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Inhibitory S-nitrosylation of the deacetylase SIRT1 blocked EMT by Honokiol and inhibited gastric cancer peritoneal dissemination

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The Epithelial-to-Mesenchymal Transition (EMT) may play a key role in tumor peritoneal dissemination of epithelial tumors that involves loss of cell - cell adhesion and increased cell mobility; however, the molecular mechanisms underlying PTM by S-nitrosylation modulates signal transduction are not fully elucidated. We previously reported that Honokiol preferentially evoked ER stress-calpain activity and degrades COX-2 via AhR cleavage. The expression of Silent Information Regulator 1 (SIRT1) has been reported to predict poor survival, associated with the clinical features and prognosis of patients with gastric cancer. Herein, we propose a novel mechanism through which the inhibitory S-nitrosylation of the deacetylase SIRT1 by Honokiol regulates EMT in gastric cancer cells through interferes with the EMT reducing transcription factor slug. Importantly, we found that Honokiol specifically reduced iNOS and induced eNOS enzymatic activity and protein expression. eNOS drive nitrosylation of Sirt1. Honokiol-induced S-nitrosylation of the deacetylase SIRT1 by direct methods analyzed by LC/MS/MS using ESI quadrupole time of flight (QTOF) mass spectrometry and biotin-switch technique. In addition, over-expression of SIRT1 in gastric epithelial cells disrupts the epithelial morphology concomitant with decreased expression of the epithelial marker, E-cadherin and increased expression of mesenchymal markers. In contrast, exposure to Honokiol or silencing SIRT1 in metastatic gastric tumor cells restores cell- cell adhesion and induces a shift toward an epithelial morphology concomitant with increased expression of E-cadherin and decreased expression of mesenchymal markers. We also found that SIRT1 has a physiologically relevant role in endogenous EMT induced by kynurenine (KYN) signaling in gastric cancer cells. We propose that the regulation of EMT by SIRT1 involves modulation of and cooperation with, the EMT inducing transcription factor slug. Specifically, we show that SIRT1 silencing reduces expression of slug and that SIRT1 is recruited to the E-cadherin proximal promoter by slug to deacetylate histone H3 and to reduce binding of RNA polymerase II, ultimately suppressing E-cadherin transcription. We thus identify a necessary role for slug in SIRT1-mediated EMT. Finally, we show that S- nitrosylation of the SIRT1 or reduction of SIRT1 decreases gastric cancer cell migration in vitro and metastasis in vivo in immune-deficient mice, which is largely independent of any general effects of SIRT1 on cancer growth and survival. We therefore identify SIRT1 as a positive regulator of EMT and metastatic growth of gastric cancer cells and our findings implicate S-nitrosylation of the SIRT1 by Honokiol as a potential therapeutic target to reverse EMT and to prevent gastric cancer progression.

Biography

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