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学位論文の題名	<p>Eicosapentaenoic acid suppresses angiogenesis via reducing secretion of IL-6 and VEGF from colon cancer-associated fibroblasts.</p> <p>(colon cancer-associated fibroblast から産生される IL-6 と VEGF に対する EPA の抑制効果とそれに伴う血管新生抑制)</p> <p>Oncology Reports (in press)</p>
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Abstract

Background

Eicosapentaenoic acid (EPA) has certain effects on improving hypercytokinemia of interleukin (IL)-6 in advanced cancer patients. This causes several kinds of anti-cancer effects. While the effects of EPA on cancer cells have been investigated, especially in terms of angiogenesis, its effects on the tumor stroma remain unclear. In this study, we clarified the role of EPA in cancer angiogenesis against colon cancer-associated fibroblasts (CAFs).

Materials and Methods

With established human colon fibroblasts from normal colon stroma (NFs) and colon cancer stroma (CAFs), we evaluated IL-6 and vascular endothelial growth factor (VEGF) secretion with or without EPA treatment using ELISA. Signal blockage in CAFs by EPA was evaluated using western blotting. In vitro anti-angiogenesis effects were evaluated by the angiogenesis assay on Matrigel using human umbilical vein endothelial cells (HUVECs) cultured with the supernatant obtained from CAF cultures with or without EPA.

Results

IL-6 secretion was greater from CAFs (331.5 pg/ml) than from NFs (66.7 pg/ml, $p < 0.001$), and stimulation with lipopolysaccharide (LPS) resulted in greater IL-6 secretion from both fibroblast types than from those without LPS stimulation. While LPS stimulation increased VEGF secretion from these fibroblasts, EPA decreased both IL-6 and VEGF secretion from CAFs. Western blotting revealed that the addition of 30 μ M EPA blocked the ERK phosphorylation signal in CAFs. Furthermore, the angiogenesis assay with Matrigel revealed that the CAF culture supernatants treated with EPA significantly suppressed tubular formation in HUVECs.

General significance

EPA significantly reduced both IL-6 and VEGF secretion from CAFs. These reductions were caused due to the blockage of ERK phosphorylation by EPA. Thus, EPA reduces cancer angiogenesis associated with CAFs.