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The fate of low affinity tumor-specific CD8⁺ T cells in tumor bearing mice.

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An important issue in tumor immunology is how to best activate and mobilize the low avidity self/tumor-specific T cells that remain in the T cell repertoire after central and peripheral tolerance. To address this issue, we generated a T cell receptor (TCR) transgenic mouse that expresses a low avidity TCR (Clone 1) specific for a model self-antigen, influenza hemagglutinin (HA). This TCR was expressed by a T cell clone isolated from the HA-tolerant repertoire of an InSHA mouse expressing HA as a self antigen on the pancreatic islet β cells. Clone 1 TCR transgenic CD8⁺ T cells, when transferred into InSHA mice, exhibit very little proliferation in response to cross-presented HA, indicating that the low avidity Clone 1 CD8⁺ T cell persisted in the T cell repertoire of the InSHA mouse from which it was derived largely because it ignored the cross-presented HA self-antigen, and not because it was "tuned" or anergized. In contrast, the expression of HA as a tumor-associated antigen on spontaneous HA-expressing β cell tumors in RIP-Tag2-HA mice leads to activation and tolerance of these low affinity Clone 1 T cells. Notably, these low avidity tumor-specific T cells were tolerized by the tumors more slowly than high affinity transgenic TCR CD8⁺ T cells (Clone 4) specific for the same HA epitope, suggesting that growing tumors progressively tolerize self/tumor antigen-specific T cells with decreasing affinities. Also, the higher affinity Clone 4 T cells were much more effective in an immunotherapeutic setting when combined with tumor-specific CD4⁺ helper cells and/or vaccination with influenza. However, under certain stimulatory conditions, Clone 1 T cells are, in fact, able to exert a significant level of anti-tumor activity. This model should prove very useful in optimizing protocols for immunotherapy of solid tumors with low affinity tumor-specific T cells.

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