International Journal of Cancer
Volume139, Issue4, 15 August 2016, Pages 916-927
https://doi.org/10.1002/ijc.30119

A novel approach for targeted elimination of CSPG4-positive triple negative breast cancer using a MAP-tau based fusion protein

Amoury, M, Mladenov, R., Nachreiner, T., Pham, A.T., Hristodorov, D., Di Fiore, S., Helfrich, W.,Pardo, A., Fey, G., Thepen, T., Kiessling, F., Kolberg, K., Barth,S.

First published: 01 April 2016

Abstract

Chondroitin sulfate proteoglycan 4 (CSPG4) has been identified as a highly promising target antigen for immunotherapy of triple-negative breast cancer (TNBC). TNBC represents a highly aggressive heterogeneous group of tumors lacking expression of estrogen, progesterone and human epidermal growth factor receptor 2. TNBC is particularly prevalent among young premenopausal women. No suitable targeted therapies are currently available and therefore, novel agents for the targeted elimination of TNBC are urgently needed. Here, we present a novel cytolytic fusion protein (CFP), designated αCSPG4(scFv)-MAP, that consists of a high affinity CSPG4-specific single-chain antibody fragment (scFv) genetically fused to a functionally enhanced form of the human microtubule-associated protein (MAP) tau. Our data indicate that αCSPG4(scFv)-MAP efficiently targets CSPG4+ TNBC-derived cell lines MDA-MB-231 and Hs 578T and potently inhibits their growth with IC50 values of ∼200 nM. Treatment with αCSPG(scFv)-MAP resulted in induction of the mitochondrial stress pathway by activation of caspase-9 as well as endonuclease G translocation to the nucleus, while induction of the caspase-3 apoptosis pathway was not detectable. Importantly, in vivo studies in mice bearing human breast cancer xenografts revealed efficient targeting to and accumulation of αCSPG4(scFv)-MAP at tumor sites resulting in prominent tumor regression. Taken together, this preclinical proof of concept study confirms the potential clinical value of αCSPG4(scFv)-MAP as a novel targeted approach for the elimination of CSPG4-positive TNBC.