Self-assembled Hexameric TRAIL for Efficient Tumor Apoptosis in vitro and in vivo

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Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a cytokine that causes cell suicide, or apoptosis, when it binds to a death receptor (DR) found on the surface of tumor cells but few on normal cells. As a result, TRAIL has the potential to be used as a cancer-targeting agent. However, its functionally active form, a homo-trimer, is non-covalently linked and easy to break down. Therefore, it has been attempted to maintain trimeric conformation and to further enhance its efficacy by utilizing TRAIL oligomers which trigger DR clustering and stronger apoptotic signals. In this study, we produced a novel hexameric TRAIL scaffold assembled by two distinct single-chain TRAILs (scTRAIL) with a C-terminally fused complimentary motif. We expressed both scTRAILs separately in a bacterial culture and then coupled them together into the hexameric scaffold. The affinity of the scaffold for a death receptor and the strength of self-assembly were investigated using microscale thermophoresis. In vitro and in vivo studies have shown strong therapeutic efficacy of the scaffold in TRAIL-resistant U87-luc cells and HCT116-luc xenografted mouse model.