Letter to the Editor

A Better TRAIL Variant for Tumor Cell–Specific Targeting? – Letter

Edwin Bremer and Wijnand Helfrich

Recently, Spitzer and colleagues (1) reported on a novel recombinant TRAIL variant in which trimerisation of soluble TRAIL, known to be essential for apoptotic activity, is enforced by genetic fusion of three TRAIL monomers. This covalent single-chained TRAIL trimer, designated TR3, was also genetically fused to an erythrocyte-specific scFv antibody fragment, to produce fusion protein scFv-TR3. Erythrocytes decorated with scFv-TR3 seemed to acquire proapoptotic bystander-killing capacity toward Jurkat cancer cells.

Previously, we extensively reported on a series of similar scFv-TRAIL fusion proteins with direct tumor targeting and killing capacity, in which we exploit the strong intrinsic capacity of TRAIL to self-associate into stable noncovalent trimers. Spitzer and colleagues referred to part of this body of work (2–4), but wrongfully claim that our homotrimeric scFv-TRAIL fusion proteins are predominantly present as biologically inactive monomers and dimers (1). Contrary to this claim, our size exclusion chromatography data actually showed that scFv-TRAIL fusion proteins are present as active homotrimers, with no detectable inactive monomers or dimers present (2).

In addition, Spitzer and colleagues overlooked the fact that our scFv-TRAIL format is capable of direct trivalent target-cell binding by virtue of three scFv-targeting domains per stable trimer. Therefore, target cell–specific binding capacity by our trivalent scFv-TRAIL fusion protein format strongly benefits from the well-established avidity effect. In contrast, the scFv-TR3 format only has monovalent binding capacity, usually too weak for efficient tumor-cell targeting.

Finally, Spitzer and colleagues claim an enhanced stability of their eukaryotically produced nontargeted TR3 variant, by comparing it to a prokaryotically produced noncovalent TRAIL preparation of a remarkable low stability (>95% loss of activity at 37°C within 30 minutes). To substantiate this claim, we argue that a eukaryotically produced noncovalent TRAIL trimer should have been used. In fact, using the intrinsic capacity of TRAIL to self-associate into noncovalent trimers, we produced thermo-stable scFv-TRAIL fusion proteins, with an activity half-life of ~3 days at 37°C (5). Of note, Spitzer and colleagues evaluated thermo-stability of TR3 for a limited time-span of only 6 hours. Therefore, we argue that the data provided by Spitzer and colleagues are insufficient to warrant the claim of superior stability of TR3.

Taken together, the conclusions by Spitzer and colleagues that TR3 is more stable and a better platform for scFv-based targeting of TRAIL are, in our opinion, insufficiently substantiated by their data and warrant additional detailed side-by-side comparisons with appropriate control reagents.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References


Authors’ Affiliation: University Medical Center Groningen, Department of Surgery, Surgical Research Laboratory, Groningen, The Netherlands
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