News Release

Title

Targeting ceramide synthase 6-dependent metastasis-prone phenotype in lung cancer cells

Key Points

- The ceramide synthase protein CERS6 is significantly overexpressed in lung cancer, and promotes metastasis.
- Besides metastasis, ceramides serve as intracellular mediators of apoptosis.
- Combined treatment of L-α-dimyristoylphosphatidylcholine (DMPC)-liposome with the glucosylceramide synthase inhibitor D-PDMP induced cell death in association with ceramide accumulation in a CERS6-dependent manner.

Summary

Lecturer Motoshi Suzuki and colleagues at Molecular Carcinogenesis in Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, M.D., Ph.D.) have identified that the ceramide synthase gene CERS6 is significantly overexpressed, in part because of reduced miR-101 expression, and associated with invasion and poor prognosis. CERS6 knockdown altered the ceramide profile, resulting in decreased cell migration and invasion in vitro, which were associated with a decreased frequency of RAC1-positive lamellipodia formation and attenuation of lung metastasis in mice, while forced expression of CERS6 showed an opposite phenotype. Furthermore, combined treatment of L-α-dimyristoylphosphatidylcholine-liposome with the glucosylceramide synthase inhibitor D-PDMP was shown to be a promising synthetic lethal strategy by taking advantage of CERS6 overexpression, which induced cell death in association with ceramide accumulation in a CERS6-dependent manner. Their results suggest that CERS6-dependent ceramide synthesis and maintenance of ceramide in the cellular membrane is essential for lamellipodia formation and metastasis. Targeting this homeostasis may provide a novel therapeutic strategy for CERS6-overexpressing NSCLC.

The manuscript was published online on December 7, 2015 and will appear in the January 2016 issue of The *Journal of Clinical Investigation*.

Research Background

Altered levels of biologically active sphingolipids and enzymes have been considered to be related to types of cellular phenotypes. Ceramides, the central molecules of sphingolipid metabolism, constitute a family of closely related molecules that function as stress coordinators in response to various stress stimuli such as cytokines, ionizing radiation, and chemotherapeutic agents. In addition, they serve as intracellular mediators of apoptosis. However, ceramides' functions leading to cancer pathogenesis in tumor formation and progression have not been well documented.

Research Results

In the present study, Lecturer Motoshi Suzuki and colleagues showed that the miR-101-CERS6 pathway found in cancer cells is closely correlated with invasion- and/or metastasis-prone phenotypes in lung cancer patients, by promoting RAC1-positive lamellipodia/ruffling formation. They further hypothesized that cellular DMPC uptake may force synthesis of the downstream molecule of C14:0 acyl-CoA, which is further elongated into C16:0 acy-lCoA and used for C16:0 ceramide synthesis by the sequential actions of enzymes, including CERS6, and ultimately kill cells with cancer specific manner. In order to develop a promising synthetic lethal strategy for taking advantage of CERS6 overexpression, they screened for inhibitors that induce cancer apoptosis in a synergistic manner with DMPC. Among the ceramide catabolic pathway inhibitors, D-PDMP showed a synergistic effect.

Research Summary and Future Perspective

The present strategy for anticancer action is novel and quite distinct from conventional molecular targeting, which is usually aimed at inhibition of survival kinases, while CERS6 activity is not inhibited, but rather utilized to induce cancer cell-specific killing. Moreover, targeting the miR-101-CERS6 pathway is advantageous, because normal cells do not show obvious CERS6 expression, thus demonstrating resistance to apoptosis. Therefore, induction of synthetic lethality with the CERS6 overexpression nature of NSCLC may become a viable therapeutic choice and potentially benefit lung cancer patients in the future.

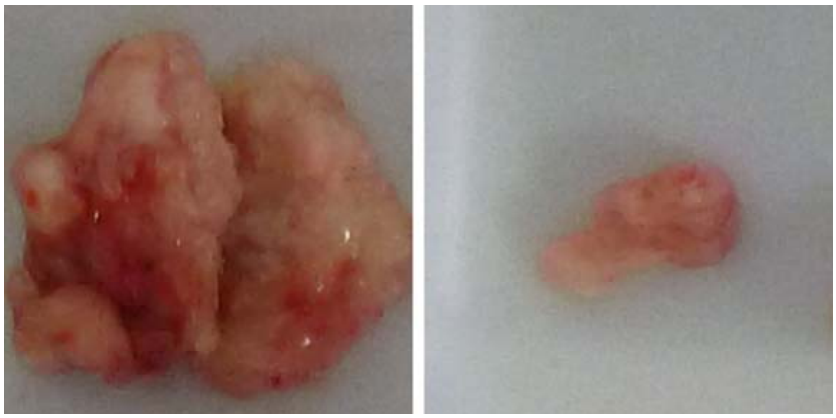
Publication

Motoshi Suzuki1, Ke Cao, Seiichi Kato, Yuji Komizu, Naoki Mizutani, Kouji Tanaka, Chinatsu Arima, Mei Chee Tai, Kiyoshi Yanagisawa, Norie Togawa, Takahiro Shiraishi, Noriyasu Usami, Tetsuo Taniguchi, Takayuki Fukui, Kohei Yokoi, Keiko Wakahara, Yoshinori Hasegawa, Yukiko Mizutani, Yasuyuki Igarashi, Jin-ichi Inokuchi, Soichiro Iwaki, Satoshi Fujii, Akira Satou, Yoko Matsumoto, Ryuichi Ueoka, Keiko Tamiya-Koizumi, Takashi Murate, Mitsuhiro Nakamura, Mamoru Kyogashima, and Takashi Takahashi. Targeting ceramide synthase 6-dependent metastasis-prone phenotype in lung cancer cells. *The Journal of Clinical Investigation*; Dec.7,2015.

Japanese ver.

http://www.med.nagoya-u.ac.jp/medical/dbps_data/_material_/nu_medical/_res/topix/2015/CERS6_20151208jp.pdf

ctrl Drug treatment



Tumor growth suppression by the drug treatment