Visualizing targeted killing of cancer cells by therapeutic T-cells at the nanoscale

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Abstract: Immunotherapy approaches which modulate the activity of cytotoxic T cells, effector cells of the adaptive immune system which selectively target and kill cancer cells, have revolutionized the treatment of select cancer types. However, efforts to generalize these approaches have been hampered by gaps in our understanding of the molecular mechanisms by which T cells engage their targets. As this engagement is mediated by the assembly of a large supramolecular signaling interface (the "immunological synapse", or IS) built by the concerted action of many proteins, traditional structure-based drug design focused on the isolation and structural characterization of individual target proteins faces fundamental limits in immunotherapy development. Here we propose to surmount this limitation by directly visualizing the IS using cutting-edge cellular cryo-electron microscopy (cryo-EM) technology which resolves the three-dimensional structures of protein molecules within their native functional context. We will analyze the nanoscale dynamics of the IS, and the impact of 2 major classes of immunotherapy which operate through this interface: Chimeric Antigen Receptors (CARs) and checkpoint blockade. We will then dissect how target cell properties facilitate evasion of these therapies, anticipating aberrant IS assembly with resistant cells. These efforts will guide the development of next-generation CARs, which we will design to optimize IS nanoscale properties for signaling output and proper T cell activation. In addition to addressing basic questions about immunotherapy mechanisms at the IS that were previously inaccessible, our studies will lay the groundwork for a novel avenue for immunotherapy optimization harnessing the promise of *in situ* structural biology.