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DeltaRex-G, tumor targeted retrovector encoding a CCNG1 inhibitor, for CAR-T cell therapy induced cytokine release syndrome

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Cytokine release syndrome is a serious complication of chimeric antigen receptor-T cell therapy and is triggered by excessive secretion of inflammatory cytokines by chimeric T cells which could be fatal. Following an inquiry into the molecular mechanisms orchestrating cytokine release syndrome, we hypothesize that DeltaRex-G, a tumor targeted retrovector encoding a cytocidal CCNG1 inhibitor gene, may be a viable treatment option for corticosteroid-resistant cytokine release syndrome. DeltaRex-G received United States Food and Drug Administration Emergency Use Authorization to treat Covid-19-induced acute respiratory distress syndrome, which is due to hyperactivated immune cells. A brief administration of DeltaRex-G would inhibit a certain proportion of hyperactive chimeric T cells, consequently reducing cytokine release while retaining chimeric T cell efficacy.

KEYWORDS

DeltaRex-G, CAR-T cell therapy, cytokine release syndrome, COVID-19, acute respiratory disease

Introduction

Chimeric Antigen Receptor-T (CAR-T) cell therapy is a novel cancer treatment wherein CARs are introduced into a patient's own harvested T cells and subsequently infused intravenously for the purpose of eradicating cancer (Kalos et al., 2011). Factors that limit the efficacy of CAR-T cell therapy include minimal or exaggerated CAR-T cell proliferation, a dysregulated inflammatory tumor microenvironment (TME) and a high baseline tumor burden (Ventin et al., 2024). Cytokine Release Syndrome (CRS) is a severe, potentially fatal, adverse event that could develop in patients receiving CAR-T cell therapy (Freyer and Porter, 2020). Hypothesis: A brief administration of DeltaRex-G, a tumor targeted retroviral vector encoding a cytocidal mutated cyclin G1 gene, would inhibit only the dividing T cells thus reducing cytokine release by hyperactive CAR-T cells while retaining their antitumor efficacy.

CAR-T cell therapy

T cells harvested from the patient are modified with chimeric antigen receptors (CARs) engineered to recognize and bind antigens specific to a patient's cancer

(Sermer and Brentjens, 2019; Korell et al., 2022). Engineered CAR-T cells equipped to target and eliminate cancer cells are intravenously infused into the patient who has undergone lymphodepletion. Upon recognizing and binding to the target antigen in cancer cells, the activated CAR-T cells eradicate tumor cells while proliferating simultaneously. CAR-T cell therapy has been proven effective in pediatric and adult acute lymphocytic leukemia, B cell lymphoma, mantle cell lymphoma, and multiple myeloma by targeting the Cluster of Differentiation 19 (CD19) or B cell maturation antigen (BCMA) on these malignant cells (Asmamaw et al., 2022).

Currently, there is only one FDA-approved CAR-T cell therapy for solid tumors. The primary challenge to implementing CAR-T cell therapy for solid tumors is tumor heterogeneity and consequent difficulty in ascertaining which antigen, ideally a mutated oncogene, should be targeted (Qin and Xu, 2022). Moreover, solid tumors are often found in tissues with reduced regenerative capacity compared to the hematopoietic system so CAR-T cell targets must be incredibly precise to preserve the maximum amount of healthy tissue (Qin and Xu, 2022; Xia et al., 2018). Two novel receptors enable inducible CAR expression to enhance tumor specificity and prevent CAR-T cell exhaustion, including Synthetic intramembrane proteolysis receptors (SNIPRs) and Signal neutralization by an inhibitable protease (SNIP) (Qin and Xu, 2022; Zhu et al., 2022; Labanieh et al., 2022). Additionally, stroma in tumors act as physical barriers and the immunosuppressive tumor microenvironment (TME) further prevents optimal CAR-T cell penetration in solid tumors (Asmamaw et al., 2022). Ongoing research has determined that intratumoral injection of CAR-T cells and a hydrogel containing cytokine and CAR-T cells can overcome the physical impediments to solid tumors and improve CAR-T cell cytotoxicity and efficacy while preserving tumor-specificity (Qin and Xu, 2022; Melero et al., 2021; Adusumilli et al., 2014; Grosskopf et al., 2022). There are currently over fifty clinical trials investigating various solid tumor targets for CAR-T cell therapy--Mesothelin, Carcinoembryonic antigen, Claudin18.2, and Cluster of Differentiation 70 (CD70) are the most common antigens in addition to dual CAR targets to increase tumor specificity (A Phase I, 2016; T Cells Armed With Chimeric, 2016; Phase I, 2017; Phase I Study of Autologous, 2018; A First in Human Phase, 2018; A Phase I Investigation of the Safety, 2019; An Open Label, 2019; An Exploratory Study of αPD1, 2020; A Phase I Trial to Assess Safety, 2020; Open, 2020; B7-H3-Specific Chimeric Antigen Receptor Autologous, 2021; Phase I Study of EGFR, 2021; A Single, 2021; A Phase 1 Dose Escalation, 2022; A Phase 1 Study to, 2022; Clinical Trial to Evaluate the, 2022; A Single, 2022; A Phase Ia/Ib, 2022; An Exploratory Study of αPD1, 2022; Open-Label, 2022; Single-center, 2022a; A Phase I Clinical Study, 2022a; A Safety and Efficacy Clinical, 2022; A Phase I Clinical Study, 2022b; GD2/PSMA Bi, 2022; A Phase I Clinical Study, 2022d; Clinical Study of CLDN18, 2022; An Open, 2022; A Phase I Clinical Study, 2022c; Chimeric Antigen Receptor T Lymphocytes CAR-T, 2022; Clinical Study to Evaluate the, 2022; Exploratory Clinical Study of PD, 2022; Single-center, 2022b; FIH and Arm, 2022; Efficacy and Safety of Claudin18, 2022; Phase, 2022; A Phase 1, 2023; A Phase1/phase2 and Single-arm, 2023; Mesothelin/GPC3/GUCY2C Targeted CAR, 2023; A Clinical Study on the, 2023; Exploratory Clinical Trial on the, 2023b; A Study to Evaluate the Safety et al., 2023; Phase I, 2023; Exploratory Clinical Trial on the, 2023a; FTiH, 2023; A Phase I Clinical Study, 2023; A Safety and Efficacy Clinical, 2023; An Exploratory Clinical Study Evaluating, 2023a; Phase I Clinical Study of, 2023; A Seamless Phase 1, 2023; An Exploratory Clinical Study Evaluating, 2023b; A Phase 1 Study of, 2024; An Exploratory Study on the, 2024; Exploratory Study of MSLN, 2024; Exploratory Study on the Treatment, 2024; Brudno and Kochenderfer, 2016; Maude et al., 2014) (A Phase I, 2016; T Cells Armed With Chimeric, 2016; Phase I, 2017; Phase I Study of Autologous, 2018; A First in Human Phase, 2018; A Phase I Investigation of the Safety, 2019; An Open Label, 2019; An Exploratory Study of αPD1, 2020; A Phase I Trial to Assess Safety, 2020; Open, 2020; B7-H3-Specific Chimeric Antigen Receptor Autologous, 2021; Phase I Study of EGFR, 2021; A Single, 2021; A Phase 1 Dose Escalation, 2022; A Phase 1 Study to, 2022; Clinical Trial to Evaluate the, 2022; A Single, 2022; A Phase Ia/Ib, 2022; An Exploratory Study of αPD1, 2022; Open-Label, 2022; Single-center, 2022a; A Phase I Clinical Study, 2022a; A Safety and Efficacy Clinical, 2022; A Phase I Clinical Study, 2022b; GD2/PSMA Bi, 2022; A Phase I Clinical Study, 2022d; Clinical Study of CLDN18, 2022; An Open, 2022; A Phase I Clinical Study, 2022c; Chimeric Antigen Receptor T Lymphocytes CAR-T, 2022; Clinical Study to Evaluate the, 2022; Exploratory Clinical Study of PD, 2022; Single-center, 2022b; FIH and Arm, 2022; Efficacy and Safety of Claudin18, 2022; Phase, 2022; A Phase 1, 2023; A Phase1/phase2 and Single-arm, 2023; Mesothelin/GPC3/GUCY2C Targeted CAR, 2023; A Clinical Study on the, 2023; Exploratory Clinical Trial on the, 2023b; A Study to Evaluate the Safety et al., 2023; Phase I, 2023; Exploratory Clinical Trial on the, 2023a; FTiH, 2023; A Phase I Clinical Study, 2023; A Safety and Efficacy Clinical, 2023; An Exploratory Clinical Study Evaluating, 2023a; Phase I Clinical Study of, 2023; A Seamless Phase 1, 2023; An Exploratory Clinical Study Evaluating, 2023b; A Phase 1 Study of, 2024; An Exploratory Study on the, 2024; Exploratory Study of MSLN, 2024; Exploratory Study on the Treatment, 2024; Brudno and Kochenderfer, 2016; Maude et al., 2014)

Cytokine release syndrome

CAR-T cell therapy stimulates a robust immune response that can cause cytokine release syndrome (CRS) in patients, which can be fatal. CRS begins as a fever and myalgia two to 3 days after CAR-T cell infusion but can progress to capillary leak, hypoxia, hypotension, tachycardia, pulmonary edema, and pleural edema within 2 weeks of treatment (Sermer and Brentjens, 2019). In dire cases, organ failure and death may ensue. The molecular basis for CRS is excessive secretion of cytokines by T cells (Brudno and Kochenderfer, 2016),. One of the core cytokines elevated in CRS patient serum is the inflammatory interleukin-6 (IL-6) produced by monocytes, macrophages, and T-cells (Maude et al., 2014). Patients with high IL-6 levels and large baseline tumor burdens have inflammatory TMEs that prime myeloid cells and macrophages to induce an immune response, and this condition is amplified by CAR-T cell treatment. Elevated IL-6 levels post-treatment have been correlated with diminished response to CAR-T cell therapy and severe CRS (Sermer and Brentjens, 2019). Tocilizumab, an anti-IL-6R antibody, is the current standard of care for mild CRS but corticosteroid therapy like dexamethasone is often required in cases of severe CRS. Recent studies have shown that high dose corticosteroid treatment and early CRS intervention with Tocilizumab and preemptive corticosteroids decreased the risk of severe CRS without adversely affecting CAR-T cell therapy efficacy (Gardner et al., 2019; Liu et al., 2020). Anakirna, an IL-1 receptor antagonist has been identified as

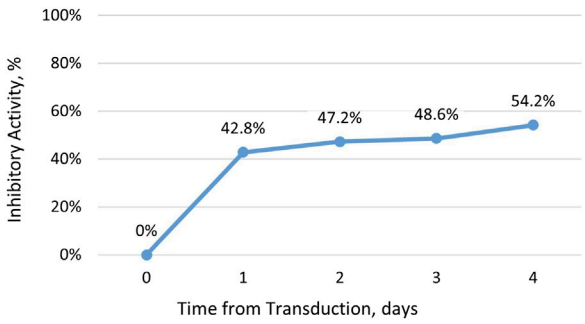

FIGURE 1
Inhibitory activity of DeltaRex-G in $CD4^+$ $CD8^+$ T cell cultures. The percent inhibitory activity of DeltaRex-G is plotted on the vertical axis as a function of time (days) from retroviral transduction of $CD4^+$ $CD8^+$ T cell cultures.

another therapeutic for severe CRS (grade 3 or 4) when administered with corticosteroids, and if administered early in combination with Tocilizumab, can prevent CRS (Ferreros and Trapero, 2022; Gazeau et al., 2023). Siltuximab, another anti-IL-6 antibody, has also shown promising results in treating mild CRS (Bajwa et al., 2024). However, these treatments are not universally effective and as such, a demand for a CRS treatment that will not only mitigate the potentially devastating progression of CRS but could also maximize the potency of the administered CAR-T cell therapy persists (Chawla et al., 2022).

DeltaRex-G for cytokine release syndrome

Originally developed as a cancer drug, DeltaRex-G (formerly named Rexin-G, Mx-dnG1) is a tumor targeted retrovector encoding a cytocidal CCNG1 inhibitor gene which inhibits cyclin G1 expression, and consequently, blocks the cancer cell cycle in G0-G1 phase, aborting the cell cycle and resulting in cell death via the apoptosis-mediated pathway (Morse et al., 2021; Chawla et al., 2019). The membrane gp70 envelope of DeltaRex-G was molecularly engineered to display a signature (SIG) protein-binding decapeptide that recognizes and binds to abnormal anaplastic collagenous SIG proteins in the TME, then fuses and enters via the innate amphotropic Pit2 receptor and inhibits/destroys only highly proliferative cells including cancer cells, neoangiogenic cells and stroma-producing fibroblasts (Morse et al., 2021; Chawla et al., 2019). Phase I/II studies in patients with pancreatic adenocarcinoma, sarcomas, and metastatic breast cancers have established a significant association between DeltaRex-G dosage and tumor control/survival advantage (Chawla et al., 2019; Chawla et al., 2016; Liu et al., 2021). During the COVID-19 pandemic, DeltaRex-G was granted FDA Emergency Use Authorization for severe COVID-19 induced CRS and acute respiratory distress syndrome (ARDS) (Larkin, 2021). CRS from CAR-T cell therapy and COVID-19 develop from excessive stimulation and activation of immune cells and consequent cytokine release resulting in tissue damage.

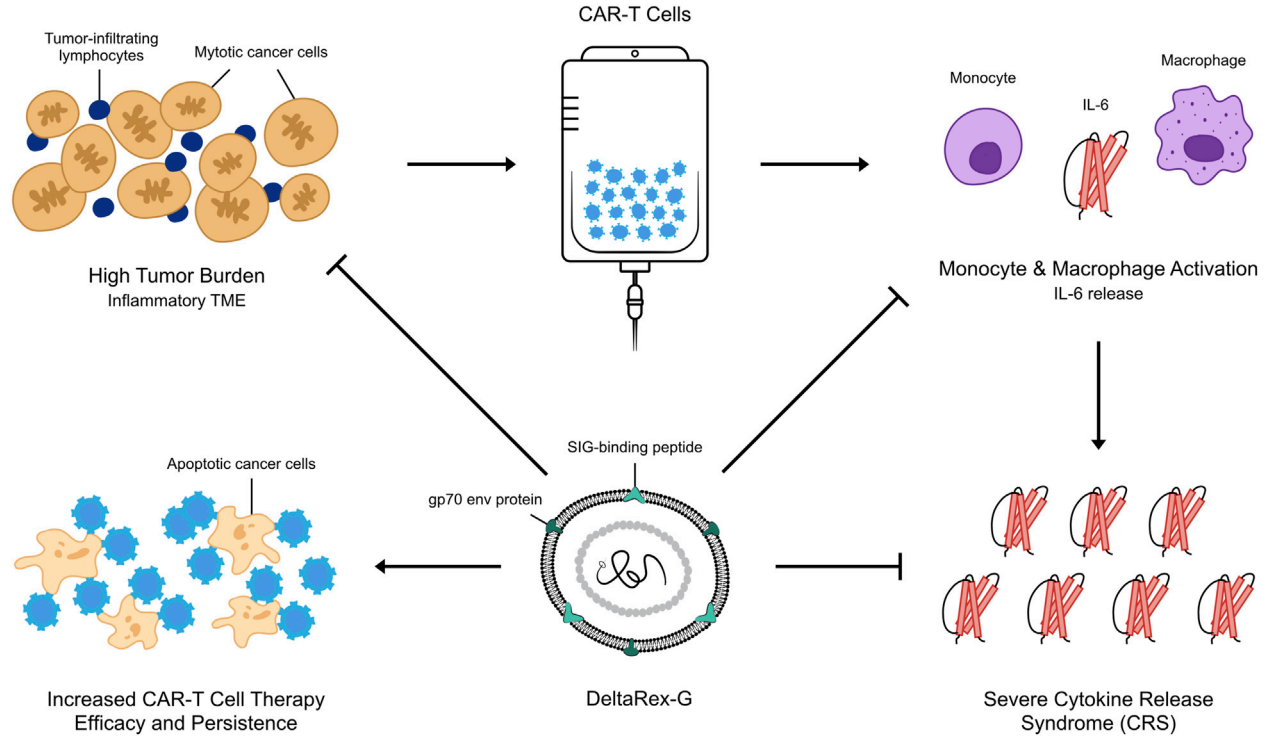

FIGURE 2
An artist's illustration of DeltaRex-G mechanism of action in CAR-T cell induced severe CRS. By killing a certain proportion of actively dividing CAR-T cells and cancer cells, the secretion of inflammatory cytokines by chimeric T cells is reduced while retaining the efficacy of remaining CAR-T cells in reducing tumor burden.

Recently, we demonstrated the inhibitory activity of DeltaRex-G in cultures of $CD4^+$ $CD8^+$ T cells (See Figure 1). This led to the hypothesis that DeltaRex-G could also inhibit the activity of activated CAR-T cells that cause CRS while retaining CAR-T cell efficacy (See Figure 2). The fact that DeltaRex-G (a retroviral based vector) only integrates in the chromosome of rapidly dividing cells, a property that is common in rapidly dividing cancer cells and proliferating CAR-T cells, is the rationale for using DeltaRex-G in CAR-T induced CRS. Further, DeltaRex-G is not immunogenic, so excessive immune responses are not expected to result from DeltaRex-G treatment. In fact, previous studies in cancer patients showed no development of CRS in DeltaRex-G treated patients and is not expected to cause any serious adverse events, including B-cell aplasia and neurotoxicity which are major sequelae of CAR-T cell therapy (Chawla et al., 2022; Chawla et al., 2019; Chawla et al., 2016; Liu et al., 2021; Bruckner et al., 2023).

Discussion and conclusion

Our hypothesis that a brief administration of DeltaRex-G would reduce the severity of CAR-T cell therapy-induced CRS is supported by the inhibitory activity of DeltaRex-G in transduced CD4 CD8 cell cultures (Figure 1). DeltaRex-G may be used to treat CRS by inhibiting a certain proportion of the proliferative cytokine-releasing immune cells, hence reducing production of IL-6, while retaining the efficacy of unaffected CAR-T cells (Figure 2). Clinical data from cancer patients treated with DeltaRex-G have shown an initial control of tumor growth with eventual tumor shrinkage and attainment of clinical remission after 8 months of DeltaRex-G therapy. Albeit DeltaRex-G has not yet been used to treat CRS, DeltaRex-G has not been reported to cause hematologic nor organ dysfunction in Phase 1 and Phase studies using DeltaRex-G in advanced sarcoma, pancreatic cancer and carcinoma of breast (Chawla et al., 2019; Chawla et al., 2016; Liu et al., 2021; Bruckner et al., 2023). Further no vector neutralizing antibodies have formed with prolonged DeltaRex-G therapy, indicating that DeltaRex-G is not immunogenic (Chawla et al., 2019; Chawla et al., 2016; Liu et al., 2021; Bruckner et al., 2023). Additionally, no delayed adverse events have been reported in long term (>15 years) cancer survivors with DeltaRex-G treatment (Liu et al., 2021). Nevertheless, a phase 1/2 clinical study is warranted to show the safety and inhibitory activity of DeltaRex-G in patients suffering from steroid-resistant cytokine release syndrome following CAR-T cell therapy.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

GH: Data curation, Formal Analysis, Writing–original draft, Writing–review and editing. EG: Conceptualization, Data curation, Formal Analysis, Supervision, Writing–original draft, Writing–review and editing.

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Conflict of interest

EMG is co-inventor of the targeted gene delivery system represented by DeltaRex-G which was created and developed at USC Keck School of Medicine, Los Angeles, CA.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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