Chapter 18
Exploiting Hyaluronan-CD44 Network in Tumor Therapy

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Abstract Cancer is one of the leading causes of death worldwide. During tumor development and progression, extracellular matrix is being intensively re-organized. One of the most abundant molecules in the extracellular matrix is the polysaccharide hyaluronan. Hyaluronan accumulation and high CD44 expression—the major hyaluronan cellular receptor—correlate with higher malignant states of cancer cells, increased incidence of metastases and poor prognosis of the patients in a wide array of tumor types. Thus, hyaluronan interaction with CD44 emerges as an important target for cancer treatment. In this chapter, recent efforts to exploit hyaluronan/CD44 network for tumor therapy are being discussed. Overall, there is a wide variety of tools available to target this system like anti-CD44 antibodies and peptides, gene therapies against CD44, nanotechnology and modified-hyaluronan. Initial in vivo evidence shows promising results, nominating hyaluronan/CD44 network targeting as a potent candidate to be introduced into clinical settings for tumor therapy.

18.1 Introduction

Cancer is one of the most common-occurring diseases and one of the leading causes of death worldwide. During cancer development, progression, and metastasis, the extracellular matrix is extensively re-organized (Theocharis et al. 2016; Larsen et al. 2006). One of the most abundant molecules in the extracellular matrix is the polysaccharide hyaluronan, which is differentially regulated during tumorigenesis. Physiologically, hyaluronan is found in many tissues such as the skin and the cartilage, where owing to its viscoelastic properties regulates several physiological characteristics of the tissues as well as proper cell function. In cancer, hyaluronan

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metabolism is altered compared to normal tissues and contributes to acquirement of tumor cell malignant properties (Skandalis et al. 2020; Karousou et al. 2017; Heldin et al. 2019). One of the main hyaluronan receptors, CD44, is considered a tumor promoter for most malignancies and plays significant roles in the regulation of cancer cell survival, proliferation, migration, invasion, metastasis, differentiation and drug resistance (Skandalis et al. 2019; Misra et al. 2011; Morath et al. 2016). Given the important roles of hyaluronan and its receptor CD44 in cancer, targeting this system opens a new avenue for the treatment of malignant diseases. Thereby, here we summarize the latest developments in the field of hyaluronan/CD44 network targeting for tumor therapy.

18.1.1 Hyaluronan Synthesis and Catabolism

Hyaluronan is a glycosaminoglycan consisting of repeating disaccharide units of N-acetyl-glucosamine (GlcNAc) and D-glucuronic acid (GlcUA), bound through alternate β1–3 and β1–4 linkages (Weigel 2015). Hyaluronan is synthesized in the plasma membrane by specific enzymes termed hyaluronan synthases (HASes). Three hyaluronan synthases have been described in the human genome, HAS1–3, which are encoded by distinct genes. HAS1 is found in 19q13.41 (www.genecards.org, GCID: GC19M054887), HAS2 in 8q24.13 (www.genecards.org, GCID: GC08M121594) and HAS3 in 16q22.1 (www.genecards.org, GCID: GC16P069105). Currently there is no information regarding their protein structure, but it is known that they have six transmembrane domains as well as UDP-sugar binding regions (Weigel 2015). Although the three hyaluronan synthases are structurally related they display different spatio-temporal expression and activities. For example, higher expression of HAS1 can be found in adipose tissue and the ovary, HAS2 is highly expressed in the adipose tissue, while HAS3 is expressed in urinary bladder, esophagus, and the lung (proteinatlas.org). Hyaluronan synthases synthesize hyaluronan of different molecular weights. Specifically, HAS2 synthesizes hyaluronan with molecular weight higher than 2×10^6 Da, in contrast to HAS1 and HAS3 which produce hyaluronan ranging from 2×10^5 to 2×10^6 Da (Itano et al. 1999). Furthermore, HAS1 displays the lowest catalytic activity compared to the other HASes, while HAS2 is less active than HAS3. Moreover, HAS1 exhibits higher Km values for both UDP-GlcUA and UDP-GlcNAc compared to HAS2 and HAS3 (Itano and Kimata 2002).

These membrane-embedded glycosyl-transferases utilize as substrates UDP-GlcUA and UDP-GlcNAc which are derived from various metabolic pathways inside the cells (Vigetti et al. 2012; Flores-Diaz et al. 1997). Accordingly, the availability of UDP-sugars is a major factor that regulates hyaluronan biosynthesis (Hascall et al. 2014; Rilla et al. 2013). This in turn suggests that specific microenvironment conditions regulate hyaluronan production, since it has been shown that high glucose upregulates hyaluronan synthesis (Wang et al. 2014). Moreover, the presence of Mg^{2+} is crucial for hyaluronan production (Weigel 2015). The

enzymatic activity of HASes is also regulated by their sub-cellular localization and trafficking from and toward the plasma membrane, where hyaluronan is normally synthesized. HAS1 is mainly localized in Golgi, HAS3 in Golgi and membrane protrusions, while HAS2 is found in the endoplasmic reticulum. The fact that HASes mainly reside inside the cells suggests that there is a reservoir of enzymes ready to translocate in plasma membrane and produce hyaluronan upon stimulation (Torronen et al. 2014). Indicative of this notion is the finding that HAS3 synthesizes a pericellular hyaluronan stroma after its translocation to the plasma membrane (Deen et al. 2014). Furthermore, hyaluronan synthase activity is also regulated by post-translational modifications such as *O*-GlcNAcylation (Vigetti et al. 2012), poly- and mono-ubiquitinylation (Karousou et al. 2010; Mehic et al. 2017) and phosphorylation (Vigetti et al. 2011), while homo- and hetero-dimerization of HAS2 with any of the other synthases leads to concomitant increase in hyaluronan production (Karousou et al. 2010; Bart et al. 2015).

HAS gene regulation is another crucial factor that controls hyaluronan production by the cells in different tissues. Different transcription factors bind to the promoter of each *HAS* gene and control their expression. Specifically, *HAS1* gene contains binding elements for SP1/3, SMAD, and E2F-myc. *HAS2* is regulated by the binding of CREB, NF-κB, RAR, STAT3, YY1, ZEB1, E2F-myc, and SP1, while HAS2-AS1 encoding—a long non-coding RNA that also regulates hyaluronan production by HAS2—is controlled by NF-κB, SP1/3, SMAD and HIF1α. Finally, *HAS3* expression is controlled by binding of ΔN-p63, NF-κB, C/EBP and SP1 in its promoter regions (Heldin et al. 2019).

Furthermore, hyaluronan synthesis is tightly regulated by several growth factors that by inducing intracellular signaling pathways control the expression of several HAS isoforms. The effect of each growth factor on hyaluronan synthesis is cell- and tissue-type-specific. Such growth factors include PDGF-BB, TGF-β, TNFα and IL-1, among others (Heldin et al. 2019).

Hyaluronan amount in the tissues is also modulated by catabolism from specific hyaluronan-degrading enzymes termed hyaluronidases (HYALs). In human, hyaluronan is recycled with high rates. Almost one-third of the total hyaluronan amount can be found in the skin and its half-life ranges from one to one and a half day (Pandey et al. 2008). Hyaluronan in the tissues has initial size about 1000–10,000 kDa and is degraded in the extracellular space in smaller fragments (10–100 kDa) (Fraser et al. 1997). Next, most of these generated fragments are drained through the lymphatic system and degraded in the lymph nodes. The remaining fragments enter the bloodstream and are finally removed by the liver, kidneys, and spleen (Pandey et al. 2008).

In the human genome, several hyaluronidase genes have been found and are encoded by different genes. HYAL-1 and HYAL-2 are widely expressed in several tissues.

HYAL-2 bears a glycosyl-phosphatidyl-inositol (GPI) tail which anchors the protein to the outside of plasma membrane mainly in lipid rafts, together with hyaluronan receptor CD44. HYAL-3 function despite its wide expression has not been fully deciphered (Shuttleworth et al. 2002; Flannery et al. 1998), HYAL-4

degrades chondroitin sulfate (CS) chains, while PHYAL-1 is a pseudogene and is not expressed in human. PH-20/SPAM1 is a hyaluronidase that is expressed in the testis and displays significant hyaluronan degrading activity (Cherr et al. 2001; Baba et al. 2002). Until recently, the widely recognized model for hyaluronan degradation suggested that hyaluronan residing in the extracellular space is degraded initially by HYAL-2 in 20 kDa fragments which then enter the cell by endocytosis through caveolae pathways in endosomes and transported to lysosomes for further degradation to disaccharides by HYAL-1 and exoglycosidases (Montanari et al. 2018). Recently, two new hyaluronidases that need to fit into the scheme of hyaluronan catabolism were discovered, HYBID/CEMIP/KIAA1199 and TMEM2. The transcription and translation of *CEMIP/KIAA1199* gene produces a 153 kDa protein that contains a 30 amino acid N-terminal domain that is required for hyaluronan degradation (Yoshida et al. 2013b). Moreover, it contains seven *N*-glycosylation sites, one G8 domain, two GG, and four PbH1 regions. The GG regions seem to be implicated in the process of hyaluronan degradation, G8 domain in interaction with other proteins and PbH1 in poly-saccharide hydrolysis (Guo et al. 2006; He et al. 2006; Birkenkamp-Demtroder et al. 2011; Yoshida et al. 2013a). Hyaluronan degradation by HYBID is performed by endocytosis in clathrin-coated vesicles with acidic pH, while the resulting hyaluronan fragments are released in the extracellular space (Yoshida and Okada 2019). The *TMEM2* gene product is a transmembrane protein of 154 kDa. The hyaluronidase TMEM2 contains one G8, one GG, and three PbH1 domains in the extracellular region, a transmembrane region, and a cytoplasmic tail (Yamaguchi et al. 2019). In contrast to HYAL-1/-2 which degrade hyaluronan in acidic pH, TMEM2 has optimal pH of enzymatic activity at 6–7. TMEM2 is located in plasma membrane and degrades extracellular hyaluronan in fragments of intermediate size, which then are endocytosed and degraded further in the lysosomes. The enzymatic activity of TMEM2 requires Ca^{2+} as a co-factor (Yamaguchi et al. 2019; Yamamoto et al. 2017). Finally, hyaluronan can be degraded by non-enzymatic ways by the action of reactive oxygen species (ROS) produced by diverse cellular metabolic pathways (Soltes et al. 2006; Agren et al. 1997).

18.1.2   CD44

Hyaluronan synthesized in the plasma membranes is subsequently extruded to the extracellular space where it can interact with several extracellular proteins, such as the proteoglycan family hyalectans, or plasma membrane receptors, and thus regulate several cell functional properties. The hyaluronan receptors discovered so far include CD44 (Cluster of Differentiation 44), RHAMM (Receptor for Hyaluronan-Mediated Motility), HARE/STAB2 (Hyaluronic Acid Receptor for Endocytosis/Stabilin-2), Laylin, Stabilin-1 and LYVE-1 (Lymphatic Vessel Endothelial Hyaluronic Acid Receptor 1).

The major and best characterized receptor for hyaluronan is CD44, which is expressed in various cell types and tissues. *CD44* gene is located in 11p13

(genecards.org) and its transcript mRNA is subjected to alternative splicing which after translation leads to encoding of several different isoforms of the receptor. Human *CD44* gene contains 19 exons, 10 standard (S1–10) and 9 variants (V2–10). The S1–10 exons are retained in all CD44 isoforms. CD44s (CD44 standard) isoform does not contain any of the V2–10 exons, while alternative splicing of V2–10 gives rise to CD44v (CD44 variants). From the mRNA translation the final product is a transmembrane protein with an extracellular region containing a LINK domain—which is responsible for hyaluronan/CD44 interactions—and a stalk-like domain—in which the exons V2–V10 are introduced—a transmembrane region, and a small cytoplasmic tail. The extracellular domain is modified by *O*- and *N*-glycosylations, while specific CD44 isoforms, such as CD44v3, bear covalently bound glycosaminoglycan chains (chondroitin sulfate or heparan sulfate chains), contributing further diversity to the resulting proteins. The cytoplasmic tail of CD44 despite not containing intrinsic kinase activity regulates several signaling pathways through interactions with cytoplasmic proteins such as Src, ERM (Ezrin, Radixin, Moesin) and IQGAP1 (Zoller 2011; Skandalis et al. 2010). Moreover, CD44 intracellular domain can be cleaved by γ-secretase and translocated to the nucleus where it regulates the expression of several genes (e.g., MMP9) (Miletti-Gonzalez et al. 2012). Apart from cellular signaling, CD44 can also participate in the endocytosis of hyaluronan, leading to its degradation (Thankamony and Knudson 2006; Skandalis et al. 2020).

18.2   Roles of Hyaluronan-CD44 Network in Tumors

Apart from the diverse roles of hyaluronan and its receptor CD44 in physiological processes like embryogenesis and cartilage function they play significant roles in tumor development and progression. In tumors, hyaluronan creates a highly hydrated extracellular matrix with specific physicochemical properties which allows cancer cells to proliferate and migrate. Moreover, hyaluronan synthesized by tumor stromal cells or cancer cells themselves, engages CD44 on the surface of cancer cells to regulate biological processes like growth/survival, epithelial-to-mesenchymal transition (EMT), differentiation, invasion, metastasis, drug resistance and cancer stem cell properties.

18.2.1   *Growth/Survival*

For tumors to successfully form, cancer cells need to deal with several stressful events, such as anchorage-independent growth, hypoxia and limited nutrient availability. Therefore, it is critical for cancer cells to take advantage of physiological molecular mechanisms and pathways allowing them to cope with such stressful events. One of the major cellular receptors correlated with survival and

anti-apoptotic signaling in cancer cells is the hyaluronan receptor CD44. CD44 regulates the expression and activation of proteins involved in resistance to apoptosis and cell growth like Fas, caspase 3/9, Bcl-xl/Bak, Akt, pRb and Bcl-2 (Lakshman et al. 2004; Yasuda et al. 2001; Park et al. 2012b). For example, overexpression of CD44s, CD44v3–10, and CD44v8–10 in human colon cancer cells successfully attenuated etoposide-induced cell death (Lakshman et al. 2004). On the other hand, inhibition of CD44 expression in colon carcinoma cells reduced the expression of Bcl-2, Bcl-xL, while simultaneously increased the expression of apoptosis proteins Bax and caspase-3/8/9 (Park et al. 2012b). Furthermore, CD44 controls downstream activation of Akt, a major survival pathway, and cell cycle-regulating proteins p21 and pRb in many types of cancer cells, like breast, colon and lung cancer cells (Lakshman et al. 2004). In lung cancer cells, interaction of hyaluronan with CD44 reduced Fas expression and subsequent Fas-mediated apoptosis (Yasuda et al. 2001). In chronic lymphocytic leukemia (CLL) patients CD44 was found to promote cancer cell survival. The crucial importance of CD44 in CLL was further certified by the fact that CD44 knock-down reduced survival even in Akt-overexpressing cells. In that model, CD44 regulated the expression of MCL1 anti-apoptotic protein through Akt and Erk pathways (Fedorchenko et al. 2013). Hyaluronan engaged to CD44 also induced phosphorylation of FAK, which associates with PI3K to protect against apoptosis (Fujita et al. 2002). Furthermore, hyaluronan-CD44 interaction activated ErbB2 signaling through Hsp90, cdc37, p110 and p85 proteins (Chanmee et al. 2015).

18.2.2   Epithelial-to-Mesenchymal Transition (EMT) and Differentiation

Epithelial-to-mesenchymal transition is a dynamic process that cancer cells utilize in order to metastasize. During this process, hyaluronan synthase expression is induced and hyaluronan is synthesized to large amounts. Moreover, CD44 has been found to be overexpressed in mesenchymal cancer cells and its high expression correlates with a more undifferentiated phenotype (Misra et al. 2011; Heldin et al. 2014). In breast cancer, EMT correlates with poor prognosis and intriguingly, breast cancer cells with mesenchymal and more malignant phenotype express higher amounts of CD44, which also displays high hyaluronan-binding capacity (Bernert et al. 2011; Heldin et al. 1996). In breast epithelial cultures, TGF-β-induced EMT depends on the expression of HAS2. Specifically, TGF-β induces Smad and p38 MAPK pathways to upregulate HAS2 expression (Porsch et al. 2013). Moreover, HAS2 overexpression has been shown to promote the malignant phenotype via suppression of E-cadherin and translocation of β-catenin to the nucleus, signaling events that take place during EMT (Zoltan-Jones et al. 2003; Koyama et al. 2007). Interestingly, switching between CD44v isoforms to CD44s through alternative splicing promoted EMT by suppression of E-cadherin through PI3K/Akt pathways. Inhibition of splicing activity that produced CD44v occurred through downregulation of epithelial

splicing regulatory protein 1 and 2 (ESRP1 and 2) by transcription factors Snail1, Zeb1, and Zeb2 (Reinke et al. 2012). Expression of CD44 and its interaction with hyaluronan also regulate differentiation of aggressive cancer cells like acute myeloid leukemia cells, thus downregulating their aggressive properties (Solis et al. 2012).

18.2.3   *Invasion/Metastasis*

Accumulation of hyaluronan as well as high CD44 expression in the cancerous tissues has been widely correlated with advanced incidence of invasion and metastasis of various types of cancer cells. CD44 interacts with several growth factor receptors like ErbB2 and PDGFR and its interaction with hyaluronan regulates their signaling activity (Bourguignon et al. 1997; Ghatak et al. 2005; Li et al. 2006). Binding of hyaluronan induces CD44 clustering, which activates downstream signaling pathways in a cell- and tissue-dependent manner. This clustering was critical for MMP9 activation and subsequent activation of TGF-β, which in turn induced cancer cell invasion and metastasis (Yu and Stamenkovic 1999). Moreover, CD44 interacted with MT1-MMP—a major metalloproteinase responsible for extracellular matrix degradation during invasion and metastasis—to enhance its activity. In turn, MT1-MMP enhanced the shedding of CD44 variants and promoted cancer cell invasiveness (Kajita et al. 2001; Stamenkovic and Yu 2009; Mori et al. 2002). Hyaluronan fragments also have a functional role during invasion and metastasis. Specifically, hyaluronan dodecasaccharides by engaging CD44 induced secretion of CXCL1, to enhance endothelial cell sprouting, which could be critical for tumor angiogenesis, a key process in metastasis (Takahashi et al. 2005). Hyaluronan is also synthesized by stromal cells. This stromal cell-derived hyaluronan engaged CD44v6 in the surface of colon tumor cells to sustain PI3K signaling in a positive CD44v6/PI3K loop and promote invasion (Misra et al. 2011).

18.2.4   *Drug Resistance*

One of the main properties that cancer cells acquire during tumor development is resistance to several drugs. Drug resistance in the tumors is thought to be acquired through different mechanisms. First, a subpopulation of cells with pre-existing potential for drug resistance could be present inside a tumor. Second, drugs utilized for cancer therapy can induce resistance by cancer cells. In both cases, cancer cells upregulate the expression of proteins, like multi-drug resistance proteins (MDRs) that allow them to evade drug-induced apoptosis. Intriguingly, there is extensive evidence correlating CD44 expression with resistance to radiotherapy or chemotherapy of various types of cancer cells (Yaghobi et al. 2021). CD44 physically interacts with P-glycoprotein to enhance drug resistance in cancer cells (Miletti-Gonzalez et al. 2005). In malignant cells, decrease in CD44 expression ameliorated drug

resistance (Xu et al. 2015). Specifically, in hepatocellular carcinoma, inhibition of CD44 sensitized cancer cells to sorafenib (Fernando et al. 2015). Paclitaxel-resistant ovarian cells also showed increased expression of CD44 (Gao et al. 2015). It is important to note that interaction of high molecular weight hyaluronan with CD44 increased MDR expression and subsequently led to drug resistance, while low molecular weight hyaluronan-CD44 interaction led to MDR internalization, signifying that not only the presence of hyaluronan but also its size is critical for this process (Zoller 2011). Moreover, hyaluronan through CD44 binding activated PI3K signaling, which in turn induced MDR protein expression (Misra et al. 2005). In the context of CD44v, CD44v3 targeting in head and neck squamous cell carcinoma cells reduced resistance to cisplatin (Wang et al. 2007). Hyaluronan-CD44v3 interaction upregulates miRNA-302, enhanced Oct4-Sox2-NANOG signaling and increased expression of MDR1, leading to development of chemo-resistance (Bourguignon et al. 2012). CD44v3-hyaluronan interaction also regulated expression and activity of P300 which can in turn acetylate β-catenin and NF-κB-p65, resulting in upregulation of MDR1 expression (Zoller 2015). Interestingly, in prostate cancer, knocking down the expression of CD44v6 enhanced chemotherapy sensitivity (Ni et al. 2014).

18.2.5   Tumor Stem Cell Properties

In tumors, sub-populations of cancer cells, termed cancer stem cells (CSCs), have been shown to be responsible for tumor recurrence after chemotherapy or radiotherapy. Hyaluronan, like in normal stem cell niches, creates an ideal micro-environment for CSCs survival, self-renewal, and maintenance. Importantly, hyaluronan receptor CD44 is widely recognized as a stem cell marker (Skandalis et al. 2019). $CD44^{High}CD24^{Low}$ populations isolated from tumors of the breast showed stem cell properties, like self-renewal and tumor-initiating capacity (Shao et al. 2016; Li et al. 2017b; Wei et al. 2012). Mechanistically, ΔNp63 induced the expression of HAS3, HYAL-1, and CD44 to create a hyaluronan-rich environment that favored stemness of breast cancer cells (Gatti et al. 2018). The importance of hyaluronan and CD44 was further solidified by experiments in hyaluronan-based multilayer nanofilms, where pancreatic cells grown in such conditions upregulated CD44v6 and form colonies (Lee et al. 2018). In pancreatic tumor cells, the tumor suppressor KFL4 bound to CD44 promoter to block its expression and ameliorated cancer stem cell properties and metastasis (Yan et al. 2016). On the other hand, targeting hyaluronan with 4-methyl-umbelliferone—a widely utilized hyaluronan synthesis inhibitor—promoted phagocytosis of hepatocellular CSCs (Rodriguez et al. 2018). CD44 also activated Wnt/β-catenin pathway to upregulate FoxM1 and Twist, leading to enhanced stemness of lung adenocarcinoma cells (Su et al. 2016). Circulating oral squamous carcinoma cells that display CD44 expression were able to form spheres and displayed chemoresistance and self-renewal (Patel et al. 2016). For a more comprehensive analysis of hyaluronan/CD44 roles in cancer stem cell properties, refer to our previous review (Skandalis et al. 2019).

18.3   Hyaluronan/CD44 Network Targeting

Given the important roles of hyaluronan/CD44 network in tumor development, progression, and metastasis, this system emerges as a potent pharmacological target. Therefore, several efforts have been concentrated toward this purpose, such as incorporation of hyaluronan on nanoparticles for specific delivery of drugs to tumor cells, antibodies or peptides blocking CD44 actions and interactions, chemically modified hyaluronan, and utilizing gene therapies (CRISPR/Cas9 or sh/siRNAs) against CD44 (Fig. 18.1). Below, we describe recent advances in pharmacological targeting of this system for cancer treatment (summarized in Table 18.1).
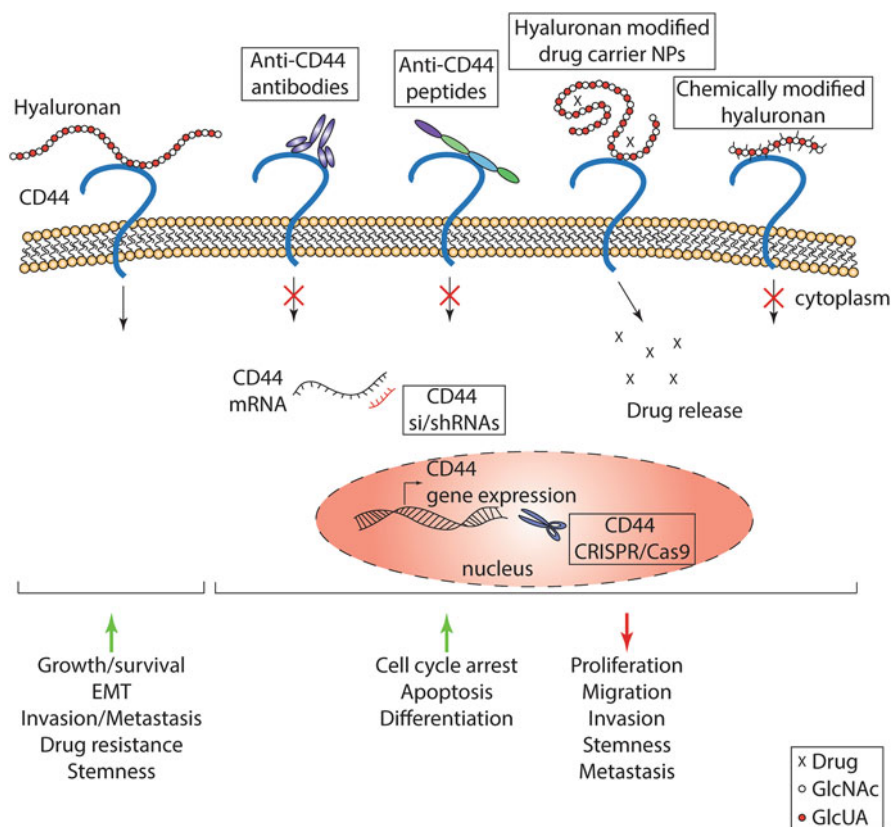
Fig. 18.1 Hyaluronan/CD44 network targeting approaches. Incorporation of hyaluronan on nanoparticles for specific delivery of drugs to tumor cells, antibodies or peptides blocking CD44 actions and interactions, chemically modified hyaluronan and gene therapies targeting CD44 mRNA (CRISPR/Cas9 or sh/siRNAs against CD44)

Table 18.1 Overview of hyaluronan/CD44 targeting tools (for further details, see text)

Approach	Tool	Tumor	Function	References
Nanomedicine	HA-PEI-PLGA-docetaxel NPs	Lung	↓ Proliferation	Maiolino et al. (2015)
	HA-PLGA-docetaxel NPs	Lung	↓ Tumor growth	Wu et al. (2017)
	HA-Dextran-modified quercetin-Cu(II) NPs with PARP inhibitor	Breast	↑ Animal survival	Cheng et al. (2021)
	HA-Resverastrol/chalcone NPs	Breast	↑ Drug cytoplasmic release	Shah et al. (2017)
	HA-Doxorubicin-super paramagnetic iron oxide NPs	Breast	↑ Drug uptake and release, apoptosis	Vyas et al. (2015)
	HA-Berberine derivative/doxorubicin NPs	Breast	↑ Mitochondrial apoptotic pathways ↓ Proliferation, migration, lung metastasis	Lin et al. (2021)
	HA-Chitosan-docetaxel NPs	Breast	↓ Cell viability	Shabani Ravari et al. (2016)
	HA-Curcumin/celecoxib NPs	Breast	↑ Apoptosis, animal survival ↓ Tumor growth, cell viability, lung metastasis	Liu et al. (2020)
	HA-Paclitaxel/curcumin PAAVB NPs	Breast	↑ Adaptive anti-tumor immunogenicity ↓ Immunosuppression, lung metastasis	Wang et al. (2021)
	HA-(PANi)-imiquimod NPs	Breast	↑ Immune responses against tumor	Yasothamani et al. (2021)
	HA-Salinomycin/curcumin NPs	Breast (CSCs)	↑ G1 cell cycle arrest ↓ EMT	Zhao et al. (2020)
	HA-NPs with saporin	Breast	↑ Apoptosis	Ding et al. (2018)
	HA-Hyaluronidase/Ce6 NPs	Breast	↑ Uptake, efficacy	Gong et al. (2016)
	HA-Gold-nanoclustered verteporfin NPs	Breast	↑ Blood stream stability, drug delivery ↓ Tumor growth	Han et al. (2016)
	Multifunctionalized iron oxide magnetic nanoparticles (MNPs) with anti-CD44 antibody and gemcitabine derivatives	Breast and pancreatic	↑ Cancer cell killing	Aires et al. (2016)
	HA-Cisplatin green tea catechin micelles	Ovarian	↑ Drug efficacy ↓ Off-target effects	Bae et al. (2017)

Formulation	Tumor type	Effects	References
Chitosan polylactic acid- coated with IM7 anti-CD44 antibody	Ovarian	↓ Toxicity	Yang et al. (2017)
HA-Serum albumin- conjugated NPs	Ovarian	↑ Drug uptake, cytotoxicity against can-cer cells	Edelman et al. (2017)
HA-Paclitaxel NPs	Colon	↑ Animal survival	Zhu et al. (2018)
HA-PTC209 NPs	Colon (CSCs)	↓ Tumor growth	Xu et al. (2019)
HA-Ce6 phosphosensitizer NPs	Colon	↓ Tumor growth	Gao et al. (2017)
HA-poly(hexamethylene biguanide) and chitosan NPS with KRAS si/shRNA	Colorectal	↑ Uptake and KRAS silencing	Tirella et al. (2019)
HA-Doxorubicin lipoic-acid encapsulated NPs	Myeloma and acute myeloid leukemia	↓ Tumor growth	Zhong et al. (2017)
A6 anti-CD44 peptide polymersomal epirubicin	Multiple myeloma	↑ Uptake, anti-cancer efficacy	Gu et al. (2019)
HA-Cabazitaxel/Silibinin liposomes	Prostate (CSCs)	↑ Apoptosis ↓ Migration	Mahira et al. (2019)
CDDP NPs	Prostate (CSCs)	↓ Stem cell properties	Jafari Malek et al. (2014)
HA-Diethyldithiocarbamate- copper NPs	Pancreatic (CSCs)	↑ ROS generation ↓ Sphere formation	Marengo et al. (2019)
HA-chitosan NPs with Bcl- 2 siRNA	Bladder	↓ Bcl-2 expression	Liang et al. (2021)
HA-HPLR- with EGFR targeted peptides	Liver	↓ Tumor growth	Liang et al. (2019)
HA NPs with Gli1 siRNA	Gastric (CSCs)	↓ Migration, invasion, tumor spheroid, and colony formation	Yao et al. (2020)
HA-docetaxel NPs with AS1411 aptamer	Glioblastoma	↑ Blood-brain barrier penetration, drug uptake ↓ Spheroid formation, tumor growth	Wang et al. (2019)
HA-Doxorubicin liposome NPs	Glioblastoma	↑ Anti-neoplastic function, doxorubicin efficacy	Hayward et al. (2016)
HA-Zinc protoporphyrin nanoprobes	Sarcoma	↑ Anti-cancer effect ↓ Side effects	Gao et al. (2021)

Table 18.1 (continued)

Approach	Tool	Tumor	Function	References
Antibodies	RG7356	Chronic lymphocytic leukemia	↑ Apoptosis	D'arena et al. (2014) and Zhang et al. (2013)
		Breast	↑ Secretion of immune cell chemo-attractants, antibody-dependent cellular phagocytosis; ↓ Tumor growth	Weigand et al. (2012) and Maisel et al. (2016)
	A3D8	Acute myeloid leukemia	↑ G0/G1 cell cycle arrest	Zada et al. (2003), Gadhoum et al. (2004a, b), and Qian et al. (2012)
		Chronic lymphocytic leukemia	↑ Caspase activation; ↓ Cell viability	Fedorchenko et al. (2013)
		Erythroleukem ia	↑ Caspase-independent apoptosis; ↓ Cell growth	Artus et al. (2006)
		Ovarian (CSCs)	↑ S phase cell cycle arrest, apoptosis	Du et al. (2013)
	F77	Prostate	↑ Apoptosis	Chen et al. (2018b)
	Hermes-1	Colorectal carcinoma	↓ Binding of hyaluronan, laminin and collagen	Ishii et al. (1993)
	IM7	Colorectal carcinoma	↓ Liver metastasis	Ogoshi et al. (1998)
		Glioblastoma	↑ Apoptosis; ↓ Hyaluronan biosynthesis	Wiranowska et al. (2010)
		Ovarian	↓ Proliferation, tumor development, and progression	Yang et al. (2017)
		Bladder	↓ NF-κB activation	Fitzgerald et al. (2000)
		Melanoma	↓ Adhesion of melanoma cells on endo-thelial cells	Ota et al. (1995)
	IM7 and S5	Natural killer cells	↑ Natural killer cell activity	Tan et al. (1993)
	IM7 conjugated to saporin	Prostate	↑ Apoptosis	Bostad et al. (2014)
	J173 and F10442	Natural killer cells	↑ CD16-mediated lysis, intracellular Ca^{2+}	Galandrini et al. (1994)

	J173	Burkitt's lymphoma and chronic myelogenous leukemia	↑ Killing activity of peripheral mononuclear cells against cancer cells	Ishizuka et al. (2008)
	HI44α	Acute myeloid leukemia	↑ Differentiation, apoptosis	Song et al. (2004)
	KMP1	Bladder	↓ Cell proliferation, migration and adhesion, tumor growth	Chen et al. (2018c)
	aCD44O$_2$LNCs with paclitaxel	Pancreatic (CSCs)	↑ Anti-tumor efficacy	Navarro-Marchal et al. (2021)
	5-mG2a-f	Oral squamous cell carcinoma	↓ Tumor development	Takei et al. (2020)
	P3D2	Breast	↓ Tumorigenesis	Lusche et al. (2021)
	Anti-CD44v9 mAb 44-IV	Colon	↓ Cancer cell capillary adhesion, liver metastasis	Seki et al. (1997)
Peptides	RP-1	Gastric	Detection of CD44$^+$ cancer cells, prognosis prediction	Zhang et al. (2015) and Li et al. (2017a)
	CV-1	Gastric	Detection of CD44v3–10$^+$ cancer cells	Zhang et al. (2016)
	PFT	Prostate	Detection of CD44v6$^+$ cancer cells	Peng et al. (2017)
	PDPP	Breast	Detection of CD44$^+$ CSCs	Cho et al. (2015)
	A6	Chronic lymphocytic leukemia	↑ Toxicity	Finlayson (2015)
		Ovarian and breast	↓ Migration	Piotrowicz et al. (2011)
		Melanoma	↓ Lung metastasis	Piotrowicz et al. (2011)
	A6 with reduction-sensitive polymersomal vincristine sulfate	Acute myeloid leukemia	↑ Animal survival, ↓ Leukemia burden in the circulation, bone marrow, liver, and spleen	Gu et al. (2021)
	v6	Pancreatic	↑ Animal survival, ↓ Tumor growth	Matzke-Ogi et al. (2016)
	NLN and NEW	Breast and pancreatic	↑ CD44v6 internalization, ↓ c-Met/Erk activation, migration, invasion, metastasis	Khan et al. (2021)

Table 18.1 (continued)

Approach	Tool	Tumor	Function	References
	NLN and NEW with KLA pro-apoptotic peptides	Breast and pancreatic	↑ Tumor cell killing ↓ Tumor growth, metastasis, side effects	Khan et al. (2021)
	FKBPL and AD-01	Breast and prostate	↓ Anti-angiogenic effects ↓ Tumor growth	Valentine et al. (2011)
		Breast	↓ Migration	Yakkundi et al. (2013)
	AD-01	Breast (CSCs)	↑ Differentiation ↓ Mammosphere formation, tumor initiation, chemotherapy, and radiotherapy resistance when combined with DAPT	McClements et al. (2013)
	Peptides derived from collagen type IV with liposomes and doxorubicin	Melanoma	↓ Tumor size	Ndinguri et al. (2012)
	P3 and P9	Chronic lymphocytic leukemia	↓ Adhesion to pro-MMP9, chemotaxis, transendothelial migration	Ugarte-Berzal et al. (2014)
	PCK3145	Fibrosarcoma	↓ Adhesion to hyaluronan	Annabi et al. (2005)
	A5G27	Melanoma	↓ Metastasis	Hibino et al. (2005)
	A5G27 with siRNA particles	Lung and ovarian	↓ Tumor growth	Golan et al. (2016)
	CD44BP	Breast	↓ Tumor sphere formation	Yang et al. (2013)
	CD44 cytoplasmic tail peptides bearing phosphor-$_{Ser}$325	Melanoma	↓ Migration	Peck and Isacke (1998)
	CD44-derived peptides as immunogens	Prostate (CSCs)	↑ Sensitize dendritic cells, anti-tumor activities	Wang et al. (2020)
Chemically modified hyaluronan	Modification with Au-Ag alloy in NPs	Breast	↑ Sensitivity to radiotherapy	Chong et al. (2020)
	Modification with a hydrazide group and bisphosphonate (BP)	Colon	↑ Targeting	Varghese et al. (2009)
	Modification with sulfate groups	Pancreatic	↑ Targeting of CD44 and P-selectin	Bhattacharya et al. (2020)

Gene therapies	Modification with poly(lactic-co-glycolic acid) and loaded to transferrin-targeted nanoformulated AUY922 NPs	Brain	↑ Uptake, apoptosis, side effects ↓ Tumor growth	Debele et al. (2021)
	Modification with β-cyclodextrin and drug conjugates	Lung and prostate	↑ Toxicity against cancer cells ↓ Toxicity against normal cells	Bai et al. (2020)
	CD44 siRNA	Lung	↓ Stem cell gene expression	Nurwidya et al. (2017)
	CD44 siRNA in combination with doxorubicin	Breast	↑ Apoptosis ↓ Tumor metastasis, proliferation, invasion, migration	Vahidian et al. (2020)
	CD44 siRNA in liposomes with Apt1 CD44-targeted aptamer	Breast	↓ CD44 expression	Alshaer et al. (2018)
	CD44 shRNA	Breast	↓ Proliferation, colony formation, invasion	Zhou et al. (2018)
	PLGANPs with FAK and CD44 siRNAs	Ovarian	↑ Apoptosis ↓ Tumor size, angiogenesis, proliferation	Zou et al. (2013)
	CD44 shRNA adenovirus	Colon	↑ Apoptosis ↓ Proliferation, migration, invasion	Lee et al. (2017)
	CD44v6 shRNA	Colon	↓ Adenoma growth	Misra et al. (2009)
	CD44 CRISPR/Cas9	Osteosarcoma	↓ Proliferation, spheroid formation, migration, invasion	Liu et al. (2018)
		Osteosarcoma	↑ Drug sensitivity of drug-resistant cells	Xiao et al. (2018)
		Liver (CSCs)	↑ Tumor differentiation ↓ Tumor malignancy	Han et al. (2015)
	CD44v6 CRISPR/Cas9	Gastric	↑ Cisplatin sensitization ↓ Self-renewal	Lobo et al. (2020)
	Cosmc CRISPR/Cas9	Breast	↓ CD44 O-glycosylation and expression, proliferation	Du et al. (2020a)

HA hyaluronan, NPs nanoparticles, CSCs cancer stem cells

18.3.1 Nanomedicine

Nanomedicine therapies utilize targeted drug delivery approaches to specifically target tumor cells and avoid adverse effects in normal tissues. Accordingly, there are two types of targeted drug delivery. First, passive targeting, which takes advantage of enhanced permeability and retention effect (EPR) in tumors. The EPR effect allows for accumulation of drugs and nanoparticles in tumors that have distinct architectural features from normal tissues, such as hyper-vasculogenesis, impaired lymphatic drainage, and different abnormal interstitial pressures (Fang et al. 2011). Second, active targeting, follows passive targeting to selectively deliver specific drugs to cancer cells overexpressing the desired receptor, taking advantage of receptor-substrate interactions (Danhier et al. 2010). Due to the important roles of hyaluronan/CD44 interactions and the correlation between CD44 expression and higher states of malignancy, hyaluronan is widely utilized in nanomedicine to specifically target CD44-expressing cancer cells and cancer stem cells. In blood circulation drug bioavailability and activity is altered by the body's defense, through chemical modification or binding to serum factors. In the last years, a "3S" transition concept has emerged, which incorporates stability transition, surface transition and size transition to overcome barriers in the delivery process. Hyaluronan therefore is an excellent candidate to be incorporated to nanoparticles and drug carriers, since it fulfills all three criteria due to its biocompatibility, biodegradability, and specific targeting of CD44-expressing cancer cells (Zhong et al. 2020).

One of the main purposes of hyaluronan-coated nanoparticles is to specifically deliver encapsulated drugs in cancer cells to enhance anti-tumor efficacy and avoid adverse effects. Hyaluronan can decorate polyetheleneimine (PEI) biodegradable nanoparticles of poly(lactic-*co*-glycolic) acid (PLGA) to deliver docetaxel specifically to lung cancer cells and inhibit their proliferation (Maiolino et al. 2015). Tumor growth inhibition of lung cancer cells in vivo was also observed by using PLGA hyaluronan-coated docetaxel nanoparticles without PEI, verifying the anti-cancer efficacy of this strategy (Wu et al. 2017). In another study, docetaxel loaded in chitosan-coated hyaluronan nanoparticles was more effective than free docetaxel against CD44^{+} breast cancer cells (Shabani Ravari et al. 2016). Hyaluronan nanoparticles composed of branched cell-penetrating peptide B-mR9 could also successfully deliver methotrexate to CD44^{+} cells and exerted antitumor activity (Yoo et al. 2020). Curcumin and celecoxib loaded in hyaluronan-coated nanoparticles displayed in vitro toxicity and inhibited tumor growth, enhanced survival of mice, induced apoptosis, and abrogated the formation of lung metastasis of breast cancer cells (Liu et al. 2020). Tumor cells display higher levels of glutathione. Taking advantage of this, hyaluronan-coated redox-sensitive micelles were developed to aim CD44-expressing tumor cells and release the drugs inside the target cells (Du et al. 2020b). Furthermore, dextran-modified quercetin-Cu(II)/ hyaluronan nanoparticles with a natural PARP inhibitor could induce synthetic lethality in triple-negative breast cancer cells and extended animal survival, without displaying any adverse effects on normal organs (Cheng et al. 2021). Similarly, in

triple-negative breast cancer cells conjugation of resveratrol and a chalcone to hyaluronan enhanced their uptake (Shah et al. 2017). Doxorubicin was loaded in hyaluronan-super paramagnetic iron oxide nanoparticles to achieve better uptake and cytoplasmic release of the drug and subsequently enhanced apoptosis in triple-negative breast cancer cells (Vyas et al. 2015). In addition, hyaluronan could facilitate lipoplexes delivery in breast cancer cells that express CD44 (Surace et al. 2009). Recently, targeting mitochondrial pathways in cancer cells has emerged as a promising strategy for tumor therapy. Indeed, hyaluronan nanomedicine utilizing a berberine derivative and doxorubicin was able to target mitochondria and subsequently inhibited proliferation, migration, and enhanced apoptosis of triple-negative breast cancer cells. Importantly, lung metastasis in vivo was abrogated after this treatment. These effects were mediated by suppression of MMP-2/-9 activities and induction of mitochondrial apoptotic pathways (Lin et al. 2021). Cisplatin can be also loaded to hyaluronan-green tea catechin micellar nanocomplexes, to enhance its efficacy against ovarian cancer cells, without causing side effects in vivo (Bae et al. 2017). In glioblastoma cells, hyaluronan-conjugated liposome nanoparticles effectively delivered doxorubicin inside the cells and enhanced its anti-neoplastic function (Hayward et al. 2016). Paclitaxel is another drug that can be also delivered with hyaluronan-nanoparticle complexes to treat CD44-positive colon cancer cells in orthotopic mouse models (Zhu et al. 2018). Paclitaxel and curcumin encapsulated in poly (acrylamide-co-acrylonitrile-co-vinylimidazole-co-bis(2-methacryloyl) oxyethyl disulfide) (PAAVB) polymer-based intelligent platform coated with hyaluronan, were able to promote adaptive anti-tumor immunogenicity and inhibit immunosuppression of CD44-overexpressing breast tumor cells while simultaneously abrogating lung metastasis (Wang et al. 2021). Hyaluronan can also decorate serum albumin conjugate-based nanoparticles to enhance drug delivery and their cytotoxic effects on cancer cells expressing CD44 (Edelman et al. 2017). In addition, promising results have been obtained by using hyaluronan-modified nanoparticles for treatment of hematological tumors, where CD44 plays significant roles. Specifically, doxorubicin encapsulated in lipoic acid-crosslinked hyaluronic acid nanoparticles was used to inhibit tumor growth of multiple myeloma and acute myeloid leukemic cells in vivo (Zhong et al. 2017).

The size of hyaluronan that may be used to coat nanoparticles is apparently important. Specifically, hyaluronan nanoparticles coated with low molecular weight hyaluronan displayed low CD44-binding activity, while high binding affinity was displayed by high molecular weight hyaluronan-coated nanoparticles, suggesting that high molecular weight hyaluronan is more suitable as a coating substance (Mizrahy et al. 2011). Furthermore, high molecular weight hyaluronan-coated nanoparticles displayed enhanced circulation time and better tumor targeting specificity than low molecular weight hyaluronan-coated nanoparticles (Mizrahy et al. 2014).

As already mentioned, CD44 serves as a major cancer stem cell marker. Therefore, hyaluronan can be used to guide nanoparticle-drug conjugates to cancer stem cells. To target prostate cancer stem cells, hyaluronan was used to decorate cabazitaxel and silibinin co-encapsulated cationic liposomes to induce apoptosis

and decrease cell migration (Mahira et al. 2019). Cis-dichlorodiamminoplatium (II) (CDDP) glyconanoparticles were also coated with hyaluronan to deliver the drug in vivo and suppress stem cell properties of prostate cancer cells (Jafari Malek et al. 2014). For breast cancer treatment, co-delivery of salinomycin and curcumin in hyaluronan-coated nanoparticles was achieved in CD44-expressing breast cancer stem cells, inducing cell cycle arrest in G1 and inhibiting EMT (Zhao et al. 2020). To target pancreatic cancer stem cells, hyaluronan was utilized to coat diethyldithiocarbamate-copper complex nanoparticles. These nanoparticles were able to impair sphere formation of pancreatic cancer stem cells, probably by inducing the generation of ROS (Marengo et al. 2019). Nanoparticles can be delivered also orally. Specifically, hyaluronan-decorated nanoparticles containing PTC209, a BMI-1 inhibitor, were able to target colon cancer stem cells and abrogate tumor growth in vivo (Xu et al. 2019).

Hyaluronan-coated nanoparticles can encapsulate phosphosensitizers, like Ce6, to deliver them in human colon cancer cells in vivo. After photodynamic therapy, tumor growth was attenuated, while no side effects were observed (Gao et al. 2017). Furthermore, co-administration of hyaluronidase with such nanoparticles induced their uptake from tumor cells and enhanced their anti-cancer efficacy, probably by increasing the enhanced permeability and retention (EPR) effect inside the tumor (Gong et al. 2016). For triple-negative breast cancer treatment, photothermally targeted hyaluronan-polyaniline (PANi)-imiquimod (R837, a TLR7 agonist) nanoparticles were used to induce immune responses against the tumor (Yasothamani et al. 2021). Interestingly, hyaluronan-decorated nanoparticles could be effectively used to encapsulate and deliver hyaluronidase enzymes specifically to the tumors together with doxorubicin to enhance its efficacy (Chen et al. 2018a). Gold-nanoclustered hyaluronan nano-assemblies were also used as a platform for photodynamic or photothermal cancer therapies, by delivering the photodynamic therapy agent verteporfin in cancer cells. These nanoparticles displayed excellent stability in the blood and were able to completely inhibit tumorigenesis while displaying 100% survival rate (Han et al. 2016). Hyaluronan-conjugated zinc protoporphyrin nanoprobes were also used for photodynamic therapy against colon cancer and fibrosarcoma cells (Gao et al. 2021).

Among others, hyaluronan-coated nanoparticles can carry siRNAs or shRNAs against specific proteins expressed in cancer cells. KRAS is a known oncogene with no available small molecule inhibitors. To target KRAS hyaluronan-decorated nanocarriers [poly(hexamethylene biguanide) and chitosan] bearing KRAS-si/shRNA have been designed to specifically silence KRAS expression in CD44-expressing cancer cells (Tirella et al. 2019). Moreover, chitosan nanoparticles were conjugated with hyaluronan to target bladder cancer cells that expressed high levels of CD44, to deliver siRNA against the Bcl-2 oncogene. These particles were able to target bladder cancer cells in vivo and successfully interfere with the Bcl-2 expression (Liang et al. 2021). A new anti-cancer siRNA delivery system named by the authors HPLR was manufactured with a siRNA-peptide core surrounded by lipid bilayer, thin hyaluronan coating, and EGFR-targeted peptides to target EGFR and CD44 overexpressing cells. This system was able to successfully deliver the siRNAs

in subcutaneous liver tumors and inhibit their growth without displaying any significant toxicity (Liang et al. 2019). Additionally, hyaluronan-conjugated nanoparticles were utilized to deliver Gli1 siRNA in gastric cancer stem cells and subsequently reduced migration, invasion as well as tumor spheroid and colony formation (Yao et al. 2020).

Notably, nanoparticles can also be decorated with CD44-targeting peptides. Indeed, A6 anti-CD44 peptide conjugated to polymersomal epirubicin enhanced uptake and anti-cancer efficacy of epirubicin against multiple myeloma cells in vivo (Gu et al. 2019). Furthermore, nanoparticles can be decorated with anti-CD44 antibodies. Multifunctionalized iron oxide magnetic nanoparticles with CD44 antibodies were able to selectively target CD44-positive cancer cells (Aires et al. 2016). In breast cancer cells, conjugation of saporin, a ribosome-inactivating protein, with hyaluronan modified nanoparticles achieved intracellular release of saporin leading to enhanced apoptosis (Ding et al. 2018). Hyaluronan-coated nanoparticles have been also conjugated with AS1411 aptamer, to penetrate blood-brain barrier and deliver docetaxel to CD44- overexpressing glioma cells. Delivery of docetaxel through this pathway significantly attenuated the formation of spheroids and tumor growth in vivo (Wang et al. 2019).

18.3.2 Antibodies

Different monoclonal antibodies have been raised against CD44 standard and variant isoforms to be utilized for cancer treatment. One of the best-studied anti-CD44 monoclonal antibodies is RG7356 which binds to the constant region of CD44, abrogating hyaluronan binding. In chronic lymphocytic leukemia (CLL), interruption of hyaluronan/CD44 interaction induced caspase-dependent apoptosis, with the strongest effects being observed in ZAP-70^{+} CLL cells both in vitro and in vivo (D'arena et al. 2014). Mechanistically, RG7356 engages CD44 to induce its internalization in CLL cells, and subsequently decrease ZAP-70, which was found to be complexed with CD44 (Zhang et al. 2013). RG7356 is also effective against triple-negative breast cancer cells in mice xenografts by modifying the MAPK pathway (Weigand et al. 2012). Response to treatment with RG7356 in xenograft models and colorectal cancer patients depended on the presence of CD44s isoform, suggesting that only treatment in patients with CD44s expression could be effective (Birzele et al. 2015). RG7356 mechanism of function also involves activation of the immune system. Specifically, RG7356 treatment induced secretion of chemo-attractants responsible for recruitment of immune cells, such as macrophages, to the tumor, through activation of MAPK. Moreover, RG7356 activated antibody-dependent cellular phagocytosis (ADCP) of triple-negative breast cancer cells by macrophages (Maisel et al. 2016). In clinical trials, [89]Zirconium-labeled RG7356 was taken up by several tissues such as the spleen, liver, bone marrow, lung, and kidney in a dose-dependent manner in patients (Jauw et al. 2018), while selectively targeting CD44^{+} breast and pancreatic cancer cells in monkeys (Vugts et al. 2014). Moreover, phase

1 clinical trials with RG7356 in patients with advanced, CD44-expressing solid tumors showed that it was well-tolerated, with most side effects being mild such as fever, headache, and fatigue. Its clinical efficacy was modest with 21% of patients experiencing disease stabilization (Menke-Van Der Houven Van Oordt et al. 2016). Furthermore, phase 1 studies in acute myeloid leukemia patients verified the mild adverse effects, although only 2 out of 44 patients showed response in the treatment suggesting that this antibody cannot be utilized as monotherapy (Vey et al. 2016).

Another popular anti-CD44 antibody is A3D8. On human acute myeloid leukemia (AML) cells, A3D8 treatment caused G0/G1 cell cycle arrest through induction of p21, p27 and reduction of pRb and CdK2/4 activities. Furthermore, JNK protein expression was reduced leading to reduction in c-Jun phosphorylation after A3D8 treatment (Zada et al. 2003; Gadhoum et al. 2004a, b; Li et al. 2016). A3D8, apart from inducing apoptosis and inhibiting cell proliferation, induced differentiation of the AML cells (Gadhoum et al. 2004a). This apoptotic effect was caused by A3D8-induced CD44s lipid raft clustering leading to Fas aggregation and subsequent caspase-8 activation (Qian et al. 2012). It is important to note that bone marrow stromal cells could protect acute myeloid leukemia cells from A3D8-induced apoptosis through activation of PI3K/Akt signaling to down-regulate p27 (Chen et al. 2015). In these studies, the effects of A3D8 were verified by another anti-CD44 antibody, H90. In chronic lymphocytic leukemia, A3D8 abrogated CLL cell viability and in vivo caused reduction of MCL1 protein and activation of caspases (Fedorchenko et al. 2013). In human erythroleukemia cells, A3D8 also evoked cell growth inhibition and caspase-independent apoptosis-like cell death, through disruption of mitochondrial membrane potential and release of AIF but not cytochrome c, which is typical for caspase-dependent apoptosis. This type of cell death involves activation of PARP and calpain, since their inhibition ameliorated A3D8-induced cell death (Artus et al. 2006). CD44 ligation by A3D8 was also able to arrest ovarian cancer stem cells in S phase and induced apoptosis (Du et al. 2013).

The monoclonal antibody F77 was developed to recognize glycolipids and O-glycosylation on prostate cancer cell proteins. F77 antigen was finally identified to be glycosylated CD44v10 isoform. On functional level, F77 induced apoptosis in prostate cancer cells. Moreover, this antibody can be utilized in ELISA assays to identify this glycosylated CD44v10 isoform in prostate cancer cells and serum of patients with prostate cancer (Chen et al. 2018b).

Hermes-1 is an anti-CD44-specific monoclonal antibody that specifically interrupts hyaluronan/CD44 interactions. When compared with other anti-CD44 antibodies, like Hermes-3, J173, and 50B4, Hermes-1 was the only one capable to completely inhibit binding of hyaluronan by colorectal carcinoma cells. It is important to note that Hermes-1, Hermes-3, and J173 inhibited the adhesion of the cells on laminin and collagen, while 50B4 did not have any effect (Ishii et al. 1993). Hermes-1 can be also utilized to investigate differences between metastatic cells and cells from the original tumor. Unexpectedly, utilizing Hermes-1, it was found that primary human colon carcinoma cells expressed higher amounts of CD44 on their cell surface, than the cells in lymph node metastases (Kubens and Zanker 1998).

Inhibition of hyaluronan/CD44 interactions has been also achieved with IM7 monoclonal antibody. Despite not displaying any effect on colon carcinoma cell growth in vitro, IM7 was able to inhibit liver metastasis in vivo, although tumor cell colonies were detected in all of the livers even in mice free of nodules, suggesting that IM7 probably delayed formation of metastases, rather than completely inhibiting them (Ogoshi et al. 1998). In glioma cells, which synthesize high levels of hyaluronan, IM7 decreased hyaluronan biosynthesis, and induced apoptosis (Wiranowska et al. 2010). IM7 can be also delivered with chitosan polylactic acid-coated nanoparticles to reduce its toxicity. This modified IM7 antibody was able to reduce proliferation of ovarian cancer cells and control the development and progression of ovarian cancer in vivo (Yang et al. 2017). It is known that hyaluronan fragments that engage CD44 can activate downstream NF-κB signaling in various tumor types, which in turn promotes inflammation and tumorigenesis. IM7 by inhibiting these interactions successfully reduced NF-κB activation in bladder cancer cells (Fitzgerald et al. 2000). IM7 was also able to block adhesion of melanoma cells on endothelial cells, a critical step during metastasis formation (Ota et al. 1995). IM7 can be also conjugated to ribosome inactivating protein saporin, to specifically target CD44-expressing cancer cells. These modified antibodies can release saporin in the target cell cytoplasm, which can then display its cytotoxic effects only on prostate cancer cells with high CD44 expression (Bostad et al. 2014). IM7 also enhanced natural killer cell activity (Tan et al. 1993), suggesting that CD44 targeting with antibodies can enhance activation of immune system against cancer cells. In the same study, different anti-CD44 antibodies were also studied, Hermes-1, S3 and S5, but the same effect was only observed with S5 antibody. The effect of CD44 ligation was also investigated with J173 and F10442 antibodies, where CD44 cross-linking upregulated CD16-mediated lysis. Moreover, CD44 blocking with these antibodies led to rapid increase of intracellular Ca^{2+} (Galandrini et al. 1994). Accordingly, J173 activated MAPK signaling to enhance the killing activity of peripheral mononuclear cells against cancer cells from Burkitt's lymphoma and chronic myelogenous leukemia (Ishizuka et al. 2008).

Several other less studied anti-CD44 monoclonal antibodies have been developed. The HI44α antibody effects were investigated in acute myeloid leukemia cells derived from patients. Ligation of CD44 by HI44α was able to induce differentiation and apoptosis of AML cells, probably through inhibition of c-Myc expression (Song et al. 2004). In colon cancer cells, engagement of CD44 by a specific antibody reversed the resistance to anti-integrin antibody, altered cell morphology, and enhanced apoptosis (Bates et al. 1998). U36 is another antibody that has been raised to recognize CD44v6- expressing squamous cell-carcinomas (Van Hal et al. 1996), but whether it can be used for treatment of these tumors remains to be investigated. KMP1 is a CD44-specific antibody that shows significant anti-tumor effects against bladder cancer cells. Specifically, KMP1 inhibited the bladder cancer cell proliferation, migration, and adhesion in vivo, while suppressed tumor growth in xenograft models. Importantly, expression of the KMP1 epitope correlated with clinical severity and prognosis of bladder cancer (Chen et al. 2018c). Anti-CD44 antibody conjugated to oil liquid nanocapsules, aCD44O^{2}LNCs, to target pancreatic cancer

stem cells, has also been developed. This technology displayed high uptake of these nanoparticles by pancreatic cancer stem cells in vivo. Moreover, these nanoparticles when coupled with paclitaxel were able to enhance their anti-tumor efficacy (Navarro-Marchal et al. 2021). A defucosylated anti-CD44 antibody, 5-mG2a-f, also significantly reduced tumor development in oral squamous cell carcinoma xenograft models (Takei et al. 2020). In another study, the authors developed four anti-CD44 monoclonal antibodies, namely, P4G9, P3D2, P3A7 and P3G4 that recognized unglycosylated and conserved regions of CD44 ectodomain. P3D2 was able to inhibit breast cancer tumorigenesis in animal models (Lusche et al. 2021). Since CD44v7 is expressed in many human cancers, an antibody raised against CD44v7 is to be utilized as a diagnostic and therapeutic tool in clinical settings (Borgya et al. 1995). Whether this antibody is useful remains to be investigated. An antibody raised against CD44v9, mAb 44-IV was able to inhibit liver metastasis of human colon cancer cells by blocking their adhesion to the capillaries, a critical step in the metastatic cascade (Seki et al. 1997).

18.3.3 Peptides

Apart from antibodies, peptides have been also used to target CD44 and regulate hyaluronan binding capacity. Peptides can be used for detection of CD44-expressing tumor cells inside the tissues. Several peptides against CD44 have been described utilizing phage display libraries (Park et al. 2012a). For example, RP-1, a 12-mer peptide isolated from a phage peptide library, binds to CD44$^+$ gastric cancer cells and allows their detection inside the tissues (Zhang et al. 2015). Importantly, RP1 peptide binding can predict prognosis of gastric cancer patients (Li et al. 2017a). Another 7-mer peptide also isolated from phage display library, termed CV-1, was able to detect CD44v3-v10 protein expression in gastric cancer cells and tissues (Zhang et al. 2016). Similarly, a phage displays 15 amino acid peptide PFT marked CD44v6-expressing prostate cancer stem cells (Peng et al. 2017). Polyvalent-directed peptide polymer (PDPP) specifically traced CD44-expressing breast cancer stem cells (Cho et al. 2015).

A widely studied peptide against CD44 is A6. A6 peptide is derived from uPA, but it does not bind to uPA receptor (uPAR) nor interferes with uPA/uPAR interactions. Importantly A6 did not cause any significant toxicity in animals. Moreover, A6 showed efficacy and exceptionally good safety profile in Phase 1a, 1b and 2 clinical trials. In chronic lymphocytic leukemia, A6 displayed significant toxicity against B-lymphocytes expressing ZAP-70 (Finlayson 2015). A6 peptides loaded with reduction-sensitive polymersomal vincristine sulfate targeted CD44-expressing acute myeloid leukemia cells and reduced the leukemia burden in the circulation, bone marrow, liver, and spleen, while extending survival of mice (Gu et al. 2021). A6 also inhibited migration of ovarian and breast cancer cells. Mechanistically, A6 regulated CD44-mediated adhesion to hyaluronan and the activation of downstream

FAK and MAP/ERK signaling pathways. In vivo treating mice with A6 inhibited the metastasis of melanoma cells to the lung (Piotrowicz et al. 2011).

Peptides that bind CD44v have been also developed. A peptide mimicking a specific extracellular motif of CD44v6 reduced CD44v6-mediated activation of c-Met and VEGFR-2. Treatment with this peptide in vivo reduced angiogenesis in tumors, suggesting that targeting the co-receptor functions of CD44 is another viable possibility (Tremmel et al. 2009). Following the same notion, v6 peptide that interfered with CD44v6 co-receptor functions with these receptors, blocked tumor growth and metastasis in pancreatic tumors in mice, while extended their survival time. Of note, the v6 peptide achieved higher inhibition than c-Met or VEGFR-2 inhibitors (Matzke-Ogi et al. 2016). NLN and NEW are peptides that bind CD44v6, inducing its internalization to inhibit c-Met/Erk pathways, leading to reduction of cell migration, invasion, and metastasis. In vivo these peptides after conjugation with KLA pro-apoptotic peptides successfully killed tumor cells and impaired tumor growth and metastasis without displaying systemic side effects (Khan et al. 2021).

The FK506-binding protein-like (FKBPL) and a 24-amino acid-derived peptide AD-01 exerted anti-angiogenic effects and reduced tumor growth in vivo, effects that are dependent on the presence of CD44 (Valentine et al. 2011). Moreover, FKBPL and AD-01 bound CD44 and reduced breast cancer cell migration, through inhibition of Rac-1 activity, upregulation of RhoA and the actin-interacting proteins profilin and vinculin (Yakkundi et al. 2013). Moreover, AD-01 treatment inhibited mammosphere-forming capacity of breast cancer stem cells in vitro and reduced tumor initiation in vivo. Specifically, AD-01 induced differentiation of breast cancer stem cells, while reducing the expression of stem cell markers Nanog, Oct4, and Sox2. Importantly when combined with DAPT—a Notch inhibitor—it caused significant reduction of chemotherapy and radiotherapy resistance in breast cancer stem cells (McClements et al. 2013).

CD44, apart from binding hyaluronan, can also interact with other proteins like collagen. Consequently, there are also peptides taking advantage of collagen/CD44 interactions. Peptides derived from collagen type IV incorporated to liposomes bearing doxorubicin targeted CD44$^+$ melanoma cells and reduced tumor size (Ndinguri et al. 2012). Moreover, taking advantage of pro-MMP9 and CD44 interactions, P3 and P6 peptide were prepared from PEX9 domain of pro-MMP9, and were shown to reduce chronic lymphocytic leukemia cell adhesion to pro-MMP9 and thus abrogated chemotaxis and transendothelial migration (Ugarte-Berzal et al. 2014). The peptide PCK3145 induced CD44 shedding by increasing MT1-MMP while decreasing MMP9 secretion. PCK3145 also abrogated adhesion of fibrosarcoma cells on hyaluronan, thus antagonizing tumor metastatic processes (Annabi et al. 2005). A5G27 peptides derived from laminin could also bind CD44v3 and CD44v6, and could be conjugated to particles bearing specific siRNAs. Introduction of such particles in vivo inhibited tumor growth by lung adenocarcinoma or ovarian carcinoma cells (Golan et al. 2016). A5G27 peptide blocked melanoma metastasis by inhibiting the binding of FGF2 in the heparan sulfate chains of CD44v3, and thus reducing bioactivity of FGF2 (Hibino et al. 2005). C21, a C-terminal peptide of thrombospondin-4 competed for osteopontin and hyaluronan

binding to CD44, but its effect on tumor cells remains to be investigated (Sadvakassova et al. 2009). Another CD44-binding peptide (CD44BP) added to an engineered matrix showed significant anti-tumorigenic effect, as evidenced by reductions in tumor sphere formation in vitro (Yang et al. 2013).

Another interesting approach was synthesizing CD44 cytoplasmic tail peptides bearing phosphor-Ser^{325} which were conjugated to penetration sequences in order to enhance plasma membrane translocation. Such peptides blocked CD44-mediated cell migration without affecting hyaluronan binding or CD44 expression (Peck and Isacke 1998). CD44 could be used also as an antigen to be recognized by immune cells for cancer treatment. Specifically, CD44-derived peptides could function as immunogens to sensitize dendritic cells and enhance their anti-tumor activities against prostate cancer stem cells that expressed high CD44 levels in vitro and in vivo (Wang et al. 2020).

18.3.4 Chemically Modified Hyaluronan

Hyaluronan can be modified in several different chemical groups to inhibit binding to CD44, affect tissue architecture and to be utilized in hydrogels and as a scaffold for drug carriers. Sulfhydryl (-SH) modified hyaluronan is utilized to form hydrogels to be used as drug-loaded implant for chemotherapeutics, photosensitizer and photothermal reagent in chemotherapy, photodynamic and photothermal therapy against tumors (Xu et al. 2021). Hyaluronan modification with Au-Ag alloy can be used in nanoparticles that allow for the sensitization of breast cancer cells in radiotherapy, since ionizing radiation releases toxic Ag$^+$ and enhances production of OH$^-$ in tumor sites (Chong et al. 2020). High molecular weight hyaluronan can be also modified with a hydrazide group and bisphosphonate (BP) for selective targeting of CD44 expressing cancer cells (Varghese et al. 2009). Notably, hyaluronan—a non-sulfated glycosaminoglycan—has been modified with sulfate groups which allowed simultaneous targeting of CD44 and P-selectin, to effectively target CD44$^+$P-selectin$^+$ cancer cells (Bhattacharya et al. 2020). Hyaluronan can be also modified with poly(lactic-*co*-glycolic acid) to produce highly stable and GSH sensitive micelles. Loading of these complexes with transferrin-targeted nanoformulated AUY922 eased their uptake by brain tumor cells and induced caspase-dependent cleavage of the apoptosis marker PARP followed by upregulation of p53. Moreover, this complex was drastic against tumor growth in vivo, without displaying any toxicity to other major organs (Debele et al. 2021). β-Cyclodextrin-modified hyaluronan with drug conjugates was able to exert significant toxicity against lung and prostate cancer cells with high expression of CD44, while on the other hand showed no toxicity against normal cells with low CD44 expression (Bai et al. 2020).

18.3.5 Gene Therapies

A promising strategy to target hyaluronan/CD44 network in tumors is to silence the expression of CD44 gene, with specific siRNA and/or shRNA or the most recently developed CRISPR/Cas9 system.

Introduction of a CD44-specific siRNA in lung cancer cells reduced the expression of the stem cell-related genes CXCR4 and POU5F genes after TGF-β1/TNFα treatments but failed to reverse EMT gene signature (Nurwidya et al. 2017). A recombinant adenovirus bearing CD44 shRNA was also able to inhibit cell proliferation, migration and invasion, while induced apoptosis of colon cancer cells. These adenoviral particles inhibited Akt and GSK-3β signaling pathways. Furthermore, the expression levels of anti-apoptotic proteins Bcl-2 and Bcl-xL were reduced, while the apoptotic proteins Bax, cleaved caspase-3/−9 and PARP were increased in colon cancer cells treated with the adenovirus (Lee et al. 2017). Targeted deletion of CD44v6 with specific shRNA in colon cancer cells also reduced the adenoma growth in vivo through interruption of hyaluronan/CD44v6/pErbB2/Cox-2 pathway (Misra et al. 2009). In triple-negative breast cancer cells, knock-down of CD44 with shRNA vectors significantly suppressed proliferation, colony formation, and invasion (Zhou et al. 2018). Doxorubicin resistance is a major caveat in the treatment of breast cancer. Targeting of breast cancer cells with CD44 siRNA in combination with doxorubicin treatment effectively limited tumor metastasis, proliferation, invasion, migration, and induced apoptosis in triple-negative breast cancer cells, signifying the importance of targeting CD44 to overcome drug resistance (Vahidian et al. 2020). Targeting of CD44-expressing breast cancer cells can be also performed with CD44-targeted aptamer Apt1. This aptamer conjugated to liposomes with encapsulated CD44 siRNA was able to successfully target CD44-expressing breast cancer cells to silence CD44 in vitro and in vivo (Alshaer et al. 2018). In another study, the authors utilized biodegradable poly D,L-lacticied-*co*-glycolide acid nanoparticles (PLGANPs) to deliver FAK and CD44 shRNAs in ovarian cancer cells in vivo, since both FAK and CD44 have active roles in tumor angiogenesis and cancer metastatic processes. Double knock-down of both FAK and CD44 reduced tumor size, inhibited angiogenesis, reduced proliferation and induced apoptosis (Zou et al. 2013).

CRISP/Cas9 technology in contrast to siRNA or shRNA systems offers silencing capacity of a specific gene by completely removing the target gene from the host genome. In osteosarcomas, high expression of CD44 predicts poor survival and higher incidence of metastases in patients. Targeting CD44 with CRISPR/Cas9 system in metastatic osteosarcoma cells abrogated the proliferation and spheroid formation in 3D cultures as well as migration and invasion (Liu et al. 2018). Furthermore, in multi-drug-resistant osteosarcoma cells, silencing of CD44 with CRISPR/Cas9 system could also enhance drug sensitivity (Xiao et al. 2018). Although CD44 seems to play an important role in tumor growth, CD44 silencing in vivo with CRISP/Cas9 in HAS3-overexpressing stromal fibroblasts or CD44 knock-down with shRNA in breast cancer cells was not able to inhibit tumor growth,

in contrast with the reductions that were observed when hyaluronan production or accumulation was inhibited (Zhao et al. 2019). This rather contradicting study points out the context-dependent effects of hyaluronan and CD44 in several tumors. Given the fact that in most breast tumors HAS2 has been most extensively studied, while the role of HAS3 remains obscure, further studies are needed to clarify this discrepancy. CD44 can be also indirectly targeted, as evidenced by CRISPR/Cas9 silencing of Cosmc, an endoplasmic reticulum-localized chaperone that regulates protein O-glycosylation. Cosmc knock-out inhibited protein expression of CD44, confirming the notion that O-glycosylation is important for proper CD44 expression. Of note, reconstitution of CD44 reversed the effects of Cosmc disruption on MAPK signaling and breast cancer cell proliferation, verifying the important role of CD44 for breast tumor growth (Du et al. 2020a). In liver cancer stem cells, knock-out of CD44 utilizing CRISPR/Cas9 system resulted in less malignant and more differentiated tumors. Unexpectedly, CD44 silencing increased the expression of stem cell markers Oct4, Sox2, and Nanog. This contradictory finding warrants further investigation as in these cells CD44 was predominantly nuclear and bound in promoter regions of c-Myc and Sox2 (Han et al. 2015). The CRISPR/Cas9 system can be also utilized to target specific variants of CD44. In gastric cells, CD44 exon v6 was deleted, allowing for the rest of CD44 gene to be expressed. Removal of v6 exon from CD44 sensitized gastric cancer cells to cisplatin and abrogated their self-renewal (Lobo et al. 2020). In another study, utilizing CRISPR/Cas9 and overexpression approaches, chimeric antigen receptors (CARs) that specifically target CD44v6 from head and neck squamous cell carcinoma were expressed on T cells. Targeting CD44v6 demonstrated a direct correlation of CD44v6 expression and cytotoxic effects mediated from CAR T cells (Haist et al. 2021).

18.4   Conclusions

Conclusively, hyaluronan/CD44 network appears to offer an important target for translation into the clinic to treat tumors. However, given the omnipresent localization of hyaluronan in the body and ubiquitous expression of CD44 as well as their importance in physiological processes, targeting this system needs to be approached with caution. On the bright side, many of the hyaluronan effects depend on the expression of CD44v isoforms that are expressed specifically by tumor cells. Moreover, while many of the processes controlled by hyaluronan/CD44 network overlap with features of immune and inflammatory pathways, there are clear differences between tumor cells and physiologic events that can be exploited, like the size and interactions of hyaluronan found in cancerous tissues. Certainly, further research is needed to clarify the exact roles of hyaluronan and CD44 in tumorigenesis, but the evidence presented so far suggests that targeting of this system is a promising avenue for the development of safe and effective cancer treatment regiments in the future.

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