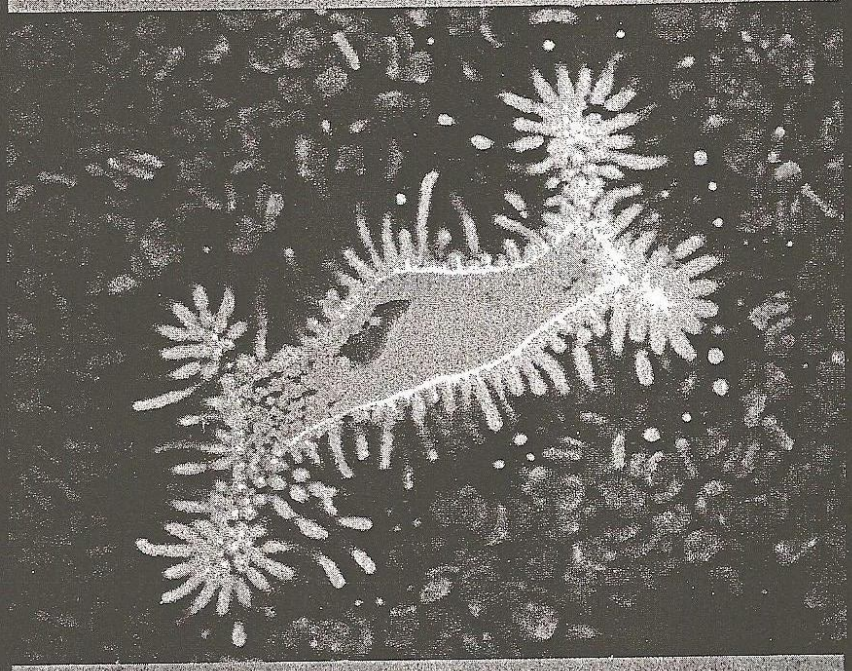
Hyaluronan in Cancer Biology



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Growth Factor Regulation of Hyaluronan Deposition in Malignancies

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OUTLINE

INTRODUCTION

The link between the stromal microenvironment and the promotion of cancer was first described in 1889 by Stephen Paget (Paget, 1889), who predicted that the interactions between tumor cells (the "seed," including secreted growth factors and cell surface proteins) and the host microenvironment ("the soil") determine the metastatic outcome. In recent years it has become accepted that the microenvironment of local host tissue provides tumor cells with a scaffold that promotes their attachment and

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serves as reservoir for regulatory signals and thereby actively participates in tumor progression and metastasis (Schor and Schor, 2001).

In this review we focus on the extracellular molecule hyaluronan, the signals that regulate its synthesis and deposition as well as its role in cellular communication. Hyaluronan is a polysaccharide containing thousands of disaccharide repeats of glucuronic acid and *N*-acetylglucosamine residues. It is abundantly found in free form or decorated by proteoglycans in the extracellular and pericellular matrices of mammals (Heldin and Pertoft, 1993; Laurent and Fraser, 1992), as well as in the surface coats of some bacteria (Weigel, 2004) and *Chlorella* virus infected algae (DeAngelis, 2001). Hyaluronan in the pericellular matrix interacts with the cell by sustained binding to its own membrane-associated synthase or to hyaluronan receptors and with other matrix molecules; these interactions influence intracellular signaling and thereby cellular functions such as cell migration, growth and differentiation (Heldin and Pertoft, 1993; Knudson and Knudson, 1993). Importantly, intracellular and nuclear hyaluronan has also been demonstrated in both normal and tumor cells (Evanko and Wight, 2001; Li et al., 2007b). Because of its remarkable physicochemical properties and hygroscopic nature, hyaluronan has important physiological properties, including tissue organization and tissue hydration. Thus, an accumulation of hyaluronan is a common feature of remodeling tissues, for example during embryonic development, followed by its clearance. However, an aberrant increase in the amount of hyaluronan of a more polydisperse character, with a preponderance of lower molecular mass forms, is seen during inflammation and tumor progression.

Both high and low molecular mass hyaluronan can function as signaling molecules through their interactions with cell surface receptors, e.g. CD44 and extracellular matrix proteins, e.g., versican (Toole, 1990; Turley et al., 2002; Wu et al., 2005). CD44 is an adhesion receptor that is found in different splice variants on immune cells and stromal cells in a low hyaluronan binding state (Aruffo et al., 1990). However, external stimuli by cytokines can induce the transition of CD44 to its high hyaluronan binding state. Active CD44 with high hyaluronan binding capacity is found on activated leukocytes and tumor cells (Cichy and Pure, 2003; Ponta et al., 2003). The ability of CD44 to bind hyaluronan is tightly controlled. High Mw hyaluronan facilitates CD44 oligomerization whereas hyaluronan fragments bind to monomeric CD44 molecules. West and colleagues were first to demonstrate that hyaluronan oligomers are angiogenic (West et al., 1985). Subsequently, a number of laboratories, including ours, revealed that hyaluronan fragments is an important initiation factor in fibrotic tissue remodeling by the induction of collagen genes (Li et al., 2000), chemokine genes (McKee et al., 1996; Teder et al., 2002), but also an angiogenic factor, by the induction of distinct and/or common sets of genes with the known angiogenic factor fibroblast growth factor-2 (FGF-2) (Takahashi et al., 2005).

Both FGF-2 and hyaluronan oligosaccharides promote tubulogenesis in a process dependent on the co-ordinated induction of ornithine decarboxylase (Odc) and ornithine decarboxylase antizyme inhibitor (Oazi) genes. Among the genes induced selectively by hyaluronan oligosaccharides was the chemokine *CXCL1/Gro1* gene (the human homolog is IL-8); the endothelial cell differentiation was CD44-mediated leading to activation of chemokine receptor 2 which is involved in endothelial cell retraction, a common phenomenon observed during angiogenesis (Takahashi et al., 2005). Thus, hyaluronan oligomers have an important function during the inflammatory and angiogenic responses in injuries and malignancies through a sustained production of chemokines.

EXPRESSION OF HYALURONAN SYNTHASES AND HYALURONIDASES

Vertebrate, bacterial and plant hyaluronan molecules have identical chemical structure. There exist three related yet distinct hyaluronan synthase (*HAS*) genes encoding the mammalian HAS-1, HAS-2, and HAS-3 isoforms (Weigel and DeAngelis, 2007). Notably, HAS-2 is required for embryonic development, but not HAS-1 and HAS-3 (Camenisch et al., 2000); moreover the *HAS-2* gene is under tighter regulatory control than the other *HAS* genes (Nairn et al., 2007). The expression patterns of the *HAS* genes was found to vary between normal mesenchymal cells, and between normal and their transformed counterparts. In general, the expression was higher in sub-confluent than in confluent cultures (Jacobson et al., 2000; Li et al., 2007b). Each one of the *HAS* genes encodes plasma membrane proteins that are independently active, with multiple transmembrane and membrane-associated domains; the majority of the protein is inside the cell and possesses consensus sequences for phosphorylation by protein kinases (Shyjan et al., 1996; Spicer et al., 1996; Spicer et al., 1997). Recently, studies have demonstrated that HAS activities can be regulated through extracellular signal-regulated kinase (ERK) (Bourguignon et al., 2007). Each of the three HAS proteins synthesizes hyaluronan chains of high molecular mass, *in situ* ($\geq 4 \times 10^6$ Da). However, *in vitro*, the HAS-2 isoform synthesizes hyaluronan chains of high molecular mass ($\geq 4 \times 10^6$ Da), whereas HAS-3 produce polydisperse hyaluronan (average molecular mass of 0.8×10^6 Da), and HAS-1 even smaller hyaluronan chains (average molecular mass of 0.1×10^6 Da). Furthermore, the HAS-3 protein was catalytically more active than HAS-2 which in turn was more active than HAS-1. It is possible that different cytoplasmic proteins specifically interact with each HAS protein and may have accessory or regulatory roles in hyaluronan biosynthesis (Brinck and Heldin, 1999). The nature of these proteins have not yet been identified.

The newly synthesized and growing hyaluronan chain is extruded through the plasma membrane while the synthesis is in progress, contributing to the assembly of pericellular matrices by remaining attached to its own membrane-associated synthase before being released into the extracellular matrix (Heldin and Pertoft, 1993). The transfer process of newly synthesized hyaluronan is not yet known. It has been proposed that hyaluronan is transported through a pore-like passage and/or uses the multidrug resistance system (Prehm and Schumacher, 2004; Tlapak-Simmons et al., 1999). Hyaluronan overexpression amplifies MDR1 multidrug transporter expression and increases doxorubicin resistance in breast cancer cells MCF-7 (Misra et al., 2005; Misra et al., 2003); further studies are necessary to elucidate the inter-relationship between hyaluronan synthesis/export and multidrug transporters.

The turnover rate of hyaluronan in mammals is high; its intravenous $t_{(1/2)}$ is about 5 min and in epidermis it is less than 24 h (Fraser et al., 1981; Tammi and Tammi, 1998). Hyaluronidases, the enzymes involved in hyaluronan degradation also exist in several isoforms (*HYAL-1*, *HYAL-2*, *HYAL-3*, *HYAL-4*, and *PH-20*) and are localized in lysozomes or are glycosylphosphatidyl-inositol linked to the plasma membrane. HYAL-1 and HYAL-2 proteins are widely expressed in tissues and act in a concerted manner to degrade hyaluronan chains (Csoka et al., 2001; Lepperdinger et al., 2001).

HYALURONAN SIGNALING PROMOTES THE MALIGNANT PHENOTYPE OF TUMOR CELLS

Studies on human cancers from different origins and various malignancy grades have demonstrated a positive correlation between tumor aggressiveness and stromal hyaluronan expression (Auvinen et al., 2000; Boregowda et al., 2006). The aberrant amounts of hyaluronan in the desmoplastic stroma can be produced by the tumor cells themselves or by the stromal cells commandeered by the tumor cells (Asplund et al., 1993; Toole, 2004). Notably, a differential expression of *HAS* genes is seen during tumor progression. For example, aggressive breast cancer cells and ovarian cancer express higher levels of *HAS-2* than *HAS-3* compared to non-aggressive ones (Bourguignon et al., 2007; Li et al., 2007b), whereas metastatic prostate and colon cancer express higher levels of *HAS-3* than *HAS-2* (Bullard et al., 2003; Simpson et al., 2001). *HAS-1* was expressed only at low levels in these tumors. An important question awaiting an answer is whether there are functional differences between tumor cell-produced and stromal fibroblast- and/or mesothelial cell-synthesized hyaluronan for tumor progression. It is also important to elucidate which regulatory factors modulate the expressions and activities of HAS and HYAL proteins.

Earlier studies in our laboratory demonstrated marked differences in hyaluronan synthesis and expression of CD44 between non-aggressive and aggressive breast cancer cells. Metastatic breast carcinoma cells were found to express high levels of CD44 with high hyaluronan binding capacity and to synthesize hyaluronan. In contrast, breast cancer cell lines which have a non-invasive character synthesized much lower amounts of hyaluronan and did not express CD44 (Heldin et al., 1996). Importantly, CD44 exhibiting high hyaluronan binding capacity was expressed on malignant mesotheliomas but not on normal mesothelial cells, suggesting an up-regulation of hyaluronan–CD44 interaction upon transformation (Asplund and Heldin, 1994). In view of these observations it is possible that tumor cell invasiveness could be related to tumor cell surface CD44–matrix hyaluronan interaction or tumor cell-presented hyaluronan interaction with soluble CD44 or CD44 expressed by endothelial cells (Hill et al., 2005). However, blocking hyaluronan–CD44 interaction does not lead to complete inhibition of tumor cell migration/invasion, suggesting that also other mechanisms are involved (Fig. 3.1). Using two-photon fluorescence correlation microscopy, hyaluronan molecules were demonstrated to form continuous cage-like structures partitioning the space of melanoma tumor matrix into aqueous and viscous compartments (Alexandrakis et al., 2004), thereby facilitating cell migration.

Several approaches have been used to elucidate the importance of hyaluronan for tumor progression; manipulation of tumor cell-produced

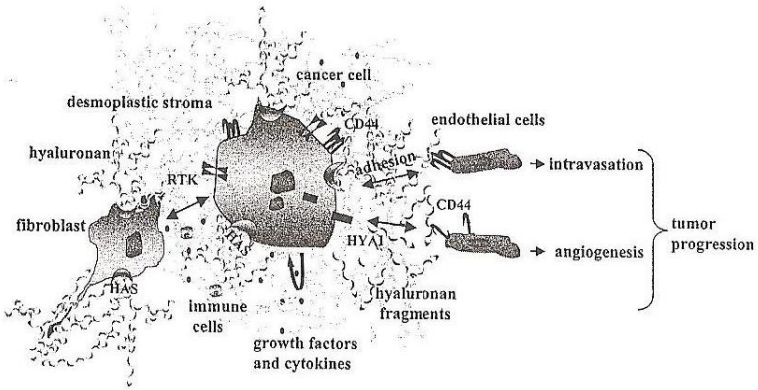

FIGURE 3.1 Tumor–host cross-talk in tumor progression. Growth factors and cytokines released by tumor cells, immune cells, and "activated" stromal cells trigger signaling events that increase the deposition of extracellular matrix macromolecules and activate tumor cell-expressed CD44 and RTK. Hyaluronan molecules form biological networks that bridges CD44 expressed by tumor and endothelial cells facilitating intravasation. Hyaluronan fragments, produced for example by the action of HYAL, bind to CD44 on endothelial cells and promote angiogenesis.

hyaluronan by overexpression of *HAS* or *HYAL* transcripts, overexpression of soluble CD44, administration of hyaluronan fragments, and treatment with antibodies that prevent hyaluronan–CD44 interactions (Toole, 2002; Toole, 2004). The impact of hyaluronan for the malignant phenotype of colon carcinomas was studied by overexpressing *HAS-2* and *HYAL-1* both *in vitro* and *in vivo*. The analysis revealed that *HAS-2* gene overexpression leads to a faster development of transplantable tumors in syngeneic rats, compared to mock-transfectants. In contrast, *HYAL-1* overexpression suppressed the growth rate of tumor cells (Jacobson et al., 2002). Similarly, inhibition of hyaluronan synthesis in prostate cancer cells impaired their growth (Liu et al., 2001; Simpson et al., 2001). Importantly, administration of hyaluronidase to mice bearing human breast cancer xenografts reduced tumor volume, hyaluronan content, and CD44 isoforms in the cancerous growth, supporting the hypothesis that loss of tumor cell-produced hyaluronan interactions is crucial for the maintenance of the malignant phenotype (Shuster et al., 2002).

Hyaluronan is abundant in highly aggressive breast cancer cells and has been shown to be a prognostic factor for patient survival of clinical breast carcinomas (Auvinen et al., 2000). *HAS-2* overexpression correlates with the promotion of the malignant phenotype of colon cancer and mesotheliomas (Jacobson et al., 2002; Li and Heldin, 2001). We therefore investigated the importance of HAS-2-synthesized hyaluronan for the malignant properties of breast cancer cells, by investigating the consequences of suppressing HAS-2 protein using specific siRNAs (Li et al., 2007b). Silencing of the *HAS-2* gene caused an about 50% reduction of the invasive and malignant phenotype of Hs578T breast cancer cells. This strong reduction of the aggressive characteristics of breast cancer cells suggests that the amount of synthesized hyaluronan influences their invasive phenotype. Similarly, antisense-mediated suppression of HAS-2 in breast cancer cells also decreased their aggressive phenotype (Udabage et al., 2005). Interestingly, addition of exogenous hyaluronan could not rescue the aggressive phenotype of breast cancer cells, suggesting that hyaluronan synthesized by neighboring fibroblasts *in vivo* is functionally not equivalent to endogenously tumor cell-produced hyaluronan. Importantly, in a mouse mammary model of spontaneous breast cancer, endogenous hyaluronan production promoted tumor epithelial–mesenchymal transition and elicited cell survival signals (Koyama et al., 2007). In addition, the aggressive phenotype could be promoted by elevated HAS activity and expression of CD44 receptors resulting in retention of hyaluronan on the surface of the neoplastic cells, facilitating their binding to the bone marrow endothelium (Draffin et al., 2004; Simpson et al., 2001). However, the involvement of hyaluronan in tumor progression is complex. Tumor cells often exhibit elevated levels of HYALs (Li et al., 2007b; Lokeshwar et al., 1999), leading to the production of angiogenic hyaluronan fragments. These observations

demonstrate a cooperativity between HAS and HYAL activities, as well as CD44 hyaluronan receptors in the maintenance of the aggressive character of breast cancer cells (Fig. 3.1).

Interestingly, hyaluronan synthesized by mammary and colon carcinomas can, through interactions with tumor cell-expressed CD44, promote activation of several receptor tyrosine kinases (RTK), including ErbB2, and thereby promote cell survival and drug resistance. Perturbating the interaction between endogenously synthesized hyaluronan and CD44, Bryan Toole and his colleagues demonstrated the necessity of hyaluronan for the malignant properties of some cancer cells; addition of hyaluronan oligosaccharides, suppressed the tyrosine kinase activities of RTKs resulting in suppression of the phosphoinositol-3-kinase/Akt survival pathway (Ghatak et al., 2002; Ghatak et al., 2005; Misra et al., 2006).

The general concept emerging from these studies is that increased hyaluronan synthesis promotes tumorigenesis and plays an important role in the local aggressive spread of tumor cells. Thus, suppression of hyaluronan synthesis and/or prevention of its binding to cell surface receptors may provide a therapeutic opportunity to suppress tumor invasion.

REGULATION OF HYALURONAN LEVELS PRODUCED BY TUMOR CELLS

The levels of hyaluronan and differences in the size of hyaluronan molecules seen in rapidly remodeling tissues, e.g. tumor tissues, are due to the concerted action of HAS and HYAL enzymes that most likely are targets of local environmental cell specific factors. During tumor development and progression, besides the epithelial malignant cells and stromal cells (fibroblasts, mesothelial cells, and endothelial cells), a large number of inflammatory cells are also present; chronic inflammation goads premalignant cells to become malignant through the influx of innate immune cells that release cytokines and chemokines, promoting the growth and invasion of tumors (Mantovani, 2005). Tumor cells themselves release a variety of growth factors, for example TGF-β and PDGF, that may function in autocrine stimulation of tumor cells or in paracrine mechanisms involving stromal cells. Importantly, these growth signals can "activate" stromal cells to produce and release growth factors and cytokines, resulting in modulation of the matrix macromolecular structure (desmoplasia). Additionally, these signals can activate adhesive receptors (CD44, integrins) so that they can transmit signals for cell survival and metastasis (Hanahan and Weinberg, 2000; Hill et al., 2005). During inflammation in malignancies a possible co-existence of reactive oxygen species and overexpression of HYALs results in the accumulation of hyaluronan fragments in tissues.

Very little is known about the hyaluronan-stimulatory activities in various carcinomas. Mesothelioma cells produce PDGF-BB- and bFGF-like factors that most likely stimulate hyaluronan synthesis by the neighboring mesothelial cells and fibroblasts, creating a matrix that supports the colonization of malignant cells (Teder et al., 1996). However, it is possible that these factors also in an autocrine manner stimulate mesotheliomas to synthesize hyaluronan and thereby acquire a more malignant phenotype than the non-hyaluronan producing mesotheliomas (Li and Heldin, 2001). Furthermore, the phosphoglycoprotein osteopontin is implicated in breast cancer progression and metastasis probably through its interaction with CD44 resulting in the induction of HAS-2 expression and hyaluronan synthesis (Cook et al., 2006). Additionally, heregulin (HRG) activates members of the epidermal growth factor receptor family of tyrosine kinases leading to ERK activation and subsequent phosphorylation and activation of HAS-1, HAS-2 and HAS-3, affecting ovarian cancer progression (Bourguignon et al., 2007). Notably, the HRG-ErbB2-ERK signaling caused a decrease in the size of hyaluronan from about 400 kDa to about 80 kDa. Whether this reduction in the size of hyaluronan is due to HRG-mediated activation of HYAL in ovarian cancer cells, remains to be elucidated. Notably, HYAL activity was upregulated in TGFβ-stimulated human dermal fibroblasts cultures (Li et al., 2007a). Furthermore, oncostatin M, TGFβ and phorbol 12-myristate 13-acetate (PMA) induce the hyaluronan binding capacity of CD44 in lung tumor cells (Cichy and Pure, 2000; Teder et al., 1995). Because the molecular mechanisms underlying malignancy-induced hyaluronan production are not well understood, further studies on the regulatory mechanisms modulating the activities of HASs, HYALs, and CD44 hyaluronan binding capacity in tumors are necessary.

REGULATION OF HYALURONAN SYNTHESIS BY PERITUMORAL STROMA CELLS

The emphasis in this section is on the regulation of hyaluronan synthesis by stromal mesothelial cells and fibroblasts, particularly in response to PDGF-BB and TGFβ released by cancer cells, endothelial cells, and immune cells during the malignant progression. A large body of studies revealed that *HAS-2* is the most abundantly expressed among the three HAS isoforms in mesothelial cells (Jacobson et al., 2000), corneal keratocytes (Guo et al., 2007), chondrocytes (Recklies et al., 2001), synovial cells (Stuhlmeier and Pollaschek, 2004), as well as in dermal, oral and lung fibroblasts (Li et al., 2007a; Li et al., 2000; Meran et al., 2007). *HAS-3* is also found in appreciable amounts in these cells, whereas *HAS-1* is hardly detected. However, the importance of each HAS isoform in the overall hyaluronan synthesis and assembly of the matrix surrounding cells is not known.

PDGF-BB had a potent stimulatory effect on hyaluronan synthesis through the induction of *HAS-2* in mesothelial, foreskin or dermal fibroblasts, and smooth muscle cell cultures (Heldin et al., 1992; Jacobson et al., 2000; Li et al., 2007a; Suzuki et al., 1995; van den Boom et al., 2006). Interestingly, PDGF-BB-mediated proliferation of human dermal fibroblasts and smooth muscle cells is promoted by the binding of hyaluronan to CD44 (Li et al., 2007a; van den Boom et al., 2006). Importantly, TGFβ stimulation suppresses *HAS-2* in mesothelial cells (Jacobson et al., 2000) and orbital fibroblasts from patients with Graves' ophthalmopathy (Wang et al., 2005), but potently activates *HAS-1* in synovial fibroblasts (Oguchi and Ishiguro, 2004; Recklies et al., 2001). The stimulatory effects of PDGF-BB and TGFβ were partly dependent on protein synthesis since the stimulations were partly inhibited by cycloheximide. Similarly, the protein kinase C stimulator PMA, powerfully induced hyaluronan synthesis probably via regulatory phosphorylation of a HAS isoform (Suzuki et al., 1995). Regulatory phosphorylation of each one of the three HAS isoforms has been demonstrated in a recently published study (Bourguignon et al., 2007). Combinations of PDGF-BB and TGFβ additively stimulated hyaluronan production in foreskin cultures (Suzuki et al., 1995). In contrast, in dermal fibroblast cultures TGFβ reduced the PDGF-BB-mediated hyaluronan production, probably because of activation of HYALs activity (Li et al., 2007a). These observations demonstrate that different cell types respond differentially to hyaluronan-modulating factors. More recently the downstream signaling pathways, through which PDGF-BB stimulates hyaluronan synthesis in human dermal fibroblasts were investigated. Using specific inhibitors for the major PDGF-BB-induced intracellular signaling pathways revealed that ERK MAPK and PI3K pathways are crucial for PDGF-BB-dependent *HAS-2* transcriptional activity and hyaluronan synthesis. Similarly, inhibition of NF-kB action completely suppressed hyaluronan production. The fact that the *HAS-2* promoter has putative transcription factor binding sites for CREB, NF-kB, and STAT (Monslow et al., 2003; Saavalainen et al., 2005), which are downstream of PDGF β-receptor signaling, is consistent with an important role of these signaling pathways in hyaluronan production (Fig. 3.2A).

The importance of high amounts of hyaluronan for PDGF-BB-mediated stromal fibroblast growth and migration were recently studied. The analysis revealed that hyaluronan-stimulated CD44 suppresses the activation state of the PDGF β-receptor, in PDGF-BB-stimulated human dermal fibroblasts, by the activation of a CD44-associated tyrosine phosphatase to the receptor, decreasing PDGF-BB-mediated fibroblast migration. Additionally, hyaluronan binding to CD44 is important for the mitogenic PDGF-BB response (Li et al., 2007a; Li et al., 2006) (Fig. 3.2B). Thus, dermal fibroblast CD44 binding to exogenous hyaluronan negatively regulates PDGF β-receptor-mediated migration, but positively

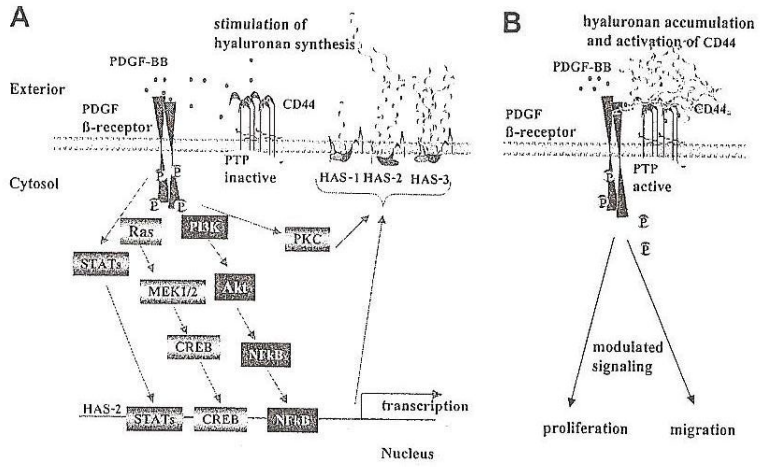

FIGURE 3.2 PDGF β-receptor-mediated hyaluronan production and its interaction with hyaluronan-activated CD44. (A) MEK1/2 and PI3K signaling pathways are important in mediating PDGF-BB-induced hyaluronan synthesis. Furthermore, activation of PKC is involved in the enhancement of HAS isoforms activities. (B) The interaction between hyaluronan-activated CD44 and PDGF β-receptor activates a CD44-associated PTP and modulates PDGF signaling, leading to cell migration and growth.

regulates its mitogenic response. Further studies are needed in order to elucidate the physiological importance of these observations during normal and abnormal tissue remodeling.

FUTURE PERSPECTIVES

Several observations support the notion that hyaluronan has an important role in tumorigenesis. Future studies should aim at unraveling the molecular mechanisms responsible for the synthesis and degradation of hyaluronan. Moreover, the mechanisms behind the expression and induction of CD44 from its low to high hyaluronan binding state as well as the functional importance of the interaction between RTK and CD44, remains to be elucidated.

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CHAPTER

4

Hyaluronan Binding Protein 1 (HABP1/p32/gC1qR): A New Perspective in Tumor Development

Anindya Roy Chowdhury, Anupama Kamal, Ilora Ghosh, and Kasturi Datta

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HYALURONAN IN CANCER BIOLOGY

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"For decades, hyaluronan researchers have followed with growing interest the slowly developing story of how cancer progression and metastasis are correlated with or regulated by hyaluronan and its catabolic degradation products. Initially trying to understand the role of hyaluronan metabolism in prostate, breast, melanoma and other carcinomas was a bit like the story of the blind men touching and describing an elephant, each with a different impression of what they found. Now, however, our understanding of how hyaluronan is related to cancer biology has come into much clearer focus and this is captured nicely in ***Hyaluronan in Cancer*** - a collection of well written research perspectives and summaries from ~20 research groups around the world. The timing of this volume edited by Dr. Stern is excellent - readers can now get an overview and understand the importance of hyaluronan in multiple cancers. The book provides the first state-of-the-field summary and should be a highly useful and cited source for cancer biologists and hyaluronan researchers for many years."

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"Hyaluronan is a major component of the fluid extracellular matrix that surrounds cells and fills the intercellular spaces of tissue. Long known for its fundamental role in tissue development and physiology, hyaluronan's involvement in cancer progression and metastasis has more recently become the subject of intense multidisciplinary efforts. This volume provides a state-of-the-art review of hyaluronan's role in the cell biology of cancer, its diagnostic and prognostic value, and its potential as a target for therapeutic intervention. Authored by leading researchers in the field, the chapters help bridge the gap between basic science and clinical oncology, providing background and context that will prove valuable to both cancer and hyaluronan researchers for years to come."

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