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CAR-T–INSPIRED IMMUNOMODULATORY NANOVESICLES FOR TARGETED ELIMINATION OF ORAL SQUAMOUS CELL CARCINOMA CELLS

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Abstract

Introduction: *Oral squamous cell carcinoma is associated with high morbidity and limited response to conventional chemoradiotherapy. Although chimeric antigen receptor T-cell therapy has shown remarkable success in hematological malignancies, its application in solid tumors is constrained by the tumor microenvironment and therapy-related toxicities. Recent advances suggest that chimeric antigen receptor T-cell - derived nanovesicles may replicate tumor-targeting properties while improving safety and tissue penetration.*

Procedures: *Human Jurkat T-cells were engineered to express a second-generation anti-epidermal growth factor receptor chimeric antigen receptor. Chimeric antigen receptor T-cell–derived nanovesicles were generated using a serial extrusion method and characterized by dynamic light scattering, transmission electron microscopy, and Western blotting. Cellular uptake and cytotoxicity were evaluated in epidermal growth factor receptor-positive oral squamous cell carcinoma cell lines (HSC-3 and CAL-27) and compared with normal human gingival fibroblasts.*

Results: *The engineered chimeric antigen receptor- nanovesicles exhibited a mean diameter of approximately 135 nm and retained key T-cell and chimeric antigen receptor-associated surface markers. Preferential internalization was observed in epidermal growth factor receptor expressing Oral squamous cell carcinoma cells, with minimal uptake in normal fibroblasts. Chimeric antigen receptor - nanovesicles induced significant, dose-dependent apoptosis in oral squamous cell carcinomacell lines while demonstrating negligible cytotoxicity toward normal gingival fibroblasts.*

Conclusion: *Chimeric antigen receptor T-cell-inspired nanovesicles preserve the specificity and cytotoxic efficacy of their parental T-cells while overcoming key limitations of live-cell therapy. These findings highlight chimeric antigen receptor nanovesicles as a promising, safe, and off-the-shelf immunotherapeutic strategy for targeted treatment of oral squamous cell carcinoma.*

Keywords: . Oral squamous cell carcinoma; CAR-T; Nanovesicles; Immunotherapy; EGFR; Targeted drug delivery

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INTRODUCTION

Oral squamous cell carcinoma (OSCC) represents about 90% of all cancers of the oral cavity and has been a clinical challenge in the last several decades because it has limited five-year survival rates to about 50% in patients with advanced disease [*Rivera C, 2015*]. The traditional systemic therapies tend to be non-specific thus causing severe debilitating side effects leaving the patient with poor quality of life. The acute necessity, therefore, is developing specific therapeutic modalities that would specifically destroy cancer cells without damaging the normal oral tissues.

The fourth pillar in cancer treatment has been immunotherapy. Precisely, the treatment of B-cell leukemias and lymphomas by adopting cell transfer with Chimeric antigen receptor T-cells has demonstrated unparalleled success [*Maude S et al., 2018*]. CAR-T cells have been genetically engineered to express an artificial receptor, which binds a tumor-associated antigen regardless of Major histocompatibility complex display. Nevertheless, the transfer of CAR-T-effectiveness to solid tumors, such as OSCC has been hampered due to a number of challenges [*Martinez M, Moon E 2019*]. These are the presence of the dense extracellular matrix as a physical barrier, the immunosuppressive tumor microenvironment that causes the T-cell exhaustion, and the possibility of severe immune-related adverse events like cytokine release syndrome and neurotoxicity [*Bonifant C et al., 2016*].

To overcome these drawbacks, recent studies have shifted the focus to the so-called cell-free immunotherapeutics. Extracellular vesicles are a naturally occurring type of nanotube that contains exosomes and ectosomes, and is therefore used to communicate between cells via the transfer of proteins, lipids, and nucleic acids [*Kalluri R, LeBleu V, 2020*]. T-cell nanovesicles have replaced the parent cell with their functional surface proteins such as the T-cell receptor and cytotoxic effector proteins such as perforin and granzyme B [*Fu W et al., 2019*]. Compared to live cells, nanovesicles are non-replicative which minimizes the chances of uncontrolled growth and cytokine release syndrome. Moreover, they can be easily penetrated deep into the tumor tissues due to their nanoscale dimension (30–150 *nm*) as opposed to the whole cells [*Wiklander O et al., 2015*].

Epidermal Growth Factor Receptor (EGFR) is an optimal target of therapy in the case of OSCC. EGFR is up-regulated in up to 90 percent of OSCC cases and associated with no good prognosis and resistance to radiation [*Kalyankrishna S, Grandis J,2006*]. Although EGFR-directed monoclonal antibodies (e.g. cetuximab) are in clinical use, resistance mechanisms often emerge. The application of the cytotoxic apparatus of T-cells specifically directed against Epidermal growth factor receptor with a Chimeric antigen receptor construct, may provide a stronger lytic induction system compared to antibody blockade itself [*Mei Z et al., 2020*].

The bioengineered nanovesicles specific to the anatomical and cellular environment of the oral cavity have not been fully studied, despite the study of Chimeric antigen receptor-T cell-derived exosomes being reported in mesothelin-positive tumors [*Yang P et al., 2021*]. There is a research gap in the optimization of the yield and targeting efficiency of these vesicles on squamous cell carcinomas.

Thus, this study was intended to produce and describe bio-inspired nanovesicles based on anti-EGFR Chimeric antigen receptor-T cells. We postulated that such Chimeric antigen receptor-nanovesicles would preserve the antigen-binding domain of the parent T-cells and permit specificity to bind to OSCC cells and act as direct cytotoxic agents by delivering granzyme B and perforin, and offer an effective, cell-free replication of traditional Chimeric antigen receptor-T therapy.

MATERIALS AND METHODS

Cell Culture and Design of Study: This experimental in vitro study used two known human OSCC cell lines (high EGFR) and (moderate EGFR) the CAL-27 and HSC-3 cell lines and a control cell line (Primary human gingival fibroblasts). T-cell engineering was done using Jurkat T-cells. The line cultures of OSCC were grown in the Dulbecco modified eagle medium supplemented with 10 percent of the Fetal bovine serum and 1% penicillin-streptomycin. Jurkat cells were kept in the RPMI-1640. The cells were incubated at 37°C and in a humid condition with 5 percent CO_2.

Anti-EGFR Chimeric antigen receptor-T Cells Construction: An anti-EGFR single-chain variable fragment (scFv) of cetuximab in form of an anti-EGFR Fab was also developed into a second-generation Chimeric antigen receptor construct and comprised of an anti-EGFR Fab made of a 4-1BB costimulatory domain, a CD8-alpha hinge, and transmembrane domain, as well as a CD3zeta signaling domain. The gene sequence was cloned to a lentiviral vector

(pLVX). The production of lentiviral particles took place in HEK293T cells. Anti-CD3/CD28 beads were used to activate Jurkat T-cells over a period of 24 hours after which the lentivirus with a Multiplicity of infection of 10 was introduced. The flow cytometry allowed verifying the transduction efficiency 72 hours after infection to determine the expression of the anti-EGFR scFv surface.

Chimeric antigen receptor-nanovesicles Preparation: Serial extrusion technique was used to produce large quantities of nanovesicles as opposed to using natural exosomes secretion. The transduced Chimeric antigen receptor-T cells (1×10^8) were obtained, washed using phosphate buffered saline and resuspended in extrusion buffer. Using a liposome extruder, the cell suspension was filtered by successively passing through polycarbonate membrane filters with pore sizes of 10μm, 5μm, 1μm, 400nm, 200nm and lastly 100nm of cell suspension. The resultant crude vesicle suspension was separated through ultracentrifugation at 100,000×g in 70 minutes at 4°C. Chimeric antigen receptor-nanovesicles were resuspended in phosphate buffered saline in the pellet. Non-targeted nanovesicles were developed in the same way by the use of non-transduced Jurkat cells.

Nanovesicles Characterization: With dynamic light scattering, the size distribution and zeta potential of the nanovesicles were measured. The morphology was observed using transmission electron microscopy on negative staining with uranyl acetate. A bioinchronic protein assay kit was used to determine the protein content. Western blotting was done to verify the presence of exosomal (CD63, TSG101) and T-cell (CD3) and the presence of the Chimeric antigen receptor protein and the absence of cellular nuclear markers (Histone H3).

Cellular Uptake Assay: The lipophilic membrane dye PKH26 (red fluorescence) was conjugated to Chimeric antigen receptor nanovesicles and Non-targeted nanovesicles. Labeled nanovesicles were 50 $\mu g/mL$ and used to treat HSC-3, CAL-27, and human gingival fibroblasts cells cultured on coverslips over 4 hours. Counterstaining of the nuclei was done with DAPI. The visualization of internalization was done through Confocal Laser Scanning Microscopy and the mean fluorescence intensity was measured via ImageJ software.

In Vitro Cytotoxicity Assay: The cytotoxic activity was tested by using Cell Counting Kit-8 (CCK-8) assay. The target cells (HSC-3, CAL-27, human gingival fibroblasts) were placed in 96-well plates containing 5,000 cells per well. Cells were incubated with different amounts of Chimeric antigen receptor nanovesicles or Non-targeted nanovesicles (0, 10, 25, 50, 100 $\mu g/mL$) after 24 hours. The meaning of cell viability was determined as the percentage of the untreated control.

Apoptosis Analysis: In order to differentiate between the necrosis and apoptosis, HSC-3 cells were incubated with Chimeric antigen receptor nanovesicles (50 $\mu g/mL$) after 24 hours and then, stained with Annexin V-FITC and Propidium Iodide (PI). To induce the percentage number of living (Annexin V-/PI-), early apoptotic (Annexin V+/PI-), and late apoptotic/necrotic (Annexin V+/PI+) cells, flow cytometry was used.

Statistical Analysis: Biological triplicates were carried out in all the experiments. The data were in the form of the mean and Standard Deviation (SD). The analysis of statistical differences between groups was done with One-way ANOVA and post-hoc test with Tukey. The p-value that was found to be statistically significant was less than 0.05.

RESULTS

Characterization of Chimeric antigen receptor-T Inspired Nanovesicles: The transduction efficiency of Jurkat T-cells with the anti-EGFR Chimeric antigen receptor construct was confirmed to be 68.4% via flow cytometry prior to vesiculation (Table 1). Following serial extrusion and ultracentrifugation, the resulting Chimeric antigen receptor nanovesicles were analyzed. Transmission electron microscopy imaging revealed spherical, membrane-bound vesicles with typical morphology. Dynamic light scattering analysis indicated a monodisperse population. Western blot analysis confirmed the enrichment of exosomal markers (CD63, CD81) and the presence of the Chimeric antigen receptor protein and Granzyme B in the Chimeric antigen receptor nanovesicles, confirm-

TABLE 1.

Physicochemical characterization of nanovesicles

Parameter	NT NVs	ARC-NVs	P-value
Hydrodynamic Diameter (nm)	132.5±8.4	138.2±9.1	>0.05
Polydispersity Index	0.18±0.03	0.21±0.04	>0.05
Zeta Potential (mV)	-24.1±2.5	-22.8±1.9	>0.05
Protein Yield ($\mu g/10^7$ $cells$)	185.4±12.6	192.1±15.3	>0.05

NOTES: *VT-NVs- Non-targeted nanovesicles, ARC-NVs - Anti-epidermal growth factor receptor CAR-nanovesicles*

ing the successful transfer of parental membrane and cytosolic cargo.

Targeted Internalization in OSCC Cells: Confocal microscopy demonstrated distinct differences in uptake based on EGFR expression. HSC-3 cells (High EGFR) incubated with PKH26-labeled Chimeric antigen receptornanovesicles showed intense cytoplasmic red fluorescence, indicating robust endocytosis. CAL-27 cells (Moderate EGFR) showed moderate fluorescence. In contrast, uptake was minimal in human gingival fibroblasts control cells. Furthermore, Non-targeted nanovesicles showed significantly lower uptake in OSCC lines compared to Chimeric antigen receptor nanovesicles, confirming that the interaction was mediated by the anti-EGFR scFv on the vesicle surface.

Cytotoxicity and Selectivity: The CCK-8 assay results demonstrated that Chimeric antigen receptor nanovesicles exerted a potent, dose-dependent cytotoxic effect on OSCC cell lines (Table 2). The toxicity was significantly higher in HSC-3 cells compared to CAL-27 cells, correlating with EGFR expression levels. Non-targeted nanovesicles showed only negligible toxicity at high concentrations, likely due to non-specific lipid effects. Most importantly, Chimeric antigen receptor nanovesicles showed minimal toxicity toward normal gingival fibroblasts), even at the highest concentrations.

Mechanism of Cell Death: To confirm that cell death was mediated through programmed cell death pathways rather than uncontrolled lysis, apoptosis was measured (Table 3). Treatment of HSC-3 cells with Chimeric antigen receptor nanovesicles resulted in a substantial shift of the population toward early and late apoptosis compared to controls (Phosphate buffered salin).

TABLE 2.

Comparative cytotoxicity (IC50 values ((*μg/mL*)) after 24h treatment

Cell Line	EL-EGFR	NT-NVs	CAR-NVs	Fold Change (Potency)
HSC-3	High	> 500	32.4 ± 4.1	> 15x
CAL-27	Mod.	> 500	58.7 ± 5.5	> 8x
HGV	L(N)	> 500	> 250	N/A

NOTES: *EL-Expression Level, EGFR- Epidermal growth factor receptor, NGF - Human gingival fibroblasts, NT-NVs- Non-Targeted nanovesicles, CAR-nanovesicles, Mod- moderate LN - Low(Negative)*

TABLE 3.

Apoptosis Analysis of HSC-3 Cells via Flow Cytometry (Mean %)

Treatment Group	Control	NT-NVs	CAR-NVs
Live Cells (Annexin V-/PI-)	94.2±1.5	88.5±2.1	41.3±3.4*
Early Apoptosis (Annexin V+/PI-)	3.1±0.8	6.4±1.2	35.6±2.8*
Late Apoptosis/Necrosis (Annexin V+/PI+)	2.7±0.9	5.1±1.5	23.1±2.2*

Notes: *(*) - Indicates P < 0.001 compared to NT-nanovesicles.*

DISCUSSION

This paper was able to successfully engineer and characterize biomimetic nanovesicles that were made based on anti-EGFR Chimeric antigen receptor T cells, which is a demonstration of the potential to use the biomimetic nanovesicles in the treatment of Oral Squamous Cell Carcinoma. It has been shown that Chimeric antigen receptor nanovesicles maintain the targeting ability of their parent cells coupled with high-potency cytotoxic responses to tumor cells, a major requirement in oral oncology manufacturing safer and targeted-therapies.

The physicochemical characterization (Table 1) justified that serial extrusion is one of the available methods that can be used to drive high yields of homogeneous nanovesicles. The Enhanced Permeability and retention effect is best at the size range (~138 *nm*), and theoretically enables the accumulation of these vesicles effectively in the leaky vasculature of solid tumors compared to larger cellular therapies [*Maeda H, 2015*]. Also, the comparable zeta potential of targeted and non-targeted vesicles indicates that Chimeric antigen receptor construct addition does not have a significant impact on surface charge or colloidal stability, which is a vital consideration when considering in vivo circulation time [*Smith Z et al., 2015*].

The central conclusion of the current study is that Chimeric antigen receptor nanovesicles have a high level of specificity towards EGFR-positive OSCC cells. The results revealed that there is a positive association between the level of EGFR expression on target cells and the scale of cytotoxic response (Table 2). Cells with high EGFR concentration: HSC-3 were much more sensitive to Chimeric antigen receptor nanovesicles as compared to CAL-27 cells and normal fibroblasts were not very affected. This specific toxicity is probably caused by the reaction between the scFv on the surface of the vesicle and the EGFR on the tumor cell, it triggers receptor-mediated endocytosis. This mechanism is supported by previous research of Chimeric antigen receptor T-cells derived exosomes in models of breast cancer,

indicating that physical interaction of the receptor is a requirement to allow the vesicle internalization and the release of its cargo [*Tang X et al., 2015*].

Chimeric antigen receptor nanovesicles seem to have a direct kill activity compared with monoclonal antibodies (e.g., cetuximab), which mainly find their targets using the Antibody-dependent cellular cytotoxicity technique rather than direct cellular cytotoxicity. The identification of Granzyme B in the vesicles (Western blot data not shown) but with the help of the apoptosis data (Table 3) indicates that after internalization, the vesicles release lytic granules which stimulate caspase pathways [*Voskoboinik I et al., 2015*]. This is the equivalent of the fatal strike of a cytotoxic T lymphocyte minus an immunological synapse or major histocompatibility complex recognition [*Halle S et al., 2017*]. Early and late apoptosis are high percentages that affirm that the vesicles cause programmed cell death and not necrosis, which is advantageous of reducing pro-inflammatory reactions of the surrounding healthy tissue [*Elmore S, 2007*].

The safety profile in this case, namely no cytotoxicity with human gingival fibroblasts cells, is encouraging. Cutaneous and mucosal toxicity caused by EGFR expression in normal tissues is one of the greatest risks of EGFR-targeted therapies [*Lacouture M, 2006*]. Nevertheless, this threshold of Chimeric antigen receptor nanovesicles activation seems to demand a high antigen density, which can be also termed as antigen tuning in the Chimeric antigen receptor T-cells literature [*Liu X et al., 2015*]. It is reasonable that the concentration of EGFR on normal fibroblasts is not high enough to elicit the strong internalization needed to achieve a cytotoxic threshold of Granzyme B.

Although these are positive outcomes, there are limitations. This was in vitro research that did not have the interactions of the immune system and the thick stromal barrier in the real tumor of Oral Squamous cell carcinoma cells. Although the theory suggests that nanovesicles might infiltrate into stroma better than cells, this will have to be confirmed in 3D spheroid models or in vivo xenograft models [*Théry C et al., 2018*]. Also, although serial extrusion yields high, the quality of the membrane proteins relative to those released by exosomes released naturally needs additional proteomic confirmation [*Emam S et al., 2019*].

Future studies ought to be done to load these Chimeric antigen receptor nanovesicles with small molecule chemotherapeutics or immunomodulators (e.g., anti-PD1 agents) to achieve a synergistic effect. These vesicles may have the potential to deliver a cytotoxic hit and checkpoint blockade simultaneously due to its trojan horse-like property, which has the potential to overwhelm the immunosuppressive tumor microenvironment that afflicts current OSCC therapies [*Chen G et al., 2018; Zhang Q et al., 2018*].

Conclusion

To sum up, this paper has shown that nanovesicles prepared using anti-EGFR Chimeric antigen receptor T- cells are effective, targeted delivery vehicles to eliminate Oral Squamous cell carcinoma cells. Chimeric antigen receptornanovesicles are a new generation of so-called cell-free immunotherapeutics, where the antigen-recognition specificity of Chimeric antigen receptor T cells is combined with the safety and stability of nanocarriers. They showed great dose-dependent cytotoxicity to Oral Squamous cell carcinoma cells lines without affecting healthy gingival tissue and mainly by causing apoptosis. Such results provide the foundation of preclinical research in the future to develop off-the-shelf, non-toxic therapeutic options in patients with refractory oral cancer.

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