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Review

Hyaluronan: A constitutive regulator of chemoresistance and malignancy in cancer cells

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ABSTRACT

Hyaluronan not only is an important structural component of extracellular matrices but also interacts instructively with cells during embryonic development, healing processes, inflammation, and cancer. It binds to several different types of cell surface receptors, including CD44, thus leading to co-regulation of important signaling pathways, notably those induced by activation of receptor tyrosine kinases. Consequently, interactions of both stromal and tumor cell-derived hyaluronan with tumor cells play important cooperative roles in several aspects of malignancy. This review focuses on cell autonomous hyaluronan–tumor cell interactions that lead to activation of receptor tyrosine kinases and enhanced drug resistance. Particular emphasis is placed on the role of hyaluronan–CD44 interactions in drug transporter expression and activity, especially in cancer stem-like cells that are highly malignant and resistant to chemotherapy. Antagonists of hyaluronan–CD44 interaction, especially small hyaluronan oligomers, may be useful in therapeutic strategies aimed at preventing tumor recurrence from these therapy-resistant sub-populations within malignant cancers.

Contents

1. Introduction: the relationships between drug resistance, malignancy and cancer stem-like cells

Invasion and metastases of cancer cells and the development of resistance to anticancer therapies are the main causes of morbidity and mortality from cancer. Recently, sub-populations of stem-like cells have been characterized within a variety of cancers. These cells are highly malignant in that they can rapidly regenerate a fully grown tumor when implanted in small numbers in an animal host [1–3] and they may be responsible for tumor metastasis [4,5]. In addition, these cells usually demonstrate resistance to chemotherapy (multidrug resistance) [6]. Expression of the hyaluronan receptor, CD44, is frequently associated with these stem-like cells [1]. Both hyaluronan and CD44 have been shown to play a role in drug resistance [7–9], as well as in malignant cell behavior and cell survival [10]. Treatment with hyaluronidase enhances the action of various chemotherapeutic agents [11,12]. Moreover, hyaluronan may be extruded from cells by ABC-family drug transporters [13]. These and other observations point towards a role for hyaluronan–CD44 interactions in the malignant and drug-resistant properties of cancer cells, and possibly cancer stem-like cells.

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2. Hyaluronan in tumor progression

Hyaluronan is a large, linear glycosaminoglycan composed of 2000–25,000 disaccharides of glucuronic acid and *N*-acetylglucosamine: [β1,4-GlcUA-β1,3-GlcNAc-]$_n$, with molecular weights usually ranging from 10^5 to 10^7 Da. Hyaluronan is distributed ubiquitously in vertebrate tissues. In adult tissues such as the vitreous, synovial fluid and dermis, it clearly plays an extracellular, structural role that depends on its unique hydrodynamic properties as well as its interactions with other extracellular matrix components. However, hyaluronan is also concentrated in regions of high cell division and invasion, e.g. during embryonic morphogenesis, inflammation, wound repair, and cancer. Thus, in similar fashion to numerous matrix constituents, hyaluronan has an instructive role in terms of cell signaling via hyaluronan receptors on the cell surface, as well as an important structural role [10,14–17]. Although underlying regulatory mechanisms are not well understood, it is clear that hyaluronan-induced signaling is "activated" during dynamic cell processes such as occur in cancer but not under conditions of adult tissue homeostasis.

Considerable experimental evidence implicating hyaluronan in tumor progression has now been obtained in animal models. Several approaches have been used, including manipulation of levels of hyaluronan and perturbation of endogenous hyaluronan–protein interactions. For example, experimental over-expression of the hyaluronan synthase, HAS2, in human fibrosarcoma cells gives rise to elevated hyaluronan production and causes increased tumor cell growth in xenografts in vivo [18]. Similar results were obtained in vivo on HAS2 over-expression in a transgenic mouse breast cancer model [19] or on over-expression of HAS3 in human prostate tumor cells [20]. On the other hand, transfection of prostate carcinoma cells with antisense *Has2* and *Has3* reduced subcutaneous tumor growth in nude mice xenografts [21]. Tumor growth and metastasis are also inhibited in animal xenograft models by perturbing endogenous hyaluronan–cell receptor interactions in various ways. For example, soluble hyaluronan-binding proteins such as the ectodomain of CD44 competitively displace hyaluronan from its endogenous cell surface receptors. Thus over-expression of CD44 ectodomain in mouse mammary carcinoma cells or in human malignant melanoma cells has been shown to inhibit growth, local invasion, and metastasis in vivo [22–25]. These effects most likely arise due to induction of apoptosis [23] or cell cycle arrest [24] in vivo. No significant effects were obtained in these studies if the CD44 ectodomain was mutated such that hyaluronan binding was reduced. A soluble form of Rhamm, another hyaluronan receptor, also induces cell cycle arrest and inhibits metastasis [26] and a soluble hyaluronan-binding complex derived from cartilage inhibits both tumor growth and metastasis [27]. Likewise, administration of antibodies that block hyaluronan binding to CD44 inhibits tumor growth and invasion [28,29]. In addition, we have found that treatment with small hyaluronan oligosaccharides (oligomers) retards growth of several tumor types in vivo [30–32]. These oligomers most likely compete for endogenous polymeric hyaluronan (see Fig. 1), thus replacing high affinity, multivalent and cooperative interactions with low affinity, monovalent receptor interactions [33,34]; oligomers containing 6–18 sugar residues are monovalent in their interaction with CD44, whereas larger polymers are multivalent [34].

Although these and many other studies have strongly implicated hyaluronan in tumorigenesis, numerous observations have been made that indicate the role of hyaluronan in cancer is complex, especially with respect to hyaluronan processing. First, lower molecular weight hyaluronan, e.g. 10–100 kDa, stimulates angiogenesis but high molecular weight hyaluronan (>1000 kDa) is inhibitory [35–37]. Second, even though elevated hyaluronan production usually promotes tumor progression, extremely high levels of hyaluronan production can be inhibitory [38]. Third, glioma progression is promoted by increased hyaluronan production only when hyaluronidase is expressed concomitantly with hyaluronan [39]. Similarly, maximum growth of prostate tumors in xenografts was observed on coexpression of both the hyaluronan synthase, HAS2, and the hyaluronidase, HYAL1 [40]. Fourth, tumor progression often correlates with both hyaluronan and hyaluronidase levels in human cancers [41]. These observations have led several investigators to propose that hyaluronan turnover is essential to the promotion of tumor progression by hyaluronan [23,39–43]. This idea is compounded by the apparent importance of partial degradation of hyaluronan in signaling pathways implicated in inflammation [17], an important factor in the progression of many tumor types [44,45].

Another complex aspect of the relationship between hyaluronan and tumor progression is the relative contribution of stromal versus cancer cell-produced hyaluronan. In human patients, correlations have been made between increased levels of either stromal or parenchymal hyaluronan and malignant outcomes (reviewed in [103]). The importance of stromal hyaluronan has been highlighted in a Neu-induced, spontaneous, mouse breast cancer model in which hyaluronan levels were increased by up-regulation of HAS2 [19] (see [104]). Using this model, it was shown that induction of hyaluronan production caused recruitment of stromal cells,

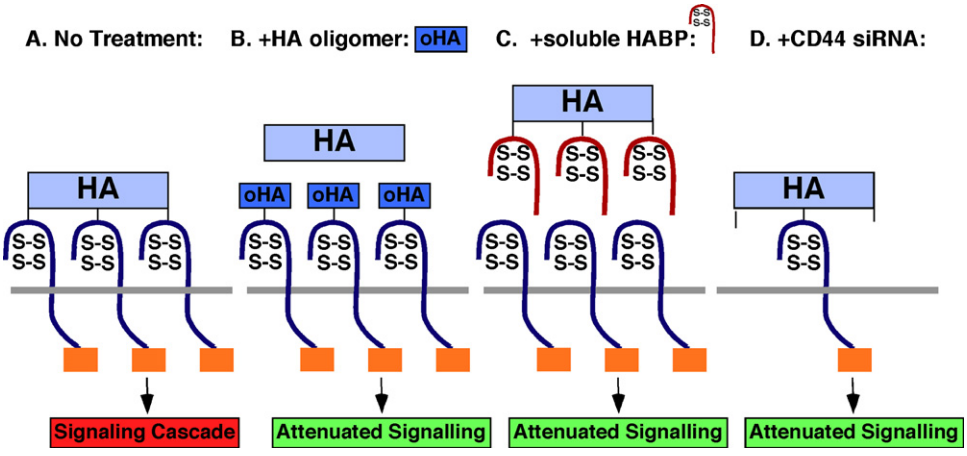

Fig. 1. Antagonists of hyaluronan–CD44 signaling (adapted from Refs. [10,51]. HA, hyaluronan; HABP, HA-binding protein.