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Targeting CD44 by hyaluronic acid-based nano drug delivery systems may eradicate cancer stem cells in human breast cancer

Navid Goodarzi[1], Mohammad Hossein Ghahremani[2,3] and Rassoul Dinarvand[1,2]

[1]Department of Pharmaceutics, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[2]Nanotechnology Research Centre, Tehran University of Medical Sciences, Tehran, Iran
[3]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

Corresponding author:
Rassoul Dinarvand
Department of Pharmaceutics, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran 1417614411, Iran
Tel: +98 21 66959095/Fax: +98 21 66959096
E-mail: dinarvand@tums.ac.ir

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Abstract

Despite the significant progress in cancer diagnosis and therapy, still invasion and metastasis of cancer cells, development of drug resistance and cancer recurrence are the main causes of mortality in cancer patients. Recent researches on cancer stem cells (CSCs) along with the role of CD44 marker in drug resistance and as the main marker of breast CSCs, highlight the importance of CD44 in cancer targeted therapy. Additionally, co-localization of MDR1 and CD44 in cancer cell population showed that one protein directly influences the expression of the other and disruption of interaction has significant effects on drug resistance, cell migration and in vitro invasion. Based on the above information, using nanotechnology-derived CD44 targeted drug delivery systems will be able to address recurrence of the disease and other major obstacles in cancer chemotherapy. Therefore, we hypotheses that using combination of cytotoxic agents and CSC specific agents anchored in hyaluronic acid (as the endogenous substrate of CD44), have the potential to develop novel drug delivery systems to eradicate breast cancer.

Keywords
Hyaluronic acid, Nanoparticles, CD44, Targeting, Cancer stem cells

Introduction

Despite the significant progress in cancer diagnosis and therapy, the prognosis of some types of the cancers remains poor (1-3). Invasion and metastases of cancer cells and the development of resistance to cytotoxic agents are the main causes of failure in therapy and mortality in cancer patients. Even after a successful sophisticated treatment, cancer recurrence has been observed in many cases (4-8).

Over the past decades, different researches have focused on drug resistance, metastasis and recurrence. Development of MDR1-mediated drug resistance results in failure of treatment in breast cancer and it is known as the main cause of drug resistance in breast cancer and many other types of cancers (9, 10). Indeed, resistance to chemotherapy

is believed to cause treatment failure in over 90% of patients with metastatic breast cancer (5). On the other hand, several hypotheses have been proposed to explain the recurrence mechanisms (11-13). The progression of cancer stem cells represents the most recent hypothesis (13). With the recent identification of sub-populations of tumor cells, have higher in vivo tumorigenicity than the total mass of cancer cells and the major role in the initiation, maintenance, and clinical outcome of different types of cancers, researchers interested in specifically targeting these "tumor-initiating cells" (14, 15). In breast cancer, these cells are characterized by the expression of CD44 marker and lack of expression of CD24 marker ($CD44^+/CD24^-$) (16).

The importance of CD44

Before its identification as the main marker of cancer stem cells (CSCs) in breast cancer, CD44 was proposed as receptor for tumor targeting (17). Miletti-Gonzalez et al found a novel interaction and coexpression between CD44 and MDR1 in breast cancer cell lines, which showed that the two proteins co-localize within the cell membrane (18). Recently, it was demonstrated that MDR1 and ABCG2 were up-regulated in $CD44^+/CD24^-$ side population in breast cancer (19).

Co-localization of MDR1 and CD44 in cancer cell population showed that one protein directly influences the expression of the other and that a disruption of this interaction has significant effects on drug resistance, cell migration and in vitro invasion (18).

The expression of CD44 in drug resistant cells and cancer stem cells and the functional interactions between CD44 and P-glycoproteins, show the importance of CD44 targeting in cancer chemotherapy.

Targeting cancer stem cells by novel drug delivery systems

Recent studies have suggested that eradication of CSCs is an important goal towards the cure of cancer by overcoming drug resistance (20-22). These data suggest that the side population related to CSCs is associated with chemotherapeutic resistance of breast cancer. It highlights the importance of targeting CSCs, rather than eliminating the bulk of rapidly dividing and terminally differentiated cells, in novel anti-cancer strategies (19). Targeted therapy using stem cell-specific targets, may offer the best chance of eliminating cancer stem cells, leading to cancer cure.

Therefore, new drug development should focus not only on the drugs and their specific targets, as most efforts was on finding the old/new drug molecules (20), but also on novel drug delivery systems to target the cancer stem cells.

Although there are many drug delivery systems to target cancer cell population and some of them as nanoparticles and drug-conjugates have reached the market, to the best of our knowledge, there are few reports about targeting CSCs based on novel drug delivery systems.

The role of nanomedicine

Because of the similarity in surface markers and cellular properties between cancer stem cells and normal stem cells, targeting the CSCs can also eliminate the normal stem cells.

As stated by Andreas G. Schätzlein (23), in this situation, nanomedicine improve control on pharmacokinetics and distribution of CSCs-specific agents, thus lead to safe, efficient and selective therapies to address the challenges posed by CSCs.

Taking advantages of combinational therapy

Because of difference between CSCs and non-stem cancer cells, many of the cytotoxic agents, which affect rapid dividing cells such as paclitaxel, does not affect CSCs efficiently. Although taking advantages of novel drug delivery systems may improve their efficacy, it seems necessary to use CSCs specific agents (such as salinomycin, rapamycin etc.) along with typical cytotoxic medicines.

Combined eradication of both CSCs and non-stem cell cancer cell populations may be the main strategy to eradicate cancer cells (13). In fact, combination chemotherapy by cytotoxic agents proved to be more effective than single or adjuvant chemotherapies in the clinic (13) and it will be reasonable to combine CSC specific therapies and routine anti-cancer therapies. However there are some concerns about the concept of eradication of the disease via CSCs targeting (24).

The hypothesis

Hyaluronic acid (also called Hyaluronan) is an anionic, nonsulfated glycosaminoglycan distributed widely throughout connective, epithelial, and neural tissues. One of the chief components of the extracellular matrix contributes significantly to cell proliferation and migration by interacting with receptors such as CD44 and RHAMM (17, 25).

Breast cancer cells are known to have greater uptake of HA than normal tissues (26), requiring HA for high P-glycoprotein expression, primary contributor to drug resistance (27). The classical stem cell marker CD44 itself is a receptor for hyaluronic acid. CD44 targeting of routine cytotoxic agents in cancer cells will reverse drug resistance. In addition targeting CD44 in CSCs will reduce the chance of recurrence of the disease (28, 29).

Based on above information, we hypothesize that developing HA-drug conjugates using combination of cytotoxic agents (such as docetaxel, doxorubicin, etc.) and CSC specific agents, in a manner that targeting properties of HA is maintained, have the potential to develop novel drug delivery systems to eradicate breast cancer cells (Figure 1). In this case, preparing drug conjugate, which carry just one type

of drug molecule, give the chance to use HA-drug conjugates in more effective dosing schedules.

Evaluation of the hypothesis

In order to confirm or dispute our hypotheses, we suggest preparing HA-drug conjugates using combination of cytotoxic agents and CSC specific agents (such as salinomycin and rapamycin), and evaluation of the drug delivery system on the isolated cancer stem cell side population. In this way, we recommend evaluation of the efficacy and mechanism of action to check the CD44 targeting properties, CSCs cytotoxicity, and ability to reverse drug-resistance. Apparently, it will be possible to use intact cytotoxic drugs (e.g. docetaxel) and drug conjugates (e.g. HA-docetaxel and HA-salinomycin) in different dosing schedule to find the best performance.

In this case, HA-drug conjugate will be prepared by using carbodiimide chemistry to conjugate carboxylic groups on hyaluronic acid backbone to a suitable functional group (e.g. amine, hydroxyl) in small drug molecules. In parallel with preparation of macromolecular-drug conjugate as drug delivery system (DDS), cancer stem cell will be sorted and isolated via presence or absence of their surface markers ($CD44^+/CD24^-$) from MCF-7 and MDA-MB-231 CD44-overexpressing cancer cell lines. This sub-population can be subjected to in vitro cell culture studies to evaluate cell proliferation and apoptosis in different experimental groups including free drug solution, DDS dispersion and negative/positive controls (HA, DMSO, etc.). In comparison to free drug solution, selective toxicity in CSC sub-population could be an index to assess the efficacy of DDS. If the efficacy measures are being met, developed drug delivery system could then go further to animal experiments in xenograft models via isolated cancer stem cells.

Discussion and Conclusion

The hypothesis integrates advantages of the nanomedicine, CSCs targeting at present researches and combinational chemotherapy in the clinic. Therefore, it presents many merits for targeted drug delivery for cancer treatment, such as selectivity, reversing drug resistance and eradication.

Apparently, it has its limitations while the normal stem cells such as mesenchymal cells express CD44 marker. This will be the major concern about CSC targeting by hyaluronic acid-based drug delivery system. Although the use of nanotechnology enhances permeation and retention of nanomedicine (EPR effect), even the affected parts of normal counterparts will be recovered considering the large population and the self-renewal properties of normal stem cells.

As stated above, the eradication of breast cancer upon treatment with hyaluronic acid-based drug delivery systems supports the concept that agents targeting CD44 will lead to better therapeutic approach and may completely eradicate cancer cells.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Overview Box

What do we already know about the subject?

Eradication of cancer stem cells (CSCs) has been suggested to be an important goal towards the cure of cancer. It highlights the importance of targeting CSCs, rather than eliminating the bulk of rapidly dividing and terminally differentiated cells, in novel anti-cancer strategies. Targeted therapy using stem cell-specific targets, may offer the best chance of eliminating CSCs, leading to cancer cure.

What does your proposed theory add to the current knowledge available, and what benefits does it have?

The classical stem cell marker CD44 itself is a receptor for hyaluronic acid (HA). In addition targeting CD44 in CSCs will reduce the chance of recurrence of the disease, and will reverse drug resistance. Therefore, we hypothesize that developing HA-drug conjugates using combination of cytotoxic agents and CSC specific agents (e.g. salinomycin) have the potential to eradicate breast cancer cells.

Among numerous available studies, what special further study is proposed for testing the idea?

This is a novel idea, and it will bring great benefits to develop CSCs-targeted drug delivery system if it is proved. Systematic cell culture studies would be suggested to evaluate the efficacy and the mechanism. If the safety and efficacy measures are being met, the developed drug delivery system could then go further to animal experiments.

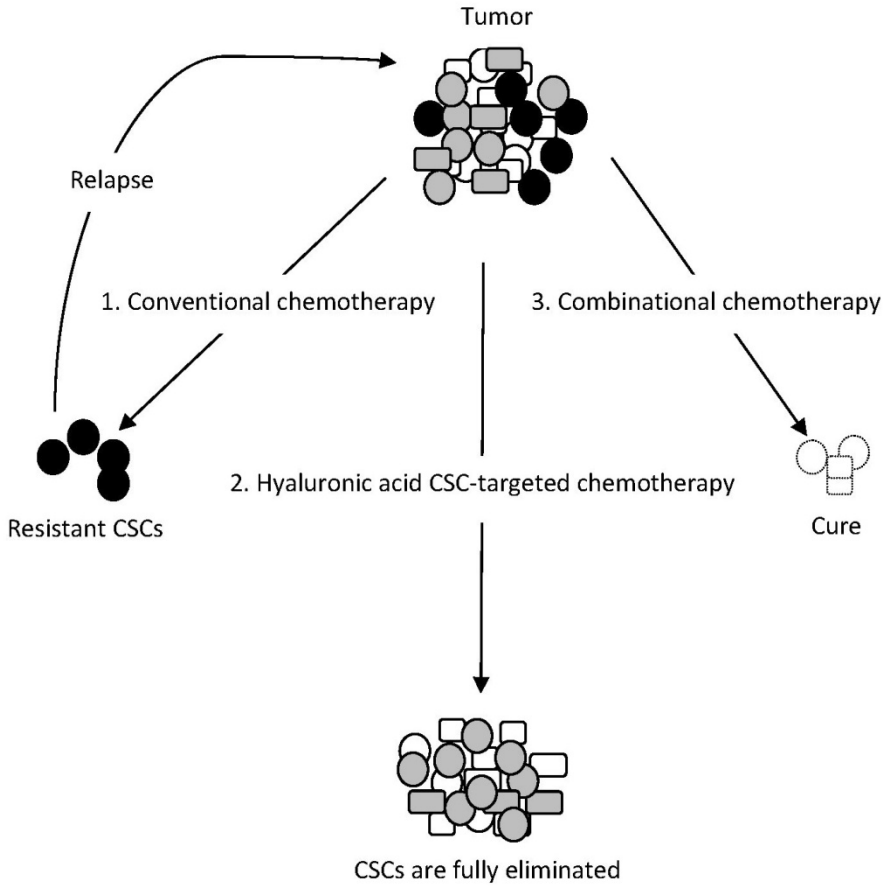

Figure 1. Application of hyaluronic acid-based targeted drug delivery systems in cancer chemotherapy. CSCs: cancer stem cells

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