Modulating T Cell Cytotoxicity to Enhance Anti-tumor Immunotherapy

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Abstract: Cytotoxic T lymphocytes (CTLs) can recognize and eliminate both incipient and established tumors. As such, there is a great deal of interest in using CTLs for anti-cancer immunotherapy. Because the efficacy of these treatments depends on the intrinsic cytolytic activity of CTLs, understanding how they destroy target cells and how to potentially augment this response is of paramount importance. We have found that perturbations in phosphoinositide 3-kinase (PI3K)-dependent cytoskeletal remodeling can both diminish and dramatically enhance CTL-mediated killing. Our preliminary results suggest that this PI3K pathway controls cytotoxic efficiency by modulating the structure and molecular composition of the immunological synapse, the specialized cell-cell interface that forms between a CTL and its target cell during killing responses. Specific Aim 1 of our proposed studies will investigate this hypothesis using a combination of high-resolution single cell imaging and targeted proteomic studies. In Specific Aim 2, we will use a mouse immunotherapy model to determine if boosting PI3K signaling in CTLs enhances anti-tumor responses *in vivo*. We anticipate that our work will reveal how PI3K-dependent cytoskeletal dynamics influences tumor cell killing both *in vitro* and *in vivo*. We also expect that our studies will provide general insights into the molecular and cellular mechanisms of cytotoxicity. Taken together, these results should aid the development of novel strategies to optimize the efficacy of adoptive CTL therapy in clinical settings.