Medical Hypotheses 129 (2019) 109241

Contents lists available at ScienceDirect

Medical Hypotheses

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

CD133 receptor mediated delivery of STAT3 inhibitor for simultaneous elimination of cancer cells and cancer stem cells in oral squamous cell carcinoma

ARTICLE INFO

Keywords:
Oral squamous cell carcinoma
Cancer stem cells
STAT 3
CD 133
Epithelial mesenchymal transition
Niclosamide
Metastasis

ABSTRACT

Oral Squamous Cell Carcinoma (OSCC) is one of the major causes of cancer related deaths worldwide. Presence of chemoresistant cancer stem cells is the major reason behind metastasis, tumor relapse and treatment resistance in OSCC. STAT 3 signalling plays a key role in survival of cancer stem cells (CSC's), Epithelial Mesenchymal Transition (EMT) mediated metastasis in OSCC. CD 133 is the surface marker for identification of cancer stem cells. In the present study we hypothesise the selective targeting of CSC's using CD 133 mediated delivery of STAT 3 inhibitor, Niclosamide to specifically target CSC's and Non CSC's.

Background

Squamous cell carcinoma comprises of 90% of oral malignancies. Oral cancer holds eight most position in incidence of cancer worldwide and third position in South East Asia. Oral Squamous Cell Carcinoma (OSCC) is the most common malignant neoplasm [1]. The conventional chemotherapeutic agents eliminate only the rapidly dividing bulk tumor cells without affecting relatively quiescent and small population of cancer stem cells (CSCs) [2–4]. Recently, it was identified that these CSCs which are spared by conventional chemotherapeutic agents, result in tumor recurrence and metastasis [5]. There is a need, therefore, for elimination of CSCs in addition to bulk tumor cells (non-CSCs). Epithelial-to-mesenchymal transition (EMT), is a regulatory program implicated for reversion of non-CSCs to CSCs [6,7]. During EMT, epithelial cells lose their intercellular adhesion, accompanied by gain of invasive and migratory properties, which is a prerequisite for metastasis [8]. Although CSC targeted therapies result in elimination of CSCs, however, the non-CSCs are left unaffected. In addition, if non-CSCs are not killed it will once again may result in survival of the tumor as these cells have the ability to spontaneously convert into CSCs through induction of EMT [9]. Therapies that eradicate CSCs and inhibit EMT, therefore, became an attractive strategy to prevent tumor relapse, drug resistance and metastasis [10].

Signal transducer and activator of transcription factor 3 (STAT3) mediated signaling plays a pivotal role in regulating the self-renewal and maintenance of CSCs. It was reported that STAT3 inhibition resulted in elimination of CSCs. In addition, it was recently reported that, STAT3 activation also results in induction of EMT in cancer cells. Therefore, development of novel therapeutics targeting STAT3 can eliminate CSCs and also prevent EMT in non-CSCs. Niclosamide (Niclo), an FDA-approved anthelmintic drug was recently identified as a potent inhibitor of the STAT3 signaling pathway. Niclo is, therefore, effective in elimination of CSCs. In addition, Niclo reverses conversion of non CSCs to CSCs and also sensitizes drug resistant oral cancer cells to chemotherapy by preventing EMT [11]. However, the clinical translation of Niclo as anticancer agent is limited due to its poor water solubility, non-stealth property and reduced bioavailability. To overcome this problem we propose to formulate stealth solid lipid nanoparticles (SLNs) of Niclo, which is expected to improve the stability (stealth property) of Niclo and improve the bioavailability. In addition, the requirement of STAT3 for differentiation of normal healthy cells and stem cells is the major limitation for STAT3 targeted therapies. Selective inhibition of STAT3 in CSCs and non-CSCs is, therefore, required to minimize off-target effects. CD133 or prominin-1 a pentaspan membrane glycoprotein is an unique biomarker in CSCs and differentiated non-CSCs which are prone to EMT in OSCC. It was also reported that CD133 + cells are associated with aggressiveness in OSCC. CD133 aptamer (A15), therefore, can be employed as an effective targeting ligand to deliver drugs to CD133 + CSCs and cancer cells in OSCC. In this study we propose to prepare solid lipid nanoparticles (SLNs) of Niclosamide surface modified with CD133 aptamer (CD133-Niclo-SLNs), to achieve active targeting to oral squamous cell carcinoma so as to inhibit the STAT3 signaling in both CSCs and non-CSCs to eliminate these cells, and also to prevent stem cell and epithelial-to-mesenchymal transition (EMT) mediated relapse.

Hypothesis

In this study we propose to prepare solid lipid nanoparticles (SLNs) of STAT3 inhibitor, niclosamide, surface modified with CD133 aptamer (CD133-Niclo-SLNs). The drug delivery system proposed here is a novel approach for treating OSCC and expected to have following advantages (Fig. 1).

(1) Encapsulation of Niclo in stealth SLNs will provide stability and permit systemic administration of Niclo through intravenous route which is not previously achievable with conventional dosage forms of Niclo (due to its poor water solubility and non-stealth properties).
(2) Surface modification of Niclo-SLNs with CD133 aptamer will

https://doi.org/10.1016/j.mehy.2019.109241
Received 6 April 2019; Accepted 19 May 2019
0306-9877/

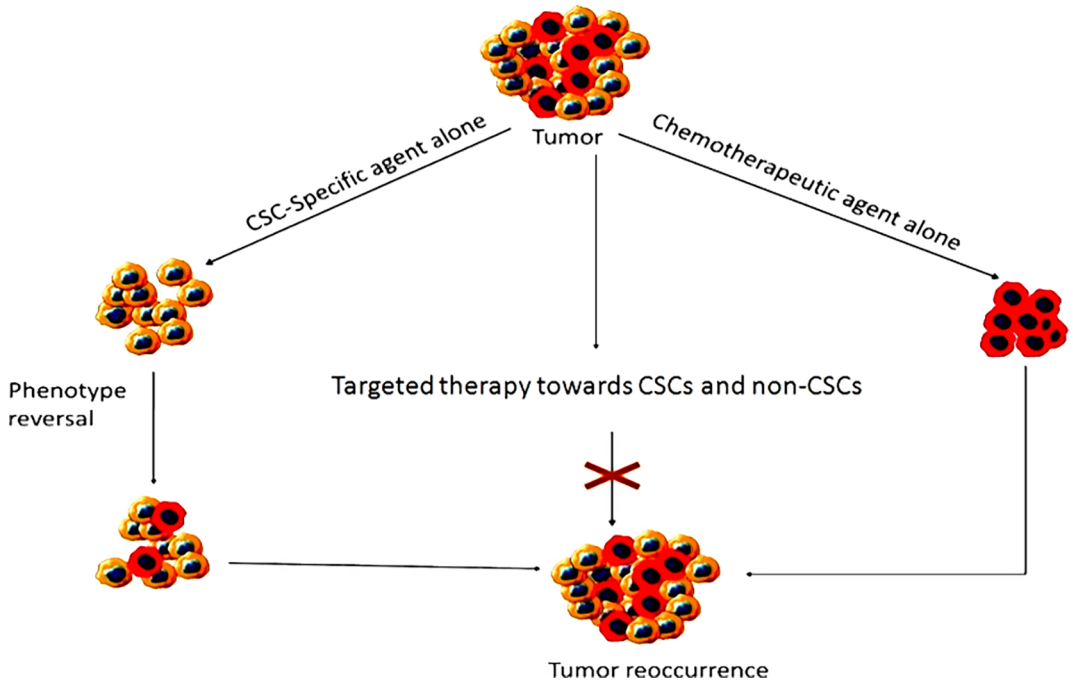

Fig. 1. Conventional chemotherapeutic agents eliminates bulk tumor cells (non-CSCs), leaving behind CSCs. This results in relapse of tumor. CSC specific agent alone eliminates CSCs, however, it results in phenotype reversal in bulk tumor cells and also results in tumor recurrence. Targeted therapies towards both CSCs and non-CSCs, therefore, can result in radical cure by eliminating both CSCs and non-CSCs.

achieve active targeted delivery in OSCC and hence avoids off target effects

(3) CD133-Niclo-SLNs in combination with conventional chemotherapeutic agents expected to have additive/synergestic proapoptotic activity.

Justification of proposed hypothesis

OSCC remained as one of the major cause of cancer related deaths worldwide in spite of therapeutic interventions. The reason includes, cancer metastasis, drug resistance and tumor recurrence [11]. The identification of CSCs in 1997 by Bonnet and Dick changed the view of cancer treatment. Later, it was found that CSCs play a crucial role in spread of tumor to other tissues, drug resistance and tumor relapse. It was, therefore, identified that CSCs are potential target for effective treatment of oral cancer [12]. The CSCs were identified using the presence of their surface markers like CD44, CD24, EpCAM and CD133 [13]. In recent years, therefore, the search for CSCs specific agents began and as a result agent like, Salinomycin, Notch inhibitors, STAT inhibitors, Wnt inhibitors are reported as CSC specific agents [14]. Recent drug screening identified Niclosamide as a potential anti-CSC agent that can effectively eliminate CSCs. It was also found that niclo inhibits multiple signaling pathways in CSCs. Despite this the clinical efficacy of these agents is limited due to their low bioavailability and off-target side effects. From past two-decade nanotechnology based formulations of anticancer agents have been extensively studied. For example, Abraxane, an albumin bound paclitaxel formulation, has been developed to overcome the solubility issues of paclitaxel. Likewise, BR96-doxorubicin, an immunoconjugate consisting of antibody that recognizes Lewis-Y antigen (expressed on ~75% of cancer cells) and doxorubicin drug, has been developed and tested in animal models of cancer. Few other studies have developed doxorubicin loaded PEGylated-liposomes (Doxil) and tested preclinically as well as in clinical trials. Some of these nanoliposomal drugs (like Doxil, Abraxane etc.) have been approved by FDA to treat cancers [15,16] (see Fig. 2).

CD 133 targeted approach towards cancer stem cells using nanocarriers initiated very recently in the year 2011 for cancers like glioblastoma and Hepato carcinoma [17]. Among the CSCs surface markers, CD133 is becoming an emerging target for immuno-therapy for killing CSCs. For the first time Smith et al unravel the potential of CD 133 as a They used CD 133 antibody drug conjugates for the treatment of hepatocellular and gastric cancer. However, this strategy failed due to instability of the formulation. Although this study gave the idea that CD 133 can be utilized as drug delivery target [18]. TJLiu et al. (2012) at Department of Pathology, Tianjin Medical University, Tianjin, China, demonstrated that CD133 expression was the highest in cancer specimens. They have also proved that CD133+ expression might be central for tumor relapse and progression. Thus gave the idea that CD 133 related molecular pathways may be used as novel therapeutic targets for the inhibition of angiogenesis and metastasis in oral squamous cell carcinoma [2,19,20].

Conclusion

Oral Squamous Cell Carcinoma (OSCC) therapy is challenged by the presence CSCs, which are responsible for metastasis, resistance and EMT mediated relapse. To achieve radical cure it is required to eliminate both CSCs & non-CSCs, unfortunately current drugs can only target non-CSCs. Blocking STAT3 signaling can be utilized to achieve this. We therefore, propose to prepare and evaluate CD133 aptamer surface modified solid lipid nanoparticles (SLNs) of Niclo (CD133-NicloSLNs). The CD133 receptors on OSCC cells will be used for active targeting. The stealth Niclo SLNs will overcome the intrinsic drawbacks of Niclo (solubility, non-stealth and bioavailability) and also provides opportunity for active targeting. The above formulation, is therefore, expected to achieve radical cure through active targeting and will have additive/synergistic effect with conventional therapies.

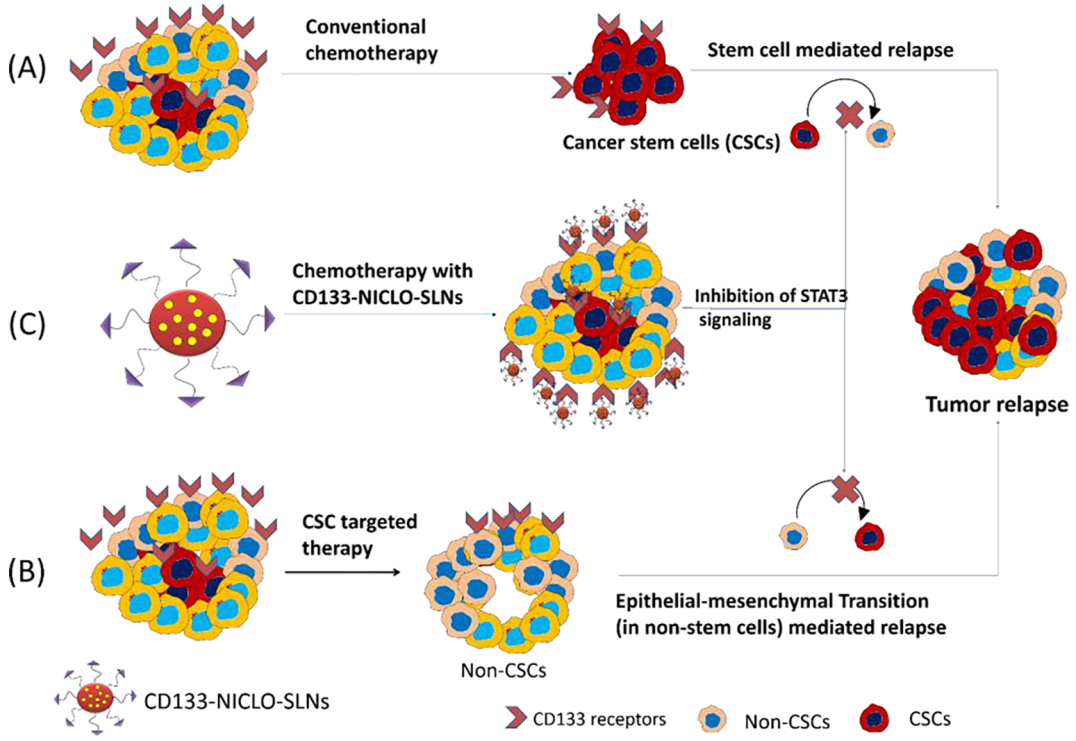

Fig. 2. (A) Conventional chemotherapy results in elimination of cancer cells, leaving behind CSCs. These CSCs which are left behind will result in tumor relapse; (B) CSC targeted treatment initially result in tumor shrinkage and regression due to the elimination of CSCs. Some residual non-CSCs undergo EMT leading to re-population of CSCs, subsequently resulting in treatment failure and metastasis; (C) We propose to prepare CD133-Niclo-SLNs to inhibit STAT3 signaling in both CSCs and non-CSCs to eliminate these cells, and also to prevent stem cell and EMT mediated relapse.

Declaration of Competing Interest

None to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.109241.

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