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Docosahexaenoic fatty acid favorably alters inflammatory pathways and macrophage polarization in the aorta of atherosclerotic mice

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The omega 3 PUFA docosahexaenoic acid (DHA) has potent anti-atherosclerotic properties but its molecular action at the vascular level remains poorly explored. Knowing the broad range of DHA targets at the cellular and molecular levels, microarray analysis was chosen to evaluate the effect of DHA intake on the overall gene expression in the aorta of atherosclerosis prone LDLR^{-/-} mice. Mice were fed (20 wks) an atherogenic diet and received daily oral gavages with either oleic acid-rich oil or a mixture of oils providing 2% of energy as DHA. As anticipated, DHA intake exerts a potent cardioprotective effects, i.e. reduced systolic blood pressure (-16 mmHg, p<0.01), plasma levels of cholesterol (-28%, p<0.001) and triacylglycerols (-37%, p<0.01), and lowered the extent of atherosclerosis measured in the aortic root (-35%, p<0.001). Bioinformatics analysis of microarray data (functional enrichment and canonical pathway analysis) of the aortic gene expression revealed that DHA supplementation mostly affected inflammatory processes and innate immunity, with a remarkable number of down-regulated genes associated with pro-inflammatory activity of immune cells (e.g. CCL5, CCR7), cell movement (e.g. ICAM-2, SELP, PECAM-1), and antigen presentation (e.g. HLA-DQA1, HLA-DRB1, HLA-DQB1, H2-Q8). Interestingly, the expression of several significantly modulated genes were identified as markers of macrophage phenotype, suggesting their preferential orientation towards a M2 reparative phenotype. This hypothesis was confirmed by the immunohistological analysis of a specific biomarker of M2 macrophage (arginase 1), which abundance was increased in the aortic root of the DHA supplemented group (+111%, p=0.01). All together, these results suggest that DHA mainly interfere with atherosclerosis progression by limiting inflammation probably through the orientation of macrophages towards a M2 reparative phenotype.