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"Investigating tissue-resident memory T cell differentiation of CAR T cells reveals an unexpected role for CD69"

By

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Friday, March 15th, 2024
12:00 P.M.
Cancer Center, G1196

Join Zoom Presentation:
https://rutgers.zoom.us/j/94163032474?pwd=V3o2Z1hsbWQzck01VW5NWWhyaXVodz09

Meeting ID: 941 6303 2474
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ABSTRACT

Adoptive cell therapy using chimeric antigen receptor-expressing (CAR) T cells has revolutionized the treatment of liquid tumors; however, CAR T cells have had more limited success against solid tumors. CD8+ tissue-resident memory T cells (Trm), which are characterized by surface expression of CD69 and CD103 and a unique transcription factor circuit, are found within solid tumors and associated with improved tumor control. However, it is unclear whether CAR T cells adopt Trm features in the tumor microenvironment and how enhancing Trm differentiation of CAR T cells might impact their efficacy against solid tumors. Using the murine colorectal tumor model MC38, we identified both CD69+CD103- and CD69+CD103+ subsets that express Trm signature genes. To examine if CAR T cells follow a similar differentiation pattern, human carcinoembryonic antigen (hCEA)-specific CAR T cells with either a CD28 or 4-1BB costimulatory domain were transferred into hosts bearing MC38-hCEA tumors. We found the CD28 domain drove expansion of the CAR T population while delaying Trm marker expression compared to 4-1BB and non-CAR T cells. The persistence of a CD69-CD103- subset of CD28 CAR T cells strongly correlated with the number of hCEA-CD28 CAR T cells within the tumor. CD69-CD103- hCEA-CD28 CAR T cells were more proliferative and expressed lower levels of surface markers associated with dysfunction, including PD-1, LAG3, and CD39. We hypothesized CD69 could negatively regulate T cell proliferation and function. Indeed, deletion of CD69 in hCEA-CD28 CAR T cells enhanced their proliferation and accumulation within tumors. CD69 deficiency also leads to higher granzyme B and granzyme A expression on tumor infiltrated transferred cells, compared to the wildtype control, suggesting enhanced cytotoxicity. In summary, hCEA-CD28 CAR signaling delayed Trm differentiation and CD69 expression in solid tumors resulting in prolonged T cell proliferation. CD69 is a tumor microenvironment-induced CD8 T cell suppressor, limiting cell proliferation and granzyme-mediated cytotoxicity within the tumor.