European Journal of Pharmaceutics and Biopharmaceutics 97 (2015) 400–416

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Review Article

Hyaluronic acid and its derivatives in drug delivery and imaging: Recent advances and challenges

Giuseppe Tripodo [a], Adriana Trapani [b], Maria Luisa Torre [a], Gaetano Giammona [c], Giuseppe Trapani [b], Delia Mandracchia [b,*]

[a] Department of Drug Sciences, University of Pavia, Viale Taramelli 12, 27100 Pavia, Italy
[b] Department of Pharmacy-Drug Sciences, University of Bari "Aldo Moro", via Orabona 4, 70125 Bari, Italy
[c] Department of "Scienze e Tecnologie Biologiche, Chimiche, Farmaceutiche (STEBICEF)", University of Palermo, via Archirafi 32, Palermo 90123, Italy

ARTICLE INFO

Article history:
Received 30 January 2015
Revised 21 March 2015
Accepted in revised form 23 March 2015

Chemical compounds studied in the article:
Hyaluronic acid (PubMed CID: 3084050)
Paclitaxel (PubMed CID: 36314)
Doxorubicin (PubMed CID: 31703)
Irinotecan (PubMed CID: 60838)
Docetaxel (PubMed CID: 148124)
Curcumin (PubMed CID: 969516)
Chitosan (PubMed CID: 71853)
Mitoxantrone (PubMed CID: 4212)
All-trans retinoic acid (PubMed CID: 444795)
Etoposide (PubMed CID: 36462)

Keywords:
Hyaluronic acid
Drug delivery
Intracellular delivery
Theranostics
Carbon nanotubes
Quantum dots

ABSTRACT

Hyaluronic acid (HA) is a biodegradable, biocompatible, nontoxic, and non-immunogenic glycosaminoglycan used for various biomedical applications. The interaction of HA with the CD44 receptor, whose expression is elevated on the surface of many types of tumor cells, makes this polymer a promising candidate for intracellular delivery of imaging and anticancer agents exploiting a receptor-mediated active targeting strategy. Therefore, HA and its derivatives have been most investigated for the development of several carrier systems intended for cancer diagnosis and therapy. Nonetheless, different and important delivery applications of the polysaccharide have also been described, including gene and peptide/protein drugs delivery. The aim of this review was to provide an overview of the existing recent literature on the use of HA and its derivatives for drug delivery and imaging. Notable attention is given to nanotheranostic systems obtained after conjugation of HA to nanocarriers as quantum dots, carbon nanotubes and graphene. Meanwhile, attention is also paid to some challenging aspects that need to be addressed in order to allow translation of preclinical models based on HA and its derivatives for drug delivery and imaging purposes to clinical testing and further their development.

1. Introduction

Hyaluronic acid (HA) is a naturally occurring linear polysaccharide constituted by repeating units of *N*-acetyl-D-glucosamine and D-glucuronic acid with the monosaccharides linked together by alternating β-1,3 and β-1,4 glycosidic bonds (Fig. 1) [1]. Since the pK_a value of the carboxyl groups of HA is 3–4, these functional groups are predominantly ionized at pH 7.4 and, therefore, upon physiological conditions, HA is a polyanion denoted as hyaluronan [2]. HA is found in a wide range of molecular weights, typically, from 20 kDa to 4000 kDa; its presence in pharmaceutical formulations is also characterized by a broad range of molecular weights [3,4]. In solution, the chains of HA adopt random-coil conformations. In these conditions, it is highly hydrophilic and surrounded by water molecules linked through hydrogen bonds. Due to this conformational features as well as due to its high molecular weights, the solutions of this polysaccharide are very viscous and elastic [5].

In nature, HA mainly occurs in the extracellular matrix (ECM) of connective tissues ant it is most abundant in the vitreous body of the eye. In addition, HA also plays important roles in intracellular functions because it influences cell proliferation and migrations as well as it is engaged in the modulation of intracellular signaling [6]. Some of the HA-receptors involved in these intracellular

* Corresponding author. Tel.: +39 (0)805442046; fax: +39 (0)805442724.
E-mail address: delia.mandracchia@uniba.it (D. Mandracchia).

http://dx.doi.org/10.1016/j.ejpb.2015.03.032
0939-6411/

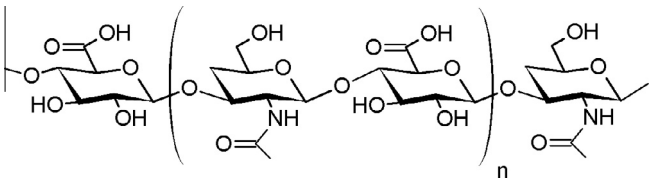

Fig. 1. Structure of hyaluronic acid.

functions have been well identified such as the cluster determinant 44 (CD44) [7,8], the lymphatic vessel endothelial HA receptor (LYVE-1) [9], the receptor for hyaluronate-mediated motility (RHAMM) [10] and the HA receptor for endocytosis (HARE) [11,12]. In particular, CD44 is involved in the interaction between HA and the surface of specific cells, in cell proliferation, in cell migration, angiogenesis, in cell survival and endocytosis of HA [7,13]. Moreover, it has been proved that the CD44 receptor is overexpressed in many types of tumors and this overexpression is related to tumorigenesis and tumor metastasis [14]. More precisely, an isoform of CD44 receptor, named CD44v6, occurs in metastatic but not in non-metastatic tumors [15]. The interaction between HA and CD44 receptors, overexpressed on the surface of some tumor cells, represents another distinct advantage of HA because, based on that interaction, a receptor-mediated targeting strategy may be accomplished useful for tumor diagnosis and therapy. Hence, it can be stated that, although HA binds CD44, LYVE-1, RHAMM, and HARE receptors in non-specific way, the polymer may act as an active targeting moiety for intracellular delivery of anticancer drugs [4,16]. However, the CD44 targeting by delivery systems is affected by the HA hepatic clearance mediated by the HARE receptor, in turn located mostly in endothelial cells of liver and spleen [3]. On the other hand, HA chain length notably influences intracellular signaling pathways and biological effects. Thus, it is hypothesized that various length of HA molecules may function as both tumor suppressors or tumor growth promoters as indicated in Fig. 2 [4].

From a pharmaceutical view point, HA is a biodegradable, biocompatible, nontoxic, and non-immunogenic polymer. Moreover, HA can be chemically modified by crosslinking or conjugation reactions exploiting the available functional groups of HA, that are the carboxylic acid and the hydroxyl ones [5,17–19]. Due to the favorable physico-chemical and biological features of HA, this polymer has been widely used for various biomedical applications such as in the treatment of osteoarthritis, in ocular and plastic surgery and in tissue engineering. However, HA has also been used for several drug delivery applications. Actually, HA has been widely investigated as carrier for receptor-mediated drug targeting in cancer therapy and delivery of protein, peptide, and nucleotide therapeutics as well as the delivery of imaging agents due to its peculiarity to recognize receptors whose expression is increased in various diseased cells.

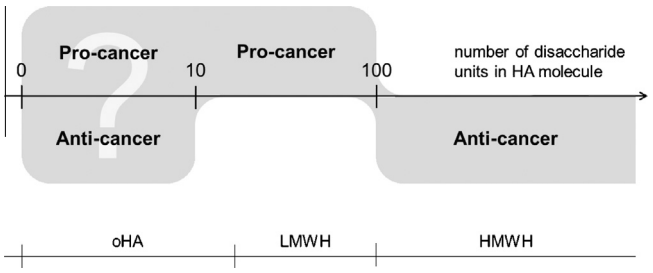

Fig. 2. The hypothesized pro- and anti-cancer activity of various length of HA molecules. The number of disaccharide units in HA molecule corresponds to the number of *N*-acetyl-D-glucosamine and D-glucuronic acid units in HA molecule. Adapted with permission from Elsevier [4].

The purpose of the present review was to discuss various advances made in the last few years on the application of HA and its derivatives in drug delivery and as tools for disease diagnosis. The information provided is mainly taken from PubMed, Scopus and ISI Web of knowledge databases. In the last decades, it is apparent a growing research interest toward the therapeutic action of HA and in developing new diagnostic tools based on this polymer (Fig. 3 for bibliographic analysis details related to the topic HA in drug delivery; a similar trend occurs for the topic HA and imaging). HA has been presented in several pharmaceutical forms including nanoparticles (NPs), nanocomplexes, matrices and hydrogels. Excellent reviews have recently summarized the progress made in this area and the reader is referred to [4–6,20–22].

In the present review, we first describe the advances made in the last few years on the formation of hydrogels by crosslinking reactions of HA. Next, taking into account the increasing number of citations and papers, we present some relevant applications of the combination HA with various polymers for cancer and gene therapy as well as for disease diagnosis. It should be noted that there are several reasons for which HA could be combined with other polymers (*i.e.*, conjugated or coated) for drug delivery or diagnostic applications, including reduction of the HA turnover (degradation)and the formation of drug delivery systems such as NPs or self-assembled systems as core–shell micelles. In addition, the combination of HA with polycations leads to polyelectrolyte

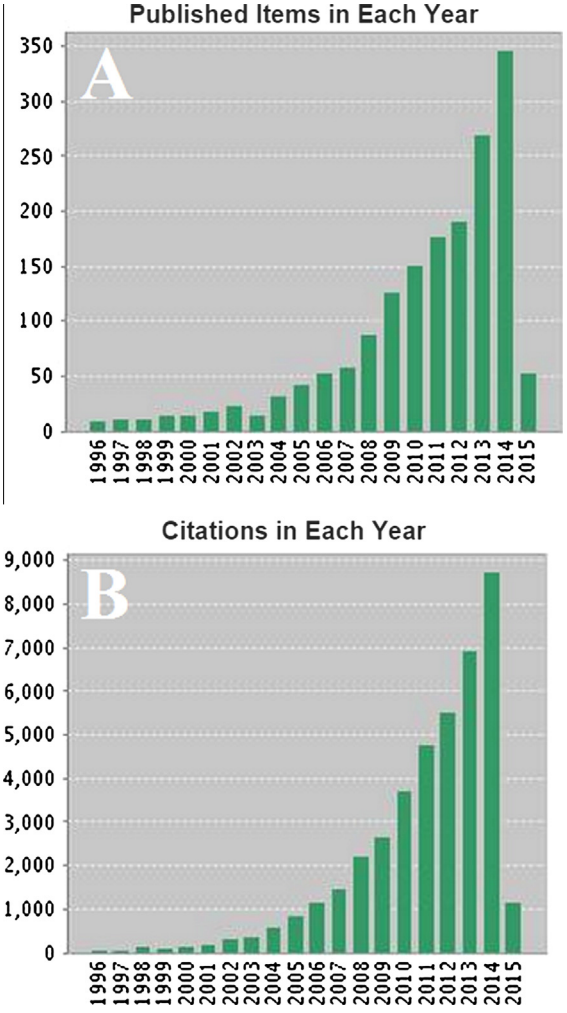

Fig. 3. (A) Number of articles published by years on HA in drug delivery; (B) number of citations related to papers on the same topic. Data from Web of Science® (Thomson Reuters).