Omega-3 fatty acids differentially reduced expression of neutrophil degranulation-associated proteins in endothelial cells during IL-6 exposure

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Background: Neutrophil degranulation contributes to atherogenesis and tissue injury. Mixed omega-3 fatty acid (n3-FA) formulations of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have failed to reduce CV events compared to EPA only (REDUCE-IT), but the mechanisms are not understood.

Purpose: The purpose of this study was to compare the effects of EPA and DHA on expression of proteins linked to neutrophil degranulation in the vascular endothelium in vitro.

Methods: Human umbilical vein endothelial cells (HUVECs) were pretreated with EPA or DHA at equimolar levels (10 μM) for 2 h, then challenged with IL-6 at 12 ng/ml for 24 h. Proteomic analysis was performed using LC/MS to measure relative protein expression. Only significant ($p<0.05$) changes between treatment groups >1-fold were analyzed.

Results: In the Reactome "neutrophil degranulation" pathway, EPA and DHA downregulated 27 and 14 proteins, respectively, (p=9.97E-9 and 5.30E-4, respectively) relative to IL-6 alone. There were 12 protein changes common to both n3-FAs, including heme oxygenase-2 and ferritin light chain. EPA downregulated 15 proteins unlike DHA, including peroxiredoxin-6 and mitogen-activated protein kinase-1 (MAPK1). A combined 21 proteins downregulated by EPA and DHA versus IL-6 were upregulated by IL-6 alone relative to vehicle. EPA also increased expression of Rho-associated protein kinase-1 (ROCK-1), a protein downregulated by IL-6 alone and unaffected by DHA.

Conclusions: EPA and DHA differentially modulated expression of proteins linked to neutrophil degranulation. The distinct effects of EPA on protein expression may contribute to reduced inflammation in vascular injury compared to DHA.