Implantation of engineered adipocytes suppresses tumor progression in cancer models

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Background:

A hallmark of tumors is metabolic reprogramming to sustain rapid growth and survival. Most cancers accelerate aerobic glycolysis and increase lipid utilization under hypoxia. Targeting tumor metabolic pathways is therefore a potentially effective therapeutic strategy. Although pharmacologic interventions are under development, prior studies have shown that activating brown adipose tissue by cold exposure can markedly suppress tumor growth; however, keeping cancer patients in prolonged cold environments is impractical. Thus, there is a need for a controllable, cold-exposure–free metabolic therapy.

Objective:

To develop a novel cell therapy termed Adipose Manipulation Transplantation (AMT), which uses engineered adipocytes or adipose organoids to compete with tumors for nutrients, thereby inhibiting cancer progression.

Results:

Using CRISPRa to upregulate UCP1, PPARGC1A, or PRDM16 successfully “browned” adipocyte, increasing glucose uptake and fatty acid oxidation. In co-culture system, CRISPRa adipocytes significantly suppressed proliferation of multiple cancer cell lines and reduced metabolic rate. In xenograft models, co-implantation of UCP1-CRISPRa human adipose organoids adjacent to tumors reduced tumor volume, and also significantly decreased the proliferation, hypoxia, and angiogenesis markers, while increasing apoptosis. Next, they fed mice a high-fat diet or high-glucose water to support nutrient competition as the primary mechanism. In genetic mouse models of pancreatic cancer and breast cancer, AMT markedly suppressed tumor growth. Notably, distal implantation provided similar anti-tumor effects, suggesting systemic activity. In clinical applications, they developed a tetracycline-inducible AAV vector to control UCP1 expression and a cell-scaffold delivery platform to provide a stable 3D microenvironment that allowed the implant to be removed or replaced, enhancing the controllability and personalization of AMT. In the end, it also showed the customization in uridine-dependent pancreatic ductal adenocarcinoma.

Conclusion:

Given that adipocytes can be readily obtained and transplanted via liposuction, and it demonstrates the therapeutic efficacy across multiple cancers, systemic activity, inducible platform and customizable metabolic targets, AMT might be a promising clinical therapy.