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REVIEW ARTICLE

Hyaluronan Metabolism and Tumor Progression

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Abstract—Hereditary and somatic mutations initiating the origin of cancer cells are the key but not the only factor of tumor progression. Activation of tumor growth needs tight interaction with the microenvironment. The extracellular matrix functions simultaneously as biomechanical a supporting medium and active link in signal communications of cells. Hyaluronan is the major elastic component of interstitial tissue. Proliferation and metastasis of tumors are accompanied by preliminary accumulation of hyaluronic acid. The ratio between hyaluronan synthase and hyaluronidase activities is an important factor of tumor malignization. Hyaluronan synthases localized on plasma membrane form a high-molecular-weight copolymer of D-glucuronic acid and *N*-acetyl-D-glucosamine. Megapolymers of hyaluronan inhibit proliferation and migration of cells. Fragmentation of hyaluronan is performed by hyaluronidases. The increased level of expression of hyaluronidase HYAL1 forming low-molecular-weight hyaluronan is observed in tumors. By contrast to high-molecular-weight forms, low-molecular-weight hyaluronan activates intracellular transduction of proliferative signals. The hyaluronan regulatory effects are realized through interaction with specific membrane receptors. Receptor CD44 takes part in all metabolic and signal transduction reactions of hyaluronan. The action of hyaluronan–CD44 receptor complexes depends on linear dimensions of the polymeric ligand. Binding of low-molecular-weight hyaluronan to CD44 activates protein kinase B and cascade of mitogen-activated protein kinases and initiates local angiogenesis and tumor growth. Hyaluronan megapolymer molecules have an inverse inhibitory effect on tumors due to high-valent CD44 clustering and competition with low-valent hyaluronic acid oligomer. Angiogenic effect is observed for hyaluronan fractions from 4 to 30 kDa. Oligomers of hyaluronic acid stimulate proliferation by activation of CD44 interaction with receptors of epidermal growth factor ErbB2 and focal adhesion kinase FAK. Tissue-specific receptor proteins execute more narrow functions. Receptors LYVE-1 and HARE take part in hyaluronan endocytosis and catabolism in lymphatic system, liver, kidney, and spleen. RHAMM controls migration and adhesive effects of hyaluronan in tumors. Toll-like TLR4 receptors stimulate tumor angiogenesis by activating the NF-κB signaling pathway in endothelial cells.

Keywords: hyaluronic acid, hyaluronan synthase, hyaluronidase HYAL1, receptor CD44, LYVE-1, RHAMM, HARE, TLR4, NF-κB

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CONTENT

INTRODUCTION

Hyaluronic acid is a major macromolecular component of connective tissue. For the first time, the compound has been isolated from vitreous humor, which is reflected in its name (*hyalos* is Greek for glass) [1]. In an aqueous medium, hyaluronic acid adopts an intermediate polyanionic form, hence "hyaluronan" is widely used as a synonym [2]. Chemically, the structure of the molecule is a copolymer of alternating residues of D-glucuronic acid and *N*-ace-

Abbreviations: AKT, protein kinase B (AKR thymoma oncogene); CD44, cluster of differentiation 44; ERK1/2, extracellular signal-regulated kinase 1/2; ERM, ezrin, radixin, moesin; EGFR, epidermal growth factor receptor; ErbB2, erythroblastic leukemia oncogene homolog B2; FAK, focal adhesion kinase; HARE, hyaluronan receptor for endocytosis; HAS1, 2, 3, hyaluronan synthases 1, 2, 3; HYAL1, 2, hyaluronidases 1, 2; IGF1R-β, insulin-like growth factor-1 receptor β; IκB, inhibitor kappa B; IKK, IκB kinase; LYVE-1, lymphatic vessel endothelial hyaluronan receptor 1; MAPK, mitogen-activated protein kinases; MD-2, myeloid differentiation factor 2; MEK1, mitogen-activated protein kinase; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PDGFR-β, platelet-derived growth factor receptor β; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; RHAMM, receptor for hyaluronan-mediated motility; TGFR, transforming growth factor receptor; TIR, Toll-interleukin-1 receptor; TIRAP, Toll-interleukin 1 receptor (TIR) domain containing adaptor protein; TLR4, Toll-like receptor 4; VEGFR3, vascular endothelial growth factor receptor 3.

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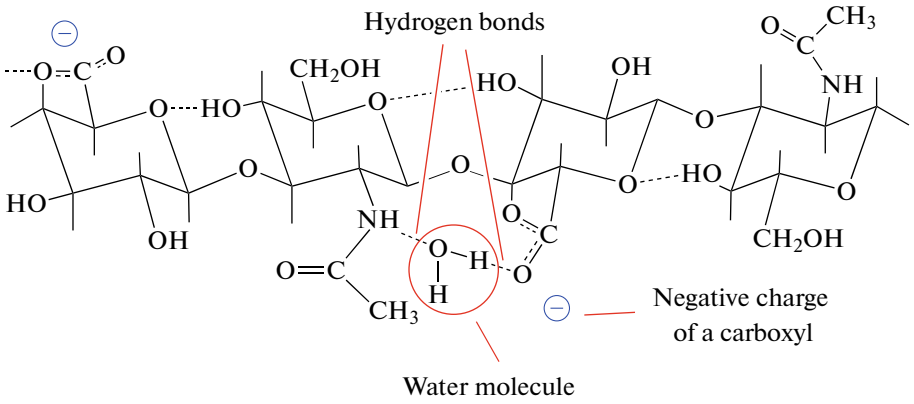

Fig. 1. Structure of hyaluronan in aqueous solutions. Dashed lines show intramolecular and intermolecular hydrogen bonds. Adapted from Fallacara et al. [3].

tyl-D-glucosamine linked via alternating β-1,4- and β-1,3-glycosidic bonds. β-Conformation of monosaccharides promotes the formation of energetically favorable configuration of the molecule with optimal arrangement of functional groups. Hyaluronic acid is the only non-sulfated linear glycosaminoglycan. In contrast to sulfated glycosaminoglycans, which interact with proteins predominantly through formation of covalently bound proteoglycans, hyaluronic acid mainly binds water in the interstitial tissue. Carboxy, hydroxy, and acetamide groups of the anionic heteropolysaccharide impart the molecule with hydrophilic properties. Water is fixed due to formation of intermolecular hydrogen bonds with carboxy and acetamide groups located in neighboring monomers of hyaluronan (Fig. 1) [3]. The number of solvated molecules depends on the length of the polymer.

Hyaluronan acts as the major depot of water in the extracellular matrix. High hygroscopicity determines such unique physicochemical properties of hyaluronan as elasticity as part of the hyaline cartilage, wettability of synovial fluid, and the ability to form gels. Gel viscosity depends on the size of the hyaluronan molecule and hydration shell mass [4]. Hyaluronan gels are nontoxic and actively used for synthesis of three-dimensional scaffolds in cell and tissue engineering. Scaffolds based on hyaluronan modified with vinyl groups are used in cellular therapy of skin burns [5]. The effects of molecular forms of hyaluronic acid include signaling mechanisms accompanying cell division, migration, and adhesion. Regulatory effects of hyaluronan are implemented upon interaction with specific receptors and influence nearly all stages of morphogenesis of normal and tumor tissues, participating in the activation or inhibition of cell proliferation in the function of the molecular weight of the ligand [6, 7]. Various types of hyaluronan molecules are formed as a result of the balanced effect of enzymes involved in the synthesis and hydrolysis of hyaluronic acid. Hyaluronan is characterized by a rather high rate of metabolism; approximately one third of hyaluronan content in the body is renewed daily [8].

BIOSYNTHESIS AND BIODEGRADATION OF HYALURONIC ACID

Enzymatic synthesis of hyaluronan is performed by homologous hyaluronan synthases HAS1, HAS2, and HAS3 integrated in plasma membrane of fibroblasts, macrophages, endotheliocytes of connective tissue, and epidermal keratinocytes [9, 10]. In contrast to most glycosaminoglycans, which are formed in the Golgi apparatus in parallel to structural proteins, hyaluronic acid is assembled from monosaccharides into a polymer chain directly at the surface of cell on the inner side of cell membrane. Synthesized molecules cross the membrane to enter the extracellular space through channels formed by hyaluronan synthases. The polymerization reaction utilizes uridine triphosphate (UTP) as an energy source. Monosaccharides react with UTP prior to polymerization, and after cleavage of one of the phosphate groups form a UDP-activated substrate. Addition of a monosaccharide unit to the chain and movement across the membrane is accompanied by UDP cleavage [11]. Genes encoding hyaluronan synthases HAS are localized on different chromosomes and are characterized by a different level of expression in function of cell type [12]. Hyaluronan synthase isoenzymes synthesize products of various lengths and provide for wide variability of physiological effects of hyaluronan in tissues. In mammalian cell cultures, HAS1 has been shown to synthesize a polymer with a mass in the range from 2×10^2 to 2×10^3 kDa. HAS2 produces larger molecules exceeding 2×10^3 kDa. Shorter chains of $\sim 1 \times 10^2$ kDa are typical of HAS3 [13]. In human and mouse, HAS1 and HAS2 synthesize polymers up to 4×10^3 kDa long, while HAS3 synthesizes rather short chains below 3×10^2 kDa. HAS3 possesses the highest enzy-

matic activity [14]. At the same time experiments in knockout mice showed that HAS2 plays the key role: the absence of the enzyme may cause preliminary death of the embryos [15]. Mice with knockout of *HAS1* and *HAS3* did not have deviations in the development and produced fertile offspring [16].

Hyaluronidase transcription level is regulated by growth factors and cytokines. Expression of HAS1 and HAS2 in dermal fibroblasts is activated by transforming growth factor TGF-β1 and chemokine SDF-1 [17, 18]. Epidermal growth factor EGF stimulates the expression of HAS2 and secretion of hyaluronan in epidermal keratinocytes [19]. In many tumor tissues individual isoforms of hyaluronan synthases are overexpressed and hyaluronan is accumulated prior to structural rearrangement and neovascularization of the tissue. Inhibition of the activity of HAS2 and HAS3 has been demonstrated to change the structure of pericellular matrix and stop mitotic activity of prostate tumor cells [20]. There are regulatory feed-back loops between synthesis and degradation of hyaluronic acid. For example, the work of the HAS1 and HAS2 enzymes leads to the increase in higher-molecular-weight hyaluronan concentration, in turn the high-molecular-weight fractions are capable of activation of hyaluronidases, the enzymes catalyzing hydrolysis of the macromolecules [21].

Hyaluronic acid is biodegraded through consecutive cleavage under the effect of several enzymes in function of initial parameters of the polymeric substrate. In human and mouse genomes, six homologous genes encoding enzymes with hyaluronidase activity have been located [22]. The function is mainly performed by ubiquitously expressed hyaluronidases HYAL1 and HYAL2 [23]. At the initial stages of hydrolysis of high molecular weight hyaluronan, the HYAL2 enzyme is active. At its *C* terminus, HYAL2 has a glycolipid, glycosylphosphatidylinositol, which fixes the enzyme in cell membrane. HYAL2 cuts extracellular hyaluronic acid into fragments of ~2 × 10 kDa. Then, hyaluronan molecules interact with membrane-bound receptor proteins, gather into clusters, and are packed into lipidic endosomes [24]. Internalization and endocytosis of the glycan–receptor complexes are clathrin-dependent processes [25]. Endosomes are being pulled inside the cell, where they lose the clathrin coating and fuse with lysosomes [26, 27]. In lysosomal vesicles, hyaluronan hydrolysis continues. The HYAL1 enzyme cleaves the molecules down to tetramers, and lysosomal hydrolases β-glucuronidase and β-*N*-acetylglucosaminidase transform them into individual di- and monosaccharides [8, 21, 22]. In tumors, hyaluronidase HYAL1 expression is often elevated. The enzyme is most active under conditions of acidosis typical of tumor tissues [28, 29]. Expression of the *HYAL1* gene in tumors has been shown to be regulated by epigenetic factors—methylation or demethylation of the promotor region [30]. Under normal physiological conditions, the activity of hyaluronidases is balanced. The HYAL2 enzyme forms hyaluronan fragments that can be pulled to endocytosis caveolae, and intracellular hyaluronidase HYAL1 reduces them to the size of the substrate used for synthesis of new hyaluronic acid [31].

Several proteins are involved in enzymatic reactions of biosynthesis and biodegradation of hyaluronan. The group comprises proteins that are able to form ionic bonds with hyaluronan. The proteins exhibiting this property form a heterogenous family of hyladherins. Hyladherins are present in the extracellular matrix, on cell membranes, and inside cells. They interact with hyaluronan via specific binding domains present in their structures. Usually, the binding domains contain a peptide fragment ~100 aa long that has been first isolated from cartilage proteins and then identified as a consensus-binding module. The ternary structure of the binding module is a globule of two α-helices and two antiparallel β-fold three-chain sheets, stabilized by two conservative disulfide bridges and capable of high-affinity binding with hyaluronan [32]. The structure of aggrecan binding module has been studied the most. Aggrecan is a proteoglycan that fixes hyaluronic acid together with water in the hyaline cartilage. *N*-Terminal globular subdomain G1 consists of an immunoglobulin module and a tandem of consensus-binding modules. Homologous subdomains G2 and G3 following the G1 subdomain are separated by glycosaminoglycan insert and participate in processing and secretion of aggrecan. At the *C* terminus, the transmembrane domain is located. Binding domains of most hyaluronan-binding proteins have a structure homologous to globular subdomain G1 of aggrecan in various combinations with immunoglobulin and transmembrane domains. Hyladherin BRAL1 specific for brain tissue is an aggrecan binding domain truncated at the C terminus with retained globular subdomain G1 at the N terminus. Binding domain of integral protein CD44 consists of a single consensus-binding module flanked by a transmembrane domain, a glycosaminoglycan insert, and a cytoplasm domain [33]. Hyladherins localized in cell membranes function as transmembrane receptors mediating the signaling effects of hyaluronan.

HOW HYALURONAN RECEPTORS SIGNAL

The most important membrane receptor of hyaluronan is the ubiquitously expressed integral glycopeptide CD44 involved in the binding of free molecules of extracellular hyaluronic acid for its further incorporation in endosomes [34]. In addition to endocytosis, the CD44 receptors are involved in transduction of proliferative signals of hyaluronan. Signaling function of the CD44–hyaluronan receptor complex is manifested through the ability to regulate cell proliferation, migration, and adhesion both independently and as a coreceptor of growth factors. In normal tissues, the standard isoform of CD44 is mainly pro-

duced. In keratinocytes, macrophages, and most often tumors, alternatively spliced CD44 variants are revealed. Additional exons are included in the transcript region encoding the extracellular domain [35]. For malignant tumors, constitutive expression of CD44 and alternative splicing are typical. Alternative isoforms of CD44 increase adhesion and survival of tumor cells through apoptosis inhibition [36]. Elevated concentration of hyaluronic acid is observed in tumors. Hyaluronan is the major ligand for all CD44 isoforms. Interaction of CD44 with high-molecular-weight hyaluronan promotes the formation of glycocalyx, which protects the cell from cytotoxic factors, while receptor complexes with low-molecular-weight hyaluronan fragments initiate cell migration and angiogenesis [37]. The action of CD44 is coupled to tyrosine kinase receptors and is switched to the proliferative cascades inside the cell. The ectodomain of CD44 that is posttranslationally modified with chondroitin sulfate, is able to bind the fibroblast growth factor FGF, vascular endothelial growth factor VEGF, and hepatocyte growth factor HGF [38, 39]. Post-translational phosphorylation of the transmembrane and cytoplasmic domains of CD44 increase its affinity to ectodomains of epidermal growth factor receptor EGFR, insulin-like growth factor receptor IGF1R-β, platelet-derived growth factor receptor PDGFR-β, and transforming growth factor receptor TGFR. Interaction of CD44 with growth factors and receptors thereof activates the phosphoinositide-3-kinase/AKT signaling pathway and the mitogen-activated protein kinase cascade, providing for higher survival and growth of tumor cells [40].

Effects of CD44 on migration are mediated by changes in cortical actin cytoskeleton. Cytoplasmic domain of CD44 can bind proteins of the Erm family. Three closely related protein paralogues—ezrin, radixin, and moesin—function as cross-linkers that bind plasma membrane to actin cytoskeleton [38]. In free state, ERM proteins form a closed ring inside which the *N*-terminal domain is linked to the *C* terminus of the same protein. Interaction of the *N*-terminal domain with the PIP2 phospholipid and phosphorylation of the conservative threonine at the *C* terminus breaks the ring and activates membrane-binding site at the *N* terminus and actin filament-binding site at the *C* terminus [41, 42]. *N*-Terminal domains of the ERM proteins are attached to the CD44 receptor through the ankyrin site. Ankyrins are involved in the attachment of cortical actin cytoskeleton to transmembrane proteins in erythrocytes and nervous tissue [43]. The central part of the molecule of the ERM proteins is represented by an α-helical segment that binds regulatory subunits of protein kinase A, while the *C*-terminal domain is fixed directly on β-actin [44]. An important signaling function of the ERM proteins is activation of protein kinase A and, at the same time, spatiotemporal compartmentalization of cAMP-dependent processes inside cells [45].

The CD44–hyaluronan receptor complexes possess the ability to interact with fibrillar proteins of connective tissue and matrix metalloproteinases involved in proliferative processes [40]. Membrane matrix metalloproteinase MT1-MMP cleaves the cytoplasm domain of CD44 that is translocated into the nucleus and activates transcription of the *NOTCH1* and *MMP-9* genes. The NOTCH1 protein contains multiple EGF-like repeats recognized by receptors of epidermal growth factor. Metalloproteinase MMP-9 destroys collagen of the extracellular matrix and participates in metastases development and tumor vascularization [35, 46].

Interaction with various growth factors, receptors of growth factors, cytokines, and proteins of connective tissue allows one to consider the CD44 receptor as a multifunctional regulator of primary importance with wide range of effects in inflammatory and regeneration processes in normal tissues and progressing tumors [24, 47, 48]. There are several membrane receptors of hyaluronan involved in regulation of proliferation together with CD44. First of all, these include glycoproteins LYVE-1, RHAMM, HARE, and Toll-like receptor TLR4, which perform more specialized functions [28]. Figure 2 shows the scheme of signaling effects of receptors regulating cell proliferation [49].

Glycoprotein LYVE-1 is a homolog of CD44 expressed primarily in blood and lymph vessels. LYVE-1 molecules work as ligand-specific transporters of hyaluronan from the surface of the plasma membrane to intracellular organelles in lymphatic endothelial cells and are involved in catabolism of hyaluronan in lymph nodes. Affinity of LYVE-1 to hyaluronan is higher than that of CD44 [50]. The binding domain of LYVE-1 is arranged in the same manner as the similar domain of the CD44 receptor. Composition of functional subdomains of the LYVE-1 molecule is identical to that of CD44, while the glycosaminoglycan subdomain is typical only for CD44 [51]. Despite the maximum likeness, the binding domain of LYVE-1 can have a more compact structure and higher susceptibility to ionic strength of the medium, which affects the formation of hydrogen bonds. While soluble CD44 monomers can interact with hyaluronan individually, LYVE-1 receptors first need to form dimers. Supposedly, in contrast to CD44, dimers of the LYVE-1 receptors bind and transport primarily high-molecular-weight hyaluronan inside cells, thus initiating intracellular catabolism. Coexpression of LYVE-1 and vascular endothelial growth factor receptor VEGFR3 has been demonstrated. The VEGFR3 receptors are markers of lymphatic endothelium; simultaneous detection with LYVE-1 can be used for diagnostics of tumor lymphangiogenesis [52].

Migration and mitogen effects of hyaluronan are associated with the participation of the second most important receptor after CD44, RHAMM. In experiments with CD44-deficient mice RHAMM has been established to activate and maintain inflammation

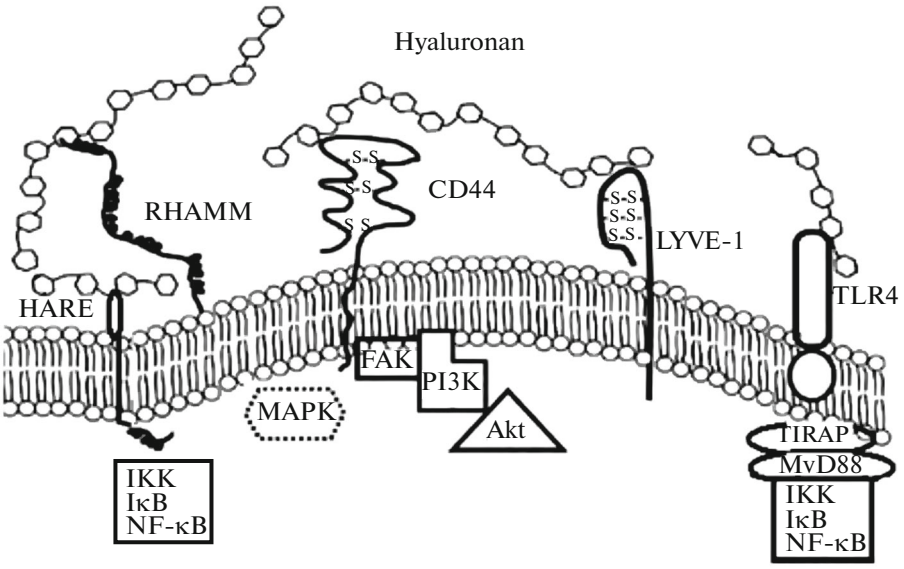

Fig. 2. Membrane receptors of hyaluronan participating in progression of tumors. HARE, hyaluronan endocytosis receptor; RHAMM, receptor of hyaluronan-mediated motility; CD44, primary hyaluronan receptor; LYVE-1, lymphatic endothelial receptor of hyaluronan 1; TLR4, Toll-like receptor; IKK, inhibitor of transcription factor κB kinase; IκB, inhibitor of transcription factor kappa B; NF-κB, transcription factor κB; MAPK, mitogen-activated protein kinase; FAK, focal adhesion kinase; PI3K, phosphoinositide-3-kinase; Akt, protein kinase B; TIRAP, adhesion protein comprising the Toll-like receptor and IL-1 homology domain TIR; Myd88, adaptor protein containing the TIR domain. Adapted from Alaniz et al. [49].

processes even more efficiently than CD44 [53]. Progression of tumors is usually accompanied by overexpression of RHAMM and alternative splicing. Alternatively spliced variants of RHAMM have various localizations within the cell. RHAMM proteins are fixed both on the outer membrane and inside the cell in the cytoskeleton and nucleus. The effect of RHAMM molecules is aimed at stimulation of cell motility [54, 55]. The function of the RHAMM binding domain is performed by a tandem of unique BX_7B motives representing a sequence of seven positively charged amino acids flanked by lysine or arginine [56]. The RHAMM protein lacks a transmembrane domain and is usually localized inside the cell. The exit to the external membrane occurs under the effect of cytokines, particularly the transforming growth factor TGF-β. On the surface of the cell, RHAMM can form receptor complexes with CD44 and EGFR and initiate tumor progression [57]. In cytoplasm, RHAMM molecules are found in association with the tubulin cytoskeleton and interact with cancer susceptibility proteins BRCA1, participating in joint regulation of mitosis. Inside cells, the hyaluronan–RHAMM complex activates the MEK1/ERK1/2 signaling the cascade and transport of mitogen-activated kinases inside the nucleus [58, 59].

The HARE receptor is expressed in sinusoidal endothelial cells of liver, spleen, and lymph nodes, as well as the eye lens epithelium, renal collecting tubules, and ovary duct [60]. Liver, kidney, and spleen, together with lymph nodes, form a common system of recirculation of hyaluronic acid in the body. Hyladherin HARE functions as a membrane adsorbent of hyaluronan that purifies the blood and lymph of the catabolism products. The effect of the HARE receptors is based on clathrin-mediated endocytosis of hyaluronic acid. Clusters of the hyaluronan–HARE receptor complexes aggregate the AP2 adaptor proteins bound to phosphoinositides of the plasma membrane and clathrin shell. In contrast to other hyaluronan receptors, HARE are primarily found in the state of adhesion with proteins of clathrin vesicles and continuously circulate between extra- and intracellular compartments [61]. The binding module of HARE contains a transmembrane domain and four unique motifs in the cytoplasm compartment directly involved in hyaluronan binding. Binding motifs have the following amino acid compositions: M1, $YSYFRI^{2485}$; M2, $FQHF^{2495}$; M3, $NPLY^{2519}$, and M4, DPF^{2534}. Deletion analysis showed that the M3 motif is the most important for hyaluronan endocytosis [62]. The signaling function of the HARE receptors has been demonstrated in the experiments on ligand specificity of the hyaluronan–HARE receptor complexes. The HARE receptors activated the ERK1/2 mitogen cascade and stimulated the expression of NF-κB-induced genes in a dose-dependent manner. The stimulatory effect of the HARE receptors is implemented exclusively upon the interaction with intermediate fractions of hyaluronic acid of 40–400 kDa [63, 64]. The HARE receptors are active only as dimers. Presumably, binding of megamolecular hyaluronic acid distorts and impairs the functionally active conformation of dimers. In turn, too short fragments are not capable of activation and stabilization of dimers due to insufficient size. Possessing the

properties of a signaling receptor reacting to intermediate products of hyaluronan degradation, HARE can perform the function of a detector of connective tissue degradation under stress conditions and oncogenesis [65].

Antigen-presenting, epithelial, and endothelial cells express Toll-like receptor TLR4 [66, 67]. Recently, data on TLR4 expression in tumors have been reported [68, 69]. Degradation of connective tissue in the course of inflammatory processes and carcinogenesis is accompanied by accumulation of low-molecular-weight hyaluronan. TLR4 receptors are capable of binding low-molecular-weight fractions of hyaluronic acid. The ectodomain comprising tandem copies of leucine-rich repeats (LRR) functions as the binding module [70]. Interaction of TLR4 with hyaluronan is mediated by the MD-2 cofactor, and the TIR domains transmit the signal inside the cell [71]. Ultimately, the signaling pathway of a transcription factor NF-κB is activated [72]. Here, hyaluronan acts as an oligosaccharide ligand stimulating innate cellular immunity [73]. Reception of oligosaccharides induces formation of dimers from inactive monomers of the TLR4–MD-2 complex. Pairing of the TLR4 molecule along its whole length promotes the formation and activation of a duplex of homologous TIR domains in the cytoplasmic part of the complex. Activated TLR4 receptors interact with intracellular adaptor proteins TIRAP and MyD88, which contain similar TIR domains. TIR domains of TLR4, TIRAP, and MyD88 form intermolecular bonds and switch the signal of TLR4 receptors onto the IKK complex. Kinase IKK phosphorylates the IκB inhibitor of a transcription factor NF-κB. Phosphorylation of IκB releases and translocates inside the nucleus the NF-κB dimers for participation in regulation of transcription of genes responsible for cell proliferation and apoptosis [74]. Reception of oligomeric hyaluronan has been shown to cause antiapoptotic effect and increase cell survival [75]. In mutant mice, in the absence of TLR4 receptors in the lung epithelium, decrease of basal activity of NF-κB signaling pathway, and increase in cell apoptosis was observed [76, 77].

CARCINOGENIC EFFECTS OF LOW-MOLECULAR-WEIGHT HYALURONAN

An important feature of interaction between hyaluronic acid and hyladherins is the ability of the macromolecular polyvalent ligand to bind simultaneously dozens of various receptors and proteins. This is accompanied by integration of intracellular processes and the spread of signals to adjacent cells [28, 78]. As a substrate and simultaneously a ligand, hyaluronic acid molecule physically connects hyaluronan synthase HAS2 and hyaluronidase HYAL2 with the CD44 receptor localized on plasma membrane of cells. This complex controls fragmentation of hyaluronan and functions as a means of autocrine regulation of cell motility, which plays an important role at first stages of tumor metastasis [79]. Another important parameter for functioning of hyaluronan–receptor complexes is the dependence on the ligand size [8]. Under normal physiological conditions hyaluronan is represented primarily by megapolymers with molecular weight above 10^3 kDa. Native hyaluronic acid possesses anti-inflammatory and antiangiogenic properties due to the ability to inhibit intercellular interactions [80]. Insusceptibility to cancer in *Heterocephalus glaber* correlates with increased content of high-molecular-weight hyaluronan in tissues. In this case, accumulation of the compound is associated with a particularly stable structure of hyaluronan synthase HAS2 simultaneously with decreased activity of hyaluronidases [81]. Most epithelial and mesenchymal cells to one degree or another have the ability to synthesize and secrete high-molecular-weight hyaluronan [11, 82]. Hyaluronidase HYAL2, acting together with the CD44 receptor, forms intermediate fractions of hyaluronan cutting the native hyaluronic acid into fragments of ~10^1–10^3 kDa [83]. Low-molecular-weight hyaluronan is generated by hydrolytic activity of HYAL1. The enzyme localized in lysosomes is involved in intracellular catabolism of hyaluronan. The free soluble form of HYAL1 is present in blood serum, synovial fluid, and urine [84]. Hyaluronan oligomers have a rigid linear structure, while megapolymers can bend and adopt a helical shape [85]. Taking into account the differences in their properties, hyaluronans are usually divided into several categories. High-molecular-weight hyaluronans are 10^3–10^4 kDa and higher. Intermediate length hyaluronans are 10^2–10^3 kDa. Smaller fractions are referred to low-molecular-weight hyaluronan and the oligomers [63].

In many tumors, overexpression of hyaluronan synthases and accumulation of high-molecular-weight hyaluronan is observed at the initial stages of tumor growth. One of the specific features of gastrointestinal carcinomas and adenocarcinomas is the ectopic production of hyaluronan. Further development of pathological processes is accompanied by enhanced activity of hydrolytic enzymes. Acidosis of the environment typical of a progressive tumor stimulates the expression of hyaluronidase HYAL1. At low pH, the HYAL1 enzyme generates an additional pool of short-chain oligomers of hyaluronan, which trigger reorganization of the extracellular matrix [28]. The formation of low-molecular-weight fragments of hyaluronan in connective tissue is tightly linked with tumor malignization [86]. Interaction of hyaluronan oligomers with CD44 initiates phosphorylation and activation of tyrosine kinase receptors of growth factors and is involved in the formation of a signaling complex phosphoinositide-3-kinase (PI3K)/protein kinase B (AKT), which is responsible for the escape from apoptosis and proliferation of tumor cells [87]. The signaling process of protein kinase B is directed at activation

of cell migration [88]. At the same time, the hyaluronan–CD44 receptor complex activates FAK (focal adhesion kinase), which regulates the structure of cortical cytoskeleton and polarity in migrating cells [89]. The action of low-molecular-weight hyaluronan through TLR4 receptors stimulates the NF-κB signaling pathway and secretion of metalloproteinase involved in reorganization of the extracellular matrix [90].

Currently, several variants of involvement of hyaluronic acid in tumor progression are being considered. Freshly synthesized hyaluronic acid forms a glycocalyx layer, which protects the tumor cell from mechanical damage and cytotoxic effects. The hyaluronan glycocalyx takes part in communication and adhesion of metastasizing cells. Short fragments of hyaluronan activate proliferation and angiogenesis in tumor cells. Mitogenic and angiogenic effects are implemented through receptors CD44, RHAMM, and TLR4. After recognition of low-molecular-weight hyaluronan, dendritic cells carrying the TLR4 receptors are activated and transformed into mature form capable of synthesis and secretion of vascular endothelial growth factor VEGF [91]. VEGF stimulates tumor angiogenesis. Interaction of hyaluronan with the RHAMM receptors localized on endotheliocytes enhances the growth and migration of cells acting through the MEK1/ERK1/2 signaling cascade [58, 92]. In tumor cells constitutively expressing the CD44 receptor, the binding of low-molecular-weight hyaluronan induces phosphatidylinositol-3-kinase pathway and multiplies the production of metalloproteinases 2 and 9. Metalloproteinases destroy the components of extracellular matrix and promote further growth and germination of blood vessels into tumor tissue [93, 94]. Detailed analysis of the dependence of angiogenesis on the size of the ligand in the CAM (chicken chorioallantoic membrane) model of hematopoiesis showed that hyaluronan weighing 4–20 kDa possesses the most pronounced angiogenic properties. Smaller fragments do not cause the effect, while larger molecules inhibit proliferation and migration of endotheliocytes [95]. Interaction of low-molecular-weight hyaluronan with receptors CD44 and RHAMM initiates cell migration to blood and lymphatic vessels and the formation of secondary metastases [96]. The high concentration of metabolites of hyaluronic acid in connective tissue is the factor stimulating tumor progression.

CONCLUSIONS

Hyaluronic acid (hyaluronan) is the major macromolecular component that determines physicochemical properties of the extracellular matrix. Hyaluronan is a linear nonsulfated glycosaminoglycan possessing hygroscopic properties and polyaffinity involved in migration, adhesion, and aggregation of proliferating cells. Interaction with membrane receptors determines signaling functions of hyaluronic acid. First of all, secreted hyaluronan molecules bind a ubiquitously expressed receptor CD44. The CD44–hyaluronan receptor complexes participate in intracellular transduction of proliferative signals of cytokines and growth factors. Regulatory effects of the receptor complexes depend on the molecular weight of hyaluronan. In tumor cells, the elevated level of the HYAL1 hyaluronidase and high concentration of low-molecular-weight fragments (<100 kDa) of hyaluronic acid are observed. In contrast to high-molecular-weight hyaluronic acid, low-molecular-weight hyaluronan stimulates proinflammatory and angiogenic processes in tumors. Tissue-specific membrane receptors of hyaluronan, which do not possess the universal properties of CD44 and perform specialized functions, are involved in the implementation of signaling effects of hyaluronan. Receptor LYVE-1 is expressed in lymphatic vessels and functions as a ligand-specific transporter of hyaluronan from the cell surface to lysosomes. Dimers of LYVE-1 receptor possess higher affinity to hyaluronan than CD44 molecules and interact primarily with high-molecular-weight hyaluronan. The RHAMM receptors are localized both outside and inside cells providing for migration and adhesion effects of hyaluronan in tumors. Endothelial receptors HARE, together with CD44, are involved in clathrin-mediated endocytosis in the liver, kidney, and spleen. The HARE receptors adsorb and purify blood and lymph from intermediate products of hyaluronan catabolism, continuously circulating between extracellular and intracellular compartments. Toll-like receptors TLR4 bind low-molecular-weight hyaluronan. Short oligomers initiate the formation of active TLR4 dimers, interaction with cytoplasmic adaptor proteins, activation of transcription factor NF-κB, and enhancement of transcription of genes responsible for proliferation and antiapoptosis. Regulation of hyaluronic acid metabolism is a significant factor in tumor progression. The effect of high-molecular-weight hyaluronan is linked primarily to the formation of protective adhesive glycocalyx. Low-molecular-weight hyaluronan performs the function of a receptors' ligand that activates proliferation, migration, and antiapoptotic processes in tumor cells.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any research involving humans or animals as research objects.

Conflict of Interests

The authors declare no conflicts of interest.

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