ABSTRACT

Age-related accumulation of senescent cells drives tissue dysfunction, fibrosis, and chronic inflammation across multiple diseases. T cells themselves undergo senescence characterized by metabolic decline, mitochondrial impairment, and loss of stem-like properties limiting both natural immune surveillance of senescent cells and therapeutic approaches including autologous CAR-T cell therapy. Although CAR-T cells have achieved remarkable success in hematologic malignancies, older cancer patients exhibit inferior clinical responses potentially due to age-related T cell dysfunction. While CAR engineering has focused on optimizing antigen recognition and signaling architectures, the metabolic regulatory systems that sustain T cell fitness, prevent exhaustion, and enable serial cytotoxic function remain unexploited. SIRT7, an NAD^+-dependent deacetylase and desuccinylase, is a central regulator of T cell metabolism through post-translational modification of branched-chain amino acid (BCAA) catabolic enzymes. Emerging clinical evidence demonstrates that SIRT7 expression declines by 70% between ages 20-80 in human leukocytes. In preliminary work, we find that SIRT7 deficiency promotes exhaustion marker expression (PD-1, TIM-3) and reduces cytotoxic capacity. Building on our premise that SIRT7 integrates metabolic enzyme regulation and chromatin remodeling, we hypothesize that age-related SIRT7 decline drives premature CAR-T exhaustion and metabolic dysfunction, yielding cells with compromised infiltration, reduced serial killing capacity, and accelerated senescence. Compounding these intrinsic T cell defects, senescent cells accumulate in aging tumor microenvironments, particularly in desmoplastic malignancies that frequently overexpress MET, where they create fibrotic stromal barriers and secrete immunosuppressive factors that further impair CAR-T infiltration and function. This proposal employs two complementary approaches to systematically address how SIRT7 orchestrates metabolic fitness, stemness preservation, and cytotoxic execution in CAR-T therapy. Aim 1 will define SIRT7's complete succinylation and acetylation regulatome in aged versus young human T cells through integrated acetyl-proteome, succinylation proteome, and ATAC-seq analyses, revealing how SIRT7 coordinates metabolic enzyme activity with chromatin accessibility at stemness and metabolic gene loci to prevent age-related T cell dysfunction. Aim 2 will determine how SIRT7 overexpression enhances aged senolytic CAR-T function by restoring stem-like properties and, improving serial killing capacity. We will use aged human T cells engineered with SIRT7 overexpression and either uPAR-targeted senolytic CARs or our novel MET CAR platform. Our recently developed MET CAR uses a nanobody-recognition domain that has multiple advantageous biochemical properties to overcome the tonic signaling and exhaustion limitations of prior scFv-based MET CARs. We will test combination therapy of SIRT7-armed uPAR CAR T cells and MET CAR T cells against MET-overexpressing solid tumors embedded in senescent stromal barriers. These studies will establish SIRT7 as an overlooked but central metabolic regulator of T cell aging and introduce SIRT7 overexpression, through co-expression with CAR constructs, as a generalizable strategy to enhance aged CAR-T infiltration, persistence, and efficacy against both cancer and senescent cells, orthogonal to CAR receptor design strategies. This work addresses critical translational geroscience priorities by enhancing autologous CAR-T therapy for elderly cancer patients and advancing senolytic CAR-T approaches for age-related diseases including metabolic dysfunction, inflammatory fibrosis, infections, and autoimmune disorders where senescent cell accumulation drives pathology.