurensis*), PHA (*Phaseolus vulgaris*), SNA (*Sambucus nigra*), VVA (*Vicia villosa*) and others[10,30,43,56,65,70,74] a number of lectins from higher and lower plants induce apoptosis of tumor cells[5,10,70] intelligin1 (omentin1).[32,37] Galectins-1, 3, 9, others[15,31,40,49,55] new lectins with rare specificity (for example, L-Rha-alpha-binding WCL lectin from the caviar of the white-spotted pike *Salvelinus leucomaenis*.[71] or oligosaccharide specificity to glycans in the case of Siglecs (recognition of alpha-2,3- (or alpha-2,6-)-sialylated glycans).[50] phytolectins (recognition of core glycans with exposed residues of Fuc-alpha-1,6-[5] and oligomannoside glycans – ligands for the C-type mannose receptors.[18,20]

- Lectins of symbiotic and probiotic microorganisms are promising as complex systems of targeted action on mucosal immunity, including in the antitumor direction. Such lectins co-

function with other proteins in the modulation of cytokine production by the body, which may be important in the schemes of interconnection of pro- and anti-inflammatory cytokine cascades.[39]

• The use of lectinomimetics (natural and synthetic peptides, including cyclic peptides, and others) and glycomimetics (mimics of ligand GC with respect to RL) in targeted action on cells involving lectin—glycan recognition (soluble lectinomimetic—receptor glycan, soluble glycomimetic—RL) and binding.[52,57]

• The introduction of lectin short RNA forming hairpins (hairpin 3D patterns) (Clec4a2 shRNA [Small Hairpin RNA]) into tumors is promising for enhancing $CD8^+$ immunity *in vivo*.[73]

• Chimeric NK derivatives of tumor-attacking cells with a wide range of RL[46] (such as CAR-T cells[9,68] are used, as well as other antitumor chimeras[71] Table 1.

• There is a specific delivery directed to the cell (sub) population with the participation of the resulting lectin—GC pattern complexes and ensembles using the examples of macrophages M2, mDC, pDC and MoDC.[1,33]

• It is widespread (T cells with a modified affinity surface)-targeted killer effects on tumor (sub)populations.[46,68]

• RL-dependent selective action is performed on cell cascade chains/ sequences in order to reprogram and switch selective subpopulations of body cells (for example, in cases of associated with tumors macrophages M2 [CD163] and M1 [CD11c])[1]

• The delivery of effectors to intestinal mucosal M cells is important in order to initiate antitumor cell cascades.[43,65]

• Multitropic enhancement of the immune response is achieved through the use of glycoadjuvants, cross-presentation of antigens, and injectable co-stimulation (including with lectins).[39]

• Allogeneic cell-stem (cells characterized by RL markers) transplantation is used for the treatment of hematological tumors.[66]

• It is advisable to further enhance the immune response by choosing ways to administer lectin—GC interaction drugs (intradermal.[65] vaginal, oral, rectal [via suppositories], nasal [spray], and other options (Table 1).

• The strategies of combined antitumor effectors on the TME is often used[7,15,16,21,24,45,47,54,55] including through T cells and tumor-associated macrophages (TAM, including pan-macrophages with CD68 marker and M2 macrophages with CD163 and CD206 markers) in order to inhibit, reduce and eliminate metastases.[17,54] Table 1.

• The functioning of lectins with other PRR and pattern-recognizing molecules (for example, TLR, ROS and others) is used.[17]

• Cancer antigens are the first to signal in the body to the network of "antigens—(RL subpopulations of DC and macrophages, killer and other protective cells of the rapid response of innate immunity)—(antibodies–response cells)". Evolutionarily justified ways of control in the opposite direction are required – when choosing antigens signals, in the variants of accumulation of a "critical amount of positive signals" (the transition from quantity to quality), prolongation of the intercellular communication memory of signals and their effects resulted in a massive combined prolonged attack on tumors by cytokines, chemokines and antibodies are under consideration.

• TLR agonists and ligands (many types of TLR exhibit RL properties) and other RL categories, combinations of GC-containing adjuvants can improve cancer immunotherapy (Table 1).

• GC-dependent initiation of responses by lectins (receptor and soluble ones) plays an important role, which are involved in the final enhancing general anti-cancer immunity, arresting tumor growth and metastasis (Table 1). RL control specific intercellular communications of APC with tumor antigens, which contribute to the resulting growth inhibition, possible rejection or involution of tumors.

• PRR signatures play a special role in the identification, control, and signaling of protective cells (TAM, DC, others) in TME, in the regulation of antitumor events, and in the development of antitumor strategies. Siglecs – RL, involved in the control of cancer-related and recognizing Sialoglycans, such as antigens Sialyl-Thomsen (SiaTn, CD175s[soluble]) and others (Table. 1).[29,50,52,63] Most metaplastic/metastatic carcinomas (including breast

cancer) are characterized by targets containing spatial patterns of combinations of sialic acid residues. Gangliosides (including within the composition of patterns) cooperate with Siglecs, that can be used in antitumor strategies. At the same time, the heterodimeric forms of RL and other receptors are the basis for rapid and reliable receptor co-functioning.[77] Such assemblies contribute to the manifestation of new intermolecular lectin specificities – extended patterns ("megapattern") and particle ones. Siglecs are involved in the formation and functioning of spatial depressions and protrusions of the inter-receptor recognition of glycoantigenic "megapatterns" of sialic acid residues (their special space clusters). Other Sia-specific lectins with antitumor activity, such as the phytolectins mentioned above, are also promising.

• Anti-cancer vaccines containing tumor-specific antigens (Tn, others) usually include specific GC adjuvants that increase the ability of antigens to stimulate the immune response.[22] Recognizing patterns of mannans and glucans, Dectin1 (on DC and macrophages) interacts with N-glycans on the surface of tumor cells, promotes the antitumor effect of beta-glucans. Human MGL recognizes other tumor antigens. RL-dependent delivery to cells is considered as co-stimulation of immune responses with RL ligands (for example, with alpha-GalCer loading of the RL system). Other natural and synthetic tumor antigens (including their glycomimetics) and lectins (including lectinomimetics) are promising for use in combination with PRR in antitumor therapy.[28,43] (Table 1).

• Other examples of RL combinations include the co-functioning of Endo180 and LOX-1, activation of Dectin1 on macrophages by Galectin, and the involvement of Siglec-7 and Siglec-9 in limiting MoDC activation via the TLR signaling pathway.[8,15] Card9 lectin controls Dectin-1-induced cytotoxicity of T cells and tumor growth, protecting mice from tumors (but not Card9-deficient animals).[26]

Table 1 systematizes data on the use of lectins in the study and therapy of malignant tumors, including solid, bloodstream-related, metastatic and other types.

Table 1: The current anticancer procedures, technologies, therapy and strategies involved lectins and their recognized glycoconjugates.

Tumors, features, lectin(s), target cells, results, prospects, references

SOLID TUMORS

Cancer of the nervous system

Brain cancer

U373-GSC glioma stem cells obtained from the patient's U373 glioma cell line; MAL-II (*Maackia amurensis* lectin) for targeting alpha2,3-sialylated glycans on U373-GSC.[56]

Glioblastoma; targeting of RL, including C-type lectins such as MGL/CLEC10A, and Siglecs; use of Galectins, including Galectin-9.[54]

Cancer of the sympathetic nervous system in children under 5 years of age

Neuroblastoma (NB), primary tumor of the adrenal gland (NB cell line SJNB-7), bone marrow metastases in children at high risk of NB (NB lines SK-N-AS and SK-N-DZ); use of RL: NKG2D.[12]

Cancer of the bone system

Osteosarcoma (progressive with bone metastasis and osteolysis); the use of lectins: collagen receptor – Endo180 (CD280, MRC2 uPARAP) in antibodies targeting Endo180 to prevent osteolysis and bone destruction; Endo180 to develop advanced bone cancer treatment technologies.[64]

Cancer of the pulmonary system

LLC (*Lewis* lung carcinoma) in mice; lectins from *Bacillus subtilis* IMV B-7724; antitumor and antimetastatic activity of lectin from *B. subtilis* IMV B-7724 ensured the preservation of cytotoxic activity of antitumor immunity at the level of functioning of macrophages, NK cells and CTL throughout the growth of LLC; combination of *B. subtilis* lectins and *Bifidobacterium animalis* cells was the most effective.[11]

Mouse lung tumor; the use of lectins: Clec4a2; the introduction of Clec4a2 shRNA (Small Hairpin RNA) slowed down tumor growth; elimination of Clec4a2 expression by delivering shRNA through the skin provided enhanced $CD8^+$ immunity *in vivo*; Clec4a2 shRNA has the potential of an adjuvant for cancer immunotherapy.[73]

Cancer of the glandular systems

Breast cancer: Breast cancer; Dectin-1 (RL of C-type) can stimulate immune responses against breast cancer, enhancing both innate and adaptive immunity; in the future, Dectin-1 as a target for the treatment of tumors.[7]

Breast cancer: MCF7, MDA-MB-231, MDA-MB-468 (highly metastatic), T47-D and ZR cell lines-75-1 – from ATCC (Manassas, VA, USA); soluble lectins – antagonists of RL; mice were immunized with antigens (reactive to phytolectins) of breast cancer cell lines; GS-I- (group I lectins from *Griffonia simplicifolia* seeds) and VVA- (phytolectin *Vicia villosa* agglutinin) depleted fractions significantly delayed tumor formation and inhibited pulmonary metastases.[49]

Metastatic breast cancer: MDA-MB468 (ATCC HTB-132) and SKBR3 (ATCC HTB-30) cell lines; peptides-1, 3 were identified that bind similarly to AAL (lectin from the mycelium of the fungus *Aleuria aurantia*) and are capable of inhibiting migration of metastatic breast cancer cell lines; synthesized lectinomimetics based on odorran-1 (cyclic lectins-like peptide of the skin of the frog *Odorrana graham*) were used; targeting of cancer-specific glycans using cyclic peptide lectinomimetics is promising.[57]

Thyroid cancer

Anaplastic thyroid carcinoma (ATC), ATC cells: Siglec-15^{low} and $Siglec15^{high}$; $Siglec15^{high}$ ATC are characterized by high expression of the serine protease PRSS23 and the "cancer stem cell" marker - CD44; members of the family of RL - Siglecs: CD33, Siglec-1, Siglec-10, Siglec-15; treatment of antibodies against Siglec-15 significantly increased the cytotoxic capacity of $CD8^+$ T cells in a model of co-cultivation with an ATC xenograft obtained from zebrafish; antibodies against Siglec-15 significantly inhibited tumor growth and increased mouse survival in an immunocompetent mouse ATC model, which was associated with an increase in M1/M2 in macrophages, NK cells, and $CD8^+$ T cells, as well as a decrease in the number of myeloid suppressor cells (MDSC); Siglec-15 inhibited T cell activation, reducing signals NFAT1, NFAT2 and NF-kB; blocking Siglec-15 increased the secretion of cytokines IFN(interferon)-gamma and IL(interleukin)2.[4]

Liver cancer

Hepatocellular carcinoma (HCC); lectins: phycolin3 (FCN3); FCN3 expression was associated with higher patient survival, significantly inhibited proliferation, migration, and attachment-independent growth of HCC cell lines, as well as xenograft tumor growth, and induced apoptosis of HCC cells.[80]

HCC; RL: ASGPR1 for targeting CAR-T cells with high levels of cytokine secretion and proliferation and the ability to apoptose tumor cells.[9]

HCC; RL: LOX1; $LOX1^+$ $CD15^+$ PMN-MDSC (polymorphonuclear myeloid-derived suppressor cells) blood cells were associated with HCC tissues and were a prognostic criterion for HCC (LOX1 was practically undetectable in peripheral blood neutrophils from healthy donors); stress (marker sXBP1) induced a significant increase in $LOX1^+$ expression in patients $CD15^+$ PMN-MDSC caused suppression of T cell proliferation.[51]

HCC: HepG2 cells; (alpha1,6-Fuc-)-specific lectins: CSL (*Cephalosporium curvulum* lectin), LCA (*Lens culinaris* agglutinin), AOL (*Aspergillus oryzae* lectin); CSL induced caspase-dependent apoptosis of HepG2; all lectins inhibited the growth of HepG2 (mucin as blocker).[5]

Pancreatic cancer

Pancreatic carcinoma; lectins: Dectin-1 (RL) and soluble Galectin-9 (an activator of functioning Dectin-1).[15]

Pancreatic ductal adenocarcinoma (PDAC); RL: CD206 CD163 - on macrophages; associated with tumor fibroblasts promoted polarization of macrophages M2 in PDAC; M2 macrophage expression of CD163 and CD206 was enhanced; pancreatic fibroblasts CAF induced monocyte production of ROS (PRR) that supports possibility of complex pattern strategy of TME treatment.[17]

PDAC, modified tumor T cells: CAR H84T; BanLec (oligomannoside-specific phytolectin) expressed in T cells H84TCAR as chimeric receptor construction with antigen H84T; H84TCAR destroyed 3D architecture of PSC (pancreatic stellate cells) of TME and decreased number of tumor cells and TME non-tumor cells in mixed cultures.[45]

Human PDAC, Capan-1 cells; soluble recombinant lectin: rBC2LCN, labeled by IRDye700DX photoabsorber (rBC2LCN-IR700); intake of rBC2LCN-IR700 and its gross cytotoxicity in respect of Capan-1 cells upon rBC2LCN-IR700 glycan targeting; cytotoxic rBC2LCN-IR700 action also upon treatment of subcutaneous mouse PDAC xenograft obtained from patient.[36]

Cells PANC-1; (alpha1,6-Fuc-)-specific phytolectins: CSL (fungus *Cephalosporium curvulum* lectin), LCA (plant *Lens culinaris* agglutinin), AOL; these lectins inhibited the growth of PANC-1 (mucin as a blocker).[5]

Prostate cancer

Metastatic prostate cancer: PC3, VcaP, and DU145 cell lines; use of targeting into cells via RL: Endo180.[8]

Rat prostate cancer: highly metastatic MatLyLu tumor, weakly metastatic AT1 tumor; prostate cancer marker – RL: Siglec1^{+}/CD169^{+} is an indicator of aggressive/high degree of prostate cancer metastasis; there was a decrease in CD169 expression on macrophages in the sinuses of regional lymph nodes, a prognostic indicator of increased risk of death from prostate cancer after prostatectomy; decreased the number of macrophages CD169^{+} in premetastasized lymph nodes is associated with subsequent tumor metastasis (in the rat model of prostate cancer) and poor outcome for patients with prostate cancer.[63]

Prostate cancer; RL: CD59 is a candidate ligand for Siglec-9 in the case of prostate cancer; blocking interactions between Siglec-7/9 and sialic acids inhibited prostate cancer xenograft growth and increased immune cell infiltration in humanized mice; the CD59/Siglec-7 and CD59/Siglec-9 axes are promising in the treatment of prostate cancer.[72]

Cancer of other internal organ systems

Cancer of the gastrointestinal system

Stomach cancer

Stomach cancer; use of RL: MR and CD163.[18]

Stomach cancer; RL: CLEC2; a correlation was found between the severity of CLEC2 in stomach cancer tissues and the depth of invasion, metastasis to lymph nodes, TNM stage, and 5-year survival of patients; CLEC2 suppressed AKT kinase signaling and invasive activity of stomach cancer cells in respect of blocking the expression of phosphoinositide-3-kinase subunits; CLEC2 suppressed metastasis of stomach cancer cells injected into mice.[69]

Stomach cancer; potential targeting of Siglec-15 in stomach cancer immunotherapy.[14]

Stomach cancer; SRC (signet ring cell carcinoma) cell lines: NUGC-4 and KATO-III with reduced alpha exposure of alpha-2-6-sialic acid residues; among 96 tested lectins, 11 were highly affinity and 8 low affinity for SRC; lectins: rBC2LCN and algal BPL (*Bryopsis plumosa*) showed maximum affinity for SRC; cytocidal the effect of rBC2LCN and pseudomonas exotoxin A in respect of SRC as well as regression of the model xenograft in mice were established; rBC2LCN is promising in alternative treatment of patients with SRC.[74]

Rectal cancer

Human rectal cancer (and related tumors) caused by obesity; cells from the patient rectal mucosa; the prospect of using the expression of Intelectin-1 ("intestinal lectin", TLN-1, Omentin-1 – one of the adipokines), a cancer suppressor in targeting tumors of the gastrointestinal tract.[32]

Cancer of the urogenital system

Kidney cancer

Macrophages M2 (RL: CD163 [marker for M2] and CD206, in combination with CD68) are perspective for RL-targeting therapy.[1,35]

Bladder cancer

Bovine bladder cancer: (papilloma virus type 2 or type 13)-associated 8 bovine tumors, urothelial cancer cells; RL: Mincle (no Mincle expression in healthy cattle); perspective – Mincle-DC-targeted immunotherapy of non-muscle invasive human bladder cancer.[58]

Bladder cancer; Siglec-15 is promising in a new strategy as a therapeutic target in the treatment of bladder cancer.[16]

Mouse bladder cancer; RL: CLEC4A2; the introduction of Clec4a2 shRNA (Small Hairpin RNA) slowed down tumor growth; elimination of Clec4a2 expression by delivering shRNA through the skin provided enhanced $CD8^+$ immunity *in vivo*; Clec4a2 shRNA has the potential of an adjuvant for cancer immunotherapy.[73]

Ovarian cancer

Ovarian cancer (A2780 tumor transplanted into mice); RL: Galectin-3 expressed on CD68 cells - for targeting ovarian cancer stem cells at the stages of tumor progression; Galectin-3 for improving anti-cancer therapy.[31]

Ovarian cancer; SNA (*Sambucus nigra* agglutinin); targeted apoptosis of ovarian cancer cells as a result of a mitochondrial response to SNA with further suppression of tumor growth *in vivo*; SNA as a promising candidate for inhibiting the progression of ovarian cancer.[10]

Ovarian cancer; AAL (*Aleuria aurantia* lectin) for M-cell targeting into intestinal-associated lymphoid tissue during oral immunization of animal antibodies against cancer antigen.[43]

Ovarian cancer: mouse ovarian cancer cell line; AAL as a targeting ligand bound to M cells in *Peyer's* plaques of the small intestine; as part of a transdermal oral microparticle combination vaccine to enhance targeted uptake from M cells into the tumor.[65]

Ovarian cancer as a progressive (metastatic, disseminated) epithelial; suppression of the mannan receptor: LY75 (DEC205, CD205) in ovarian cancer induced the transit of mesenchyma into the epithelium, accompanied by a decrease in cell migration and invasiveness *in vitro*.[20]

Cervical cancer

(human papilloma virus-16)-associated cervical cancer; RL kit; promising targeting vaccine for the presentation of antigen cervical cancer associated with (human papilloma virus-16) through CD40 on DC (in comparison with RL: LOX1, Dectin-1, DEC205, DC-ASGPR, DC-SIGN, DC-SIGN/L, DCIR, CLEC6).[77]

Cancer of the skin system

Melanoma; RL: DEC205 for targeting via MoDC.[60]

Melanoma; SLN (sentinel lymph node)-resident (BDCA3/CD141$^+$ cDC)-subpopulations (T cells-stimulating, capable of cross-priming); RL: BDCA3/CD141 and CLEC9A; BDCA3$^+$ cDC were recruited into SLN in an interferon-type-I dependent manner, expressed CLEC9A; exposure local administration of CpG-B and GM-CSF to melanoma lymph nodes led to the recruitment and activation of BDCA3/CD141$^+$ cDC, increased cross-presentation; melanoma-induced suppression of DC in SLN lymph nodes interfered with the generation of antitumor immunity.[61]

Melanoma; RL: Dectin-1 can stimulate immune responses against cancer, enhancing both innate and adaptive immunity; in the future, Dectin-1 is a target for the treatment of tumors.[7]

Squamous carcinoma cells from squamous cell carcinoma of the skin in the last stages in patients; the TIPE2 pattern regulates tumor-associated macrophages (TAM).[41]

Melanoma and tumors of the rectum and endometrium of the vagina; RL: CD169 on macrophages of the sinuses of lymph nodes - for the development of antitumor vaccines targeting lymph nodes.[34]

Tumors due to blood flow

Leukemia, leukemia (red bone marrow lesion)

Acute myeloid leukemia (AML), chronic lymphoid; the use of RL on antileukemic invariant NK-T cells.[6]

AML; RL: CLL1 on $CLL1^+$ CAR-T cells [LSC: leukemic stem cells, absent in hematopoietic stem cells]; CAR-T were specifically lysed, as well as samples with AML from patients; CLL1 targeting is promising for AML therapy.[68]

Myeloma (a form of lymphocytic chronic leukemia), multiple myeloma; RL: MR, CD209.[2,13]

Multiple myeloma; using the E-selectin/CD62E lectin ligand; GMI-1271 (a specific glycomimetic antagonist of E-selectin/CD62E) for targeting E-selectin in order to overcome tumor metastasis.[52]

Chronic lymphocytic leukemia (CLL), RL: CD69 as a marker of cell activation; CD69 expression was accompanied by decreased sensitivity to bendamustine, could be a prognostic sign of patients' response to the drug and its modulation by ibrutinib and idelalisib (by destroying the TME supporting tumor growth, the release of tumor cells from lymphoid tissues into the peripheral bloodstream, where the signals of the TME are much stronger weaker, and bendamustine may have a greater effect); both drugs reduced CD69 expression and thereby increased the sensitivity of CLL to bendamustine; combinations of these drugs undergoing clinical trials may serve as a treatment strategy for poorly predicted cases of CD69high type CLL.[48]

Chronic myeloid leukemia (CML); phases: initiatory chronic, accelerated, progressive blasts; proportional increase in RL (CD163 and CD206) expression on macrophages M2; strategies – therapy using macrophages M2 ($CD163^+$ and $CD206^+$) in combination with CD68 immunoreceptor (macrophage pan-antigen) and targeting.[62]

Acute human myeloid leukemia: B-cell leukemia; CLL1 targeting.[37]

Lymphoma (cancer of the lymphatic system)

Lymphoma, CLL1 targeting.[37]

Follicular lymphoma (large diffuse B-cell lymphoma, *Burkitt* lymphoma), also CLL; prospects for therapeutic targeting of RL: DC-SIGN (recognizes altered Asn-glycans of tumor B-cell antigen receptors); blocking the therapeutic effect of 4-1BB co-stimulation through the PD-1 pattern.[28,44]

Other hematological tumors

Hematological tumors; RL: BDCA1 mDC, BDCA3 mDC; allogeneic cell stem transplantation (alloSCT) as *hematological tumors* therapy; (hematopoietic stem cells)-obtained (mDC and pDC)-basic vaccines – highly potent inducers of anti-tumor T- and NK-cell responses *ex vivo*; significant amounts of $BDCA1^+$ mDC and $BDCA1^+$ pDC were generated, sufficient for multiple vaccination cycles; $BDCA1^+$ mDC outperformed other subpopulations in enhancing T-cell responses; prospects – mDC vaccines.[66]

Tumor angiogenesis and metastatic dissemination; RL for therapeutically targeting tumor vasculature: CD93, CD248/endosialin, CLEC14A, and thrombomodulin/CD141 (all RL from the group XIV subfamily of CTLDs).[75]

The data presented in the table demonstrate the current variety of technologies in which RL and soluble lectins participate in enhancing the final anti–cancer immunity, which is the basis for creating new promising strategies for the prevention and treatment of tumors.

3. CONCLUSION

To fight tumors (including metastatic ones), the use of selective RL in combination with TLR and immunoreceptors for targeting (targeted selective [inter]cell-delivery cascades of the body communicative network) procedures involving lectin-adequate sets of GC, GC adjuvants, GC complexes (simple or fused, chimeric), other GC-constructions and GC-3D patterns (with unique properties, different from contributors) is particularly promising. It is important to take into account selective populations of DC, macrophages, NK cells and M cells labeled with lectins and/or glycans, as well as to take into account the cell/tissue/organ tropism in treatment of TME. In the case of tumor-type receptor glycans, their targeting by phytolectins and soluble recombinant human lectins is also promising.

Disclosure of conflict of interest

The authors declare no conflict of interest.

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