Available online at www.sciencedirect.com
ScienceDirect
Drug Resistance Updates 11 (2008) 110–121
DRUG RESISTANCE Updates
www.elsevier.com/locate/drup

Hyaluronan, CD44 and Emmprin: Partners in cancer cell chemoresistance

Bryan P. Toole *, Mark G. Slomiany

Department of Cell Biology and Anatomy, Medical University of South Carolina, USA

Received 29 March 2008; received in revised form 7 April 2008; accepted 8 April 2008

Abstract

Hyaluronan not only is an important structural component of extracellular matrices but also interacts with cells during dynamic cell processes such as those occurring in cancer. Consequently, interactions of hyaluronan with tumor cells play important cooperative roles in various aspects of malignancy. Hyaluronan binds to several cell surface receptors, including CD44, thus leading to co-regulation of signaling pathways that are important in regulation of multidrug resistance to anticancer drugs, in particular anti-apoptotic pathways induced by activation of receptor tyrosine kinases. Emmprin, a cell surface glycoprotein of the Ig superfamily, stimulates hyaluronan production and downstream signaling consequences. Emmprin and CD44 also interact with various multidrug transporters of the ABC family and monocarboxylate transporters associated with resistance to cancer therapies. Moreover, hyaluronan–CD44 interactions are critical to these properties in the highly malignant, chemotherapy-resistant cancer stem-like cells. Perturbations of the hyaluronan–CD44 interaction at the plasma membrane by various antagonists result in attenuation of receptor tyrosine kinase and transporter activities and inhibition of tumor progression in vivo. These antagonists, especially small hyaluronan oligomers, may be useful in therapeutic strategies aimed at preventing tumor refractoriness or recurrence due to drug-resistant sub-populations within malignant cancers.

Keywords: Hyaluronan; CD44; Emmprin; CD147; Cancer stem cells; Multidrug resistance; Receptor tyrosine kinases; ABC-family drug transporters; Monocarboxylate transporters

1. Introduction

A close association between the extracellular polysaccharide, hyaluronan, and malignant tumor progression has been known for some time, where hyaluronan concentrations are usually higher in malignant tumors than in corresponding benign or normal tissues (Knudson et al., 1989; Toole et al., 2002). Several studies have reported enrichment of hyaluronan in the stroma that surrounds tumors (Bertrand et al., 1992; Koyama et al., 2007; Toole et al., 1979), and other studies have shown that hyaluronan production by stromal cells is stimulated by interactions with tumor cells (Asplund et al., 1993; Edward et al., 2005; Knudson et al., 1984). However, hyaluronan synthesis is also increased in malignant tumor cells themselves (Calabro et al., 2002; Kimata et al., 1983; Zhang et al., 1995).

Hyaluronan is distributed ubiquitously in adult vertebrate tissues where it clearly plays a structural role that depends on its unique hydrodynamic properties and 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 and wound repair, as well as in cancer. In these contexts, hyaluronan has an instructive, cell signaling function in addition to its structural role (Jiang et al., 2007; Slevin et al., 2007; Toole, 2001, 2004; Turley et al., 2002). Though hyaluronan signals through interaction with several cell surface receptors, CD44 is the best characterized of these receptors in cancer cells. Variant forms of CD44 are commonly up-regulated in cancers and CD44 has been implicated in numerous aspects of cancer progression (Hill et al., 2006a; Liu and Jiang, 2006; Marhaba and Zoller, 2004; Slevin et al., 2007).

* Corresponding author. Department of Cell Biology and Anatomy, Room BSB620, Medical University of South Carolina, 173 Ashley Avenue, PO Box 250508, Charleston, SC 29425, USA. Tel.: +1 843 792 7004; fax: +1 843 792 0664.
E-mail address: toolebp@musc.edu (B.P. Toole).

1368-7646/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.drup.2008.04.002

Emmprin (extracellular matrix metalloproteinase inducer; CD147; basigin), which was originally characterized as an inducer of matrix metalloproteinase synthesis (Biswas et al., 1995), is a multifunctional glycoprotein that is also up-regulated on the surface of many types of cancer cells (Yan et al., 2005). Emmprin has now been shown to stimulate hyaluronan production and many of its signaling effects (Toole, 2004). In addition, we have recently shown that Emmprin co-localizes with CD44 in a variety of carcinoma cell lines (unpublished results).

Resistance of cancers to multiple classes of chemotherapeutic agents, i.e. multidrug resistance, can arise in numerous ways, e.g. by decreased uptake of drugs due to cell and tissue barriers, activation of repair and detoxification mechanisms, altered metabolic phenotype, increased activities of cell survival/anti-apoptotic signaling pathways, or enhanced drug efflux via cell membrane transporters of the ATP-binding cassette (ABC) family (Cheng et al., 2005; Dai and Grant, 2007; Gottesman et al., 2002; Assaraf, 2006; Landis-Piwowar et al., 2006; Li and Dalton, 2006; Moretti et al., 2007; Broxterman and Georgopapadakou, 2007; Tredan et al., 2007). A relatively new paradigm with respect to solid tumors is the likely contribution of cancer stem-like cells to chemoresistance. Like normal hematopoietic and other adult stem cells, cancer stem-like cells are enriched in ABC-family drug transporters. As these cells may be responsible for resistance of cancer to various therapies and for recurrence after treatment, their unique properties may comprise a novel therapeutic target (Ailles and Weissman, 2007; Dean et al., 2005; Fojo, 2007; Neuzil et al., 2007; Raaijmakers, 2007).

In recent years, inter-related activities of hyaluronan, CD44 and Emmprin have been shown to influence drug resistance at several of these different levels, i.e. through cell survival signaling pathways, drug transporter expression and activity, glycolytic phenotype, and cancer stem-like cell characteristics. Their contributions to multidrug resistance are examined in this review.

2. Hyaluronan, CD44 and Emmprin

Hyaluronan is a very large, linear glycosaminoglycan composed of 2000–25,000 disaccharides of glucuronic acid and *N*-acetylglucosamine: $[\beta1,4\text{-GlcUA-}\beta1,3\text{-GlcNAc-}]_n$, with molecular weights usually ranging from 10^5 to 10^7 Da. In addition to its structural role, which is dependent on its unique hydrodynamic properties and its interactions with other extracellular matrix components, hyaluronan has an instructive role in signaling via receptors on the cell surface. These receptors include CD44, Rhamm, TLR1/4, Hare and LYVE-1 (Jiang et al., 2007; Slevin et al., 2007; Toole, 2004; Turley et al., 2002). CD44, the most widely studied hyaluronan receptor, exists in numerous spliced forms due to insertion of several exon products into a single position in its ectodomain (Fig. 1). The standard form, which has none of these additional spliced-in exon products, is the most

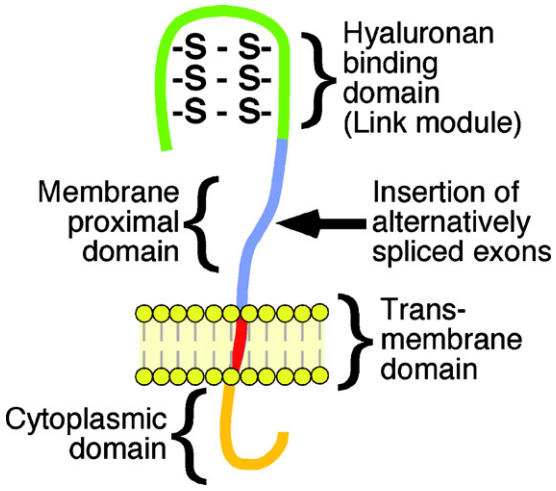

Fig. 1. Structure of CD44. The major domains of the standard form of CD44 are shown. These are the hyaluronan-binding domain, which is related to the so-called link modules of other hyaluronan-binding proteins (Day and Prestwich, 2002); the membrane proximal domain, which includes the single site into which additional exon products are spliced to form numerous CD44 variants; the transmembrane domain; and the cytoplasmic domain, to which numerous signaling molecules bind directly or indirectly on activation and engagement of the link module by hyaluronan.

widely distributed in normal tissues. However, so-called variant forms are expressed by several epithelia and are widely expressed in cancers.

Hyaluronan-receptor interactions mediate at least three important physiological processes, i.e. signal transduction, receptor-mediated hyaluronan internalization, and assembly of pericellular matrices (Knudson et al., 2002; Toole, 2001). Each of these general functions is most likely shared by more than one receptor. For example, CD44 and Rhamm can mediate many aspects of hyaluronan-induced signal transduction (Turley et al., 2002). It is not yet clear which specific signaling functions overlap, although interchangeable CD44 and Rhamm signaling has been demonstrated in some systems (Naor et al., 2007). Also, CD44 and Rhamm exhibit cooperative effects in that Rhamm-CD44 interaction can activate hyaluronan-induced signaling (Hamilton et al., 2007; Maxwell et al., 2008). 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, and considerable experimental evidence implicating hyaluronan in tumor progression has now been obtained in cell and animal models. Several approaches have been used, including manipulation of levels of hyaluronan production and perturbation of endogenous hyaluronan–protein interactions (Stern, 2005; Toole, 2004).

In our own studies, we have focused on manipulating constitutive hyaluronan–tumor cell interactions. To inhibit these interactions we commonly use treatment with small hyaluronan oligosaccharides (oligomers), experimental expression of soluble hyaluronan-binding proteins (HABPs), or transfection with siRNA against CD44 (Fig. 2).