ICoLA 2019
The 8th International Congress on Lipid &Atherosclerosis(ICoLA)
The 58th Conference of the Korean Society of Lipid & Atherosclerosis
September 5(Thu.) ~ 7(Sat.), 2019, Conrad Hotel Seoul, Republic of Korea

Inhibition of inflammation and tumor progression in mouse model by SMS2 deficiency

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Abstract

Sphingomyelin (SM) synthase is a key enzyme to generate SM and diacylglycerol by converting phosphocholine of phosphatidylcholine to ceramide. SM synthase (SMS) genes consist of three homologs, SMS1, SMS2 and SMSr. SMS1 acts as a homeostatic enzyme to maintain the level of SM in the membrane, whereas SMS2 seems to work when the SM level in the membrane was changed by a diverse stresses such as inductions of apoptosis and autophagy-related cell death. We established SMS2-deficient mouse embryonic fibroblasts (MEF) and conventional SMS2-KO mouse. SMS1-deficient MEF did not grow well, but SMS2-deficient MEF can grow similar to wild type MEF. SMS1 increases SM content, and SMS2 also increases SM but the level is lower than SMS1 does. In addition interestingly SMS2 can increase glucosylceramide content in MEFs. As compared to SMS1-KO mouse SMS2-KO mouse looks normal in terms of ordinary phenotypes.

Dextran sodium sulfate (DSS)-induced mouse acute colitis model has been used to investigate the mechanism of inflammation in colon and by addition of azoxymethane (AOM) adenomatous colon tumor is produced in mice. In SMS2-KO mice DSS-induced colitis was inhibited by increasing of ceramide/SM balance, which suppressed the expression of inflammatory cytokines such as IL-6 and TNF and the recruitment of T lymphocytes to the inflammatory lesions. In addition DSS/AOM-induced polypoid tumors was also inhibited in SMS2-KO mice. Next we examined the effect of SMS2-deficiency in progression of T lymphoma (EL4)-xenograft model. EL4 cell growth was inhibited and overall survival time was prolonged in SMS2-KO mice. Then we investigated the mechanism of tumor inhibition by SMS2-deficient condition and found that the infiltration of host T cells into tumor-microenvironment was suppressed because of increase of ceramide in TIL (tumor-infiltrating lymphocytes) and decrease of SM.

Keywords

Sphingolipids, sphingomyelin synthase, inflammation and cancer