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FROM DYNAMIC STRUCTURES TO FUNCTIONAL MATERIALS

Intracellular Peptide Assemblies as Synthetic Regulators of T Cell Function

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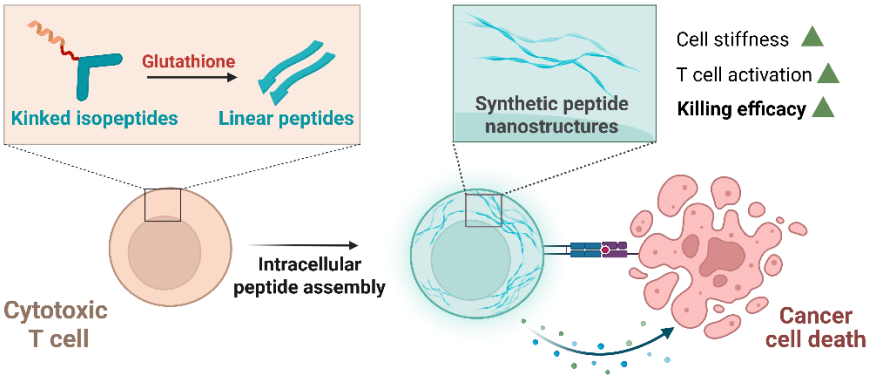

Intracellular peptide assembly enables the bottom-up construction of synthetic architectures within living cells. To date, however, most intracellular assembly systems have been designed to disrupt cellular homeostasis and induce cell death. Here, we demonstrate that intracellular peptide assembly can instead be harnessed to enhance the function of therapeutically relevant immune cells.

We designed glutathione-responsive isopeptides that undergo reductive cleavage and rearrangement into linear self-assembling peptides within activated human cytotoxic T cells. The resulting peptide monomers assemble into synthetic intracellular nanostructures with dimensions comparable to natural cytoskeletal filaments. Correlative light and electron microscopy revealed extensive intracellular assemblies throughout the cytosol and perinuclear regions. Importantly, assembly formation occurred without compromising cell viability or subcellular integrity of the treated T cells.

Intracellular peptide assembly altered the mechanical phenotype of cytotoxic T cells, increasing cellular stiffness and reducing deformability. In parallel, we observed enhanced activation of MAPK and PI3K/Akt/mTOR signalling pathways together with transcriptional changes associated with metabolic fitness. These assembly-driven effects translated into biological function: T cells containing synthetic peptide nanostructures exhibited a ten-fold increase in cytotoxic potency against HER2-positive breast cancer cells in a co-culture model.

This work establishes a new role for intracellular peptide assembly. Rather than acting directly as disruptive synthetic assemblies, intracellular peptide nanostructures can function as active regulators of cellular behaviour, providing a supramolecular strategy for enhancing beneficial cell functions and opening new opportunities for peptide-based cell engineering.