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

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ABSTRACT

Oropharyngeal 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. STAT3 signaling plays a key role in survival of cancer stem cells (CSCs), 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 STAT3 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...
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/synergistic proapoptotic activity.

Justification of proposed hypothesis

Oral Squamous Cell Carcinoma (OSCC) therapy is challenged by the presence of 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. 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.

Fig. 2. (See Medical Hypotheses 129 (2019) 109241)
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-Nico-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.

References


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