Rescue of Dendritic Cell Metabolism from Glycolysis Inhibition for Cancer Immunotherapy
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Introduction: Cancer cells have accelerated glycolysis for ATP generation even in aerobic conditions (Warburg effect), which starves immune cells in tumor microenvironment. Moreover, under depleted nutrient (e.g. glucose) availability, the metabolic intermediates of glycolysis play a major in macromolecular biosynthesis, thereby giving the cancer cells a selective advantage over immune cells. Therefore, inhibition of glycolysis is known to be a viable strategy for inhibiting tumor growth. Although, numerous strategies have been implemented by targeting this pathway, some of the disadvantages include system toxicity, precise targeting of cancer cells and chemoresistance. Importantly glycolysis is also utilized by immune cell for their function, which is also blocked by these inhibitors. Herein, we report a novel strategy to inhibit tumor growth by rescuing primary immune cells (dendritic cells-DCs) from systemic glycolytic inhibition (PFK15) by providing metabolite (Fructose1,6 biphosphate) based polymeric microparticles while simultaneously priming the adaptive immunity (T cells) against tumor cells as well as using adoptive cell transfer.

Methods: Fructose 1,6 biphosphate (F16BP) metabolite-based calcium phosphate microparticles incorporating poly I:C, (analog of dsRNA) and mRNA (from cancer cells – YUMM1.1) in the backbone were synthesized (termed Vaccine) and characterized using scanning electron microscopy (SEM) and dynamic light scattering (DLS). Seahorse assay were used to determine the extracellular acidification rate (ECAR) and oxygen consumption rate (OCR) of DCs. Flow cytometry and enzyme-linked immunosorbent assay (ELISA) determined the activation of DCs in vitro. Immunocompetent mice were inoculated with YUMM1.1 melanoma cells and treated with 25 mg/kg PFK15 and 0.2 mg of PD-1 (i.p.) and 50 mg/kg of Vaccine (s.c.) to determine survival. Lymph nodes, tumor and spleen were harvested and used for determining immunological profile.

Results: F16BP MPs were successfully able to rescue mouse bone marrow derived DCs from glycolytic inhibition of PFK-15 as observed by upregulated ECAR and OCR, in vitro. DCs were activated as indicated by a higher population of MHCII+CD86 cells and upregulated production of TNF-alpha, a pro-inflammatory cytokine in presence of Vaccine in vitro. Interestingly, administration of the vaccine led to significant reduction of subcutaneous melanoma tumor (YUMM1.1) growth in immunocompetent mice attributable to increased tumor infiltrating lymphocytes (Tc1, Tc17, proliferating Tc1 and Tc17). Notably, mice survived >60 days after tumor inoculation in this highly aggressive melanoma model.

Conclusion: This novel strategy of rescuing innate immune cells by intracellular delivery of key metabolites and subsequently modulating the adaptive immunity provides a paradigm shift in the field of immunometabolism based immunotherapy with potential applications in the field of oncology, wound healing and autoimmune diseases.