Presenting trimer-mimetic TNF superfamily ligands with self-assembling nanocages

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Presentation of an endogenous bioactive ligand in its native form is a key factor in determining its bioactivity, stability, and therapeutic efficacy. In this study, we developed a novel strategy for presenting trimeric ligands on nanocages by designing and optimizing based on the rational design and high-resolution structural analysis. We successfully designed a nanocage that presents the TNF superfamily member, TRAIL (TNF-related apoptosis-inducing ligand) in its native-like trimeric structure. The efficacy of TTPNs as an anti-tumor agent was confirmed in vitro studies, which revealed up to 330-fold increased affinity, 62.5-fold enhanced apoptotic activity, and improved stability compared with the monomeric form of TRAIL. In addition, TTPNs effectively induced apoptosis of tumor cells in vivo, leading to effective inhibition of tumor growth. All members of the TNF superfamily share the TNF homology domain and have similar distances between each ecto-domain C-termini, thus the TRAIL ligand can be genetically substituted with other TNF superfamily ligands on the surface of this nature-mimetic delivery platform.