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Abstract 4140419: Targeting Cardiac Fibrosis with Chimeric Antigen Receptor Neutrophils from Human Pluripotent Stem Cells

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Abstract

Cardiac fibrosis is a pathological hallmark of almost all forms of heart disease, characterized by excessive deposition of extracellular matrix (ECM) proteins by activated fibroblasts, leading to cardiomyocyte hypertrophy, arrhythmias, and heart failure. Current treatments, predominantly pharmacological, target signaling pathways involved in fibroblast activation but often come with side effects such as cardiac toxicities. There is a critical need for therapies that specifically target activated cardiac fibroblasts to mitigate these adverse effects.

Recent advances have shown that chimeric antigen receptor (CAR)-T cells targeting fibroblast activation protein (FAP), expressed by activated fibroblasts, can significantly reduce fibrosis and improve cardiac function in mouse models. However, CAR-T cell therapies face challenges such as the requirement for large quantities of healthy primary immune cells, lengthy process, and the high cost of personalized treatments. To address these issues, we propose an innovative strategy using off-the-shelf CAR-neutrophils derived from human pluripotent stem cells (hPSCs).

We hypothesize that hPSC-derived CAR-neutrophils engineered to target FAP will effectively reduce cardiac fibrosis and improve cardiac function post-injury due to their potent cytotoxic effects and ability to infiltrate infarct regions. To test this hypothesis, anti-FAP CAR hPSCs were generated by CRISPR/Cas9 genome editing and differentiated into neutrophils. The differentiated anti-FAP CAR hPSC-neutrophils exhibited molecular characteristics comparable to unmodified hPSC-neutrophils. We also established an in vitro cardiac fibrosis model utilizing a previously reported protocol for the generation of hPSC-derived epicardial fibroblasts. Importantly, our anti-FAP hPSC-neutrophils exhibited significant cytotoxicity against activated epicardial fibroblasts, while unmodified hPSC-neutrophils showed no/minimal killing efficiency.

This study suggests a proof-of-concept therapeutic approach against cardiac fibrosis utilizing FAP-targeting CAR-neutrophils. This strategy can potentially be adapted to treat fibrosis in other organs, thereby having a broad and significant impact on the treatment of various fibrotic diseases, ultimately contributing to longer, healthier human lives.

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