Dokumenttyp: journal article

Autor(en) des Beitrags:
Geyer, Philipp Emanuel; Maak, Matthias; Nitsche, Ulrich; Perl, Markus; Novotny, Alexander; Slotta-Huspenina, Julia; Dransart, Estelle; Holzof, Anne; Johannes, Ludger; Janssen, Klaus-Peter

Titel des Beitrags:
Gastric Adenocarcinomas Express the Glycosphingolipid Gb3/CD77: Targeting of Gastric Cancer Cells with Shiga Toxin B-Subunit.

Abstract:
The B-subunit of the bacterial Shiga toxin (STxB), which is nontoxic and has low immunogenicity, can be used for tumor targeting of breast, colon, and pancreatic cancer. Here, we tested whether human gastric cancers, which are among the most aggressive tumor entities, express the cellular receptor of Shiga toxin, the glycosphingolipid globotriaosylceramide (Gb3/CD77). The majority of cases showed an extensive staining for Gb3 (36/50 cases, 72%), as evidenced on tissue sections of surgically resected specimen. Gb3 expression was detected independent of type (diffuse/intestinal), and was negatively correlated to increasing tumor-node-metastasis stages (P = 0.0385), as well as with markers for senescence. Gb3 expression in nondiseased gastric mucosa was restricted to chief and parietal cells at the bottom of the gastric glands, and was not elevated in endoscopic samples of gastritis (n = 10). Gb3 expression in established cell lines of gastric carcinoma was heterogeneous, with 6 of 10 lines being positive, evidenced by flow cytometry. STxB was taken up rapidly by live Gb3-positive gastric cancer cells, following the intracellular retrograde transport route, avoiding lysosomes and rapidly reaching the Golgi.
apparatus and the endoplasmic reticulum. Treatment of the Gb3-expressing gastric carcinoma cell line St3051 with STxB coupled to SN38, the active metabolite of the topoisomerase type I inhibitor irinotecan, resulted in >100-fold increased cytotoxicity, as compared with irinotecan alone. No cytotoxicity was observed on gastric cancer cell lines lacking Gb3 expression, demonstrating receptor specificity of the STxB-SN38 compound. Thus, STxB is a highly specific transport vehicle for cytotoxic agents in gastric carcinoma. Mol Cancer Ther; 15(5); 1008-17. ©2016 AACR.