

Socs3 induction by PPAR γ restrains cancer-promoting inflammation

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The presence of proinflammatory cytokines in the tumor microenvironment can support further growth of established cancers. Docosahexaenoic acid (DHA), a peroxisome proliferator-activated receptor-gamma (PPAR γ) ligand, has been shown to suppress inflammation and limit tumor progression in vivo. Are the anticancer properties of DHA relying on its ability to prevent inflammation? If so, what are the molecular links between the anti-inflammatory properties of DHA and its anticancer effects?

DHA is an n-3 polyunsaturated fatty acid mainly found in fish oil that was shown to contribute to inflammation resolution by preventing the release of proinflammatory mediators in vivo.¹ DHA has also been associated with health benefits in chronic inflammatory diseases such as cancer. However, the molecular links between the anti-inflammatory effects of DHA and its clinical activity remain elusive. In a cancer setting, the existence of an inflammatory milieu within the microenvironment of established cancers is known to further support tumor cell survival and neoangiogenesis.² Interleukin-17-producing CD4 T cells (Th17 cells) have been shown to trigger inflammatory responses and tissue inflammation in vivo. We and others have shown that Th17 cells can support cancer progression.³⁻⁵ We also found that IL-17a secretion from CD4 T cells could compromise the efficacy of anticancer chemotherapies.⁶ We have thus explored whether DHA could prevent the cancer-promoting activity of Th17 cells.

We first tested in vitro the effect of DHA on Th17 cell generation from na  ve mouse CD4 T cells. For this, differentiation of na  ve T cells was performed in absence of antigen-presenting cells

to investigate the cell-intrinsic effects of DHA on CD4 T cells. Addition of DHA markedly reduced mouse and human Th17 cell differentiation as assessed by dampened IL-17 secretion. Accordingly, na  ve CD4 T cells obtained from mice under a DHA-enriched diet had reduced ability to differentiate into Th17 cells. We have uncovered the molecular sequence of events accounting for the ability of DHA to prevent Th17 cell differentiation. We found that DHA interfered with the signal transducer and activator of transcription 3 (Stat3) signaling pathway in developing Th17 cells.⁷ Under Th17-skewing conditions, DHA first activates PPAR γ , which binds to the suppressor of cytokine signaling 3 (Socs3) promoter and favors the expression of SOCS3, which eventually prevents Stat3 phosphorylation and *Il17* gene transcription (Fig. 1).⁷ Finally, in the mouse B16 melanoma and the 4T1 mammary adenocarcinoma tumor models, we found that the anticancer effect of a dietary DHA intake was dependent on IL-17 secretion from CD4 T cells, thereby establishing a link between the ability of DHA to inhibit the secretion of proinflammatory IL-17 and its in vivo anticancer effects.

Dietary supplementation of DHA has been shown to alleviate the severity of intestinal inflammation in experimental models of colitis and in inflammatory bowel disease in humans. Accordingly, olive oil supplemented with fish oil rich in DHA also exhibited a therapeutic effect in the DSS-induced colitis model through the reduction of inflammation. The anti-inflammatory effects of DHA have also been illustrated in experimental autoimmune encephalomyelitis, where mice under a DHA-enriched diet featured decreased

autoimmunity symptoms. While the crucial role of Th17 cells in promoting tissue inflammation and autoimmunity has been documented in the aforementioned autoimmune disorders, whether the beneficial effects of DHA in vivo were attributable to a direct action of DHA on differentiating Th17 cells has remained unclear. Our study has shown that DHA directly suppresses mouse and human Th17 cell differentiation. Not only do these results extend DHA anti-inflammatory properties to a cancer setting, but they also suggest that DHA may suppress inflammation, at least in part, by directly preventing the induction of pathogenic Th17 cells.

Activation of PPAR γ has been shown to reduce inflammation and the PPAR γ agonist troglitazone has been clinically used as an anti-inflammatory drug in diabetes. Activation of PPAR γ has been associated with reduced inflammation. PPAR γ ligands such as pioglitazone are currently used to manage insulin resistance but the molecular mechanisms involved remain elusive. Some studies have even proposed that PPAR γ ligands might act independently of PPAR γ activation. In this regard, given that Th17 cells have been proposed to contribute to diabetes development, the recent identification of the ability of PPAR γ ligands to suppress Th17 cell induction possibly provides a mechanistic explanation of the anti-inflammatory activity of Troglitazone in humans.^{7,8} However, Troglitazone hepatotoxicity has limited its clinical use. In this regard, our observations suggesting that DHA, a nutrient relatively devoid of toxicity, mirrors the effects of PPAR γ activation on Th17 cells might represent an attractive alternative approach for treatment of Th17-related diseases.

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Submitted: 06/10/13; Accepted: 06/11/13

<http://dx.doi.org/10.4161/cc.25370>

Comment on: Berger H, et al. Cancer Res 2013; 73:3578-90; PMID:23619236; <http://dx.doi.org/10.1158/0008-5472.CAN-12-4018>

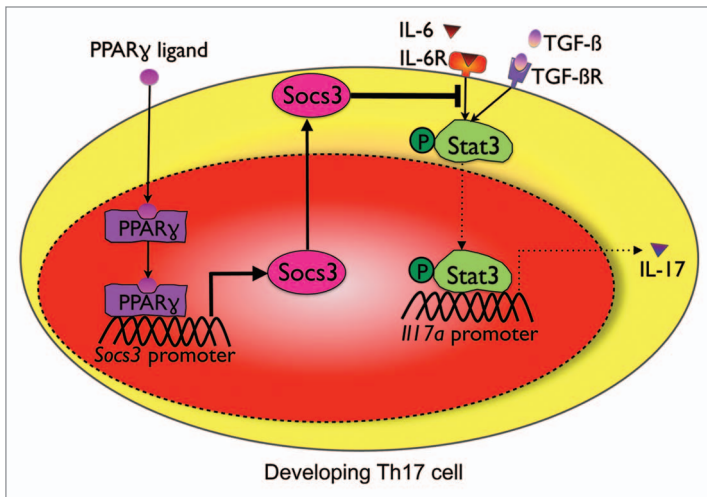


Figure 1. PPAR γ -induced SOCS3 expression represses Th17 cell differentiation. Initiation of Th17 cell differentiation with TGF- β and IL-6 leads to phosphorylation of Stat3. Phosphorylated Stat3 binds to the IL17a promoter and favors IL-17 secretion. However, in the presence of a ligand of PPAR γ such as Docosahexaenoic acid, PPAR γ binds to and transactivates the Socs3 promoter, thereby driving Socs3 expression. Socs3 subsequently prevents the phosphorylation of Stat3, resulting in decreased IL-17 secretion from developing Th17 cells.

Despite its proinflammatory activity, IL-17 exerts contrasting effects on cancer cell growth depending on the cancer cell type. In humans, IL-17 was associated with poor prognosis in colorectal, lung

and hepatocellular cancers. Conversely, the presence of intratumor IL-17 is a good prognostic factor for gastric, ovarian and prostate cancer. While the molecular mechanisms underlying these

discrepancies require further investigations, these observations suggest that, in vivo, downregulation of IL-17 levels using DHA will not be beneficial for all cancer types. We thus speculate that the use of DHA for the treatment of established malignancies should be restricted to cancers where IL-17 is detrimental.

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