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REVIEW ARTICLE **OPEN ACCESS**

A Review on Hyaluronic Acid Based Nanomaterials for Cancer Therapy

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ABSTRACT
Hyaluronic acid (HA) is a nonsulfated glycosaminoglycan and it is a important component of the extracellular matrix. HA is overexpressed by numerous cancer cells, especially tumor-initiating cells. Nanomaterials based on HA play an importance role in drug delivery systems. HA is used in various types of nanoformulations which include micelle, polymersome, hydrogel, and inorganic nanoparticle formulations. Many drug-resistant tumors and cancer stem cells (CSC) express elevated levels of CD44 receptor, a cellular glycoprotein binding hyaluronic acid (HA). Here, we report the synthesis of nanoformulation–drug conjugates for efficient targeting and suppression of drug-resistant tumors. These conjugates significantly increased the bioavailability of poorly soluble drugs with previously reported activity.
Keywords: *Hyaluronic acid (HA); nanoparticles (NPs); Cancer; Target therapy; Chemotherapy*

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INTRODUCTION

Hyaluronic acid is an mucopolysaccharide naturally occurring glycosamino glycan. It can be certain thousands of carbohydrates (sugar) when it not bounds to other it gets bind with water and form viscous as like gel. HA contains biological functions such as to maintain the elasticity or elastoviscosity of liquid connective tissues e.g.: joint synovial

HA have various properties like biodegradability, compatibility, various opportunities for chemical modification and inherent targeting properties due to the nature HA has vital role in drug delivery. To use in the drug designing, chemical modification of HA can be carried out three functional regions like the acetamide, hydroxyl and carboxylic acid. These are many HA conjugated delivery systems developed for the delivery of anticancer drugs. Due to hydrophilic nature of HA results in enhanced solubility in aqueous media so as to avoid the use of formal organic solvent and anticancer drugs are hydrophobic in nature so it is more susceptible to loading the hydrophilic HA to increase their therapeutic response and reduce their side effects.

To treat the various cancer such as liver, colorectal, pancreatic, cervical, lung various HA conjugated nanomedicine are designed to target the tumor cell. These nanomedicines contain polymeric nanoparticle, metal nanocomposite, inorganic nanoparticles, liposomes, micelles, lipid barrier, nanocomposite and carbon nanotubes.[1]

Successful cancer treatment is a major element of recent medical practice. Systemic toxicity and the lack of tumor selectivity have hindered many new chemotherapeutic molecules in reaching clinical translation. The way to decrease selective harm in cancer treatment is by actively targeting tumor cells by applicating the anatomical, pathophysiological, and microenvironmental differences between malignant areas and normal bodily tissues.

Hyaluronic acid (HA) is a linear mucopolysaccharide consisted of alternately repeated ***N***-acetylglucosamine and glucuronic di-saccharide, and it makes up a major part of extracellular matrix. HA has hydroxyl and carboxylic groups, as well as an ***N***-acetyl group, which can be used for further chemical modifications. A large variety of cells, such as fibroblasts, synthesize HA. HA shows superior physiochemical natures, such as a high water-binding capacity, nontoxicity, biodegradability, cytocompatibility, and non-immunogenicity. Due to these biological abilities of HA, there is a great interest in the development of HA-

based nanomaterials for diverse biomedical applications, including drug delivery systems (DDS) and molecular imaging.

Many cancer cells are known to overexpresses HA-biding receptors, such as CD44, LYVE-1 receptors, and Hyaluronan-mediated motility receptor (RHAMM). HA is degraded to low molecular weight components by hyaluronidase after being taken up by cancer cells through CD44 receptor-mediated endocytosis. CD44, a glycoprotein ubiquitous throughout the body, carries great potential for fulfilling the promise of active targeting. Overexpressed CD44 receptor showed in various cancer cells, including those of colon, ovarian, breast, and squamous carcinoma

Hyaluronic acid (HA) is a linear anionic polymer composed of repeating disaccharide unites of β-1,4-D-glucuronic acid-β- 1,3-N-acetyl-D-glucosamine. HA with different MWs play different roles in the body. Low-MW polymers typically induce receptor-mediated intracellular signaling, while high molecular weight polymers maintain cell integrity and matrix organization. This biocompatible, biodegradable, and nonimmunogenic biomaterial has been extensively studied in pharmaceutical and biomedical applications, including cancer therapy, when various drugs have been conjugated to HA, like paclitaxel or doxorubicin.[2,3,4] Many drug-resistant cancer cells and CSCs display elevated levels of CD44 receptors that bind HA. Potentially, CD44 can be targeted for the treatment of drug-resistant tumors and CSCs. Previously, it was shown that HA grafted liposomes have an increased cellular uptake through CD44-mediated endocytosis, which is a highly regulated process of binding, internalization, and ligand transfer through a series of intracellular compartments.[5]

In this review, we focus on the recent methodological developments in HA-based nanomaterials to treat tumors. In addition, this review demonstrates nanodelivery systems using HA for encapsulating and targeting active molecules

HA-Based Nanomaterials

HA has several functional groups used for various conjugations and modification. These properties make HA a major component of multifunctional NPs to deliver synergistic cancer therapies.[6] Several approaches for producing HA NP formulations have developed to take advantage of the targeting properties of HA. Reported HA-based nanomaterials for cancer treatment include polymeric drug-conjugated HA and nanomaterials, such as micelles, polymersome, hydrogels, and inorganic NP systems. HA nanomaterials have several merits that are low to no immunogenicity, non-inflammatory reactions, biodegradability, biocompatibility, and bioavailability.[7]

Drug-Conjugated HA

HA is a large hydrophilic biopolymer of repeating disaccharide units, and it can be directly conjugated to drugs. Direct conjugation of HA to anticancer drugs generates new compounds with promising antitumor effects.[8] Such simple yet effective NP formulations can be used to improve treatment efficacy because HA-targeted receptors (CD44) are overexpressed in many cancers. Aside from this targeting ability, drug-conjugated HA provides merits in terms of increasing circulation time, drug stability, solubility, and cancer-targeting ability. Once internalized, drug-conjugated HA is hydrolyzed by intracellular enzymes and releases the drug to the target cell.

The chemical modification of HA can be used on three available functional components in the carboxylic, hydroxyl, and acetamido groups. There are many modification methods for HA crosslinking or conjugation due to HA solubility. The carboxylic group of HA could be exploited for controlled chemical modification with different hydrazides to obtain polymers that could be used for many biomedical applications, including developing prodrugs. Another approach is activation of the hydroxyl group of paclitaxel with carbodiimide for conjugation with 4-bromobutyric acid to form ester-linked 4-bromobutyric-paclitaxel. The commonly used chemotherapy drugs in the clinical field, paclitaxel (PTX) and doxorubicin (DOX), have also shown great results. PTX is one of the leading compounds and has tremendous potential as an anticancer compound. However, intravenous injection of PTX is difficult due to hydrophobicity and side effects. PTX conjugation with hydrophilic HA can overcome these limitations.[9]

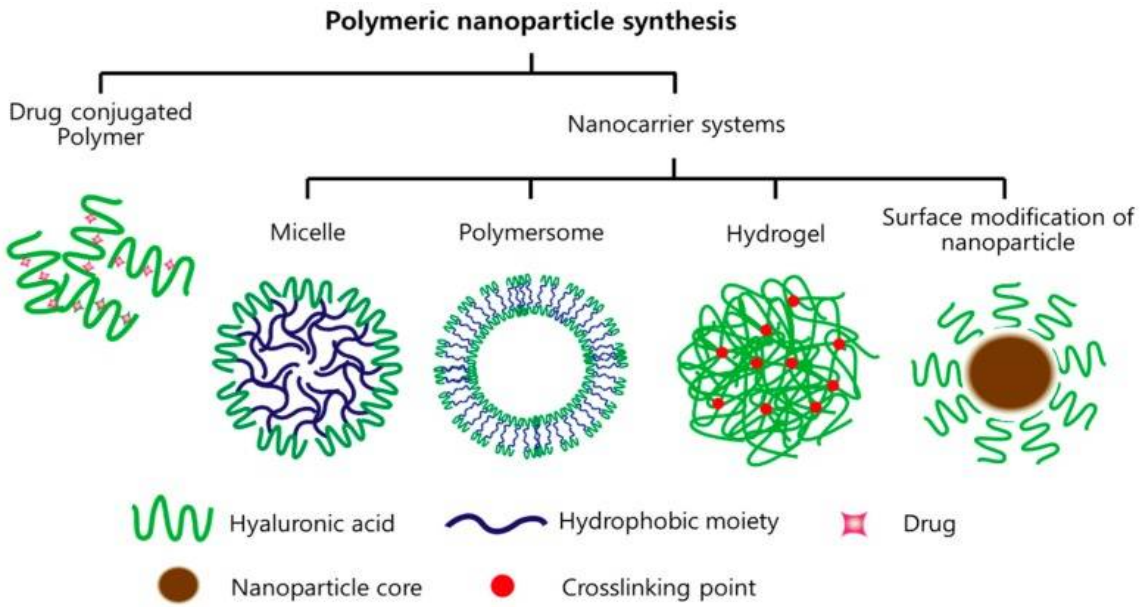

Fig No 1. Formulations of hyaluronic acid (HA)-based nanomaterials.

Micelles

HA can form self-assembling micelles to generate amphiphilic nanocarriers. Micelles that are 20–80 nm in diameter are colloidal dispersions that constitute an amphiphilic molecule. Smaller size of micelles could limit the ability to administer large doses of chemotherapeutic agents to tumors. Besides, the hydrophilicity of HA micelles increased circulation times of drugs in vivo, so they accumulated within cancer cells. HA micelles can efficiently carry hydrophobic drugs to target cancer cells, thus enhancing the bioavailability and half-life of the drugs. The solubilization of hydrophobic drugs is an important factor to decrease the risk of drug aggregation and embolism formation during intravenous injection. HA micelles might have great tumor tissue penetration compared with the large size of liposomes. [10,11,12]

Polymersome

HA has been used as a surface ligand to exploit CD44-targeted liposomal anticancer therapies. Liposomes have been widely used as a nanodelivery system. Polymersomes, that are a self-assembly of amphiphilicdiblock copolymers in an aqueous environment, are similar to liposomes that form synthetic bilayer vesicles. Polymersome is able to encapsulate water-soluble drugs as well as lipophilic drugs . Biocompatible polymersomes do not respond with blood components, and do not affect nontarget tissues. The polyethylene glycols (PEG) are the most commonly used biopolymer to produce biocompatible polymersomes. Polymersomes offer significant advantages over other bilayer vesicles. Compared to liposomes, the advantages of polymersomes are high membrane stability and low membrane permeability, resulting from varying the block lengths.

DOX-loaded polyglutamate-HA polymersomes were introduced. In this system, the HA-based polymersomes have advantages in both solubility and the targeting ability of CD44 receptors expressing cancer cells. [13,14,15]

Hydrogels

HA modification using click chemistry or supermolar assemblies is widely used to produce the covalent or physical hydrogels. Covalent crosslinking of HA is important to enhance the stability and function. Conventional HA-based hydrogels are macroscopic networks consisting of randomly interconnected HA chains at the crosslinking points established by covalent bonds.[16]

HYALURONIC ACID CONJUGATES IN COLON CANCER:

5-Fluorouracil is used as a first-line anti-cancer drug in colorectal cancer. It is a thymidylate synthase inhibitor (Interfere DNA synthesis) & blocks the cell growth at the S phase of the cell cycle. But, intravenous administration of 5-FU leads to large systemic distribution, therefore a very small fraction of the dose reaches the site of action. Hence, there is a need to developed a nano-drug delivery system to increase the therapeutic effect of 5-FU. However, when HA is conjugated with nanoformulation included with drug have the advantage that excellent biocompatibility, high hydrophobicity, systemic stability & resistance to pH changes.[17]

Sarbjeet Makkar et al, reported that Hyaluronic acid HA is a ligand for TLR4, a receptor of significance in colorectal cancer and interacts with CD44 and TLR4 in colon tumorigenesis. Colorectal cancer models included $Apc^{Min/+}$ mice, azoxymethane/dextran sodium sulfate (AOM-DSS), and CT26 tumor isografts. Knockout mice and CT26 colorectal cancer cells with CRISPR knockdown of CD44 and TLR4. HA activity

was modulated by PEP1 (a 12-mer peptide that blocks HA from binding its receptors), hyaluronidase (which promotes HA degradation), or 4-MU (HA synthesis inhibitor). Blockade of HA binding via PEP1 decreased growth in all colorectal cancer models and in cell culture. The effects were significant in WT and with CD44 deletion, but not with TLR4 deletion. In the AOM-DSS model, mice deficient in CD44 or TLR4 had fewer tumors. CD44- and TLR4-deficient CT26 isografts grew more slowly, exhibiting decreased tumor cell proliferation and increased apoptosis. *In vitro*, endogenous HA blocked LPS binding to TLR4 suggesting that HA is a relevant TLR4 ligand in colon cancer. Finally, PEP1 enhanced tumor radiation sensitivity in the isograft model. Together, these results indicate that HA binding to TLR4, as well as CD44, plays a key role in colon tumorigenesis. These findings also raise the possibility that an agent that blocks HA binding, such as PEP1, may be useful as an adjuvant therapy in colon cancer.[18]

Kai Liu et al. formulated 5-FU-loaded hyaluronic acid (HA)-conjugated silica nanoparticles (SiNPs) to target to colon cancer cells. It is reported that specific binding and intracellular accumulation of targeted nanoparticles based on HA surface modifications in colon carcinoma cells. The particles had spherical shapes with sizes of approximately 130 nm. HA-conjugated nanoparticles showed a sustained release pattern for 5-FU and continuously released for 120 hours. The cytotoxicity potential of targeted and nontargeted nanoparticles in colo-205 cancer cells. IC50 value of 5-FU/hyaluronic acid-conjugated silica nanoparticles (HSNP) were 0.65 μg/mL compared with ∼2.8 μg/mL for 5-FU/SNP after 24 hours of incubation. The result clearly showed that HA-conjugated NP was more effective in inducing apoptosis in cancer cells than nontargeted NP. The 5-FU/HSNP showed 45% of cell apoptosis (early and late apoptosis stage) compared with only 20% for 5-FU/silica nanoparticles (SNP)-treated group. The HA-conjugated nanoparticles provide the possibility of efficient drug transport into tumors that could effectively reduce the side effects in the normal tissues. 5-FU/HSNP was highly efficient in suppressing the tumor growth in xenograft tumor model. The proportion of Ki67 in 5-FU/HSNP-treated group was significantly lower than that of either free drug or non-targeted SiNPs. So, it concludes that conjugation of HA to SiNPs could result in enhanced uptake of 5-FU through CD44-mediated endocytosis uptake and could result in significant antitumor efficacy. Thus, 5-FU/HSNP could be a promising drug delivery system for colon cancer therapy.[19] Daniel C. Pan, Vinu Krishnan et al formulated hyaluronic acid–doxorubicin nanoparticles for targeted treatment of colorectal cancer and it reported that doxorubicin complexed to hyaluronic acid (HA) (HA-Dox) exhibits an unusual behavior of high accumulation in the intestines for at least 24 hr when injected intravenously. Intravenous administrations of HA-Dox effectively preserved the mucosal epithelial intestinal integrity in a chemical induced colon cancer model in mice and treatment with HA-Dox decreased the expression of intestinal apoptotic and inflammatory markers. HA-Dox possessed a zeta potential of −4.8 ± 1.06 mV, In vitro release rates of HA-Dox indicated a slow and steady release of the drug from HA. Approximately, 20.6 ± 0.8 wt% Dox was released at the end of 120 hr and the formulation inhibited proliferation of ex-vivo cancer cells. The study reported that HA-Dox could effectively inhibit the development of colorectal cancer in a safe manner, which potentially be used a promising therapeutic option.[19]

Hyaluronic acid in pancreatic cancer therapy.

Carla Serri , Vincenzo Quagliariello, et al formulated hyaluronic acid-decorated nanoparticles loaded with quercetin and gemcitabine. Aim of their study was to combine chemotherapy by means of two or more drugs is prone to suppressing or discouraging the inception of multidrug resistance, exploiting the fact that diverse drugs act in different points of the cellular cycle of amplifying tumor cells. The combination of gemcitabine (GMC) with quercetin (QCT) showed a synergistic effect in inhibiting the migration of pancreatic cancer cells and when GMC and QCT have been loaded within biodegradable nanoparticles (NPs) based on poly (lactic-co-glycolic acid), externally decorated with hyaluronic acid (HA; viz., PPHA NPs), which plays a major role in drug targeting to tumors due to its ability to specifically interact with CD44 receptor, that is overexpressed in many tumors. The produced HA-decorated NPs loaded with GMC and QCT showed an improved cytotoxicity and cellular uptake toward two cell lines of pancreatic ductal adenocarcinoma, namely Mia-PaCa-2 and PANC-1, compared with both the bare drugs and the drugs loaded in NPs which do not expose HA on the surface. HA-decorated NPs were also able to improve the anti-inflammatory properties of QCT, therefore leading to a decrease of interleukin cellular levels in both cell lines, preliminarily stimulated with lipopolysaccharides. This result is of special interest also considering the crucial role of interleukins in progression, metastatic processes, and drug resistance of human pancreas cancer cells.[17]

Carla Seri et.al concluded that the encapsulation of CD/QCT or GMC in PP and PPHA NPs enhanced the cytotoxic response against Mia-PaCa-2 and PANC-1 pancreatic cancer cell lines. More in detail, cell death was further intensified by NP decoration with HA, loaded with either active molecule. After the combined treatment with a fixed concentration of CD/QCT, a time-dependent increase in cell death with increasing GMC concentration was found out, in particular after coculture with HA-decorated NPs, thereby highlighting the chemosensitizing effect of HA. [20]

CONCLUSION

HA-based nanomaterials can target and enter cells more efficiently through the HA receptor-mediated endocytosis pathway. HA provides a simple and attractive approach for the active targeting of tumor cells with minimal toxicity. HA nanomaterials are attractive systems for the effective delivery of antitumor agents. Much research has demonstrated the ability of HA to target CD44-overexpressing cancer cells. Interestingly, HA can easily be chemically modified and used as a target-specific DDS or in various carrier systems for cancer therapy.

The advancement of nanomedicine has offered new and promising solutions and insights for the prevention and theranostic option of cancer. HA-based nanomaterials might give new opportunities for the widespread use of biomedical applications. As research in HA nanomaterials progresses, we expect more innovative strategies for expanding their biomedical applications. HA-based nanomaterials show great promise for future biomedical applications in cancer therapy.

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