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Review

Hyaluronan-mediated CD44 activation of RhoGTPase signaling and cytoskeleton function promotes tumor progression

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ABSTRACT

Hyaluronan (HA), a major component of the extracellular matrix (ECM), is enriched in many types of tumors. In cancer patients HA concentrations are usually higher in malignant tumors than in corresponding benign or normal tissues, and in some tumor types the level of HA is predictive of malignancy. HA is often bound to CD44 isoforms which are ubiquitous, abundant, and functionally important cell surface receptors. This article reviews the current evidence for HA/CD44-mediated activation of the ankyrin-based cytoskeleton and RhoGTPase signaling during tumor progression. A special focus is placed on the role of HA-mediated CD44 interaction with unique downstream effectors (e.g., the cytoskeletal protein, ankyrin and/or various GTPases (e.g., RhoA, Rac1 and Cdc42)) in coordinating intracellular signaling pathways (e.g., Ca^{2+} mobilization, Rho signaling, PI3 kinase-AKT activation, NHE1-mediated cellular acidification, transcriptional upregulation and cytoskeletal function) and generating the concomitant onset of tumor cell activities (e.g., tumor cell adhesion, growth, survival, migration and invasion) and tumor progression. I believe this information will provide valuable new insights into poorly understood aspects of solid tumor malignancy. Furthermore, the new knowledge concerning HA/CD44-mediated oncogenic signaling events will have potentially important clinical utility, and could establish CD44 and its associated signaling molecules as important tumor markers for the early detection and evaluation of oncogenic potential. It could also serve as ground work for the future development of new drug targets to inhibit HA/CD44-mediated tumor metastasis and cancer progression.

Contents

Abbreviations: HA, hyaluronan; ECM, extracellular matrix; ARD, ankyrin repeat domain; ERM, Ezrin/Radixin/Moesin; IP_3, inositol 1,4,5 trisphosphate; GEFs, guanine nucleotide exchange factors; RGS, regulator of G-protein signaling; DH, dbl homology; PH, pleckstrin homology; ROK, Rho-kinase; PI3 kinase, phosphatidylinositol 3-kinase; Gab-1, Grb-2-associated binder-1; NHE, Na^+–H^+ exchanger; LARG, leukemia-associated Rho guanine nucleotide exchange factor; Tiam1, T-lymphoma invasion and metastasis; PLCε, phosphoinositide-specific phospholipase C-ε; CaMKII, Ca^{2+}/calmodulin-dependent kinase-II; ERKs, extracellular signal-regulated kinases.

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1. Hyaluronan (HA) and CD44 in tumor progression

Tumor invasion and metastasis are the primary causes of morbidity in patients diagnosed with solid tumors such as breast cancer [1], ovarian cancer [2] and squamous cell carcinomas (SCC) [3]. It is now certain that both oncogenic signaling and cytoskeleton functions are directly involved in tumor cell growth, migration, invasion of surrounding tissue, and metastasis [4,5]. A number of studies have aimed at identifying these molecules which are specifically expressed by epithelial tumor cells which correlate with metastatic behavior. Among such molecules is hyaluronan (HA), a major component in the extracellular matrix (ECM) of most mammalian tissues. HA is a nonsulfated, unbranched glycosaminoglycan consisting of repeating disaccharide units, D-glucuronic acid and *N*-acetyl-D-glucosamine [6,7]. HA is synthesized by specific HA synthases [7,8] and digested into various smaller-sized molecules by various hyaluronidases [9]. HA is enriched in many types of tumors [10,11]. In cancer patients, HA concentrations are usually higher in malignant tumors than in corresponding benign or normal tissues; and in some tumor types the level of HA is predictive of malignancy [11]. For example, HA levels have been shown to be elevated in the serum of breast cancer patients [12].

HA interacts with a specific cell surface receptor, CD44, which belongs to a family of multifunctional transmembrane glycoproteins expressed in numerous cells and tissues including tumor cells and carcinoma tissues [13–28]. CD44 is often expressed in a variety of isoforms, products of a single gene generated by alternative splicing of variant exons inserted into an extracellular membrane-proximal site [29,30]. In fact, the expression of certain CD44 variant (CD44v) isoforms has been found to be closely associated with tumor progression [13–28]. All CD44 isoforms contain a HA-binding site in their extracellular domain, and thereby serve as a major cell surface receptor for HA [31]. Recently, it has been demonstrated that HA is rich in stem cell niches [32]. CD44 is expressed in both normal and tumor stem cells (displaying unique ability to initiate normal and/or tumor cell-specific properties) and CD44 has been suggested as one of the important surface markers for both normal stem cells and cancer stem cells [33]. The fact that both CD44 and HA are overexpressed at sites of tumor attachment and HA binding to CD44 stimulates a variety of tumor cell-specific functions and tumor progression [13–28] suggests that HA–CD44 interaction is a critical requirement for tumor progression.

2. HA–CD44 interaction with the cytoskeletal protein, ankyrin

CD44 interacts with a number of membrane-associated cytoskeletal proteins, such as ankyrin, which are expressed in a variety of biological systems [14,34]. Ankyrin contains three functional domains: a conserved N-terminal ankyrin repeat domain (ARD) (consisting of 22–24 tandem repeats of 33 amino acids with a consensus sequence such as -G-TPLH-AA–GH—V/A–LL–GA–ND—); a spectrin binding domain; and a variably sized C-terminal regulatory domain [35] (Fig. 1). CD44 binds directly to the ARD of ankyrin through a conserved ankyrin-binding domain in the CD44 cytoplasmic region. This CD44–ankyrin interaction causes cytoskeleton activation and results in several important HA-mediated functions such as cell adhesion, proliferation and migration [14,34,36–38].

In most cell types the plasma membrane contains specialized microdomains, called lipid rafts that have distinct lipid and protein compositions [39]. One type of lipid raft forms invaginated plasma membrane domains, termed caveolae, and is known to contain caveolin, flotillin, cholesterol and sphingolipids [39]. The functional importance of lipid rafts is clearly indicated by the recruitment of key signaling molecules into raft structures during the propagation of signal cascades [39]. Both CD44 and ankyrin have been found to be co-localized with caveolin in lipid rafts [40,41]. Ankyrin also binds to intracellular Ca^{2+} channels such as the inositol 1,4,5 trisphosphate (IP_3) receptor. Most importantly, ankyrin binding to IP_3 receptors is known to modulate IP_3 binding and Ca^{2+} activity [36,42–44]. In addition, ankyrin is involved

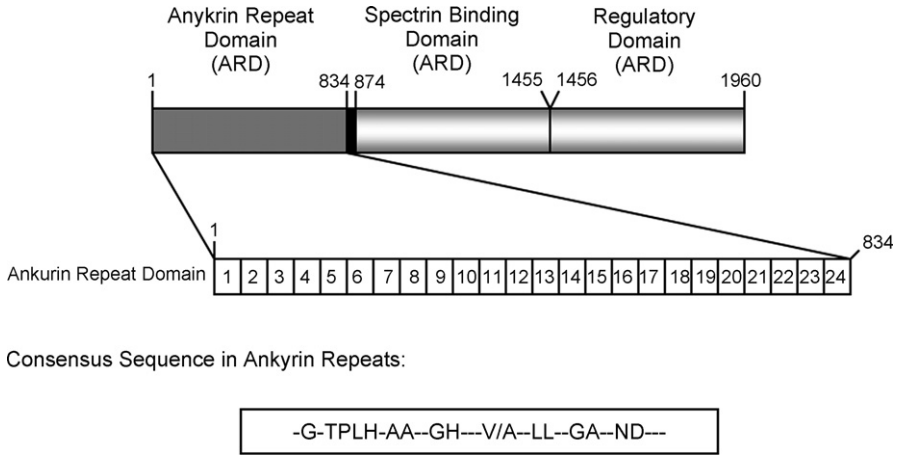

Fig. 1. Schematic illustration of ankyrin structure. Ankyrin contains ankyrin repeat domain (ARD) (with consensus sequence -G-TPLH-AA–GH—V/A–LL–GA–ND—), spectrin binding domain (SBD) and regulatory domain (RD).