930 PROTEIN HOMEOSTASIS PROMOTES T CELL STEMNESS AND ENABLES EXHAUSTED TIL FUNCTION IN CANCER

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Background In malignancies, $CD8^+$ tumor-infiltrating lymphocytes (TIL) can target tumor cells, but often fail to cure disease due to chronic TIL activation in the tissue's immunosuppressive tumor microenvironment, resulting in differentiation into an exhausted T cell state. In healthy tissues, T cells differentiate into tissue-resident memory (T_{RM}) in response to infection, and after clearance of antigen can remain to survey and protect from reinfection. When T_{RM}-like TIL are found in cancerous tissue, improved responses to immunotherapy and better patient outcomes are observed; therefore, understanding the connection between exhausted TIL and T_{RM} can inform efforts to manipulate T cell fates towards T_{RM}-like TIL to benefit cancer immunotherapy.

Methods To better understand the relationship among T_{RM}-like TIL, exhaustion states, and T_{RM}, we directly compared T_{RM} from acute viral infection and exhausted TIL from tumors to find proteomic and transcriptional differences between these distinct T cell states. Focusing on genes highly expressed by T_{RM} that may mediate their enhanced functions in tissues, we looked at genes that became downregulated as T cells transitioned to terminal exhaustion. This approach identified numerous genes related to protein homeostasis (proteostasis), including multiple under-characterized E3 ubiquitin ligases.

Results Protein regulation by the ubiquitin-proteosome system is an essential biological process, crucial for cell differentiation, and by investigating proteostasis in TIL, we found that exhausted T cells have an excess of misfolded proteins accumulated in their cytosol. CRISPR knockout studies in acute infection showed that loss of our E3 ubiquitin ligases decreased T cell stemness in tissues, and accelerated differentiation to their terminal fate via decreased ubiquitin-mediated proteasomal protein recycling. When we enforced expression of these ligases in tumor-specific T cells in cancer, we found the transduced T cells showed a decrease in cytosolic misfolded proteins and showed enhanced anti-tumor function: increased accumulation in the TME, upregulation of T_{RM} markers, and increased IFN-gamma production, which resulted in better tumor control and improved mouse survival.

Conclusions These data highlight an underappreciated relationship between proteostasis and T cell stemness, and provide novel avenues of immunotherapeutic approaches for cancer.

Ethics Approval The study was approved by UCSD's Institutional Animal Care and Use Committee, protocol number S04105.

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