Background

Despite intensive effort, current chimeric antigen receptor modified T cells (CARTs) do not work well for solid tumors. In blood cancers, CARTs easily access to target cells and can “take a break” after each killing of individual tumor cells. In contrast, solid tumor mass limits CART infiltration and create a persistent and multi-dimensional engagement between CART and tumor cells. After CARTs manage infiltrate into tumor mass, they are surrounded by tumor cells, and their movement is further restrained by tumor stroma matrix, which force them under constant stimulation and drive them into exhaustion and death. Conventionally, most CARTs are built from high-affinity monoclonal antibodies (mAb). While such high-avidity CARTs may detect and kill tumor cells of low antigen, they are more prone to exhaustion and death in solid tumors. The aims of this study is to develop proper intermediate-affinity mAbs and intermediate-avidity CARTs for hepatocellular carcinoma (HCC), the 3rd leading cause of cancer death and to test the hypothesis that intermediate-avidity CARTs can resist exhaustion and apoptosis and maintain functions in solid tumors, generating more durable antitumor effects.

Methods

We developed 3 new human glypican-3 (hGPC3)-specific mAbs from immunized mice. The mAbs only stained HCC tumors, but not the adjacent normal liver tissues. One of them, 8F8, bound an epitope close to that of GC33, the frequently used high-affinity mAb, but with ~17 fold lower affinity. We then built and compared the intermediate-avidity 8F8 CARTs to high-avidity GC33 CARTs for their in vitro function and antitumor effects (1).

Results

In vitro, 8F8 CARTs killed both hGPC3high and hGPC3low HCC cells to the same extent as GC33 CARTs, but produced lower cytokines. However, the expansion of 8F8 CARTs was 3-5 folds more than GC33 CARTs after engaging with target cells. 8F8 CARTs were less exhausted and less apoptotic than high-avidity GC33 CARTs. The expansion advantage of 8F8 CARTs was maintained under hypoxia culture condition. Importantly, the 8F8 CARTs also expanded and persisted to a greater extent than GC33 CARTs in vivo, resulting in durable responses against HCC xenografts. Compared to GC33 CARTs, there were 5 folds more 8F8-BBz CARTs in the tumor mass for a longer period of time (figure 1). Remarkably, the tumor infiltrating 8F8 CARTs were much less exhausted and apoptotic, and more functional than GC33 CARTs.

Conclusions

The novel intermediate-avidity 8F8-BBz CART resists exhaustion and apoptosis inside solid tumors, demonstrating a greater and durable therapeutic potential than high-avidity CARTs.

REFERENCE