Hyperactive (Autoimmunity) vs. Dysfunctional (Cancer) T Cells: Two Sides of the Same Coin

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Cancer and autoimmune diseases present an immunological paradox: T cells adopt opposing functional states. In cancer, T cells become dysfunctional and lose effector function, failing to eliminate malignant cells. In autoimmune diseases like type 1 diabetes (T1D), T cells become hyperactive and inappropriately destroy healthy tissue. Despite chronic antigen stimulation in both inflammatory environments, we observe divergent T cell fates. This study examined what drives T cell dysfunction versus hyperactivation and how hyperactive T cells may behave in the tumor environment (TME) under chronic antigen stimulation. To test this, I utilized a novel mouse model that contains both autoimmunity (T1D) and cancer (SL01-fibrosarcoma). I engineered the SL01 cell line to overexpress IGRP, the target antigen for hyperactive T cells. SL01/IGRP and empty vector control cell lines were implanted; IGRP-expressing tumors regressed, while controls grew progressively. Immunophenotyping of tumors showed a progressive infiltration of IGRP-specific T cells in IGRP-expressing tumors, which were absent in the empty vector tumors. These results suggest that IGRP-specific T cells maintain a hyperactive/cytotoxic state in the tumor despite chronic antigen stimulation in the TME, which is known to drive T cell dysfunction. These findings suggest that there are intrinsic regulatory mechanisms that allow the hyperactive T cells to persist under conditions that normally lead to dysfunction. Programs that drive hyperactivation or dysfunction could be harnessed to reverse or prevent T cell dysfunction in cancer or hyperactivation in autoimmunity. Future studies will utilize ATAC-seq and transcriptomics to better understand the unique regulators of T cell fates.

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